SECTION 11

The patient with acute kidney injury (and critical care nephrology)

CHAPTER 220

Definitions, classification, epidemiology, and risk factors of acute kidney injury

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Introduction: the changing concept of acute kidney injury

Since the early days of medical descriptions of acute kidney injury (AKI, previously known as acute renal failure) different definitions have been used, ranging from very sensitive to very specific (Eknoyan, 2002) (Table 220.1). One of the earliest descriptions in medical literature was by William Heberden in 1802 (Heberden, 1802; Kellum et al., 2002). 'Ischiuria renalis', as AKI was named then, was defined by the very specific definition of 'atotal suppression' of urine output. A much more sensitive definition was used during World War I to describe 'trench or war nephritis', a condition of probably post-infectious (viral) aetiology, and characterized by proteinuria (Raw, 1915; Dunn and McNee, 1917). During World War II, rhabdomyolysis-induced AKI was defined by anuria (Bywaters and Beall, 1941). In the modern era, small decreases in glomerular filtration rate (GFR), as observed in contrast nephropathy, nowadays called contrast induced AKI (CI-AKI) are considered clinically relevant (Harjai et al., 2008). Recently, the concept of tubular damage without decreased GFR, so-called subclinical AKI, was introduced (Murray et al., 2008; Bellomo et al., 2012; Haase et al., 2012) (see below).These examples illustrate that application of more sensitive or specific definitions will have an important impact on the incidence of AKI. Nowadays AKI is a heterogeneous syndrome of different aetiologies, and often multifactorial, with several different insults occurring in the same individual. The multiple aetiologies of AKI obviously need specific diagnostic tools. The clinical profile of AKI patients has shifted over the years, in particular during the period 1970 to 1990 (Lameire et al., 2006). During that period, the patients with AKI were older and had more comorbid diseases. AKI frequently developed as a consequence of major surgery, exposure to potentially nephrotoxic agents, such as iodinated contrast media, and during treatment with angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (ACEIs/ARBs) or non-steroidal anti-inflammatory drugs (NSAIDs).

Definition and gradation of acute kidney injury

A literature review in 2002 found that at least 35 different definitions of AKI were used, ranging from very sensitive to very specific (Kellum et al., 2002).

The RIFLE classification

Following this review, the Acute Dialysis Quality Initiative (ADQI) expert group developed the RIFLE classification for AKI, which was later modified by the Acute Kidney Injury (AKIN) group, and the Kidney Disease: Improving Global Outcomes (KDIGO) group (Table 220.2) (Bellomo et al., 2004; Mehta et al., 2007; Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group, 2012).

Given the ambiguities of traditional methods of diagnosing AKI and the need to have a more practical definition that included earlier, less severe stages, the ADQI experts proposed, based on a broad consensus, a system for diagnosis and classification of acute functional impairments over a wide range of kidney dysfunction (Bellomo et al., 2004). The acronym RIFLE denotes increasing severity classes *R*isk, *I*njury, and *F*ailure; and the two outcomes, *L*oss and *E*nd-stage renal disease (ESRD). The three severity grades are defined on the basis of changes in serum creatinine (SCr) or urine output where the worst of each criterion is used, whereas the two outcome criteria, Loss and ESRD, are defined by the duration of kidney failure. Around the world, studies including many thousands of patients have evaluated the RIFLE criteria to classify patients with AKI (Hoste and Schurgers, 2008; Ricci et al., 2008). Large series from the United States, Europe, and Australia, each including several thousands of patients, have consistently shown that AKI defined by RIFLE is associated with significantly decreased survival and that increasing severity of AKI defined by RIFLE stage leads to increased risk of death (Uchino et al., 2006; Ostermann and Chang 2007a; Bagshaw et al., 2008a, 2008b, 2008c, 2008d; Hoste and Schurgers, 2008).

The AKIN classification

More recently, AKIN, an international network of AKI researchers, endorsed the RIFLE criteria but proposed some small modifications by (1) broadening of the 'Risk' category of RIFLE to include an increase in absolute SCr concentration of at least 0.3 mg/dL (26.4 μmol/L) even if this does not reach the 50% threshold as long as it is documented to occur within a 48-hour window (this modification increases the sensitivity especially for patients with underlying renal disease) and (2) categorizing patients as 'Failure' if they are treated with renal replacement therapy (RRT), regardless of what their SCr or urine output is at the point of initiation

Table 220.1 Changing concept of acute kidney injury

1802 W. Heberden (Heberden, 1802)	Ischiuria renalis—anuria
1915 Raw (Raw, 1915)	War or trench nephritis—proteinuria
1941 Bywaters and Beal (Bywaters and Beall, 1941)	Crush injury—oliguria caused by myoglobin
1945 W. Kolff	First successful kidney dialysis
1960 Teschan (Teschan et al., 1960)	Concept of early initiation of RRT for AKI
1996 Levy (Levy et al., 1996)	Contrast nephropathy associated with mortality serum creatinine increase of ≥ 25% or 0.5 mg/dL
2004 Acute Dialysis Quality Initiative (ADQI) (Bellomo et al., 2004)	RIFLE classification for AKI 6-hour oliguria or SCr increase ≥ 50%
2008 Acute Kidney Injury Network (AKIN) (Murray et al., 2008)	Concept of kidney damage, occurring before glomerular filtration rate is decreased (AKI)

of RRT (Mehta et al., 2007). These refined consensus definitions are based on studies linking poor patient prognosis to even a small absolute increase of 0.3 mg/day (26.4 μmol/L) SCr (Lassnigg et al., 2004; Chertow et al., 2005; Newsome et al., 2008). Finally, an additional modification to the RIFLE criteria is proposed for paediatric patients in order to better classify small children with acute-on-chronic disease (Akcan-Arikan et al., 2007).

Similar to the RIFLE classification, the AKIN modification has been validated in several large studies, and increasing severity grade of AKI defined by AKIN, is associated with increased risk of mortality (Bagshaw et al., 2008a; Ostermann and Chang 2008; Joannidis et al., 2009; Mandelbaum et al., 2011). Although there was presumed increased sensitivity by the AKIN classification, RIFLE shows better robustness and a higher detection rate of AKI at least during the first 48 hours of admission to the intensive care unit (ICU) (Joannidis et al., 2009).

The KDIGO classification

The KDIGO workgroup on AKI amalgamated these various modifications into a single definition and staging system (see Table 220.2) (Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group, 2012). In the KDIGO definition, the time frame for an absolute increase in SCr of 0.3 mg/dL (26.4 μmol/L) is retained from the AKIN definition (48 hours) while the time frame for a 50% increase in SCr in the 7 days, was originally suggested by the RIFLE criteria. The KDIGO criteria only utilize changes in SCr and urine output, and not changes in GFR for staging, with the exception of children under the age of 18 years, for whom an acute decrease in estimated GFR to < 35 mL/min per 1.73 m^2 is included in the criteria for stage 3 AKI (Akcan-Arikan et al., 2007). As with the RIFLE and AKIN staging systems, patients should be classified according to criteria that result in the highest (i.e. most severe) stage of injury.

Not many studies have validated the definitions and classification proposed by the KDIGO guidelines; some critical remarks on the KDIGO proposal have been formulated by other guideline-making bodies such as the ad hoc working group of the

Table 220.2 The definition and staging system for AKI

(A) AKI is defined by either an increase of SCr or an episode of oliguria:

- Increase of SCr > 0.3 mg/dL within 48 hours, or
- Increase of SCr by > 1.5-fold above baseline, known or assumed to have occurred within 7days, or
- Urine volume < 0.5 mL/kg/hour for 6 hours.

(B) AKI severity is staged by the worst of either SCr changes or oliguria

Stage	SCr	Urine output
1	≥ 1.5–1.9 times baseline *Or* > 0.3 mg/dL increase	< 0.5 mL/kg/hour for 6–12 hours
2	≥ 2.0–2.9 times baseline	< 0.5 mL/kg/hour for ≥ 12 hours
3	≥ 3.0 times baseline *Or* Increase of Scr to ≥ 4.0 mg/dL *Or* RRT *Or* In patients < 18 years, decrease of eGFR to < 35 mL/min per 1.73 m^2	< 0.3 mL/kg/hour for ≥ 24 hours *Or* Anuria for ≥ 12 hours

Notes:

- A relative increase of SCr is measured to a so-called baseline SCr. Baseline SCr is defined as the SCr concentration occurring before the episode of AKI.
- When baseline SCr is unknown and the patient has no history of CKD, the RIFLE classification suggested the use of a so-called MDRD derived baseline Cr. This is based upon the assumption that baseline GFR is > 75 mL/min/1.73 m^2. It has been proven that this renders a less reliable estimate.
- In the RIFLE classification, Risk and Injury could also be assessed by changes in GFR. This was not withheld in the two modifications, and should therefore, not be used at present.

European Renal Best Practice working party (Fliser et al., 2012), the Canadian Society of Nephrology (James et al., 2013), and the KDOQI US Commentary (Palevsky et al., 2013). Most of the concerns about the KDIGO definitions of AKI focus on the clinical application in the individual patient of small increases in absolute SCr values, the added value of considering urine output, the determination of the baseline SCr, and the suggestion of stage-based diagnostic and therapeutic interventions. A recent study (Wang et al., 2013) proposed a 'novel' approach to classification and staging of AKI using 'absolute' rather than relative increases in SCr. Compared with the current KDIGO consensus AKI staging, delta-creatinine staging was found to be relatively simple and of better utility for large-scale epidemiologic studies. In this proposal, using delta-SCr allows for use of an index SCr derived from samples mostly obtained on admission of the patient rather than referring to pre-hospitalization baseline values, which are indeed not always readily available. Of course, making a classification simpler not necessarily means that it is more exact. As explained below, the use of an admission SCr is less sensitive for diagnosing AKI and the admission index SCr is even more susceptible to the same potential confounding influences such as fluid overload and eventually decreased creatinine production.

To the best of our knowledge there is only one study where the three classical definitions and classifications for AKI (RIFLE, AKIN, and KDIGO) have been compared with a more traditional

worsening renal function (WRF) definition, as used in the particular case of acute cardiorenal syndrome (Roy et al., 2013). The comparison revealed that there was a stepwise increase in primary outcome with increasing stages of AKI severity using RIFLE, KDIGO, or AKIN ($P < 0.001$). In direct comparison, there were only small differences in predictive abilities between RIFLE and KDIGO and WRF concerning clinical outcomes at 30 days (area under the curve (AUC) 0.76 and 0.74 vs 0.72) as well as for KDIGO and WRF at 1 year (AUC 0.67 vs 0.65).

Another recent study compared the incidence and the early and late mortality of AKI diagnosed by RIFLE and KDIGO criteria (however, without the urine output criteria) in the first 7 days of hospitalization due to an acute myocardial infarction (AMI) (Rodrigues et al., 2013). It appeared that KDIGO criteria detected substantially more AKI patients than RIFLE among AMI patients. Patients diagnosed as AKI by KDIGO but not RIFLE criteria had a significantly higher early and late mortality. In this study, KDIGO criteria were thus more suitable for AKI diagnosis in AMI patients than RIFLE criteria.

Despite these efforts to standardize the definition and classification of AKI, there is unfortunately still inconsistency in their clinical application and most studies actually use a variation of the definition. Only a minority of studies have included the precise urinary output criteria despite its apparent ability to identify additional cases (Hoste et al., 2006; Cruz et al., 2007; Mandelbaum et al., 2011), and many studies have excluded patients whose initial SCr is already elevated. Many cases of community-acquired AKI would be missed by limiting analysis to documented *increases* in SCr. Although, in the future, biomarkers of renal tubular cell injury may identify patients with AKI, the current gold standard uses specific changes in SCr and urine output.

Specific comments on the definition and grading of acute kidney injury

Time frame

In order to define acute changes in kidney function the patient should fulfil the criteria within a limited time frame. This time frame is only for the *definition* of AKI, and is not applicable for the *staging* of the AKI severity grade. Only a patient who has an increase of SCr ≥ 0.3 mg/dL (26.4 μmol/L) within a 48-hour period, or who within a 7-day period shows a ≥ 50% increase of SCr above the reference SCr or who has a 6-hour period of oliguria, defined as < 0.5 mL/kg/hour of urine output, fulfils the definition of AKI. If the increase of SCr or decrease of urine output takes place over a longer period, the patient has no AKI according to the KDIGO definition of AKI. This means that for every increase of SCr, one should compare it to all SCr measurements in the preceding 7-day period.

Baseline and reference serum creatinine

Although all these consensus criteria (RIFLE, AKIN, and KDIGO) have helped standardize the approach to the diagnosis and staging of AKI, there still remain specificity limitations. One of the most discussed limitations is the importance of determining the baseline kidney function in patients admitted in AKI and in whom this baseline value is not known. The lack of a uniform approach to estimate this baseline has recently been shown to compound the risk for AKI misclassification, hindering effective comparisons of this disease between settings (Bagshaw et al., 2009; Lafrance and Miller, 2010b; Siew et al., 2010). A standard definition for baseline SCr does not exist, leading to heterogeneity across research studies (Gaiao and Cruz, 2010) and the potential for misinterpreting the true nature of perturbed kidney function in hospitalized patients (Lafrance and Miller, 2010b). The choice of the estimation technique used to obtain the baseline SCr value has an effect on the prevalence of AKI, the severity (or stage) of disease, and on the mortality risk associated with various stages of AKI (Cruz et al., 2009; Gaiao and Cruz, 2010).

Several strategies for estimating the basal SCr have been proposed (Pickering and Endre 2010; Siew et al., 2010; Zavada et al., 2010; Candela-Toha et al., 2012), ranging from the use of an estimation of SCr by backward calculation from a presumed 'standard GFR' of 75 mL/min/1.73 m^2, use of the SCr value at admission, or the peak SCr in the AKI episode under consideration. Whereas RIFLE and KDIGO suggest using the back calculation, AKIN recommends using the evolution of SCr relative to the first observed value in that episode, while the European Renal Best Practice position statement and others (Wang et al., 2013) recommend using the admission SCr (Fliser et al., 2012).

However, Siew et al. (2010) reported that the use of the admission SCr value as a baseline resulted in a nearly 50% reduction in the detection of AKI compared with that using a known baseline SCr. It appeared that the MDRD-estimated baseline SCr had a significantly higher sensitivity for 'detecting' AKI than the two other methods. Although the use of SCr levels at admission resulted in the least amount of misclassification, this parameter also had the lowest sensitivity (38.9%) for diagnosis of AKI. When admission SCr levels were used, nearly half of the 'true' AKI cases were missed: 25.5% of the cohort had AKI when true baseline SCr levels were used, versus 13.7% with use of admission SCr levels. This decrease is perhaps best explained by the missed diagnosis of community-acquired AKI that improves or stabilizes during hospitalization (Srisawat and Kellum, 2011). Zavada et al. (2010) found that use of a Modification of Diet in Renal Disease (MDRD) equation-estimated baseline creatinine could result in either overestimation or underestimation of some mild (Risk) AKI cases but is unlikely to misclassify patients in Injury and Failure RIFLE classes. Thus, it is important to consider the goal of AKI classification when selecting a baseline. For clinical purposes, it may be important 'not to miss' any cases of potential AKI. Therefore, using the MDRD equation to estimate a baseline kidney function, at least provisionally, makes sense. The same may hold true for epidemiologic studies where some degree of overestimation or underestimation may average out and not affect overall rates. On the contrary, for research studies where precise case adjudication is critical, estimated creatinine should be used with caution, if at all, especially for defining mild (stage 1) AKI (Srisawat and Kellum, 2011).The accuracy of commonly used methods for estimating baseline SCr was compared with that of a reference standard adjudicated by a panel of board-certified nephrologists in 379 patients with AKI or chronic kidney disease (CKD) admitted to a tertiary referral centre (Siew et al., 2010). It was found that agreement between estimating methods and the reference standard was highest when using SCr values measured 7–365 days before admission, suggesting that the mean outpatient SCr measured within a year of hospitalization most closely approximates nephrologist-adjudicated

basal SCr values. A follow-up study confirmed that the use of these averaged outpatient SCr values also yields a reliable value among high-risk patients, already suffering from pre-existing CKD (Siew et al., 2012).

Caveats in using the serum creatinine

Reduction in creatinine production

A first caveat relates to recent findings that reduction in GFR can occur in critically ill patients with unchanged creatinine levels because of a reduction in creatinine generation rate correlating with the degree of illness severity (Wilson et al., 2012; Pickering et al., 2013).Thus in sicker patients, increases in creatinine concentration could be smaller and occur more slowly than in less sick patients with the same AKI severity. Such reductions in creatinine generation rate could have a major impact on the timing of AKI diagnosis and the assessment of its severity, in particular in critically ill, septic patients.

Dilution of serum creatinine by volume overload

A second caveat further adding to the uncertainty is the identification of changes in the patient's fluid balance as an additional confounder impacting the SCr concentration. Liu et al. (2011) examined the occurrence of AKI in critically ill patients with the acute respiratory distress syndrome (ARDS) randomized to a fluid conservative versus fluid liberal management strategy in the ARDS Network Fluid and Catheter Treatment study. After adjusting SCr measurements for fluid balance, notable increases in the incidence of stage 1 AKI were noted in each study arm (conservative, 57% vs 51%; liberal, 66% vs 58%). No impact of the different fluid management strategies on the incidence of AKI in AKI stages 2 or 3 was noted. Comparable mortality rates between those patients in whom the AKI diagnosis was 'masked' versus those with known AKI before fluid correction were also observed (31% vs 38%). These findings suggest that in addition to being an important prognostic factor (Bouchard et al., 2009; Grams et al., 2011), variations in fluid balance can cause the diagnosis of AKI to be missed or delayed in high-risk patients when using SCr-based definitions alone. As further iterations of these definitions are refined, these limitations continue to underscore the need to effectively segregate evolving aspects of injury from changes in function.

Urine output criteria

The use of urine output criteria implicates precise hourly measurement of urine output. The definition requires that urine output is < 0.5 mL/kg *every hour* for a 6-hour period. This limits its use to ICU patients with a urinary catheter. Many studies have used variants of the original urine output criteria, for example, urine output < 3 mL/kg in a period of 6 hours, use of fixed blocks of 6 or 8 hours similar to the nurses' shift, back calculation of 24-hour urine output, etc. (Macedo et al., 2011).

Finally, there is no indication what patient weight should be used for the oliguria criterion. It seems reasonable to use the 'baseline' weight of the patient, as actual patient weight in critically ill patients is not only rarely measured, but varies according to fluid overload and weight loss/muscle wasting secondary to critically illness. In patients with morbid obesity, antibiotic dosing is recommended according to adjusted body weight. Although this adjustment may also be reasonable for the definition of AKI, there are no data to support this.

Practical example of defining AKI

Table 220.3 shows two examples of patients with changes in renal function that are difficult to diagnose. Patient A has prior SCr recorded in her medical record while patient B does not. Both patients present with the exact same SCr. Patient A is a 65-year-old white female. She does not fulfil the SCr criteria for AKI on presentation because her SCr is < 50% higher than her baseline. Furthermore, she never has a *documented* increase in SCr of ≥ 0.3 mg/dL within any 48-hour period. 'Documented' is a key term here because the AKIN modification requires a documented increase in SCr. However, on day 3 the patient reaches a 50% increase from the value she had 6 months prior. Here the clinician must determine if he/she believes that the value of 1.8 mg/dL (159 μmol/L) is the patient's true baseline and should thus be used as the reference creatinine to define (and stage) AKI. The clinical context as well as physical examination and laboratory findings will have to be considered. If patient A was being seen for an acute condition known to be associated with AKI (e.g. sepsis) it would be more likely that this is indeed a case of AKI. The urine output may also be helpful even if it does not meet the threshold for diagnosis. For example, if the patient made very little urine in the first 2–3 hours of hospital care and only started to pass urine after fluid resuscitation, the clinician might reasonably infer that the urine output had to be low for some time prior to presentation. In addition, the microscopic appearance of the urine (e.g. casts) might provide additional clues to whether this is an acute event. Conversely, if the patient was seen for a routine visit in the clinic, one would be inclined to attribute the creatinine pattern shown in Table 220.3 to something other than AKI (e.g. progression of underlying CKD).

Patient B represents a different challenge because no baseline value for SC is known. Here, the clinical context and other clues become critical. If patient B was an otherwise healthy 25-year-old lady with no past medical history, normal-sized kidneys on ultrasound, and presenting from a motor vehicle accident where she was trapped for several hours, one might reasonably assume that her baseline SCr was < 1.0 mg/dL (88.4 μmol/L) and infer a diagnosis of AKI based on an acute change in SCr. However, if the patient was a 50-year-old black male with a history of hypertension and diabetes who was being seen for elective surgery, one might well come to a different conclusion. Example B is also interesting because the SCr is improving. Certainly by day 6 one makes a retrospective diagnosis of AKI since the baseline creatinine was likely not > 1.3 mg/dL (> 115 μmol/L) and the value of 2.5 mg/dL (221 μmol/L) on presentation was in fact consistent with AKI.

Epidemiology of acute kidney injury

Incidence of AKI

Prior to the publication of the RIFLE classification for AKI criteria, a whole range of definitions for AKI was used, limiting the possibility

Table 220.3 Creatinine in mg/dL for two hypothetical patients presenting with kidney impairment

	6 months ago	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6
Patient A	1.8	2.5	2.6	2.7	2.5	2.4	2.4
Patient B	??	2.5	2.6	2.2	1.9	1.7	1.3

to compare results across studies (Kellum et al., 2002; Hoste and Schurgers, 2008). In recent years, virtually all studies have used the RIFLE or AKIN or KDIGO consensus definitions for AKI, and the use of alternative definitions has become negligible (Bellomo et al., 2004; Mehta et al., 2007). In the past, many studies reporting on epidemiology of severe AKI used the number of patients who were treated with RRT as a convenient way of counting cases. Although this may seem to be an objective criterion at first glance, it is in fact highly subjective since there are no agreed upon criteria for initiation of RRT. Over the years, criteria for initiation of RRT have indeed shifted from 'rescue therapy' for life-threatening uraemic complications, such as pulmonary oedema, uraemic encephalopathy, or pericarditis (i.e. 'renal function replacement'), to a therapy that is initiated earlier in the course of AKI in this way facilitating other therapies such as parenteral nutrition (i.e. 'renal support'). Approximately 5–10% of general ICU patients will be treated with RRT (Metnitz et al., 2002; Uchino et al., 2005; Nisula et al., 2013). Depending on the patient case mix this may vary from 2% to 20% of ICU patients. This reflects a population incidence of 110–295 patients per million inhabitants per year (pmp/year) (Bagshaw et al., 2005; Waikar et al., 2006; Ali et al., 2007; Hsu et al., 2007; Prescott et al., 2007;). This incidence is comparable to that of ARDS, severe sepsis, and acute myocardial infarction (Goss et al., 2003; Harrison et al., 2006; Steg et al., 2012).

Community-acquired AKI, and hospitalized non-ICU patients

The incidence data on community-acquired AKI are relatively scarce, and most are generated in developed countries. In recent years, some large laboratory-based studies have been published on the epidemiology of AKI. Although these will identify all patients in whom a blood sample for SCr was analysed, the true incidence of community-acquired AKI will still be underestimated. Less severe cases, for example, as in outpatients with severe gastroenteritis, or, on the other end of the spectrum, in terminal patients who are given palliative care, will not be included in these databases.

Older data on the incidence of AKI showed a large discrepancy of the incidence of community-acquired AKI in developed countries. This could probably be attributed to differences in study population and management strategies. Liano and Pascual found an incidence of AKI of 209 pmp/year in 1992 in Madrid (Spain) when AKI was defined by a sudden increase of SCr > 177 μmol/L (> 2 mg/dL) or a sudden increase of 50% or more in patients with previous mild-to-moderate chronic renal failure (Scr < 264 μmol/L (< 3 mg/dL)) (Liano and Pascual, 1996). In this study, only hospitalized patients were included. Another study in Scotland during the same study period used a more specific definition for AKI (SCr ≥ 300μmol/L or 3.3 mg/dL) and included also non-hospitalized patients. In this study, the incidence of AKI was 650 pmp/year (Khan et al., 1997). Because it seems plausible that the incidence of AKI was comparable in these two regions, these data suggest that a large proportion of AKI patients in Scotland were treated as outpatients.

Similar to the increase of AKI defined by RRT, the incidence of less severe AKI has also increased over the years. In a series of two studies in 1979 and 1996, Hou and Nash found that hospital-acquired AKI increased from 4.9% to 7.2% in the same institution in the United States (Hou et al., 1983; Nash et al., 2002). In both studies, AKI was defined as an SCr increase > 0.5 mg/dL or > 44.2 μmol/L when baseline SCr < 1.9 mg/dL or < 166 μmol/L; and an increase of SCr > 1.0 mg/dL or 88.4 μmol/L when baseline SCr 2–4.9 mg/dL or 188–431 μmol/L, and increase > 1.5 mg/dL or 132.6 μmol/L when baseline SCr ≥ 5.0 mg/dL or ≥ 442 μmol/L.

Recent data illustrate that AKI is among the most prevalent of diseases. Uchino et al. found an incidence of 18% in a sample of 20,126 hospitalized patients in Australia when AKI was defined by the RIFLE classification (only SCr criteria) (Uchino et al., 2006). The population incidence of AKI in the Grampian region of Scotland in 2003 was 2147 pmp/year (Ali et al., 2007)—a figure still lower than that reported in a study in a northern California cohort of Kaiser Permanente beneficiaries in the period 1996 to 2003 (Hsu et al., 2007). The definition used in this study was similar to that used by Hou et al. (1983). The incidence in the Californian cohort of non-dialysis-requiring AKI increased from 322.7 to 522.4 whereas that of dialysis-requiring AKI increased from 19.5 to 29.5 per 100,000 person-years. This is comparable and even higher than the estimates for the incidence of sepsis in the United States, ranging from 2404 to 3000 pmp/year (Angus et al., 2001; Martin et al., 2003).

AKI in the ICU

AKI occurs in approximately one-third of ICU patients in the first 48 hours of ICU stay (Bagshaw et al., 2008c; Joannidis et al., 2009). The reported incidence of AKI defined by the RIFLE or the AKIN classification during the whole ICU stay varies between 10.8% to 78.2% of ICU patients (Lin et al., 2006; Cruz et al., 2007). This large variation can be explained by the specific case mix studied, but also by the duration of the study period (48 hours to whole ICU stay) and how the RIFLE or AKIN definitions are applied (full criteria, or a version without urine output or with variant urine output criteria, or with variant baseline SCr estimates) (Hoste and Schurgers, 2008). The largest retrospective studies in general ICU patients studied during the whole ICU stay report an AKI incidence (defined by RIFLE or AKIN classification) of 35.4–67% (Ostermann and Chang, 2007b, 2008; Bagshaw et al., 2008c; Joannidis et al., 2009; Mandelbaum et al., 2011; Nisula et al., 2013). This high incidence found in retrospective studies was confirmed by preliminary results from a recent, prospective, multicentre, international study that showed a 55.3% incidence of AKI during the first week of ICU admission (Hoste and Kellum, 2011). AKI severity staging by the RIFLE/AKIN allows early identification of patients at risk for progression to more severe AKI. In one study, 55% of patients, who developed the least severe stadium of AKI according to the RIFLE classification, progressed to more severe AKI (Hoste et al., 2006).

Epidemiology of AKI in low-income countries

The true epidemiology of AKI in low-income countries is not well understood due to the late presentation of patients to tertiary centres, underreporting, and reduced capacity to provide intensive care to critically ill patients (Adhikari and Rubenfeld, 2011; Gokulnath and Ram, 2012). It was estimated that AKI-related problems represent up to 3% of admissions in general health facilities (Naicker et al., 2008). AKI occurs rather in young, previously healthy individuals and/or in the context of a single disease or condition (Cerda et al., 2008). AKI complicates malaria in 1–5% cases, with incidences up to 60% among patients with heavy parasitaemia or HIV/AIDS (Mishra and Das 2008). AKI develops in 20–85% of patients with leptospirosis (Andrade et al., 2008) and in 3.3–10.8% adults and 0.9% children admitted with dengue haemorrhagic fever and dengue

shock syndrome (Laoprasopwattana et al., 2010; Mehra et al., 2012). Hantavirus-associated haemorrhagic fever and AKI are common in certain parts of Asia and Latin America (Clement et al., 2012) (see Chapter 241 and also specific infection chapters in Section 8).

In these countries, many AKI patients die because treatment, including dialysis, is often not available and epidemics of AKI occur subsequent to severe gastroenteritis (typhus, cholera) affecting large populations, or with leptospirosis subsequent to floods. The incidence of specific diseases that may lead to AKI in emerging or tropical countries often varies seasonally. During times of peak incidence, limited local health resources may be overwhelmed especially in rural areas, and more patients will develop AKI, often as a result of acute post-infectious glomerular disease or following dehydration (Etuk et al., 2009).

Epidemics of AKI may also occur following disasters and are to a large extent due to crush syndrome after earthquakes (see Chapter 252); they are associated with a completely different distribution of causes versus non-disaster conditions (Sever et al., 2004).

Aetiology of acute kidney injury

A classic classification of AKI defines prerenal, intrinsic renal, and postrenal causes of AKI (Table 220.4). In some particular causes of AKI, specific therapy is necessary. The aetiology of AKI should, therefore, be determined because in patients with decreased perfusion of the kidneys, acute glomerulonephritis, acute interstitial nephritis, and urinary tract obstruction, specific measures are necessary for treatment of AKI (see Chapter 222).

As explained above, AKI in critically ill patients is a heterogeneous condition with in most patients a multifactorial aetiology. In a minority of patients, AKI is the consequence of acute kidney disease like acute glomerulonephritis, acute interstitial nephritis, or obstructive nephropathies. In the majority of patients, AKI will be the consequence of another extrarenal condition, for instance, shock, severe infection, or sepsis. Typically, several causes can be identified and these may also occur at different time points.

In some of the above mentioned particular causes of AKI, specific therapy is necessary.

Aetiology of AKI in low-income countries

The distribution of the causes of AKI is determined by local conditions; AKI patients in emerging or tropical countries have, compared to more developed and non-tropical countries, less sepsis, and more gastrointestinal or systemic infections (e.g. severe malaria, leptospirosis, dengue, or haemolytic-uraemic syndrome (HUS)), pregnancy-related complications (severe preeclampsia, puerperal sepsis, intrauterine death, ante- or postpartum haemorrhage, acute fatty liver of pregnancy), surgical complications, snake poisoning, and AKI following intake of traditional and nephrotoxic medicines without medical supervision (Luyckx et al., 2005; Cerda et al., 2008; Luyckx and Naicker, 2008; Naicker et al., 2008; Mathew and George, 2011; Jha and Parameswaran, 2013) (see Chapter 241 and also chapters in Section 8).

Drug-induced haemolysis may occur in patients with deficiency of the enzyme glucose 6-phosphate dehydrogenase, which is frequent (15–20%) in East Africa and Nigeria (Sakhuja and Sud, 1998). Patients with HIV/AIDS may develop AKI in association with infections, hypovolaemia, and use of nephrotoxic antiretroviral agents, including tenofovir and indinavir (Cohen et al., 2008).

An often-used classification of AKI defines prerenal, intrinsic renal, and postrenal causes of AKI. In prerenal AKI, decreased kidney perfusion is the underlying mechanism for AKI. Similar to postrenal AKI, obstruction of the urine outflow tract is the cause of AKI. Finally, in intrinsic AKI, the kidney itself is affected (e.g. acute tubular necrosis or acute interstitial nephritis).

Table 220.4 Aetiology of prerenal, intrinsic, and postrenal causes of acute kidney injury

(A) Aetiology of prerenal causes of acute kidney injury	
Intravascular volume depletion	Gastrointestinal fluid (vomiting, diarrhoea, fistulas) Haemorrhage Renal fluid loss (diuretics, osmotic diuresis, salt-wasting renal diseases, primary adrenal insufficiency Third space (burns, pancreatitis, peritonitis, crush injury, malnutrition Nephrotic syndrome Cirrhosis of the liver
Decreased cardiac output	Cardiogenic shock, myocardial infarction, arrhythmias, severe cardiomyopathies (cardiorenal syndromes), valvular diseases, constrictive pericarditis, pericardial tamponade, cor pulmonale, massive pulmonary embolism
Systemic vasodilatation	Sepsis Vasodilating drugs, antihypertensive drugs Cirrhosis of the liver Anaphylaxis Adrenal cortical insufficiency Electrolyte disturbances (hypermagnesaemia, hypercapnia)
Renal vasoconstriction	Drugs (NSAIDs, ACEIs/ARBs, calcineurin inhibitors, vasopressors) Hepatorenal syndrome Early sepsis/endotoxin release Acute hypercalcaemia
(B) Aetiology of intrinsic causes of acute kidney injury	
Vascular	*Anatomic*: Aorta dissection, traumatic renal artery dissection, artery or vein thrombosis, surgery renal artery, thromboemboli (cholesterol, blood) *Inflammatory*: Vasculitis, malignant hypertension, thrombotic thrombocytopenic purpura, haemolytic uraemic syndrome, scleroderma crisis, disseminated intravascular coagulation
Glomerular	*Nephritis/vasculitis*: Rapidly progressive GN, post-infectious GN, IgA nephropathy Infective endocarditis GN Wegener's granulomatosis, Churg–Strauss disease, microscopic polyangiitis cryoglobulinaemia, Henoch–Schönlein purpura *Nephrotic syndrome*: Minimal change nephrotic syndrome, collapsing focal segmental sclerosis, membranoproliferative GN

(*continued*)

Table 220.4 Continued

Interstitial	*Drugs*:
	Penicillin, methicillin, cephalosporins, sulphonamide, rifampin
	Ciprofloxacin, phenindiones, cimetidine, proton pump inhibitors (omeprazole, lansoprazole)
	Azathioprine, phenytoin, carbamazepine, captopril
	Thiazides, furosemide, bumetanide
	Allopurinol, NSAIDs including selective cyclooxygenase-2 inhibitors, 5-aminosalicylates
	Hypercalcaemia
	Infections:
	Non-specific due to septicaemia
	Organ involvement (*Staphylococcus, Streptococcus*, bacterial endocarditis, visceral abscesses),
	Specific infections: *Legionella, Leptospira, Rickettsia, Hantavirus, Candida*, malaria, dengue, yellow fever, and other tropical infections
	Infiltration:
	Sarcoid, lymphoma, leukaemia
(C) Aetiology of postrenal causes of acute kidney injury	
Intratubular obstruction	Crystal deposition—uric acid, oxalic acid, methotrexate, aciclovir, indinavir, tenofovir, triamterene, sulphonamides
	Protein deposition—myoglobin, haemoglobin, light chains
Ureteral obstruction	Nephrolithiasis
	Malignancy
	Debris, blood clots, sloughed papillae, fungal balls
	Strictures—radiation, granulomatous diseases
Extrinsic ureteral/ pelvis obstruction	Retroperitoneal fibrosis, pelvis malignancy, fibrosis, ligation, abdominal aortic aneurysm
Lower urinary tract obstruction	Benign prostate hypertrophy, prostate cancer
	Bladder carcinoma, bladder stones, intravesical blood clots, bladder retention due to neurogenic bladder or drugs
Urethral obstruction	Stricture
	Phimosis

ACEIs = angiotensin converting enzyme inhibitors; ARBs = angiotensin receptor blockers; GN = glomerulonephritis; NSAIDs = non-steroidal anti-inflammatory drugs.

Risk factors for development of acute kidney injury

AKI is most often a consequence of another severe disease. In the large, international, multicentre BEST Kidney study in critically ill patients, sepsis was indicated as the most prevalent underlying cause for AKI (47.5%), followed by major surgery (34.3%), cardiogenic shock (26.9%), hypovolaemia (25.6%), drug-induced causes (19.0%), hepatorenal syndrome (5.7%), and obstruction (2.6%) (Uchino et al., 2005). In addition, a patient may also have increased susceptibility for development of AKI. For instance, gene polymorphisms for a number of factors (ACE, cytokines, hypoxia-inducible factor 1α and others) may play a role in increased susceptibility for AKI and outcome (Stuber et al., 1996; Jaber et al., 2004a, 2004b, 2005; du Cheyron et al., 2008; Kolyada et al., 2009; Payen et al., 2012).

AKI occurs also more often in medical patients compared to surgical patients. Older patients and men also appear to be at greater risk for developing AKI (Hsu et al., 2007). However, in other setting such as cardiac surgery, women are at greater risk for AKI (Thakar et al., 2003). The presence of multiple co-morbidities, including diabetes mellitus, cardiovascular disease, chronic liver disease, malignancy, complex surgery, resulting in high severity of illness scores, has been associated with AKI in community-, hospital-, and critical care-acquired AKI (Ali et al., 2007; Cruz et al., 2007; Piccinni et al., 2011; Thakar et al., 2009). Many of the risk factors for CKD (e.g. diabetes, African descent, hypertension) have also been attributed to AKI.

Pre-existing CKD is one of the most potent risk factors for AKI. The reduced functional nephron mass and impaired renal autoregulation increase susceptibility to renal insult; the incidence of acute-on-chronic kidney disease is increasing and is associated with poorer long-term survival compared to patients with AKI without CKD (Lafrance et al., 2010; Pannu et al., 2011; Wu et al., 2011). In the Grampian cohort study, acute-on-chronic AKI had a lower population incidence compared to AKI in non-CKD patients (336 vs 1811 pmp/year) (Ali et al., 2007). However, the denominator of this study was the whole population. The incidence of AKI in a cohort of CKD patients with eGFR < 30mL/min/1.73 m^2 in Canada was as high as 44.9% (Lafrance et al., 2010). Also more severe CKD was associated with greater odds for AKI treated with RRT (odds ratio for CKD 3 was 2, and increased to 40 for CKD stage 5) (Hsu et al., 2008).

Proteinuria, albuminuria, and elevated urine albumin-to-creatinine ratio are associated with progressive increase in risk of AKI, even after adjustment for estimated GFR (eGFR) and cardiovascular risk factors (Grams et al., 2010; James et al., 2010; Hsu and Hsu, 2011). (See also Chapter 224.)

Non-recovery and partial recovery of kidney function

AKI patients treated with RRT have a considerable risk of non-recovery of kidney function. Two recent, large, prospective randomized studies on intensity of RRT reported 28-day non-recovery of RRT rates of 13.3% and 25.8% (Palevsky et al., 2008; Bellomo et al., 2009). Explanations for this important difference may be the modality of RRT that was used (continuous RRT versus intermitted and continuous RRT), a difference in baseline characteristics, and difference in timing of initiation of RRT (Kellum and Ronco, 2010).

The ANZICS study reported also a 90-day non-recovery rate of 5.6% (Bellomo et al., 2009). Others have reported 90-day non-recovery in survivors as high as 13% in patients without previous CKD, and up to 53% in patients with previous CKD (Prescott et al., 2007). Finally, Bagshaw and colleagues reported a 1-year non-recovery rate of 22% in Canada (Bagshaw et al., 2005). It is believed that patients who had CKD before AKI are at greater risk for non-recovery or partial recovery of kidney function. In the United States, currently, one-third of patients who are started in a chronic dialysis programme had an episode of AKI in the previous 2 years. Risk for this complication appears to be greatest in patients with underlying CKD (Hsu et al., 2009; Ishani et al., 2009).

Even in patients with less severe forms of AKI, recovery rates may be lower than expected. In a recent study of sepsis-induced AKI, 48.6% of patients with RIFLE-Failure failed to recover renal function defined as alive, off dialysis, and with some improvement in renal function by hospital discharge (Srisawat et al., 2011). (See also Chapter 237.)

Mortality of acute kidney injury

Both severe AKI, defined by RRT, and less severe AKI stages are associated with increased mortality (Hoste and Schurgers, 2008; Ricci et al., 2008) and there is a clear stepwise relationship between increasing grades of AKI severity and short in-hospital mortality. Of course, patients with more severe AKI are more likely to have more severe underlying disease and organ dysfunction with resultant impact on mortality. However, even when corrected for covariates in multivariate analysis, all studies confirm the association of increasing AKI severity and mortality (Hoste and Schurgers, 2008).

Kidney related factors that modulate long-term mortality in AKI patients are increasing severity of AKI, recovery of kidney function, and pre-existing CKD. Increasing AKI stages are associated with stepwise decreased survival in up to 10-year follow up (Bihorac et al., 2009; Hobson et al., 2009; Lafrance and Miller, 2010a; Murugan et al., 2010; Fuchs et al., 2013). Patients who do not recover kidney function have worse long-term survival compared to patients who partially recover, and they in turn do worse compared to patients with complete recovery (Hobson et al., 2009; Schiffl and Fischer, 2008). Finally, patients with CKD before AKI have a worse long-term survival (Triverio et al., 2009; Lafrance and Miller 2010a). (See also Chapter 237.)

Improvement of outcome

Overall, unadjusted outcomes for patients receiving RRT for AKI in published studies over a 50-year time period have been remarkably stable with a mortality rate of approximately 50% (Ympa et al., 2005). However, as mentioned before, during this 50-year period patient profiles have changed dramatically. RRT is now offered to patients with severe multiple organ dysfunction, who would not have been considered for this treatment before. For instance, RRT for AKI treatments in the 1970s occurred predominantly in non-ICU patients, while in the late 1990s this was predominantly in ICU patients (Ricci and Ronco, 2005; Lameire et al., 2006). Similar observations are reported from the United Kingdom, Austria, and the United States (Abreo et al., 1986; Turney et al., 1990; Druml 1996; McCarthy, 1996).

Several detailed studies indicate that outcomes have in fact improved. From the two studies by Nash and Hou we can see that over a 17-year study period, the hospital mortality of non-ICU patients who had AKI, decreased in their institution from 25.0% to 19.4% (Hou et al., 1983; Nash et al., 2002). Administrative datasets from the United States also indicate a lower mortality for both AKI with and without RRT (Waikar et al., 2006). Finally, the large Australian-New Zealand ICU database showed that AKI defined by a SCr increase above 133 μmol/L or urine output < 410 mL/24 hours, declined over a 20-year study period, while the mortality of patients without AKI remained stable (Bagshaw et al., 2007). (See also Chapter 238.)

Diagnostic classification of acute kidney injury

As discussed in detail in Chapter 222 on the diagnosis of AKI, clinical signs and biochemical indices in urine and blood, together with technical examinations, such as renal ultrasound, are used to differentiate prerenal, intrinsic renal, and postrenal disease. Although this classification is often used, the difference between prerenal and intrinsic renal disease in particular is often not so clear.

Prerenal AKI, prerenal azotaemia

Prerenal AKI is also often named prerenal azotaemia. This class of AKI is per definition caused by inadequate blood flow to the kidneys, while the kidneys are structurally normal, and is therefore rapidly reversible when the underlying cause is corrected. Shock, leading to decreased arterial blood volume, and dehydration are the most frequent causes of prerenal AKI (Table 220.4A).

When there is associated ischaemic damage to the kidneys, the patient classifies as intrinsic renal disease. This condition is in contrast to prerenal AKI, not rapidly reversible.

Underlying aetiology of decreased kidney perfusion in prerenal azotaemia

The underlying aetiology of prerenal azotaemia is diverse (Table 220.4A). The 'prerenal' entity suggests that glomerular filtration is decreased as a consequence of renal hypoperfusion, in relation to events 'outside' the kidney, in contrast to renal parenchymal alterations ('renal') or urinary excretory obstruction ('postrenal'). The 'prerenal' term corresponds to various intricate mechanisms modifying glomerular filtration but without primary parenchymal disease, and can be seen as adapted renal responses to a variety of these 'outside' insults (Macedo and Mehta, 2009; Blantz and Singh, 2011; Payen and Legrand, 2011). In practice, one should differentiate between heart failure and volume depletion. In theory, this can easily be differentiated on basis of the clinical history, clinical examination, blood and urine chemistry, bedside echocardiography and renal ultrasound, and invasive monitoring tools such as central venous pressure, thermodilution with pulmonary artery catheter or transpulmonary catheter, or arterial pulse wave analysis. Despite these tools, volume status assessment continues to be a challenge, especially in critically ill patients who are mechanically ventilated and/or with intra-abdominal hypertension (for more details see Chapter 222).

In some patients, abnormalities of the renal vasculature, such as renal artery stenosis or cholesterol emboli, may be a cause of prerenal AKI. Renal artery stenosis is a rare cause of prerenal azotaemia in ICU patients. It should be suspected in patients with pre-existing CKD and hypertension, and can be ruled out by diagnostic imaging studies such as renal Duplex ultrasound. Less often used in ICU patients are magnetic resonance imaging, computed tomography, or classic renal angiography.

Intra-abdominal hypertension, a condition that can be easily diagnosed by measuring the intra-abdominal pressure through a urinary catheter, can lead to decreased renal perfusion secondary to the decreased cardiac output, and by pressure on the renal vasculature and parenchyma (De Waele et al., 2011) (see Chapter 222).

Certain chronic diseases, such as congestive heart failure and liver cirrhosis may present with a 'chronic' form of prerenal azotaemia.

In patients with liver cirrhosis or acute liver failure, this should be differentiated from hepatorenal syndrome. Hepatorenal syndrome is in fact an extreme form of prerenal azotaemia (see Chapter 247). The diagnosis of this condition can essentially only be made after exclusion of other causes of AKI, including other causes of prerenal azotaemia. In addition, patients with hepatorenal syndrome have no increased urine output after volume loading (see also Chapter 247).

Transient AKI

There is no consensus definition of 'transient AKI', a term which should be preferred over 'transient azotaemia' (TA), but most authors would accept a duration of renal dysfunction, usually from 24 to 72 hours after onset of AKI and reflected by a transient rise of SCr. This lack of a uniform definition explains why the incidence is reportedly different between an ICU and a hospital population. For example, in a recent cohort of 510 ICU patients with normal kidney function before admission and in whom 66 patients (13%) developed AKI according to RIFLE, 'transient AKI', defined as reaching normal SCr levels within 24 hours, was present in 19 patients (29% of AKI and 3.7% of the total cohort) (de Geus et al., 2011). Tian et al. (2009) retrospectively analysed the outcomes of 735 hospitalized AKI patients, and full or partial reversal of kidney function was determined after 48 hours. Only 197 (26.8%) returned the SCr below normal ('true transient' AKI). Strikingly, these patients with full reversal of the SCr within 48 hours had significantly higher mortality rates than patients without AKI. Uchino et al. (2010) 'pragmatically' defined 'transient' AKI' in a hospitalized population as AKI of ≤ 3 days duration. As much as 18.1% of a total of 20,126 patients experienced an episode of AKI with one-third of them having 'transient AKI'. Like in the study by Tian et al. (2009), 'transient AKI' was associated with increased odds of death. Although the causes of the morbidity and mortality in 'transient' AKI patients are not known, volume overload, acidosis, electrolyte abnormalities, and inflammation may play an important role (Hoste and Kellum, 2004). It is conceivable, although not proven, that most patients with 'transient AKI' might largely represent cases of prerenal AKI. Despite the poor outcome of these 'transient AKI' cases, it is unlikely that the kidney dysfunction in most of the prerenal AKI and/or 'transient AKI' patients as such plays a causal role in the mortality; the latter is most likely related to underlying comorbidities contributing to the development of AKI. The 'reversible' kidney ischaemia is probably a surrogate of total body ischaemia or ischaemia in other vital organs, such as the heart or brain, thereby confounding the relationship between 'prerenal AKI' and mortality (Parikh and Coca, 2010). It should be remembered that AKI that involves 'true structural kidney injury', including acute tubular necrosis (ATN), could also be of short duration if the surrounding non-injured parenchyma regains function while the injured structures are healing. By contrast, even prolonged cases of 'prerenal AKI' can exist without or with minimal kidney injury (as, for example, in hepatorenal or cardiorenal syndrome) (see Chapters 247 and 248). These diseases certainly are extreme examples of prolonged, reversible prerenal AKI.

The primary focus in the setting of an acute rising SCr should thus be to determine where the dysfunction lies on the spectrum between 'purely functional' and 'completely structural' AKI. For the clinical management of the individual patient with AKI, this determination is of great importance.

The presence or absence of structural kidney abnormalities is hard to prove, and is actually debated in the differentiation between prerenal and intrinsic renal AKI. To overcome this debate, the terminology 'transient azotaemia' was introduced (Uchino 2010; Uchino et al., 2010). While prerenal AKI and azotaemia denote the same condition, 'transient azotaemia' does not necessarily do so. As the name already discloses, it is defined by duration of GFR decrease, without the requirement of absence of structural kidney abnormalities. Most probably many patients with 'transient azotaemia' will also qualify as prerenal azotaemia, but also mild ATN can be of short duration. A major limitation of the use in daily practice of the concept of 'transient AKI' is the fact that this diagnosis can only be made after an observation period of 48 hours.

Volume-responsive AKI

The AKIN experts have proposed that terms such as 'prerenal AKI' and 'ATN' should be discarded and replaced with 'volume-responsive' and 'volume-unresponsive' AKI (Himmelfarb et al., 2008). In this proposal, AKI is characterized by a continuum of volume responsiveness and/or unresponsiveness (see Chapter 222). Applying this classification is, however, difficult because not enough detailed information on the 'responsiveness' to volume is available. In recent studies where 'volume responsiveness' was used to distinguish the 'prerenal' from the renal AKI patients, either a high number of patients could not be classified (Singer et al., 2011), or not enough information on the type and magnitude of the volume resuscitation was provided (Heller et al., 2011). In addition, the still applied clinical approach of repetitive 'fluid loading' in virtually every patient and diagnosing retrospectively those who respond as having 'prerenal' AKI has increasingly been found to be dangerous (Schrier, 2010) and should be abandoned.

In addition, the term of volume-responsive AKI defines a subgroup of patients with prerenal AKI. For example, patients with cardiogenic shock, who are not always volume responsive, are not included in this group of patients but most probably have a functional form of AKI that is rapidly reversible when heart function is restored. Further, there is much debate on fluid resuscitation and volume overload as a contributing factor for AKI (Payen et al., 2008). In common causes of prerenal AKI such as in distributive shock, or in hypovolaemia in the perioperative setting, massive fluid resuscitation may in fact contribute to development of AKI. Mechanisms that may be involved in this are intra-abdominal hypertension, the generation of hyperchloraemic metabolic acidosis as a consequence of resuscitation with sodium chloride 0.9%, and toxicity of hydroxyethyl starch and gelatin colloid solutions (for details see Chapters 222 and 225).

When prerenal azotaemia persists for a longer period, hypoperfusion of the kidneys will lead to ischaemia and ATN, or intrinsic AKI (Lameire et al., 2006). ATN is characterized by the presence of structural damage in the kidney, and is not rapidly reversible when the underlying or causal condition is corrected. The outer medullary region in particular is at risk for this, because as a consequence of the particular renal vasculature, oxygen supply in this region of the kidney is limited, while energy demands are high. It is uncertain when exactly a patients progresses from prerenal azotaemia to intrinsic AKI, because diagnosis of cellular damage is difficult to make in daily clinical practice. There is at present a growing tendency to see AKI as a continuum between prerenal AKI and AKI with renal 'structural' injury such as ATN. Prerenal AKI and ATN

can and often do coexist in the same patient (Belcher and Parikh, 2011). Because of the patchy nature of ATN, it is indeed possible that some regions of the kidneys can have both severe morphologic and functional ATN, whereas other parts may still be structurally intact, awaiting only reperfusion to resume normal filtration. As discussed in more detail in Chapter 223, recent studies (Haase et al., 2011) using the profile of novel urinary biomarkers in patients with 'prerenal' AKI seem to imply that indeed subtle tubular cellular damage can be present in the 'prerenal', subclinical phase of the AKI continuum, at least in some patients. Alternatively, some of these biomarkers may also allow a kidney injury to be diagnosed even in the absence of a subsequent manifest dysfunction (Haase et al., 2011; Nickolas et al., 2012). In addition, both studies demonstrated that patients without elevations in SCr concentration, but with elevated urinary levels of biomarkers of kidney injury, presumably reflecting presence of tubular injury, are at increased risk of adverse events (Haase et al., 2011; Nickolas et al., 2012). Such situations of biomarker positive, serum creatinine-negative cases have been termed 'subclinical AKI' (Ronco et al., 2012).

It is thus quite possible that the usage in both clinical practice and research of the terms prerenal AKI, ATN, and 'subclinical AKI' will become more and more questioned in the future. It is at present, however, still unproven whether the abnormal presence in the urine of a biomarker such as NGAL represents only tubular damage or is not also the consequence of increased filtration due to increased extrarenal production of the marker, for example, by inflammation (Pedersen et al., 2012).

Impact of acute kidney injury on healthcare resources

AKI has an important impact on healthcare resources and economics. Current studies on costs associated with AKI are limited to calculations of the costs of the procedures and the early hospitalization but not of long-term costs. Costs attributable to AKI increase as the definition of AKI broadens and with the severity of the disease.

Data from 23 Massachusetts hospitals over 2 years demonstrated that AKI, compared to non-AKI, resulted in higher hospital resource utilization, as both median direct hospital costs and hospital length of stay were increased by US $2600 and by 5 days, respectively(Fischer et al., 2005). The additional costs attributed to in-hospital AKI determined in a single Boston hospital in 2005 ranged from US $13,200 for a > 0.5–mg/dL change in SCr to US $33,161 for a 2.0 mg/dL change (Chertow et al., 2005). Similarly, in post-cardiac surgery AKI, even RIFLE-Risk disease was associated with a 1.6-fold increase in total postoperative costs compared to controls (Dasta et al., 2008). Importantly, the costs associated with AKI are largely seen in greater resource utilization and longer lengths of stay, rather than due to RRT (Dasta et al., 2008). The costs for dialysis-requiring AKI in high-income countries are setting dependent, vary widely between centres, but are generally greater for continuous RRT compared to other forms of dialysis (James and Tonelli, 2011).

The overall healthcare costs and consequences of AKI extending to CKD and ESRD have not been well quantified. Extrapolation from the study of Wald et al. (2009) suggests that AKI-precipitated CKD could account for 3% of the annual incidence of ESRD in the United States (Waikar and Winkelmayer, 2009).

Finally, information on costs of healthcare for AKI in emerging countries is scant. Direct and indirect hospital costs for 231 children with HUS in Buenos Aires, during 1987 to 2003 (Caletti et al., 2006) were estimated as US $15,400 and $7355 per patient, respectively.

Due to the direct impact of AKI on productivity, indirect costs are difficult to define. For example, of 68 patients with severe AKI in Brazil, only 28.3% could return to their jobs 3–12 months after hospital discharge (Morsch et al., 2011).

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CHAPTER 221

Pathophysiology of acute kidney injury

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(with contributions by Radovan Vasko,
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Introduction

Acute kidney injury (AKI), in the past variously referred to as 'acute haematogenic interstitial nephritis' (Kimmelstiel, 1938), 'lower nephron nephrosis' (Lucke, 1946), 'haemoglobinuric nephrosis' (Mallory 1947), 'acute tubular necrosis' (Bull et al. 1950), 'glomerulo-tubulo-nephrosis with pigmented casts' (Zollinger, 1952), and 'tubulointerstitial nephritis' (Brun, 1954) is a syndrome of graded severity of acute renal functional impairment which, depending on the nature of the insult—nephrotoxic, endotoxic, or ischaemic—may or may not be accompanied by the commensurate morphologic changes (Brun and Munck, 1966). The diversity of nomenclature is a reflection on the panoply of morphologic presentations in cases secondary to nephrotoxins, like ethylene glycol, mercury compounds, or others, which are accompanied by a conspicuous tubular necrosis, and in cases of haemorrhage, sepsis, mismatched transfusions, and others, which offer morphologic presentations far less dramatic than clinical presentation with oliguria.

As mentioned in Chapter 220, the origins of the syndrome could be prerenal, postrenal, and intrinsic renal. What is remarkable is that all three categories of diseases acutely affecting renal functions invariably injure the kidney by a combination of haemodynamic and tubular alterations varying in their intensity. Acute prerenal injury to the kidney affects predominantly the renal circulation with the attendant tubulopathy. Acute postrenal injury to the kidney affects tubules with the attendant renal circulatory abnormalities. Acute intrinsic kidney injury affects both to a variable degree. The functional coupling of these two pathogenetic mechanisms is quite remarkable; as stated by H. Valtin (Valtin, 1979), 'both the renal vasculature and the tubular system run in series and are intertwined both anatomically and functionally, initial damage to the tubules will quickly involve the vessels, and vice versa'.

Two recent reviews on the pathophysiology of AKI as a consequence of renal ischaemia were published in 2011 (Bonventre and Yang, 2011; Sharfuddin and Molitoris, 2011). In this chapter, peculiarities of disturbed renal function under different circumstances, and their cellular and molecular mechanisms, as potential diagnostic and therapeutic targets, will be summarized.

Common morphologic findings

Based on a large database of biopsies and necropsy material with fixation performed immediately after death, the key morphologic observations have been summarized by Brun and Munck (1966) as 'moderate structural changes which contrast sharply with the complete functional breakdown'. Multiple later studies (reviewed in Levinsky et al., 1981) confirmed these conclusions. The most common findings include dilation of the tubules and flattening of distal and proximal tubular epithelium with the desquamation of proximal epithelial cells; presence of granular and brownish-reddish casts; focal infiltration and oedema of the proximal tubular epithelium and the interstitium; mitotic figures in the proximal and distal epithelial cells; and occasional tubular necrosis. Whole-nephron microdissection studies by Oliver et al. (1951, 1953) confirmed previous findings and, in addition, produced direct evidence of tubulorrhexis, which was not universally spread. Although glomerular abnormalities are rare, a common finding is that of glomerular tubularization—substitution of parietal epithelia of Bowman's capsule with proximal tubular epithelia (Dunnill 1974). Described abnormalities have been confirmed by multiple investigators (reviewed in Heptinstall, 1974; Levinsky et al., 1981).

It has been known for a number of years that the renal structural changes in the human kidney differ in several aspects from those seen in small-animal models of post-ischaemic acute tubular necrosis (ATN) and the direct relevance of the animal models to human pathology has therefore been questioned (Rosen and Heyman, 2001).

A recent prospective comprehensive analysis of biopsies of human kidneys subjected to sustained clamp ischaemia over time frames typically used in the experimental models not only revealed a remarkable tolerance for even prolonged ischaemia (> 30 minutes) but also showed minor structural abnormalities, mostly only mitochondrial swelling, with little correlation to ischaemia time and creatinine increases (Parekh et al, 2013). Interestingly, urinary biomarkers did increase, but to variable degrees, and without correlation with ischaemia durations or with structural changes.

Common functional findings

Renal blood flow and glomerular filtration rate

Early demonstration of reduced renal blood flow (RBF) in AKI, using para-aminohippuric acid clearance, has been invariably confirmed in studies utilizing more precise techniques, such as Kr^{85}, Xe^{133}, or the dye dilution method (Bull et al., 1950; Brun et al., 1955). The results of these investigations help to reach a consensus that RBF is decreased to one-third to one-quarter of normal, a value insufficient to be responsible for the renal shutdown. Angiographic studies of patients with AKI showed narrowing or complete non-visualization of cortical arteries, which was present in either ischaemic or nephrotoxic forms of the disease, suggesting severe vasoconstriction. Outer cortical blood flow is disproportionally reduced (reviewed in Brezis et al., 1991). One explanation for the heterogeneity of blood flow, as well as the disproportionate reduction in glomerular filtration rate (GFR), is the shunting through the Trueta (Oxford) shunt that bypasses glomerular microcirculation and diverts blood from the afferent to the efferent arterioles (Trueta et al., 1947). In addition, a single-fibre laser Doppler flowmetry showed stagnation of flow and trapping of red and white blood cells in the outer medulla resulting in the shunting of blood flow to the inner medulla (Olof et al., 1991). Perturbation of blood flow due to endothelial swelling following restoration of reperfusion was proposed by Leaf and co-workers to be responsible for the 'no-reflow' phenomenon, a hypothesis that has been experimentally questioned or its applicability chronologically limited despite persistent 'no-reflow' (Flores et al., 1972; Frega et al., 1976). Renal oxygen uptake, although also reduced, has been found to be sufficient to avoid a pathophysiologically meaningful renal hypoxia (Kramer and Deetjen, 1960; Lassen et al., 1961). In combination with profoundly suppressed GFR in patients with AKI (Brun and Munck, 1966), it has even been argued that the decreased sodium load and reabsorption reduce oxygen demand of the kidney. Experimental suppression of transport functions, in fact, has been shown to reduce the severity of AKI (Brezis et al., 1991).

Proximal tubular pressure

Based on morphologic studies demonstrating desquamation of proximal tubular epithelia and cast formation in the distal nephron, investigators performed direct measurements of proximal tubular pressure in experimental animals. Gottschalk and co-workers measured hydrostatic pressure in the proximal tubules in rats with acute renal ischaemia (Arendshorst et al., 1975; Finn et al., 1975). Hydrostatic pressure more than doubles within the first 1–2 hours post ischaemia, then slowly declines. When agglomeration of desquamated cells and cell debris is prevented by an arginine-glycine-aspartic acid-containing peptide, elevation of the proximal tubular pressure is avoided and renoprotection achieved (Goligorsky and DiBona, 1993). [Figure 221-001]

More recently, Hall et al. (2011) performed intravital fluorescence videomicroscopy of perfused rat kidneys. After 10 minutes of ischaemia these investigators detected widespread apical membrane blebbing and desquamation of proximal tubular cells into the tubular lumen resulting in accumulation of intraluminal cellular aggregates and debris. After 30 minutes of ischaemia and reperfusion, many proximal tubules were nearly impacted by a slow-moving cell debris. These data provide powerful evidence implicating tubular obstruction in early pathophysiology of acute ischaemic injury. The data also substantiate the finding of elevated proximal tubular pressure in the course of AKI, observed by earlier investigators. Collectively, these findings delineate a putative mechanism of renal dysfunction: equilibration of filtration pressure and cessation of glomerular filtration in obstructed nephrons. In fact, this scenario has a therapeutic explanatory power: *it provides a mechanistic argument for the lack of efficacy of treatments based solely on enhancing RBF*. Eventually, some impacted tubules will undergo tubulorrhexis, as documented by elegant microdissection studies by Oliver et al. (1951, 1953). This event may have the following consequences: a decline in proximal tubular pressure and restoration of glomerular filtration, on the one hand, and elevation of interstitial pressure (as discussed below), on the other.

Interstitial pressure

This mechanism may provide an additional explanation for cessation of glomerular filtration as a result of reduced perfusion and elevated hydrostatic pressure within the renal capsule (Brun and Munck, 1966). Direct determination of the wedged renal vein pressure in patients in the oliguric and diuretic phases of AKI was performed by Brun et al. (1956), however, it failed to confirm this attractive hypothesis.

Glomerular ultrafiltration coefficient

Conflicting data exist with regard to the glomerular ultrafiltration coefficient (K_f) in experimental AKI: it has been found to be reduced early after administration of uranyl nitrate or gentamycin, but not after prolonged partial, but not complete, renal artery occlusion (reviewed in Levinsky et al., 1981). This phenomenon has been attributed to either the reduction in hydraulic conductivity of glomerular endothelial cells, which show reduced number and surface area of fenestrae (Avasthi et al., 1980), or to the contraction of capillary surface area in constricted vessels. If K_f does decline in other forms of AKI, this would further exacerbate the fall in GFR.

In summary, the most common and enduring morphologic and functional perturbations in AKI of toxic and ischaemic aetiologies are represented by (a) the loss of brush border, blebbing, and desquamation of proximal tubular epithelial cells and rapid cast formation; (b) a profound decrease in GFR mostly due to vasoconstriction and elevation of intratubular hydrostatic pressure; and (c) tubulorrhexis and 'back-leak' of tubular fluid. Within the realm of these hard facts, tightly interrelated and dependent on one another, lies the most plausible explanation of renal dysfunction and oliguria occurring in this syndrome, as schematically depicted in Fig. 221.1.

Models of acute kidney injury

The list of animal models used to study pathophysiology of AKI is long and includes uranyl nitrate, mercury chloride, glycerol, folic acid, gentamycin, cisplatin (all causing predominantly tubular injury), norepinephrine (noradrenaline) infusion, renal artery occlusion, ciclosporin, contrast media with or without nitric oxide synthase or cyclooxygenase inhibitors (all causing predominantly vascular abnormalities), lipopolysaccharide, caecal ligation, and puncture (septic models affecting both haemodynamics and tubular apparatus) (reviewed in Lieberthal and Nigam, 2000; Doi et al., 2009. It has to be emphasized that all models tend to exaggerate either vascular or tubular components of AKI. In this sense, they

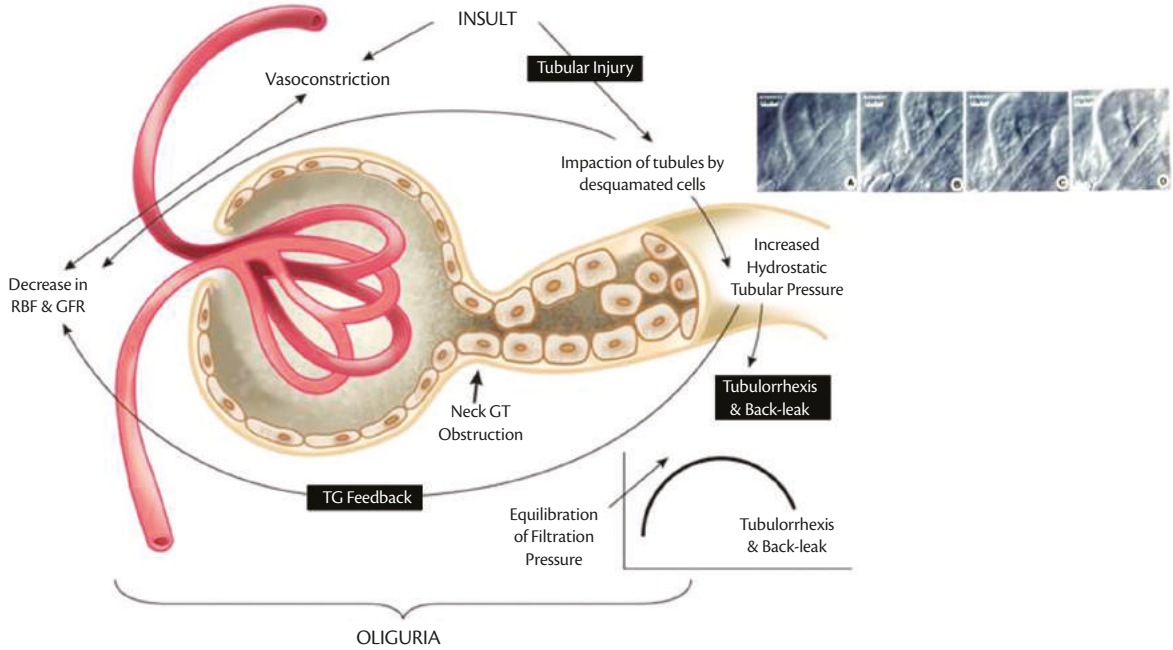

Fig. 221.1 Schematic representation of the pathophysiologic mechanisms of oliguria in AKI. Various insults inflict haemodynamic and tubular dysfunction leading to reduction of RBF and GFR and desquamation of proximal tubular epithelial cells impacting the lumen and elevation of tubular hydrostatic pressure, which counteracts filtration pressure. Tubulorrhexis relieves elevation of hydrostatic pressure and further compromises GFR. Inset: intravital videomicroscopy of the rat proximal tubule in control (A), 10 and 20 minutes after cessation of blood flow (B and C), and following reperfusion at elevated perfusion pressure (D)—note that conglomerated desquamated cells are washed-out.
Courtesy of Dr L. Moore, State University of New York at Stony Brook, USA.

are useful surrogates facilitating studies of individual mechanisms. In no way, however, do they represent facsimile copies of real-life AKI, which frequently combines several pathogenetic mechanisms. Levinsky et al. (1981) provide detailed descriptions of pathologic features of each model.

Epithelial and endothelial cell injury as a basis for tubular and haemodynamic abnormalities

Cellular response to non-lethal stress is characterized by the default 'fight-or-flight' programme (Goligorsky 2001), whereby epithelial cells develop adaptive changes in response to non-lethal stressors, desquamate and eventually obstruct tubular lumen, mediate vasoconstriction in the case of endothelial desquamation, or undergo cell death. In either situation, the integrity of these barriers becomes compromised.

Epithelial cell injury

Cell stress induces an early elevation of cytosolic calcium concentration and activation of a host of calcium-dependent events, one of which is activation of cysteine proteases, calpains. These enzymes are kept inactive in the cell by binding to a physiological inhibitor, calpastatin, which dissociates upon elevation of cytosolic calcium, binding of phospholipids, and several other proteins (reviewed in Lee and Thévenod, 2008). Substrates for calpain hydrolysis include, among others, plasma membrane and cytoskeletal proteins, especially ankyrin and α-fodrin (Inserte et al., 2009). Ankyrin is positioned between the fodrin membrane cytoskeleton and receptors or channels, one of which is the α-subunit of Na^+,K^+-ATPase (Nelson and Veshnock, 1987; Jordan et al., 1995). Calpain-induced cleavage deranges this anchorage of the sodium pump, the phenomenon occurring early in the course of many insults to the kidney (Molitoris et al., 1992). In addition, this calcium-dependent protease II, calpain, is localized in part to the focal adhesions (sites of matrix proteins interacting with integrin receptors, which in turn recruit adaptor proteins and cytoskeleton), where it is co-localized with an adaptor protein talin. Activation of calpain results in proteolytic cleavage of talin, disassembly of focal adhesions, and collapse of the membrane-anchored cytoskeleton (Beckerle et al., 1987). Furthermore, degradation of matrix proteins releases fragments of collagen, osteopontin, and laminin 5 leading, via integrin signalling, to activation of calpain and proteolytic cleavage of other components of focal adhesions, such as focal adhesion kinase and paxillin (Carragher et al., 1999). The same proteins serve as targets for inactivation by protein tyrosine phosphatases leading to the disassembly of focal adhesions (Angers-Loustau et al., 1999).

All these perturbations in focal adhesions, collapse, and remodelling of the cytoskeleton have multiple cellular consequences. The ensuing loss of epithelial cell polarity affects distribution of multiple enzymes and proteins normally segregated to apical or basolateral membranes (Molitoris et al., 1985; Wagner et al., 1995). These include not only sodium pumps, but also integrins, a family of heterodimeric proteins anchoring cells to the extracellular matrix (Gailit et al., 1993). The consequences of the hydrolysis of cytoskeletal proteins are many: these include loss of the brush border by the proximal tubular cells, their blebbing and release of blebs

into the tubular lumen that facilitates its obstruction, and finally desquamation of tubular epithelial cells, which completes tubular obstruction. Similar processes of desquamation from the basement membrane take place in endothelial cells (see below) and result in the appearance of detached cells in the circulation, on the one hand, and intimal denudation of vessels, on the other. Denuded patches of basement membrane become sites of platelet aggregation, portals for leucocyte infiltration, and foci of vasoconstriction.

Exchange proteins directly activated by cyclic AMP, Epac, and stimulating small GTPase Rap1 have recently been recognized as important contributors to the maintenance of epithelial and endothelial cell barriers. They are expressed in both cell types and the kidney has the highest expression level for Epac (de Rooij et al., 1998; Li et al., 2008). Epac activation is associated with clustering of integrins, preservation of paxillin, and maintenance of E-cadherin and VE-cadherin (Boettner and Van Aelst, 2009), all integral parts of cell–matrix and cell–cell interaction. Consequently, when proximal tubular cell cultures are subjected to stress in the presence of a cell-permeable Epac, focal adhesions and adherence junctions remain better preserved after hypoxic stress, than without this treatment (Stokman et al., 2011). *In vivo* application of Epac via the renal artery significantly reduces the loss of epithelial cells and the number of obstructed tubules. Epac pre-treatment of adoptively transferred endothelial progenitor cells improves their engraftment and regenerative potential (Patschan et al., 2010). Collectively, these data emphasize the loss of integrity of epithelial and endothelial linings in the course of AKI and the importance of maintaining these barriers in combating renal dysfunction.

Endothelial cell injury

Haemodynamic compromise is one of the hallmarks of AKI, both ischaemic and nephrotoxic. Steinhausen and co-workers were the first to perform high-speed intravital videomicroscopy of ischaemic kidneys following reperfusion (Steinhausen et al., 1973). Analysing RBC velocity 3 days (no earlier data were presented) after ischaemic episode, the authors concluded that it was decreased by about 75%.

In a series of intravital videomicroscopy imaging studies of renal ischaemia/reperfusion (I/R) in rats, we (Yamamoto et al., 2002) have demonstrated that blood flow in glomerular and peritubular capillaries becomes stagnant, retrograde, or oscillatory (alternating forward and retrograde). This pattern of oscillatory microcirculation is known to affect a host of endothelial and vascular functions. In a series of studies, Chien's laboratory has demonstrated that oscillatory shear stress, by increasing binding of c-Jun to the promoter region of microRNA-21 (miR-21), induces its expression, which in turn inhibits translation of peroxisome proliferators-activated receptor-α and leads to enhanced expression of vascular cell adhesion molecule 1 (VCAM-1) and monocyte chemotactic protein 1 (MCP-1) (Zhou et al., 2011). In addition, while laminar shear stress increases endothelial level of sirtuin 1 (SIRT1), an NAD-dependent deacetylase and master regulator of stress response and energy metabolism, oscillatory shear stress has an opposite effect on SIRT1 and, therefore, reduces the acetylation and inactivates endothelial nitric oxide synthase (eNOS) (Chen et al., 2010). The pro-inflammatory phenotype of endothelial cells subjected to oscillatory shear stress is mediated, in addition to the reduced bioavailable nitric oxide (NO), via upregulation of miR-663, which results in increased monocyte adhesion (Ni et al., 2011). Furthermore, oscillatory shear stress has been implicated in downregulation of antioxidative peroxiredoxins (Mowbray et al., 2008) and induction of mitochondrial superoxide production via activation of c-Jun NH2-terminal kinases and NADPH oxidase (Takabe et al., 2011). These multiple effects of oscillatory shear stress have a comparable time-course and could be responsible for developing endothelial cell activation and dysfunction in the course of renal I/R, as detailed in Fig. 221.2.

The causes for haemodynamic compromise in AKI are many. Endothelial activation and dysfunction develops early in the course

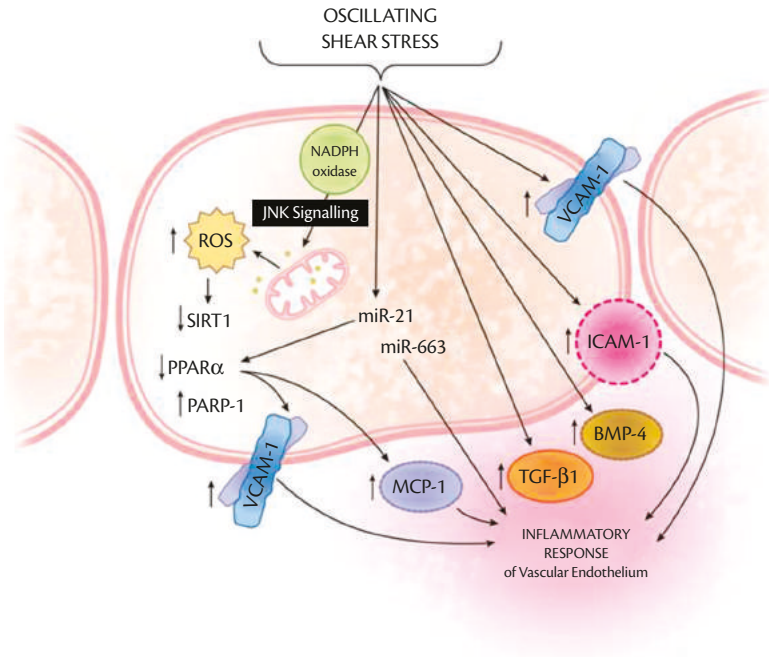

Fig. 221.2 Pathophysiologic consequences of oscillating shear stress.

Box 221.1 Endothelins, their receptors and their regulation

Endothelin 1, a 21 amino acid peptide discovered in 1988, is a member of the family of highly potent vasoconstrictors (Yanagisawa et al., 1988). All three endothelins 1-3 have 2 intramolecular disulphide bonds, all are consecutive cleavage products of pre-proendothelins, proendothelins and 38-amino acid peptide big endothelins. The enzymes responsible for the cleavage of big endothelins, endothelin-converting enzymes (ECE)-1 and -2, are present in endothelial cells, ECE-1 exhibiting neutral pH optimum, whereas ECE-2 acidic pH optimum. ECE-1 is present in secretory and storage vesicles together with big ET-1 and ET-1, while ECE-2 has been found only in secretory vesicles. ECE-2, in addition to big ET-1, cleaves bradykinin. Receptors for endothelins, ET_A and ET_B receptors, are highly selective. ET-1 and -2 activate both receptors, and ET-3 activates exclusively ET_B receptor. The function of the ET_A receptor is to initiate vasoconstrictor signalling in smooth muscle cells. In contrast, the ET_B receptor is localized predominantly on endothelial cells and serves purposes of autocrine signalling and clearance of excess ET-1. Constitutive secretion of ET-1 may represent a persistent autocrine signal activating ET_B receptor and stimulating eNOS, thus maintaining the coordinated balance between vasoconstricting and vasorelaxing agents ultimately determining the basal vascular tone.

For further information see Chapter 114, and Davenport and Maguire, 2006.

of experimental ischaemic AKI (Brodsky et al., 2002; Yamamoto et al., 2002). Laminar fluid shear stress is a physiological stimulus for endothelial production of autocoids, nitric oxide synthase (NOS) activation, and generation of NO (Rubanyi et al., 1986; Pohl et al., 1986). Stagnation of blood flow and oscillatory pattern of blood flow, as mentioned above, produce opposite effects, thus predisposing to prevailing vasoconstriction.

Furthermore, endothelial cells constitutively synthesize and release endothelin 1 (ET-1), a 21-amino acid peptide with powerful and long-lasting vasoconstrictive properties (Iijima et al., 1991; Gordienko et al., 1994) (Box 221.1; and see Chapter 114). Ischaemic, endotoxic, and nephrotoxic (ciclosporin, contrast media, tumour necrosis factor (TNF), thrombin, epinephrine) insults stimulate production and release of ET-1 from the activated endothelial cells (Kon et al., 1989; Kon and Badr, 1991; Kon and Hunley, 1995). Firth and Ratcliffe (1992) documented an increase in pre-pro-ET-1 message after 2 hours of reperfusion following 25 or 45 minutes of renal ischaemia, with elevated levels 24–48 hours later, which lasted up to 7 days.

Indeed, antagonizing ET-1 action by neutralizing antiserum results in a 40–50% increase in the single-nephron GFR (otherwise reduced to half of normal level) and the plasma flow and reduction in arteriolar resistance 48 hours after ischaemic injury. Similar observations were made in ciclosporin-induced nephrotoxicity (reviewed in Kon and Hunley, 1995).

It is worth analysing ET-1 secretory processes. ET-1 is continuously released from endothelial cells by a constitutive pathway utilizing secretory vesicles as carriers. The secretion undergoes a surge after endothelial cell activation and this pathway involves ET-1 release from the storage granules containing von Willebrand factor, thus identified as Weibel–Palade bodies (reviewed in Davenport and Maguire, 2006). It has been demonstrated, using immunoelectron microscopy and cell fractionation studies, that endothelin-converting enzyme 1, big ET-1, and cleaved ET-1 are all stored in Weibel–Palade bodies of human and bovine endothelial cells and released from these organelles upon cell activation (Harrison et al., 1995; Russell et al., 1998). Released ET-1 activates ET_B receptors on endothelial cells resulting in the stimulation of eNOS, and generation of NO, which in turn reversibly terminates ET-1 signalling (Goligorsky et al., 1994; Tsukahara et al., 1994; Goligorsky and Winaver, 1998). This interaction between two powerful vasoactive compounds provides the system with properties of an intrinsic oscillator, as schematically depicted in Fig. 221.3.

The coordination of this functional coupling between ET-1 and NO systems is lost, however, in AKI as a result of a massive release of ET-1 from endothelial cells, on the one hand, and as a consequence of oxidative stress to endothelia that 'uncouples' eNOS, on the other. eNOS is constitutively expressed in endothelial cells where it is responsible not only for vasorelaxation, but also for prevention of platelet aggregation and leucocyte–endothelial cell adhesion and transmigration, the key anti-inflammatory effects of NO. Homodimerization of the enzyme consisting of C-terminal reductase domain and N-terminal oxygenase domain is accomplished via zinc coordination of Cys 99-Cys94 motifs on each monomer. This site also participates in binding of tetrahydrobiopterin (BH4), a critical co-factor, and L-arginine, the substrate. Uncoupling of electron flux from generation of NO from L-arginine occurs as a result of substrate or BH4 deficiency and leads to preferential generation of superoxide anions over NO, formation of peroxynitrite, and further depletion of reduced biopterin pool (Rabelink et al., 2010), as schematically illustrated in Fig. 221.4. This scenario is enacted in all forms of AKI when oxidative stress depletes BH4 and reduces bioavailability of NO in endothelial cells (reviewed in Goligorsky and Gross, 1997). In parallel, inducible NOS (iNOS) is upregulated in epithelial cells and especially in infiltrating neutrophils and monocytes resulting in cytotoxicity and cytodestruction. Preventing iNOS super-induction represents one of the strategies to limit cell damage associated with AKI. This can be accomplished using oligonucleotides or selective inhibitors of iNOS (Noiri et al., 1996, 2001).

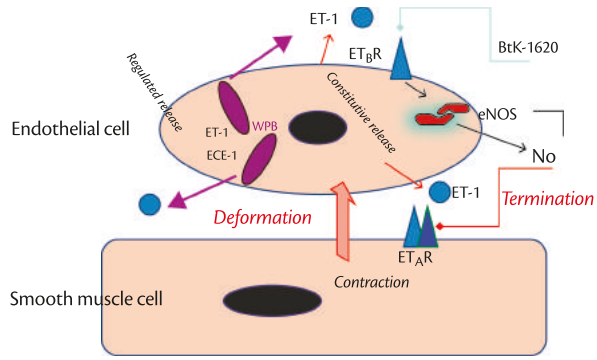

Fig. 221.3 Endothelial-smooth muscle cell interactions involving ET-1 and nitric oxide (NO) generation. Both vasoactive compounds are produced constitutively by the endothelial cells and release of both can be stimulated by various agonists. Smooth muscle cells express predominantly ET_A receptor, which mediates vasoconstriction. Endothelial cells express predominantly ET_B receptor; its activation stimulates NO production and vasorelaxation, thus counterbalancing the initiator ET-1 signalling. eNOS = endothelial nitric oxide synthase; NO = nitric oxide; BtK-1620 = inhibitor of the ET_B receptor.

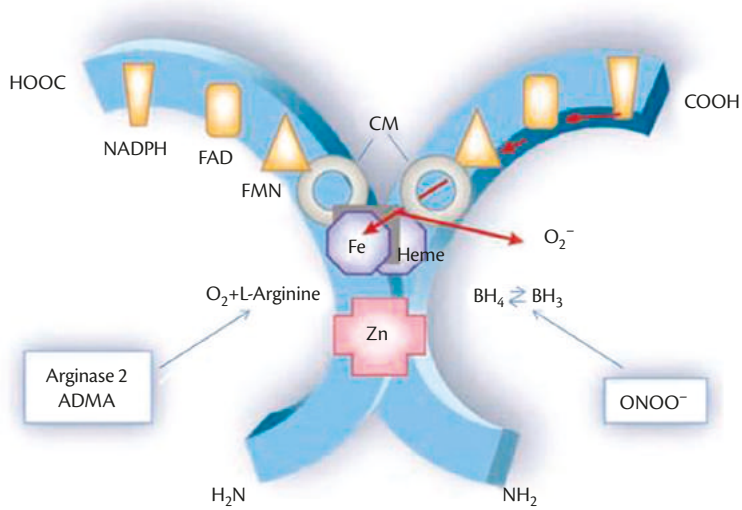

Fig. 221.4 Acute kidney injury when oxidative stress depletes BH4 and reduces bioavailability of NO in endothelial cells.

Ciclosporin nephrotoxicity is mediated in significant part by the release of ET-1 and activation of ET_A receptors leading to severe renal vasoconstriction (reviewed in Benigni, 2000) and is mitigated by administration of ET_A antagonists. In endotoxin-induced AKI, ET_B receptors mediate preservation of RBF (Nitescu et al., 2008). The blockade of ET_A receptors prevents post-cardiopulmonary bypass-associated AKI (Patel et al., 2011).

Other vasoactive compounds in AKI have been comprehensively reviewed (Conger, 1995). Activation of the cyclooxygenase system with enhanced synthesis of prostaglandins PGE_2 and PGI_2 was described in ischaemic, nephrotoxic, and endotoxic AKI (Oliver et al., 1981; Badr et al., 1986; Conger, 1995). The fact that cyclooxygenase inhibitors aggravate AKI, while infusion of prostaglandins mitigates it, argues in favour of their renoprotective effect.

Types of cell death: apoptosis, autophagy, and necrosis

When damage is severe, cells succumb to death via one of the three mechanistic pathways: type I cell death (aka apoptosis) characterized by chromatin condensation and fragmentation, cell shrinkage through formation of blebs, and apoptotic bodies containing nuclear and cytoplasmic components; type II cell death (autophagy) characterized by accumulation of autophagic vacuoles; or type III cell death (aka necrosis) characterized by cell and mitochondrial swelling and rupture of the plasma membrane (Fig. 221.5). Remarkably, these death pathways are independent of the type of insult, as the same insult can induce either type of cell death depending on the context of cell metabolism. For instance, when apoptosis or autophagy is inhibited, stressed cells undergo necrotic cell death (Kroemer and Martin, 2005). In general, however, the consensus is that the most severe damage results in necrosis, whereas damage of a lesser severity may lead to type I or II death.

Type III cell death, necrosis

Characteristic features of this type of cell death include plasma membrane permeabilization, cell swelling, mitochondrial swelling and dysfunction, ATP depletion, perinuclear clustering of organelles, and rupture of the plasma membrane (Golstein and Kroemer, 2007). Necrotic cells cannot be engulfed by phagocytes and undergo clearance through a much less efficient macropinocytosis process (Krysko et al., 2006). In the programmed form of necrosis, necroptosis, which takes place when pro-apoptotic stressors act on cells with already inhibited caspases, plasma membrane becomes permeabilized early on, in the absence of any signs of caspase-dependent cell death, and cells release soluble cyclophillin A from the cytosol (Christofferson and Yuan, 2010), a target for ciclosporin binding and inhibition. In addition, necrostatins, natural inhibitors of death receptor adaptor protein, receptor-interacting protein-1, RIP1, kinase, are released (Degterev et al., 2008). Final execution of cell death in necroptosis has similarities with autophagic cell death (see below).

Caspase-dependent, type I cell death

Apoptosis (Greek for 'falling off' like tree leaves) is typified by cell detachment from the substrate, chromatin condensation, nuclear fragmentation (karyorrhexis), retraction of pseudopodia, and shedding of apoptotic bodies (Kepp et al., 2011). Caspases, *c*ysteine-dependent *asp*artate-specific prote*ases*, are expressed as inactive enzymes which, upon activation, act as initiators (caspases-2, -8, -9, and -10) and executioners (caspases-3, -6, and -7) of apoptosis, whereas pro-inflammatory caspases-1, -4, and -5 regulate cytokine maturation (reviewed in Hellwig et al., 2011). Apoptosis can be initiated by ligands activating transmembrane death receptors (members of the TNF receptor superfamily), which directly activate caspases (extrinsic pathway), or through release of mitochondrial pro-apoptotic factors, which is triggered by DNA damage, reactive oxygen species (ROS), kinase inhibition, proteasomal or endoplasmic reticulum stress (intrinsic pathway). The extrinsic pathway leads to cell death through activated caspase 3/7, the intrinsic pathway engages Bid and Bax/Bak to induce mitochondrial outer membrane permeabilization and release of cytochrome c culminating in the formation of apoptosome followed by activation of caspase 9 and finally caspase 3/7. Importantly, these pathways not only initiate apoptosis, but, depending on the intensity of stressors, can activate survival programmes (reviewed in Yi and Yuan,

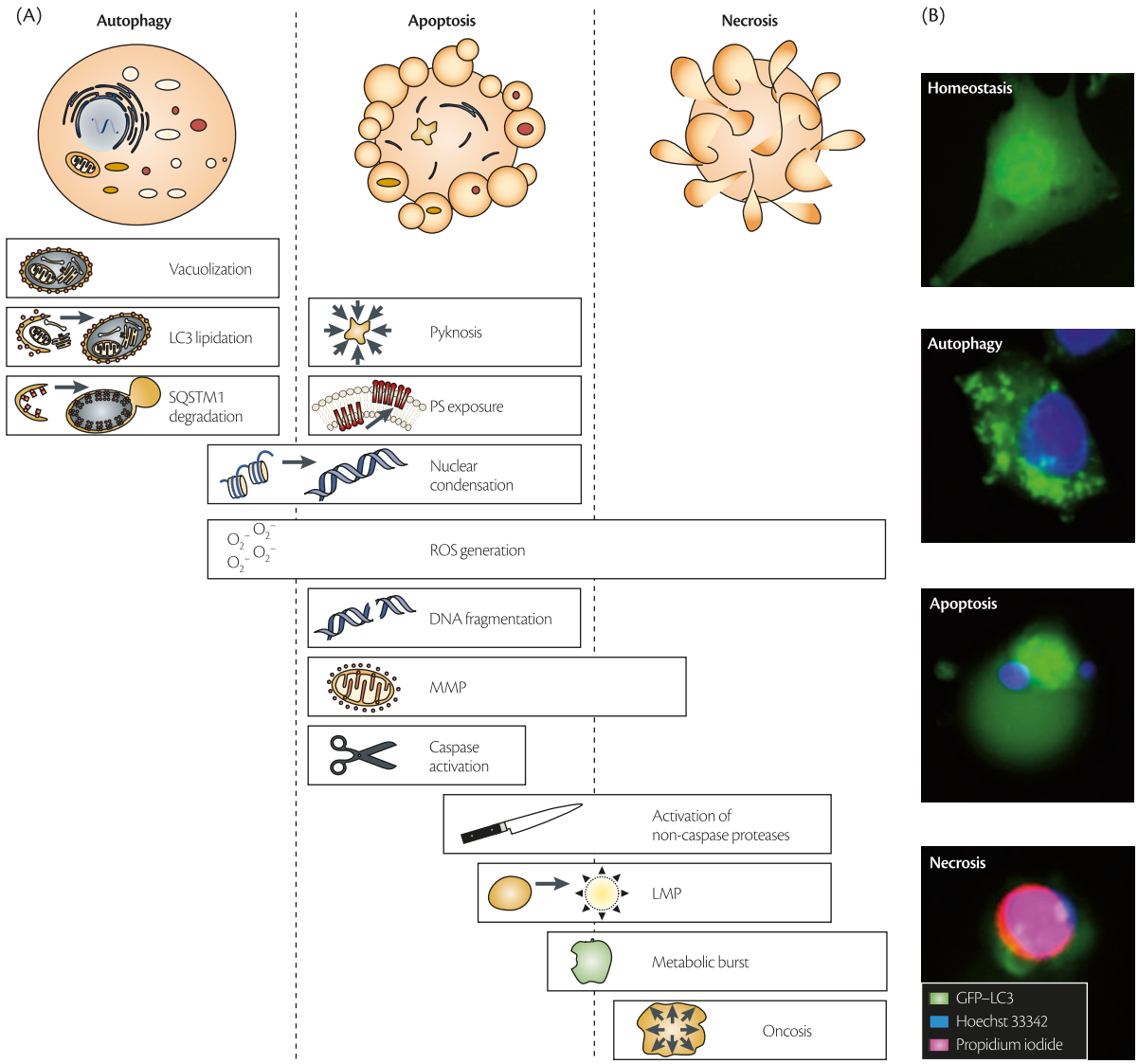

Fig. 221.5 Hallmarks of different types of cell death.
Reprinted with permission from Kepp, O., Calluzzi, L., Lapiski, M., Yuan, J., Kroemer, G. (2011). Cell death assays for drug discovery. *Nat Rev Drug Discov*, 10, 221–37.

2009) (Box 221.2). Intricate mechanisms of apoptotic cell death have been comprehensively reviewed (Kroemer and Martin, 2005).

Caspase-independent, type II cell death

Autophagy is one of the defence mechanisms protecting cells against oxidative stress. It is a highly regulated lysosomal pathway involved in the degradation and recycling of oxidized proteins and damaged organelles (Baehrecke, 2005; Codogno and Meijer, 2005). ROS can trigger autophagic processing of damaged or excessive organelles, such as peroxisomes, endoplasmic reticulum, and mitochondria (Kiffin et al., 2006). Excessive ROS may result in autophagy, apoptosis, or necrosis (Lemasters et al., 1998). Dong et al. provided *in vivo* and *in vitro* evidence that cisplatin treatment induces, in a dose- and time-dependent fashion, formation of autophagosomes in mouse kidneys and in cultured proximal tubular cells, and suggested that autophagy in AKI plays the role of a protective mechanism for cell survival (Periyasamy-Thandavan et al., 2008). Isaka et al. (2009) examined the effect of Bcl-2 on renal I/R-induced autophagy. I/R injury induced autophagosome formation. On electron microscopy, the autophagosomes contained mitochondria.

Other cells involved

Activation of vascular endothelial cells and stagnated blood flow, together with the chemoattractants released from injured tubular epithelial cells, facilitate waves of transmigration of polymorphonuclear leucocytes (PMNs), followed by monocytes/macrophages and, later on, lymphocytes. The process is driven by increased expression of adhesion molecules like ICAM-1, VCAM-1, selectins, leucocyte-endothelial integrins, fractalkine receptor CX3CR1, and its ligand (reviewed in Kinsey et al., 2008; Goligorsky et al., 2010). Most investigators find that preventing leucocytic infiltration by either depleting PMNs, macrophages, and T-lymphocytes or blocking leucocyte-endothelial interactions results in renoprotection (reviewed in Ikeda et al., 2006; Thurman, 2007; Kinsey et al., 2008; Chung and Lan, 2011). These invading cells degranulate and release

Box 221.2 The concept of hormesis

Some investigators interpret cell death as 'an ultimate but unsuccessful attempt by cells to cope with stress and re-establish homeostasis' (Kepp et al., 2011). This dichotomy is the centrepiece of the concept of hormesis. 'Stress-response hormesis' refers to the induction of stress-protective mechanisms (Gems and Partridge, 2008). The toxicological axiom states that 'the dose determines the poison'; accordingly, exposure to sublethal stressors induces a response that results in stress resistance, whereas lethal level of stressor accelerates cell demise. For instance, a non-lethal oxidative stress stimulates mitochondrial biogenesis by activating leucine zipper transcription factors, nuclear factor-E2-related factor (Nrf2) and ATF4, which regulate the expression of antioxidant response element-containing genes, such as glutathione-S-transferase, glutathione peroxidase, glutathione reductase (all involved in glutathione biosynthesis and cycling), and haem oxygenase-1 (Motohashi and Yamamoto, 2004), ultimately favouring cell survival. This process is mediated by the mitochondrial ROS stimulating Nrf2 binding to the promoter region of the nuclear respiratory factor-1 (NRF-1) (Piantadosi and Suliman, 2006). Activation of NRF-1 is a prerequisite for transcriptional activation of mitochondrial transcription factor A (Tfam) and induction of mitochondrial DNA replication/transcription and mitochondrial biogenesis (Gleyzer et al., 2005).

Another target of hypoxic stress is AMP-activated protein kinase (AMPK), a ubiquitously expressed enzyme regulating ATP production and utilization (reviewed in Hamanaka and Chandel, 2010). By activating PKC-zeta, which in turn phosphorylates α-subunits of Na/K-ATPase and leading to its endocytosis, AMPK secures parsimonious use of ATP. Other targets inhibited by AMPK are NF-κB, VCAM-1, E-selectin, JNK; targets activated by AMPK are MnSOD, catalase, thioredoxin, eNOS, FoxO1 and FoxO3, sirtuin 1, Bcl-2, and survavin. When ROS are produced in excess, calpain, caspase and p53 activation, ER stress, increase in cytosolic calcium concentration and release of HMGB1 ensue.

proteolytic products, elaborate cyto- and chemokines, reactive oxygen and nitrogen species, all participating in a well-orchestrated acute aseptic inflammation of the kidneys. This explains therapeutic benefits of curtailing the infiltration processes. Furthermore, pro-inflammatory mediators can serve as biomarkers of AKI, as will be detailed later.

Two subsets of monocytes, inflammatory $Gr1^{+}$ and 'patrolling' $Gr1^{lo}$ cells, upon infiltrating the kidney give rise to *dendritic cells* (Hochheiser et al., 2011). These cells can be recognized by co-expression of F4/80 molecule (previously considered a marker of renal macrophages, but found to be present mainly in splenic macrophages), fractalkine receptor CX3CR1, CD11c, and MHC class II. Kidney dendritic cells form an extensive network throughout the interstitium surveying renal parenchymal microenvironment for autoantigens, either tubular, or glomerular, or filtered. These professional antigen-presenting cells are activated by stimuli as diverse as hypoxia, endotoxins, and multiple drugs (the basis for drug allergy). Kidney dendritic cells represent the first line of response to ischaemia with secretion of TNFα, the function later on taken by vascular endothelial cells (Dong et al., 2007). Chemoattraction of Th cells is in part responsible for ischaemic injury. Similar pro-inflammatory functions are ascribed to kidney dendritic cells in the early phase of ureteral obstruction (Dong et al., 2008). In both cases, ablation of the source of dendritic cells with clodronate liposomes has renoprotective effect. In contrast, depleting kidney dendritic cells in cisplatin-induced kidney injury aggravates renal injury (Tadagavadi and Reeves, 2010). The underlying reasons for this discrepant effect of depletion of dendritic cells are unknown.

States of hypoxia, oxidative stress, and pseudo-hypoxia

Reduced RBF accompanying AKI of almost any aetiology (hyperdynamic state in sepsis is an exception) inevitably leads to renal hypoxia, although parallel decreases in tubular transport functions and oxygen requirement to support them, probably mitigate cellular consequences of reduced oxygen delivery. Hypoxia-inducible factors (HIFs) -1 and -2 are induced in experimental AKI (Rosenberger et al., 2005), again indicative of hypoxia. When O_2 concentration decreases below a certain threshold, HIFs accumulate and induce > 100 genes, including components of glycolytic pathway, angiogenic pathway, and detoxification pathway, among others.

One of the sensors of oxygen pressure is represented by the enzyme that hydroxylates HIF-1α on proline residues 402 and 564, prolyl hydroxylase (PHD), and this hydroxylation is obligatory for binding of von Hippel–Lindau protein marking HIF-1α for ubiquitination and proteasomal degradation. When oxygen availability is reduced, mitochondria, another ubiquitous oxygen sensor, boost their generation of ROS. Produced ROS in turn inhibit PHD activity, further stabilizing HIF-1α. Accumulation and nuclear translocation of HIF-1α results in transcriptional activation of genes responsible for glycolysis and glucose transport, lipid metabolism, angiogenesis, defence against superoxide anions, and erythropoiesis, thus orchestrating cellular adaptation to hypoxic stress, as detailed in Fig. 221.6. In addition, PHD activity can be modulated by the TCA cycle intermediate 2-oxoglutarate, its substrate, and inhibited by other TCA intermediates. Yet another oxygen sensor, an asparaginyl hydroxylase, a factor inhibiting HIF-1α (FIH1), modifies HIF-1α in a way that reduces its transcriptional activity (reviewed in Majmundar et al., 2010). Sirtuins, a family of NAD-dependent deacetylases, also modulate HIFs: sirtuin 1-induced deacetylation increases activity of HIF-2α (responsible for transcription of erythropoietin), but represses activity of HIF-1α. Under hypoxic conditions, NAD depletion reduces the activity of sirtuins, thus increasing HIF-1α transcriptional activity. Two additional oxygen-dependent regulators have been identified: microRNA-210 (miR-210) and miR-199a (Rane et al., 2009; Devlin et al., 2011).

In addition to this oxygen-dependent mechanism, there is growing appreciation of the fact that HIF-1α can be induced by other stressors, such as reactive oxygen and nitrogen species and inflammatory cytokines under non-hypoxic conditions (Kietzmann and Görlach, 2005). Indeed, ROS are overproduced in AKI (Shah, 1995), either ischaemic or endotoxic and nephrotoxic, as well as in obstructive nephropathy (Dendooven et al., 2011), and may play a central role in executing cell fate programmes. These species include superoxide anion, hydrogen peroxide, hydroxyl radicals, peroxinitrite, hypochlorous acid, and singlet oxygen and are produced in response to nephrotoxins, an ischaemic episode, or activation of cytochrome P450, arachidonic acid, xanthine oxidase,

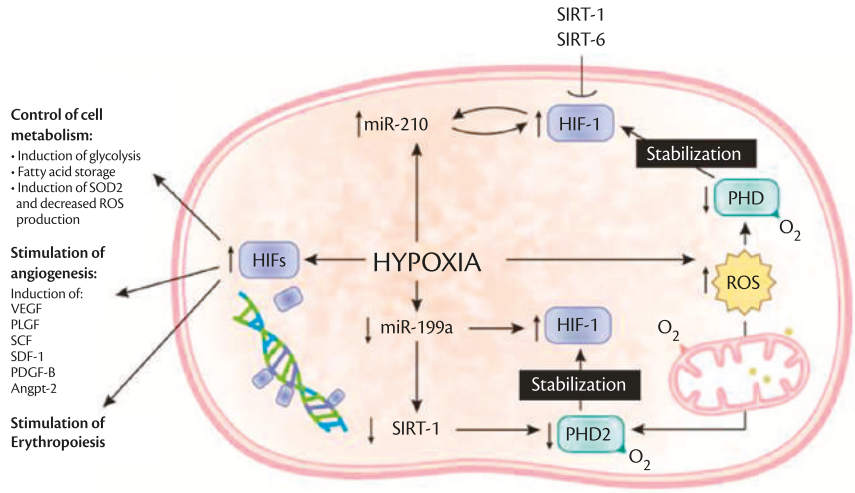

Fig. 221.6 Cellular O_2 sensors and response to hypoxia. Over 100 genes are induced by HIFs, among these are genes encoding proteins controlling cell metabolism, angiogenesis, and erythropoiesis.

NADH/NADPH oxidase, and NOS pathways. ROS overproduction results in damage to DNA, proteins, and lipids. Defences against ROS include redox systems as NAD+/NADH, NADP+/NADPH, oxidized/reduced glutathione; enzymes as SODs, catalase, glutathione peroxidase, thioredoxin peroxidases, glutaredoxins, and thioredoxin reductase, all participating in maintaining or restoring redox balance. And yet, redox imbalance is a constant companion of AKI. ROS production can be initially compartmentalized to different organelles, mitochondria or plasma membrane NADPH oxidase, and later propagate from them to other cellular compartments, such as peroxisomes, lysosomes, and nucleus (Kietzmann 2010), leading to oxidative modifications of DNA, proteins, and lipids, thus explaining the profound pathogenic nature of oxidative stress.

Mitochondrial oxidative stress in acute kidney injury

Perturbations of mitochondrial respiratory chain and production of ROS represent a part of a default response to hypoxic stress. Under physiological conditions, mitochondria are elongated filamentous structures. Upon stress, mitochondria become fragmented, develop mitochondrial membrane permeabilization, and release factors inducing apoptosis from the mitochondrial intermembrane space. Mitochondrial membrane permeabilization is directly related to the collapse of mitochondrial membrane potential. (See Box 221.3.)

ROS open mitochondrial permeability transition (MPT) pores, large non-selective channels in the inner membrane, during I/R resulting in mitochondrial swelling and depolarization. One of the key components of the MPT is represented by cyclophilin D. This component is inhibited by ciclosporin which prevents MPT pore opening. Interestingly, ischaemic preconditioning (see below) also prevents MPT pore opening and kidney injury, as does mitochondrial ROS scavenging (Szeto et al., 2011).

The dynamics of morphological changes in mitochondria may be related to cell apoptosis. Mitochondrial fission involves the constriction and scission of mitochondria by fission proteins, such as dynamin-related protein 1 (Drp1) and fission 1 (Fis1). On the other hand, mitochondrial fusion is the lengthening of mitochondria by tethering and joining together two adjacent mitochondria. Mitofusin-1 and -2 are mainly responsible for outer membrane fusion, while Opa1 is thought to mediate inner membrane fusion. AKI is associated with fragmentation of mitochondria, which involves the activation of mitochondrial fission via Drp1. Suppression of Drp1 and mitochondrial fragmentation abrogates mitochondrial damage, cytochrome c release, apoptosis, and renal/cellular injury both *in vitro* and *in vivo* (Brooks et al., 2009). On the other hand, it has recently been argued that mitochondrial morphology depends not only on the existence of a stressor, but also on the functional requirements: elongated mitochondria could facilitate signal transduction or reflect the state of active respiration, whereas fragmented mitochondria may be the preferred morphology for their recruitment to distant cellular compartments (reviewed in Chan, 2006). Hence, future work should elucidate the significance of mitochondrial fragmentation in AKI.

Box 221.3 Mitochondrial ATP production

The proton-motive force (Δp; equivalent to $\Delta\mu H^+$) responsible for mitochondrial ATP production consists of $\Delta\mu H^+$ and ΔpH. Under physiological condition, ΔpH is a small part of Δp and negligible. $\Delta\mu H^+$ is considered as the representative of Δp and its measurement is sufficient for the evaluation of mitochondrial capability to generate ATP. Under the pathological conditions, like hypoxia-reoxygenation, relative changes of ΔpH and $\Delta\mu H^+$ result in the change of Δp. ATP depletion occurs after hypoxia-reoxygenation and ATP-dependent potassium channels, localized on the inner membrane of mitochondria, become open resulting in increased potassium permeability. The increase in inner membrane potassium permeability decreases $\Delta\Psi$ and simultaneously increases ΔpH, which may leave Δp unchanged. If net Δp remained unchanged, it could not account for the energetic deficit after hypoxia-reoxygenation. Weinberg and co-workers (Feldkamp et al., 2005) measured Δp and $\Delta\Psi$ and found that mitochondrial ΔpH is abrogated after hypoxia-reoxygenation making $\Delta\Psi$ the significant portion of mitochondrial Δp. Thus, renal tubular epithelial cells become energy deficient.

Mitochondrial oxidative stress results in the accumulation of uncoupling protein (UCP2), leading to the inward proton leak which competes with the function of ATP synthase and results in reduction of ATP synthesis from ADP. This situation can be modelled *in vitro* by application of rotenone, antimycin A or diethyldithiocarbamate, all increasing mitochondrial O_2 production; in contrast, oxidants produced outside mitochondria do not affect UCP2 abundance (Giardina et al., 2008).

In renal I/R injury, the polyunsaturated fatty acyl group of membrane phospholipids is highly susceptible to O_2^- and a self-propagating chain reaction produces a wide variety of aldehydes, alkenals, and hydroxyalenals, such as malondialdehyde, 4-hydroxy hexenol (HHE), and 4-hydroxy-2-nonenal (HNE) (Kato et al., 1994; Ferri and Kroemer, 2001; Noiri et al., 2001). Membrane-permeable HNE is cytotoxic. Mitochondrial proteins are targets of HNE: it inactivates the 2-oxoglutarate dehydrogenase, pyruvate dehydrogenase complex, cytochrome c oxidase, and NADH-linked respiration in isolated mitochondria.

Another typical target of superoxide anion is represented by iron-sulphur clusters in various cellular proteins, such as the mitochondrial aconitase, leading to the inhibition of mitochondrial respiration (reviewed in Thomas et al., 2008). Reversible, covalent modification of cysteine thiol residues within active and allosteric sites of different proteins is achieved by ROS, especially hydrogen peroxide, which generate disulphides, R-S-S-R, either within a single protein between adjacent cysteines (intraprotein disulphide), between different proteins (interprotein disulphide), or between a protein and glutathione (S-glutathionylation). This redox modification of cysteine thiols is responsible for the inhibition of several phosphatises; activation of protein kinases Src and PKC; increased DNA binding and/or nuclear export of transcription factors (AP-1, nuclear factor kappa B (NF-κB), Nrf2, p53); and inhibition of antioxidant enzymes such as thioredoxin and peroxiredoxin. Furthermore, RNS are responsible for S-nitrosylative modification of several enzymes, usually resulting in their inhibition: Jnk, Akt, soluble guanylate cyclase, eNOS, and Hsp90; whereas S-nitrosylation of arginase leads to its activation, thus further perturbing the synthesis and bioavailability of NO.

Lysosomes

ROS, a constant companion of cell stress, and many other lysosomotropic agents result in lysosomal membrane permeabilization, which often precedes mitochondrial membrane permeabilization and release of cytochrome c (reviewed in Ferri and Kroemer, 2001). This leads to the activation of acidic sphingomyelinase and generation of ceramide, triggering autocatalytic proteolysis by the released cathepsins, and, when of sufficient intensity, causing type II, autophagic, cell death.

Gentamycin-induced AKI

Gentamycin-induced AKI is specifically associated with the enlargement of the lysosomal compartment where the antibiotic is concentrated together with phospholipids and the chaperone HSP73, forming so-called myeloid bodies, the typical manifestation of tubular phospholipidosis. Gentamycin binds to the peptide-binding domain and interferes with the chaperone activity of HSP73 (Miyazaki et al., 2004). A gentamycin molecule inserts into phosphatidylinositol monolayers to be surrounded by four molecules of phosphatidylinositol.

Osmotic nephrosis

Another condition typically associated with the distension of lysosomes and vacuolization and swelling of the proximal tubular epithelia is known as osmotic nephrosis (see below)—AKI initiated by contrast media, dextrans, or sucrose (Dickenmann et al., 2008). Immunoglobulin G (IgG) therapy can lead to osmotic nephrosis due to the presence of IgG stabilizers, sucrose and sorbitol, at 10% each. Volume expansion with low-molecular-weight dextran and mannitol, especially when administered with ciclosporin or furosemide, can result in osmotic nephrosis and AKI. Another volume expander, hydroxyethyl starch, results in about a 40% chance of developing osmotic nephrosis and AKI. Ionic and non-ionic hyperosmolar radiocontrast media, first and second generations of iodine-containing contrast agents, in combination with dehydration, are well-known causes of osmotic nephrosis. Clear-cell transformation can be seen in calcineurin inhibitor or rapamycin toxicity and in ischaemic injury. In all these cases, proximal tubular cells are swollen by accumulating vacuoles, presumably pinocytic in origin, which fuse with the lysosomes, but fail to undergo complete digestion. It remains to be established why the lysosome is primarily targeted, however, its permeabilization explains why lysosomal enzymuria (see below) has a potential to serve as a biomarker of damage.

Endoplasmic reticulum stress-unfolded protein response

Endoplasmic reticulum (ER) is endowed with the ability to store and release calcium, and is responsible for folding and secretion of proteins and biogenesis of lipids. These functions become impaired due to the ER stress induced in the kidney by I/R injury, non-steroidal anti-inflammatory drugs (NSAIDs), aminoglycosides, cisplatin, calcineurin inhibitors ciclosporin and tacrolimus, and some heavy metals (cadmium, mercury, lead) (Dickhout and Krepinsky, 2009). Resulting accumulation of unfolded proteins triggers a default unfolded protein response (UPR). Evolutionarily conserved UPR is a two-pronged stress response: initial cytoprotection and, if prolonged, cytodestruction. Cytoprotective effects of UPR are accomplished via upregulation of chaperones, glucose-regulated proteins GRP78 and GRP94, by inositol-requiring protein-1 (IRE1) kinase, and protein disulphide isomerase (PDI), both assisting in protein folding, and by suppression of translation through phosphorylation of eukaryotic translation initiation factor 2α (eIF2α, phosphorylated by PERK—protein kinase RNA-like ER kinase), thus reducing protein synthesis and burden of folding. These are homeostatic responses directed towards the restoration of ER function. When stress is prolonged these pathways become deactivated triggering pro-apoptotic pathways (a) IRE1-TRAF2-JNK and (b) C/EBP-homologous protein (CHOP)—outer mitochondrial membrane permeabilization and downregulation of Bcl2 (Tabas and Ron, 2011). In I/R kidney injury, PERK-dependent eIF2α phosphorylation exerts a renoprotective effect, and overexpression of the chaperone GRP78 protects cultured epithelial cells against hydrogen peroxide, iodoacetamine and 2,3,5-tris(glutathione-S-yl)hydroquinone, all potent oxidants inducing ER stress (Jia et al., 2004). It is of particular interest that a prior ER stress preconditions cells to the subsequent stress, but the mechanisms mediating this protection remain unknown.

Notably, there is a significant overlap between agents inducing mitochondrial, lysosomal, and ER stress making the idea of their intricate interactions quite probable. These interactions may represent targets for future design of therapeutic interventions. However, the integration of these various pathways remains elusive.

Peroxisomes

Different antioxidant enzymes are localized to distinct cellular compartments: glutathione peroxidase is expressed in the cytosol and mitochondria, glutaredoxin-1 in the cytosol, glutaredoxin-2 and peroxiredoxin-3 in the mitochondria, whereas catalase is localized to peroxisomes. Peroxisomes, first identified in mouse kidney, are single-membrane organelles ubiquitously present in eukaryotic cells (Box 221.4). Mammalian peroxisomes possess > 50 enzymes participating in β-oxidation of very-long-chain-fatty acids (VLCFA), α-oxidation of phytanic acid, synthesis of plasmalogens, catabolism of polyamines and purines, and decomposition of hydrogen peroxide (Wanders and Waterham, 2006). Peroxisomes can both produce and scavenge ROS and, together with mitochondria, are the key players in the tightly regulated balance of oxygen metabolites in the cell (Bonekamp et al., 2009). Many peroxisomal tasks, particularly the β-oxidation, are connected to mitochondrial metabolic pathways, confirming the close cooperation of these two organelles (Schrader and Yoon, 2007). Despite the evolutionary relationship of peroxisomal and mitochondrial β-oxidation, the rate-limiting enzymes and substrate specificities are different (Kleinman and Walker, 2008). Renal tubular cells and hepatocytes have the highest density of peroxisomes. Renal ischaemia decreases the number of peroxisomes in proximal tubules and these structural changes are accompanied by the decline of their enzymatic activity, which becomes irreversible when the duration of ischaemia exceeds a certain threshold. Gulati et al. showed that rat kidney exposed up to 60 minutes of ischaemia is able to restore normal β-oxidation after reperfusion (Gulati et al., 1992). Renal tubules rely on fatty acid oxidation as an important source of ATP synthesis, and disruption of this essential energy-generating pathway may have deleterious effects for the cell. Dysfunctional and inhibited β-oxidation in mitochondria and peroxisomes during renal ischaemia results in increased tissue levels of cytotoxic free fatty acids, accumulation of fatty acid metabolic products, and inhibition of proximal tubule Na^+K^+-ATPase (Ruidera et al., 1988; Portilla, 1999). Peroxisomes respond to various stimuli acting through peroxisome proliferator-activated receptor (PPAR)-α by increasing their enzymatic activity and proliferation. Treatment with fibrates, acting through PPAR-α, was able to maintain the oxidation of fatty acids and demonstrated renoprotective effects in animal models of I/R and cisplatin-induced AKI (Li et al., 2004). Similarly the overexpression of PPAR-α by itself, without the use of receptor ligands could prevent alterations in lipid metabolism and preserve renal function and morphology in AKI (Negishi et al., 2007; Li et al., 2009).

Modulation of the oxidative and nitrosative stress is another anticipated mechanism of PPAR-mediated renoprotection. Peroxisomal oxidases are unique in generating high amounts of hydrogen peroxide (H_2O_2), a by-product of the numerous oxidative reactions, which is subsequently decomposed by one of the most abundant peroxisomal enzymes, catalase. Whereas low quantities of H_2O_2 may function in cell signalling, overproduction or impaired degradation of H_2O_2 increases oxidative stress and may change membrane permeability with subsequent leakage of peroxisomal matrix components and H_2O_2 itself into the cytoplasm. Peroxisomal injury can also impact mitochondrial function by destabilizing the membrane potential and promoting the production of ROS by mitochondria (Koepke et al., 2008).

Box 221.4 Pathology of peroxisomes

Peroxisomes express numerous specific proteins, called peroxins. These proteins are coded by corresponding Pex genes and function as transporters and receptor in substrate transport across the peroxisomal membrane, as well as in the control of peroxisomal proliferation and division. Inherited defects of peroxins are associated with complex clinical syndromes, and renal involvement is only a part of the complex clinical picture. In Zellweger syndrome, a prototypal peroxisomal biogenesis disorder, glomerular and tubular microcystic disease is usually present and proteinuria often found (Gilchrist et al., 1976). The role of specific peroxins in renal pathophysiology, including AKI, has not been elucidated. It is plausible that temporary rather than constitutive changes of specific peroxisomal proteins accompany subcellular changes in AKI. Peroxin 14, an essential component of the peroxisomal membrane import machinery, showed significantly decreased expression in lipopolysaccharide-induced AKI. This may have a negative impact on catalase import into organelle and on scavenging function of peroxisomes during LPS challenge (our unpublished observations). Knockout of PMP70, a peroxisomal membrane transporter involved in fatty acid import, resulted in increased levels of pro-inflammatory mediators and oxidative stress (Di Benedetto et al., 2009).

Human peroxisomes do not contain urate oxidase, converting urate to allantoin, which may actually provide an evolutionary advantage, considering the antioxidant properties of uric acid (Becker, 1993). Several studies have reported on the protective effects of catalase stimulation or supplementation in AKI. The exact mechanism(s) of catalase regulation and activation in peroxisomes are still not completely understood. Transgenic mice with kidney-specific overexpression of Sirtuin 1 could maintain peroxisome number and function with upregulation of catalase, and demonstrated decreased levels of local ROS and reduced apoptosis of renal tubular epithelia during cisplatin-induced AKI (Hasegawa et al., 2010). Sirtuin 1 upregulation in the S1 segment of the proximal tubules exposed to endotoxin preserved peroxisomes, whereas the S2 and S3 segment with impaired upregulation of Sirtuin 1 exhibited severe structural and functional peroxisomal damage (Kalakeche et al., 2011).

Mechanism-based biomarker discovery

Described cellular abnormalities in AKI lay the foundation for biomarker discovery. The urine represents an ideal source for preclinical diagnosis of impending AKI because a significant number of tubular markers, both molecules and organelles, are excreted at the outset of injury. The majority of existing biomarkers originate from the brush border, lysosomes, cytoplasmic proteins, and degranulated neutrophils. The existing biomarkers of AKI have been comprehensively reviewed (Vaidya et al., 2008). Biomarkers belonging to the category of brush border membrane enzymes include alanine aminopeptidase (AAP), alkaline phosphatase (AP), sodium-hydrogen exchanger NHE3, and gamma glutamyl

transpeptidase (γ-GT); among cytosolic proteins appearing in the urine are liver-type fatty acid-binding protein, and a secretory form of clusterin; in the category of lysosomal enzymes excreted with the urine are *N*-acetyl-β-glucosaminidase (NAG) and neutrophil granules gelatinase-associated lipocalin (NGAL) which becomes detectable in the lysosomal compartment of damaged proximal tubules originating, probably, from endocytosed filtered fraction (Schmidt-Ott et al., 2007) and is highly induced in the thick ascending limb and collecting duct epithelia in the Ngal reporter mouse (Paragas et al., 2011). Kidney injury molecule 1 (KIM-1) is a membrane glycoprotein, shedding of which into the urine serves as an early signal of AKI. Another plasma membrane and secreted protein, Klotho, in contrast, disappears from the urine early in response to AKI (Hu et al., 2010). Among low-molecular-weight filtered proteins, retinol-binding protein (RBP) excretion is a sensitive indicator of nephrotoxic kidney injury (Garçon et al., 2004); β2- and α1-microglobulins, microalbumin, and cystatin C also belong to this category.

Cytokines and chemokines

Cyto- and chemokines as biomarkers are reporting on systemic propagation of local injury to the kidney. Urinary interleukin (IL)-18, an interferon-γ-inducing factor, is elevated in AKI (Parikh et al., 2004). Liangos et al. (2010) performed a nested case–control study of biomarkers predicting development of AKI in patients undergoing cardiac surgery with cardiopulmonary bypass. These investigators found that elevated levels of macrophage inflammatory protein-1β and epidermal growth factor pre-surgery and levels of soluble VCAM-1, fractalkine, and macrophage inflammatory protein-1α 2 hours after the surgery served as good predictors of impending AKI.

The clinical significance and utility of several biomarkers are discussed in Chapter 223.

Cellular actions of endotoxins: pathogenesis of sepsis-induced acute kidney injury

Despite many advances in understanding the pathophysiology of AKI in septic conditions, the development of AKI in a septic shock patient is still associated with mortality rates reaching 50–60% (Hoste et al., 2010) (see also Chapter 244). Recent studies highlighted the pathogenetic details of septic AKI. In endotoxic shock, renal ischaemia secondary to the fall of RBF and the paradoxical combination of a systemic dilatation and renal vasoconstriction has been considered for many years as the most enduring pathogenetic feature of septic AKI. However, studies in patients with sepsis, but not those in septic shock, demonstrated that RBF is maintained or even increased reflecting a hyperdynamic circulation (Bradley et al., 1976; Brenner et al., 1990; Zarjou and Agarwal, 2011). In haemodynamically resuscitated patients, RBF is mostly preserved or even increased (hyperdynamic state), but this does not preclude the development of AKI (Brenner et al., 1990). Two animal studies have recently demonstrated that early sepsis does not necessarily increase renal arterial resistance (Langenberg et al., 2007; Chvojka et al., 2008). Those data strongly suggest that renal vasoconstriction is not a prerequisite for AKI developing during sepsis. The administration of lipopolysaccharide (LPS) in animals is associated with decreased GFR. It is widely accepted that the decreased GFR is the consequence of a fall in transcapillary hydraulic pressure due to afferent arteriolar vasoconstriction (Lugon et al., 1989). Recent studies demonstrating the existence of a significantly increased RBF, decreased vascular resistance, and reduced GFR with preserved tubular functions in reanimated large animal models of sepsis support the possibility of a predominant vasodilatation of the efferent rather than afferent arterioles (Langenberg et al., 2007; Chvojka et al., 2010). The impairment of the glomerular haemodynamics secondary to the septic shock and to the imbalance in intraglomerular vasomotor control is probably only one step in the development of the sepsis-induced AKI justifying the necessary haemodynamic support of septic patients. Importantly, in the absence of septic shock, there is a dissociation between the relatively preserved or even elevated RBF and significantly decreased GFR, the latter phenomenon not dissimilar to what has been observed in AKI due to other causes.

Microcirculatory perfusion is known as an important target of sepsis (Trzeciak et al., 2007). Peritubular microcirculation is altered as early as 2 hours after the administration of LPS in mice preceding the development of AKI (Wu et al., 2007c). This alteration of the peritubular microcirculation is probably not uniform in the kidney as suggested by the inefficiency of the average pO_2 measurement to detect tissue hypoxia despite the evidence of hypoxic areas (Johannes et al., 2009). The role of reactive nitrogen-oxygen species (RNOS) and iNOS in mediating the injury of peritubular micocirculation have been demonstrated in septic rats (Wu et al., 2007b). The endotoxin induced inflammation and endothelial dysfunction lead to the RNOS production. In humans, the examination of excreted cells in urine confirmed the presence of iNOS induction in septic patients and healthy volunteers challenged with endotoxin. Moreover, in the same patients the use of a specific iNOS inhibitor (aminoguanidine) can prevent septic injury to the proximal tubule (Heemskerk et al., 2006). The integrity of the endothelial barrier is breached in sepsis, resulting in pulmonary, renal, and brain oedema, which can be life-threatening. Furthermore, a procoagulant glycoprotein, tissue factor, is released by the endothelium and, together with the disbalance between the tissue-type plasminogen activator and plasminogen activator inhibitor-1, predisposes to increased coagulation and suppressed fibrinolysis. Pioneering studies of glomerular transcriptome in LPS-treated mice (Sun et al., 2009) revealed downregulation of signalling pathways involved in the synthesis of heparin sulphate, glycan structures, adherens junctions, leucocyte transmigration, focal adhesions, actin cytoskeleton and Wnt signalling and upregulation of pathways responsible for Toll-like receptors signalling, extracellular matrix-receptor interactions, apoptosis, complement and coagulation cascades, MAPK signalling, among others, thus shedding light on several clinically relevant manifestations of sepsis. Histologic data in sepsis-induced AKI are sparse due to the potential danger of performing renal biopsy due to bleeding complications. Recently Lerolle et al. performed post-mortem kidney biopsies in 36 patients divided into three groups: 19 patients who died of septic shock with AKI, nine non-septic intensive care unit (ICU) control patients, and eight patients who died of trauma on scene (Lerolle et al., 2010). Presence of apoptosis was assessed by TUNEL and activated caspase 3 labelling. All septic patients demonstrated acute tubular lesions, intense glomerular and interstitial infiltration by leucocytes, and presence of tubular cell apoptosis (3% of tubular cells). Apoptosis in this group was significantly enhanced compared to the 0.2% and 0.5% apoptotic cells in non-septic ICU and trauma patients, respectively. Similar characteristics have also been described more recently in

a study comparing the characteristics of septic and ischaemic AKI in mice (Lee et al., 2012). The septic kidneys showed fewer tubular necrosis contrasting with more tubular apoptosis and higher caspase 3 activity. However, the role played by apoptosis is still debated and a recent post-mortem histologic study (using light and electron microscopy) of kidney biopsies in septic patients did not confirm the importance of apoptosis but rather of a likely reversible renal tubular injury (swollen injured mitochondria, tubular cell vacuolization, and shedding renal tubular cells into the tubular lumen) (Takasu et al., 2013).

Animal models have also highlighted the role of apoptosis in the development of AKI in sepsis. Four models of sepsis have been described in the literature: endotoxin infusion, caecal ligation and perforation, bacterial infusion, and intraperitoneal bacterial infusion (Heyman et al., 2002; Doi et al., 2009). Injection of LPS, a non-bacterial model of endotoxaemia, offers some advantages: simplicity, inexpensive, reproducible, and suitable to study new pharmacologic agents. The injection of LPS in mice is associated with the development of AKI even in the absence of overt haemodynamic disturbances (Cunningham et al., 2002). LPS injection induces release of several proinflammatory cytokines among which the role of TNF-α, IL-1, and IL-6 appear to be predominant. The pre-treatment of mice with a soluble receptor of TNF (TNFsRp55) protected against the development of AKI. TNF-α acts via kidney receptor TNFR1 as demonstrated by the resistance to sepsis-induced AKI in TNFR1 knockout mice (Cunningham et al., 2002). TNFR1−/− mice presented less apoptosis and fewer neutrophils infiltrating the kidney following LPS administration. Moreover, TNFR1+/+ kidney transplantation to TNFR1−/− mice was associated with the development of sepsis-induced AKI, whereas TNFR1−/− kidney transplantation to TNFR1+/+ mice led to renoprotection. In the presence of TNF-α, cultured kidney proximal tubular cells increase their expression of Fas mRNA and DNA fragmentation highlighting the possibility that TNF-α is responsible for the tubular cell apoptosis in sepsis (Jo et al., 2002). Similarly TNF-α and LPS elicit apoptotic cell death of cultured bovine glomerular endothelial cells (Messmer et al., 1999). Despite these promising findings, the use of anti-TNF monoclonal antibodies failed to protect animals from AKI (Rodriguez-Wilhelmi et al., 2003). More recently in a septic mice model, the authors underlined the role played by inflammation (Lee et al., 2012). Histologically the kidney of septic mice (caecal ligation) showed very sparse macrophage and neutrophils infiltration compared to a model of ischaemic AKI. This absence of interstitial inflammation was concomitant with a high level of anti-inflammatory cytokine IL-10, a massive immune cell apoptosis and a relative expansion of the immune suppressive regulatory T cell (Treg) lymphocytes. The authors suggest this local immune suppression characterizes and might be linked to the development of septic AKI.

The role of inflammation in sepsis is broadly acknowledged. Large cohorts of critically ill patients exhibited the relation between the IL-6 plasma concentration and the development of septic AKI (Chawla et al., 2007; Liu et al., 2009). The exact mechanisms by which cytokine storm in sepsis provokes kidney injury are only partially understood, but are probably involved in several pathogenetic steps: renal intracapillary and interstitial inflammation, direct tubular cell injury, release of proteases, activation of complement and coagulation pathways, reactive nitrogen species, and ROS, arachidonic acid, infiltration by activated leucocytes, and microcirculatory failure (Sutton 2009; Zarjou and Agarwal 2011). The role of anti-inflammatory cytokines and Treg lymphocytes was recently emphasized as discussed above (Lee et al., 2012).

Toll-like receptors (TLR) are targets of bacterial invasion and endotoxaemia. TLR-2 is ligated by Gram-positive bacteria, mycobacteria and yeasts; TLR-4 recognizes LPS, TLR-5 mediates responses to bacterial flagellin, TLR-9 recognizes bacterial DNA and TLR-3 double-stranded RNA (Peters et al., 2003).

All TLRs, except TLR-3, engage Myd88-, NF-κB- and activator protein 1-dependent pathways leading to production of pro-IL-1β and pro-IL-18, as well as the TRIF-dependent pathway resulting in the activation of type 1 interferon (Gonçalves et al., 2010). TLR-2 and -4 are upregulated on monocytes and on renal epithelial and endothelial cells in patients with sepsis, thus potentially amplifying cytotoxic effects of their ligands. Analysis of endotoxaemic mice with targeted ablation of TLR4 in the inflammatory or parenchymal cells revealed that mortality occurred exclusively in those that expressed TLR4 in parenchymal, but not inflammatory, cells and monocyte chemoattractant protein-1 predicted systemic inflammatory response (Juskewitch et al., 2012). In parallel with TLR-mediated cascade, 'endogenous danger signals' are recognized by the cytosolic Nod-like receptors (NLRs). Several NLRs are involved in the assembly of a cytosolic protein complex, inflammasome, which activates caspase-1. Activated caspase-1 in turn cleaves pro-IL-1β and pro-IL-18 to release proinflammatory IL-1β and IL-18 and initiate apoptotic cascade (Anders and Muruve 2011).

Understanding the sepsis-induced AKI pathophysiology requires integrating diverse pathways that induce inflammation as a common denominator. Systemic haemodynamic, intrarenal haemodynamic, peritubular microcirculatory alterations and the tubular and glomerular cell injury are all reliable contributors to AKI, which should be considered as co-conspirators of the sepsis-related inflammation pathway.

Cellular actions of nephrotoxins

AKI is a frequent (40–50%) and ominous (mortality reaching 50%) complication in ICU patients. The severity of critical illness requires the administration of several therapeutics, increasing the risk of a drug-related nephrotoxicity (Hoste et al., 2010). Although the incidence of AKI in ICUs has increased during the last decade, the mortality rate has simultaneously slightly decreased causing an increasing number of AKI survivors who develop chronic kidney disease (Hoste et al., 2010). The role of drugs in the development of AKI is a major contributing factor in 19–25% of AKI (Pannu and Nadim, 2008; Perazella, 2012). In the setting of severe illness those therapeutics are often unavoidable but the comprehension of their nephrotoxicity can help the physician to minimize the risk.

Some medications, like cimetidine and trimethoprim, interfere with tubular secretion of creatinine, thus leading to the elevation of its serum level without actually affecting other renal functions. These cases of pseudo-AKI are not considered herein and emphasize the problems of basing diagnostic decisions on creatinine concentration alone.

Drugs may induce kidney injury by several mechanisms: compromising intrarenal blood flow and rendering kidneys vulnerable to ischaemia or direct toxic effects on renal tubules. Renal excretion of drugs may exert direct toxicity to tubular cells or induce acute

interstitial nephritis. Age, pre-existing renal disease, the dose, and the multiple nephrotoxic agents are all risk factors of ATN. In contrast, interstitial nephritis is an allergic response to drug exposure that does not require any predisposition. Other types of nephrotoxicity have been described induced by hypertonic solutions (osmotic nephrosis) or by tubular obstruction (drug precipitation).

The non-steroidal anti-inflammatory drugs

NSAIDs are known to be associated with the development of AKI. Haemodynamically mediated renal failure is a predominant cause, but nephrotic syndrome or interstitial nephritis has also been reported (Whelton 1999). The NSAIDs block cyclooxygenase (COX), the enzyme that converts arachidonic acid into the pro-inflammatory and afferent vasodilatory prostaglandin. The concomitant administrations of efferent vasoconstriction blockers, like angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) enhance the risk of NSAID-related AKI. More recently attention has turned to the development of selective COX-2 blockers. Inhibiting the pro-inflammatory actions of COX-2 and sparing the regulatory physiological mechanism of COX-1 was intended to reduce the renal consequences of NSAIDs. Unfortunately it is now demonstrated that anti-COX-2 cause similar renal injury in high-risk patients (Ahmad et al., 2002). The mechanisms of NSAIDs renal toxicity is still the subject of research. The drop of glomerular filtration provoked by the prostaglandin inhibition is not the only hit on the kidneys provoked by NSAIDs. Direct tubular cell mitochondrial damages have been also described with diclofenac leading to MPT expression and cell death (Uyemura et al., 1997). The GSK3beta (a regulator of MPT) has been implicated in the development of many kidney diseases and its inhibition may increases COX-2 expression in the renal cortex (Wang et al., 2006). In a mouse model of diclofenac-induced kidney injury, the concomitant administration of TDZD-8 (a highly selective inhibitor of GSK3beta) increased Cox2 expression, decreased MPT, suppressed tubular cell apoptosis and improved kidney function (Bao et al., 2012).

Calcineurin inhibitors

Ciclosporin and tacrolimus are important drugs used to prevent the rejection of transplanted organs. They have widely improved the outcome of organ transplantation. Unfortunately those drugs are associated with an important risk of acute (haemodynamically mediated) or chronic (interstitial damage) renal side effects. Calcineurin inhibitors induce afferent arteriolar vasoconstriction due to an increased endothelin and thromboxane A2 production (see above) and to reduction of vasodilatory prostaglandins and nitric oxide production (Olyaei et al., 1999; Naesens et al., 2009). This will provoke a reduction of RBF and GFR. Dehydration, concomitant use of other nephrotoxic medications, or hypotension can dramatically increase the risk of renal failure. In the case of kidney transplantation, the requirement for renal biopsy is sometimes necessary to distinguish drug-related renal toxicity versus organ rejection. In such cases, graft biopsy shows arteriolar thickening, glomerular sclerosis, and proximal tubular epithelial cell atrophy (Taber and Pasko, 2008). In case of haemodynamically mediated AKI, the discontinuation of a calcineurin inhibitor can jeopardize the graft, therefore, decreasing the dose of calcineurin inhibitors is a reliable strategy, but the essential part of the treatment is to avoid coexistent nephrotoxic drugs and correct concomitant hypotension or dehydration.

Aminoglycosides

Aminoglycosides (AGs) are non-protein-bound antibiotics primarily excreted by glomerular filtration. They are used to treat Gram-negative infections, but are associated with a well-documented renal and ototoxicities. The cationic properties of AGs facilitate the fixation of the drug by the proximal tubular epithelial cells. Megalin-cubilin endocytic machinery in the proximal tubules is responsible for AG uptake. Once inside the lysosomes, AG interferes with proteolytic enzymes and can be eventually released from ruptured lysosomes (Lopez-Novoa et al., 2011). Cationic properties of AGs allow them to partition in phospholipid membranes potentially leading to phospholipidosis, including lysosomal membrane phospholipidosis that accounts for their loss of integrity. In addition, AGs have been demonstrated to stimulate the calcium-sensing receptor; the role of this pathway in inducing proximal tubular cells death has been proposed, although still remains unclear, as other cell types expressing this receptor are spared of cytotoxicity (Ward et al., 2002; Lopez-Novoa et al., 2011). Production of ROS has been associated with renal toxicity of AGs. In addition to the injury to the tubular epithelia, AGs stimulate production of several vasoconstrictors, such as endothelin-1, platelet-activating factor, and thromboxane A2 by endothelial and mesangial cells. This explains the AG-induced decrease in RBF, and even more profound decrease in GFR. The latter has been attributed to the AG effect of neutralizing the negative charge of the glomerular barrier, mesangial cell contraction, and reduction of ultrafiltration coefficient (Lopez-Novoa et al., 2011).

Cisplatin-induced nephrotoxicity

This most frequently used chemotherapeutic agent is also a potent nephrotoxin with a quarter of patients exhibiting signs of renal dysfunction (Pabla and Dong, 2008; Miller et al., 2010). The acute phase is characterized by a reversible renal vasoconstriction but the chronic injuries can be irreversible. Histological findings show tubulointerstitial fibrosis with mononuclear infiltration, tubular atrophy, and arteriolar hyalinosis. Multiple pathways have been implicated in nephrotoxicity of this chemotherapeutic agent, including cell cycle dysregulation, mitochondrial dysfunction, activation of p38 MAP kinase pathway, and TNF-α-mediated cyto- and chemokine expression, among others. Pabla et al. (2011) demonstrated that PKCδ activation and MAP kinases regulation are impaired in cisplatin-treated mice and ablation of PKCδ attenuated renal injury and cell death, on the one hand, and enhanced chemotherapeutic actions of cisplatin in several mouse tumour models. Cisplatin kidney injury is also usually associated with a renal loss of magnesium and sodium due to the downregulation in the distal convoluted tubule of TRPM6 (a Mg^{2+} ion channel) and NCC (the Na-Cl cotransporter) (Ledeganck et al., 2011). The epidermal growth factor (EGF) plays a role in the expression or activation of TRPM6 in the distal convoluted tubule and was also significantly decreased after cisplatin treatment (Ledeganck et al., 2013).

Vancomycin hydrochloride

This antibiotic is the most widely used therapy for methicillin-resistant staphylococcal infections. The nephrotoxicity of the combination of vancomycin and AG is well established. The nephrotoxicity of vancomycin has become more frequent since the high-dose therapy has

become more common (Hazlewood et al., 2010). The exact mechanism of its nephrotoxicity is unknown. Vancomycin is excreted by glomerular filtration. It is not clear if the renal toxicity is exerted on tubular proximal tubular cells or on the medullary epithelia, as suggested by the study conducted by Le Moyec et al. in a group of critically ill patients with vancomycin and/or AG therapy (Le Moyec et al., 2002). In animal models, the role of complement activation, mitochondrial dysfunction, production of oxygen free radicals, and oxidative stress in the proximal renal tubule have been suggested in different studies (Nishino et al., 2003; Celik et al., 2005; Dieterich et al., 2009). Renal tubular cell lineage LLC-PK1 exposed to vancomycin experienced a mitochondrial superoxide production, caspase activation, and cell apoptosis. Mitochondrial complex 1 seems to be responsible for this lethal super oxide production leading to tubular cells apoptosis (Arimura et al., 2012).

Amphotericin B

Amphotericin B (Ampho B) is an important antifungal therapy that has been used for several decades. However, the prescription of Ampho B is currently reduced because of its nephrotoxicity and the development of less toxic new drugs. The nephrotoxicity of Ampho B has been reported to occur in up to 80% of patients receiving this treatment. Ampho B binds directly to the proximal and distal epithelial cells and provokes an increased tubular permeability; sodium, potassium, and magnesium wasting; and an increase of the oxygen requirements (Sawaya et al., 1995; Deray, 2002). Ampho B also provokes afferent arteriolar vasoconstriction. The association of an increased oxygen demand and a decreased oxygen supply due to the arteriolar constriction causes cell necrosis (Deray, 2002). Sodium loading and reduced infusion rate have been proposed to minimize vasoconstriction and the risk of nephrotoxicity (Llanos et al., 1991; Eriksson et al., 2001). The development of liposomal formulation decreases the incidence of renal failure.

Radiocontrast dyes

Contrast media (CM) are widely used for diagnostic purposes (see also Chapter 246). The incidence of contrast-induced nephrotoxicity ranges from < 1% to 13% depending on the criteria used to define AKI (Weisbord et al., 2008). The cytotoxicity of the CM is related to the iodine itself and to the physicochemical properties of the substance (viscosity, osmolarity, and ionic strength). Iodide ion is too toxic to be used as a CM. The incorporation of iodide into a benzene ring decreases its toxicity but not completely. Iodine is a well-known cytotoxic used as a microbicidal for decades. In contact with cells, iodine disrupts the integrity of the plasma membrane through its reactions with several amino acids in cell membrane proteins (cysteine, tyrosine, and histidine) (Hsu et al., 1965). Current CM are composed of a benzene ring attached to three iodine ions and one carboxyl group (Christiansen, 2005). The design of non-ionic types of CM is based on omitting carboxyl in favour of higher hydroxyl groups, thus partially decreasing the protein binding property and the cytotoxicity. *In vitro* studies clearly demonstrate the direct toxic effect of CM (Sendeski, 2011). In cultured renal epithelial cells, CM induced a concentration-dependant formation of large cytoplasmic vacuoles and apoptosis (Andersen et al., 1994). Even when diluted, iodine povidone induces cell apoptosis, but this does not occur with application of povidone alone (Fanning et al., 2002). This demonstrates that even small amounts of iodine that are present in the modern CM possess direct cytotoxic effect. Moreover although plasma concentration of radiocontrast agents is kept low, the concentration can be very high in the urine due to the reabsorption of water and solute along the nephron. It has been shown that CM can induce an alteration of the polarized membrane proteins, disturbing the function of tubular epithelial cells (Haller et al., 1997; Schick et al., 2002). It is interesting that the disruption of the intercellular tight junction ZO-1 does not seem to be explained by the CM-related reduction of extracellular Ca^{2+} (Schick et al., 2002). The hypertonic CM generates ROS and oxidative stress that can cause apoptosis, particularly in the setting of medullary hypoxia (Hizóh et al., 1998). CM decrease RBF secondary to vasoconstriction, especially of the medullary descending vasa recta. The CM stimulate the release of several vasoconstrictors such as endothelin, activation of renin–angiotensin system, prostaglandins, and reduces NO bioavailability. Studies by Brezis et al. have demonstrated that *in vivo* AKI can be readily induced by CM in association with the use of NOS inhibition or NSAIDs (Heyman et al., 1999). Also the CM has differential effect on afferent and efferent arterioles. In an *ex vivo* study, the afferent arteriole exposed to iodixanol will experience vasoconstriction mostly due to impaired NO bioavailability although no effect was observed on the efferent arteriole (Liu et al., 2012). This afferent constriction with no change of efferent tone will provoke a decrease in GFR. The renal medulla is particularly at high risk of hypoxia and hypoperfusion after administration of CM. The vasa recta (postglomerular juxtamedullary capillaries) in the renal medulla is a structure particularly sensitive to CM (Beierwaltes, 2013). Those small capillaries composed only of endothelial cells and pericytes play an important role in the regulation of reabsorption mechanisms. Sendeski et al. showed that vasa recta exposed to CM experienced important constriction and direct endothelial injuries responsible for the endothelial dysfunction (Sendeski et al., 2012). Radiocontrast-induced nephropathy cannot be explained only by the physicochemical or by the *in vitro* direct cytotoxic effects (Haller and Hizoh, 2004). It has most likely a multifactorial pathogenesis.

Acute tubulointerstitial nephritis

Acute tubulointerstitial nephritis (ATIN) causes 15–25% of AKI (Haas et al., 2000; Praga and González, 2010) and drug-induced ATIN is thought to occur in 3–15% of all cases of AKI (Michel and Kelly, 1998) (see also Chapters 83 and 84). Histological findings are characterized by the presence of inflammatory interstitial infiltrates consisting of eosinophils, monocytes, and lymphocytes, with occasional granulomas. The principal cause is a hypersensitivity reaction related to many medications but also to a sepsis or a systemic disease (sarcoidosis, lupus erythematosus). Actually all medications can provoke ATIN, however the majority of cases are related to antibiotics, NSAIDs, and proton pump inhibitors. Classic manifestations of ATIN are renal dysfunction, fever, rash, and eosinophilia, which could appear 2 weeks after the first exposure or earlier in case of re-exposure. The renal failure is inconsistently characterized by a sterile pyuria and eosinophiluria. The interruption of the suspected drug is usually accompanied by the functional recovery, however it may take several weeks and some patients can require temporary renal replacement therapy.

The presence of extrarenal manifestations of hypersensitivity, the re-exposure with a shorter delay, the absence of dose reliance,

and the occurrence in only a small proportion of the population are arguments in favour of an immune pathogenesis of the drug-induced ATIN (Rossert, 2001). Endogenous or non-renal antigens can induce experimental ATIN. The immunization of animals with the Tamm–Horsfall protein or with megalin provokes the development of an ATIN. The daily injections of bovine serum albumin in rabbits or bovine gamma globulins in pigs or rats also provoke the development of ATIN (Wilson, 1989). In humans, some components of the tubular basement membrane (TBM), like the tubulointerstitial nephritis antigen, have been identified as endogenous antigens (Ikeda et al., 2000). The mechanisms leading to the production of such antigens in only a small group of individuals are currently lacking. In drug-induced ATIN, exogenous molecules (intact or metabolites) present in the tubulo- interstitium can elicit an immune reaction by themselves or bind to components of the TBM and induce an antigen reaction (Rossert 2001). The T-cell-mediated immunity is probably involved in the human drug-induced ATIN because of the presence of T-cell interstitial infiltrates (and sometimes granulomas) in renal biopsies. The hypothesis of a T-cell immunity is reinforced by experimental data. The immunization of SJL mice with a heterologous TBM component induces ATIN, and it can be adoptively transferred by the injection of a T cell clone, but not by anti-TBM antibodies (Neilson and Phillips, 1982; Zakheim et al., 1984). The interstitial infiltration by inflammatory cells induces release of pro-inflammatory molecules such as chemokines, growth factors, and adhesion molecules initiating interstitial fibrosis (Ong and Fine, 1994; Segerer et al., 2000).

Osmotic nephrosis

Hyperosmolar agents can be implicated in the development of AKI. Intravenous immunoglobuline (IVIg), radiocontrast media, and hydroxyethylstarch (HES) are the principal medications concerned. Renal failure appears 2-4 days after the drug administration and is usually reversible. Renal biopsy shows swollen proximal tubular cells with cytoplasmic vacuolization and oedema narrowing the tubular lumen (Dickenmann et al., 2008). Sucrose contained in the IVIg is considered to be responsible of the renal failure. For many years, the injection of sucrose has been known to be associated with the development of proximal tubular damage and renal failure (Anderson and Bethea 1940; MAUNSBACH et al., 1962). Age and preexisting renal failure seem to be associated with the IVIg renal toxicity. Safer IVIg have been developed to decrease the incidence of the related renal toxicity however several cases of renal impairment have been reported by the FDA during the recent years (Lin et al., 2011).

Postrenal (obstructive) kidney injury

Obstructive nephropathy may develop as a consequence of intratubular precipitation of drugs and metabolites, or increased resistance to urine flow in the lower urinary tract. The obstruction results in dilatation of the urinary tract above the site of obstruction, increase of hydrostatic pressure, and a decrease of GFR. Bilateral obstruction and hydronephrosis can lead to renal failure. Occasionally, ultrasound or computed tomography evidence of hydronephrosis is lacking, despite the presence of a truly symptomatic obstructive renal failure. This entity is termed *non-dilated obstructive uropathy* and can account for 4–5% of obstructive renal failure (Maillet et al., 1986). This syndrome can be the result of severe oliguria (dehydration, hypotension) or inability of the urinary tract to dilate due to infiltrative processes like cancer or fibrosis.

Intravenous high doses of aciclovir, methotrexate, sulfadiazine, and foscarnet are some of the drugs leading to tubular precipitation and potential obstructive nephropathy (Taber and Pasko, 2008). Antiretroviral therapies used to treat HIV infection (tenofovir and indinavir) can also produce obstructive nephropathy (Berns and Kasbekar, 2006). All those drugs or their metabolites are principally eliminated in the urine by glomerular filtration and/or tubular secretion; they precipitate and induce the obstruction particularly in cases of dehydration or acidic urine. Usually this obstruction can be prevented by the hydration and urine alkalinization (Taber and Pasko, 2008).

The unilateral ureteral obstruction (UUO) is the most relevant experimental rodent model mimicking the pathophysiology of obstructive nephropathy. The obstruction of the ureter provokes the increase of hydrostatic pressure above the stricture. The severity of lesions following obstruction depends on the duration of the obstruction, uni- or bilateral lesions, complete or partial obstruction. Soon after ureteral obstruction the intratubular hydrostatic pressure increases. A few hours after the ureteral obstruction, a decrease of sodium and water reabsorption and an increase of RBF have been described. RBF increases by about 25% immediately after obstruction whether uni- or bilateral, complete or partial (Moody et al., 1977; Wilson, 1980). The decrease in renal vascular resistance is a result of vasodilatation, a prostaglandin-mediated effect (Smith et al., 1979; Fukuda et al., 1985). However, if the obstruction persists, the RBF decreases and by 24 hours represents 50% of normal (Hsu et al., 1977). Several hours after the relief of a 24-hour obstruction, the intratubular pressure returns to normal in the case of UUO, but it can remain increased in the case of bilateral obstruction. RBF and GFR remain decreased due to a persistent afferent vasoconstriction (Hsu et al., 1977). Thereafter, a post-obstructive diuresis occurs as a result of altered tubular reabsorption of sodium and water. Relief of UUO results in a gradual restoration of renal parenchymal architecture and GFR (Schreiner et al., 1988) accompanied by the resolution of inflammatory infiltrate.

The potential role of oxidative stress and damage to renal epithelia triggering apoptosis and necrosis is emphasized by the finding that expression of components of NADPH oxidase (p22, p47, p67-phox) are all elevated in UUO (Cachat et al., 2003; Sugiyama et al., 2005). In view of this plausible pathogenetic mechanism, several groups have found inhibitors of NADPH oxidase as well as statins to offer certain therapeutic benefits (reviewed in Dendooven et al., 2011).

Ischaemic and pharmacologic preconditioning

The phenomenon of ischaemic preconditioning (IPC), first described by Murry et al. in 1986 (Murry et al., 1986) has been examined at the molecular level by many investigators hopeful of defining signalling repertoire of tissue protection against ischaemia (Park et al., 2001; Dana et al., 2001; Alcindor et al., 2004; Stein et al., 2004; Hausenloy et al., 2005; Bernhardt et al., 2006). These findings created the foundation for pharmacologic preconditioning and postconditioning, which target the same pathways using pharmacological agents rather than ischaemia (Fischbach et al.,

2003; Matsuo et al., 2005). IPC has been shown to be a biphasic process: an early phase lasts up to 2 hours, a late phase becomes apparent after 24 hours to several days. The delayed phase is considered to be a universal response (Bolli, 2000). With respect to the murine kidney, IPC is maximal at 1–2 weeks after the initial episode (Bonventre, 2002). Recently, endothelial progenitor cells have been shown to home to murine myocardium after short periods of IPC and protect myocardium through 'imported' NOS activity (Ii et al., 2005). Uric acid pre-treatment has been shown to serve as pharmacologic preconditioning stimulus in the mouse model of I/R injury (Patschan et al., 2006).

Remote IPC consisting of creating episodes of limb ischaemia prior to a surgery has been used for myocardial protection (Gho et al., 1996). Recently, this strategy has been adapted for prevention of AKI in patients undergoing cardiac surgery (Zimmerman et al., 2011). Producing a lower limb ischaemia by inflating a tourniquet cuff three times to a pressure of 200 mmHg for 5 minutes with 5-minute intervals resulted in the reduction of postsurgical AKI. This manoeuvre has a role in preventing an anticipated AKI (see also Chapter 225.)

From local insult to systemic inflammatory response

Epidemiologic studies disclosed a seemingly paradoxical fact: even a very mild AKI, not requiring any therapeutic intervention, is associated with a significantly increased mortality compared to those patients who have not developed AKI (Lassnigg et al., 2004; Chertow et al., 2005; Coca et al., 2007). This observation presents a powerful argument in favour of a broader view of AKI as a disease with systemic manifestations. Previous sections dealt with the local signals generated by stressed endothelial and epithelial cells. To understand the above paradox requires additional analysis of systemic signals, known to facilitate repair or to promote inflammatory reaction. Notably, the distinction between the two is blurred and context dependent.

It has been appreciated for a long time that mortality in ICU patients with AKI is better predicted by the concomitant dysfunction of other organ systems: multivariate logistic regression modelling showed that mortality increases from 12% to 100% when AKI patients have one to five failing organ systems, respectively (Schwilk et al., 1997). Adjusted odds ratio of death was 7.7, 6.3, 3.6, 3.0, 5.3, and 3.7 for cardiovascular, hepatic, respiratory, neurologic failure, massive transfusion, and > 60 years of age, respectively. In light of these epidemiologic findings in 3591 consecutive ICU patients, Kelly examined the effects of acute renal ischaemia on heart function in rats (Kelly, 2003) and described elevated systemic levels of TNFα and IL-1, increased myeloperoxidase activity and upregulation of ICAM-1 mRNA in the heart of post-ischaemic animals. This was associated with increased numbers of apoptotic cardiomyocytes, increased left ventricular end-diastolic and end-systolic diameter, and decreased functional shortening by echocardiography. These findings made at a time when animals were not severely uraemic could not be replicated by bilateral nephrectomy, suggesting that it is ischaemic insult per se that is responsible for observed distant effects. Follow-up studies demonstrated that similar distant effects are found in lungs, brain, and other organs (reviewed in Li et al., 2009).

Whilst the notion that stressed and injured cells release diverse molecular signals is well appreciated, the nature of such signals, the time course of their release, receptors involved in detection of those signals, and the short- and long-term consequences of signals released have remained a matter of contention. One of such consequences, development of systemic inflammatory response across a broad spectrum of non-bacterial diseases, has gained mechanistic explanation with the discovery of components of innate immunity against pathogenic bacteria—pathogen-associated molecular patterns (PAMPs) and pathogen-recognition receptors (PRRs) and one of their major components, TLRs—and realization that this bacterial defence system can be also employed by a host of molecules (alarmins) usually released during aseptic inflammation. This process has been conceptualized by Matzinger as the 'danger theory' (Matzinger, 2002).

TLRs have been a subject of several excellent recent reviews, thus the reader is referred to them (Bianchi, 2007; Anders and Schlöndorff, 2007; Gluba et al., 2010). The list of alarmins or danger signals, that is, endogenous signals of tissue damage, is growing and includes high-mobility group box-1 protein (HMGB1), calgranulins (S100s), hepatoma-derived growth factor, heat shock proteins, IL-1α, uric acid, thymosins, annexins, galectins, and several products released by degranulation of neutrophils (defensins, cathelicidins, and eosinophil-derived neurotoxin) (Shirali and Goldstein, 2008). A member of the TLR family, TLR4, is especially promiscuous with respect to potential ligands and has been implicated in the pathogenesis of AKI (Wu et al., 2007a; Pulskens et al., 2008).

TLR4 is activated, in addition to lipopolysaccharide, peptidoglycan and taxol, by HMGB1, Tamm–Horsfall glycoprotein, hyaluronan, heparan sulphate, fibronectin domain A, surfactant protein A, and modified low-density lipoprotein (Tang et al., 2011). HMGB1, an endogenous damage-associated molecular pattern molecule, resides in the nucleus in a deacetylated form, but translocates into the cytosol and out of the cell when acetylated upon stress (reviewed in Oliver et al., 1981). Although export pathways from the cell are incompletely understood, though HMGB1 clearly does not employ classical routes, the fact that in the process of activation HMGB1 is translocated to caveolae may suggest that it is exocytosed through those organelles. At least five cognate receptors are shared by several alarmins, including TLR2, TLR4, receptor for advanced glycosylation end-products (RAGE), triggering receptor expressed on myeloid cells-1 (TREM), and CD24, thus deletion of any one of them could blunt or even prevent signalling from several alarmins. Activation of NF-κB is a downstream event of TLR4 ligation leading to transcriptional induction of pro-inflammatory cytokines and chemokines and interferon-inducible genes. This system cooperates with the activated inflammasomes to trigger caspase-1-induced cleavage of pro-IL-1β and pro-IL-18, culminating in the secretion of these two pro-inflammatory mediators, IL-1β and IL-18.

TLR2 and TLR4 are implicated in deleterious responses to kidney injury (Leemans et al., 2005; Shi et al., 2006). More recently, it has been demonstrated that TLR4 in leucocytes, as well as in epithelial and endothelial cells, is necessary for the full-blown ischaemic response, suggesting that the release of HMGB1 from injured epithelia and endothelia activates leucocytes to generate pro-inflammatory cytokines to further exacerbate injury to ischaemic kidneys (Chen et al., 2011). The scenario proposed by Chen et al. (2011) ascribes to the release of HMGB1 from damaged epithelial and endothelial cells the role of an igniter for TLR4-induced activation of leucocytes and macrophages, which subsequently

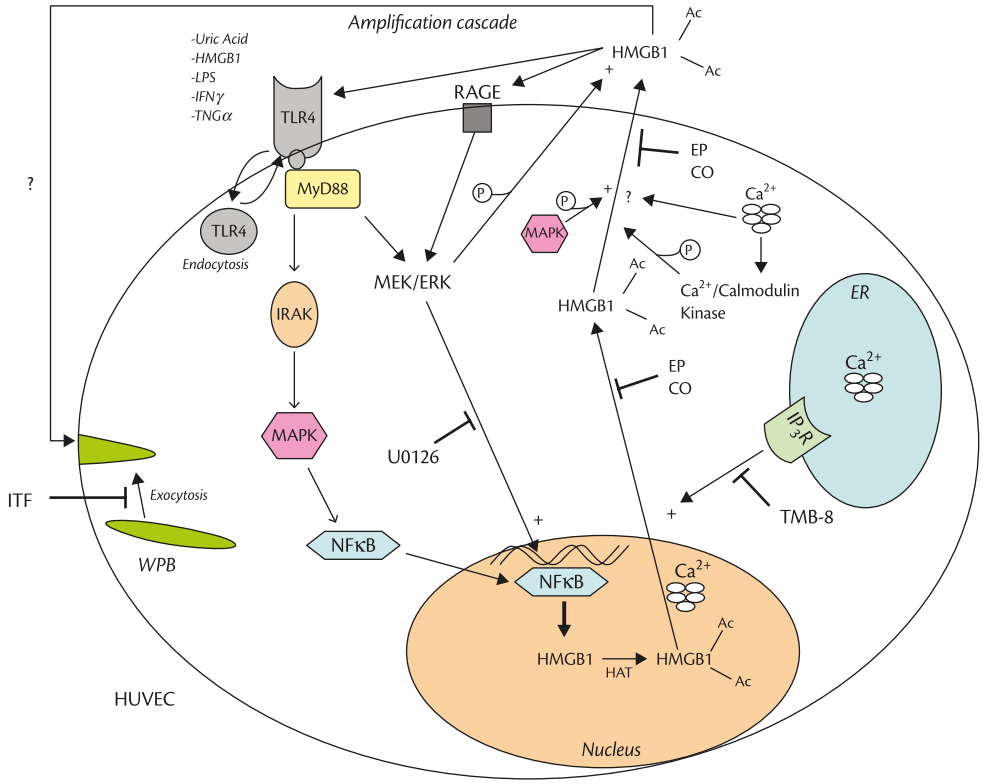

Fig. 221.7 Pathways of HMGB1-induced cell activation and the sites of action of various inhibitors. See details in the text.

secrete pro-inflammatory IL-6. IL-6 and several other members of the IL-6 family, such as IL-12, IL-10, IFNα/β, GM-CSF, as well as hypoxia per se, in turn induce a transcriptional activator of acute phase genes, signal transducer and activator of transcription 3, STAT3 (Levy and Lee, 2002). Nuclear effects of STAT3 include, in addition to transcriptional activation of c-Fos and Socs3, the induction of antioxidants MnSOD and metallothioneins 1 and 2. STAT3 is also constitutively present in mitochondria where it protects complex I-dependent respiration and cytochrome c release and reduces hypoxic generation of ROS upon ischaemic stress (Szczepanek et al., 2011). This is yet another example of a two-pronged effect of the same messenger, both pro- and anti-inflammatory.

On a broader scale, initial alarm signals in I/R could arise from xanthine oxidoreductase-stimulated production of uric acid (within minutes of hypoxia) by endothelial and epithelial cells, which via TLR4 and inflammasome activation, leads to the expression of VCAM-1 and ICAM-1 on endothelial cells and directs the traffic of leucocytes and monocytes to the post-ischaemic site. In parallel, the same alarmin stimulates the translocation of HMGB1 from the nucleus to the cytosol to be eventually exported to the extracellular environment. Released HMGB1, in turn, re-activates TLR4 and amplifies its own release (Rabadi et al., 2012). The extracellular matrix by liberating heparan sulphate and biglycan, both serving to further stimulate TLR4, can provide an additional source of stimulation. Activated macrophages produce NO and thioredoxin which modulate the redox state and the proportion of HMGB1 present in the reduced and oxidized form. Remarkably redox modifications of HMGB1 have profoundly different effects on the cells, ranging from induction of apoptosis to autophagy and survival (Fig. 221.8).

Injury-induced danger signalling elicits cyto-/chemokines response with release of pro- inflammatory (IL-1α, TNFα, IL-6, eotaxin, G-CSF) and anti-inflammatory (IL-10) molecules and stimulate mobilization of stem cells (see below).

Responses to stress: systemic signals

Reparative signals by stressed endothelial cells lead to well-orchestrated mobilization and recruitment of stem and progenitor cells that tend to restore vascular and tissue integrity (Patschan et al., 2007). For instance, hypoxia induces endothelial secretion of macrophage migration inhibitory factor (MIF): it is biphasic, initially peaking at 60 minutes (release from preformed MIF stores) and again peaking by 8 hours due to the *de novo* synthesis (Simons et al., 2011). One of the functions of MIF is to recruit EPC to the site(s) of injury; this chemotactic response is CXCR4-dependent. Importantly, increased MIF secretion cooperates with the injury- or hypoxia-induced secretion of VEGF, erythropoietin, and SDF-1, all potent inducers of regeneration and mobilisers of EPC (Gill et al., 2001; Ceradini et al., 2004). IL-8 is a potent stimulator of EPC mobilization, thus linking this response to stressors with pro-inflammatory conditions (Kuo et al., 2008). Another mechanism for EPC recruitment and differentiation has been attributed to apoptotic endothelial microparticles generated upon injury to mature endothelial cells (Hristov et al., 2004). Yet another mechanism of communication between injured and intact cells has been recently described—microvesicular transfer of genetic information from EPC to mature endothelial cells which is guided by the α4β1 integrin (Deregibus et al., 2007). There is, however, growing complexity of various particulate

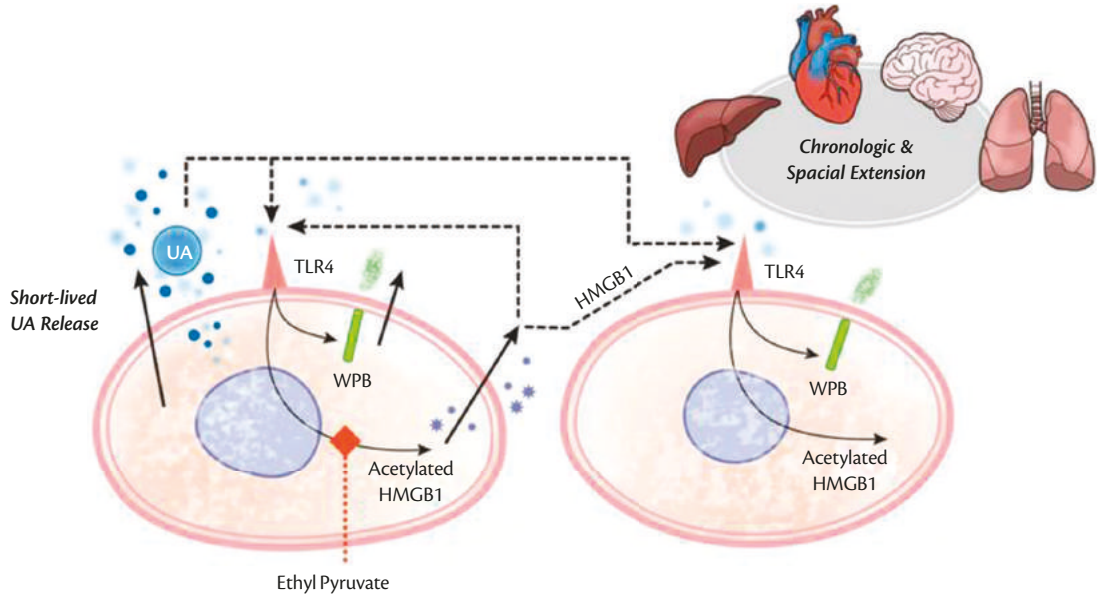

Fig. 221.8 Schematic depiction of a localized alarm signalling initiated by a rapid and transient release of the product of activated xanthine oxidoreductase, uric acid (UA), triggering exocytosis of Weibel–Palade bodies (WPB) from the endothelial cells and a broad-range secretion of HMGB1. This leads to the propagation of danger signalling via the systemic circulation, thus converting a local injury to a generalized systemic inflammatory response.

populations discharged from the cells: annexin+/DAPI-/histone- microparticles (size < 1um); annexin+/DAPI+/histone+ apoptotic bodies (size 1–3 um); secretory endocytic vesicles—exosomes (20–100 nm); and HMGB1-containing nucleosomes. Endothelial apoptotic bodies express IL-1α or its precursor (Berda-Haddad et al., 2011) and these apoptotic bodies are capable of activation of macrophages to secrete IL-1β and amplify the pro-inflammatory cytokine signalling. In fact, the key role of IL-1α in initiation of sterile inflammation in I/R injury to various organs is emerging from the recent literature and this observation underscores the use of IL-1-targeted therapy as a promising strategy (Wanderer 2008; Dinarello 2010).

Exocytosis of Weibel–Palade bodies, unique endothelial organelles containing von Willebrand factor, IL-8, angiopoietin-2, ET-1, and big ET-1 together with endothelin-converting enzyme, among other biologically active molecules, releases to the bloodstream all these previously sequestered substances. While traditionally linked to inflammation and coagulation cascades, released constituents of Weibel–Palade bodies are able to mobilize endothelial progenitors and haematopoietic stem cells and promote regeneration (Kuo et al., 2008). Intriguingly, blockade of exocytosis of Weibel–Palade bodies results in short-term benefits (better preservation of renal function following an ischaemic insult), but long-term effect of blocking their exocytosis may result in the aggravation of profibrotic processes (Yasuda et al., 2012).

This is chronologically followed by the release of HMGB1 into the circulation (Rabadi et al., 2012) resulting in further amplification of the pro-inflammatory cascade. With time, the increasing population of apoptotic cells produces large numbers of apoptotic bodies loaded with IL-1α, which results in the further propagation of a sterile inflammation and involvement of growing numbers of distant cells and organs. These consecutives waves of 'danger signalling' are depicted in Fig 221.9. Understanding the intricate biological significance of such a complex cascading evolutionary response to stress, its short- and long-term implications, and consequences of blocking any of the signals is in its infancy and a body of work is necessary to rationally utilize this knowledge for therapeutic purposes.

From injury to regeneration

In clinical practice, a typical case of recovery from oliguric AKI features conversion to the diuretic phase accompanied by a progressive increase in urine volume, followed by recovery phase, characterized by a gradual restoration of GFR, the process that may last 3–12 months and rarely results in a complete functional recovery (Fig. 221.10). In addition to the GFR remaining permanently reduced, maximal concentrating and acidification ability of the kidney sustains a lasting defect. Though recovery is incomplete, infrequently it becomes a cause of progressive renal failure necessitating chronic haemodialysis. The category of patients that do have a tendency towards defective recovery and occasional progressive renal failure is represented by elderly individuals and those with pre-existing chronic kidney disease or diabetes mellitus (Levinsky et al., 1981; Ishani et al., 2009). Mechanistic correlates of functional recovery are currently lacking.

The entire problem is, however, an aspect of a general question of post-injury tissue repair versus regeneration. Unlike tissue repair, which results in scar formation, regeneration of injured functional units results in the restoration of the tissue architecture by proliferating and differentiating resident cells, either somatic or stem cells, and/or recruitment of circulating stem cells. Adult nephron progenitors participating in kidney regeneration have been identified in zebrafish (Diep et al., 2011). Small cellular aggregates engendered these properties and were isolated based on the expression of Cdh17 and transcription factors Lhx1/Lim1 and Wt1; these cells were capable of regenerating the entire nephron. The analogue of this structure is represented in mice by the Six2-positive cap mesenchyme cells, with which they share Six2, Wt1, Meis2, Ezh2, and Tcf3 (Wnt signalling pathway). In adult mammals, however, these processes of regeneration are suppressed and alternately diverted

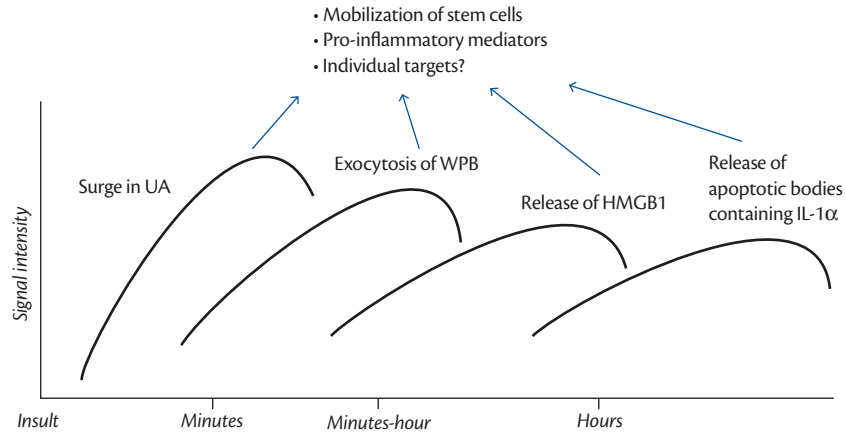

Fig. 221.9 Consecutive waves of alarm signalling in the course of AKI. Signals are coordinated in time and intensity and serve a dual purpose: to stimulate healing and regeneration, on the one hand, and induce pro-inflammatory mediators, on the other.

towards scar formation. The final result of AKI in a typical case is a variable combination of tissue scarring and regeneration, shifted more towards scarring in elderly individuals and towards regeneration in younger ones.

Diverse stem cells, such as bone marrow-derived stem cells, mesenchymal stem cells, 'side-population' cells, and endothelial progenitor cells, are not only mobilized in response to injury, but have also been used for transplantation to improve regeneration of injured kidneys. It has been demonstrated that mobilized stem and/or progenitor cells are temporarily sequestered in the spleen from where they are titrated into the circulation to engraft injured organ (Patschan et al., 2007) and/or modulate its ambient microenvironment by diverse secretory products. There is a reasonably strong consensus that transplantation of bone marrow-derived mesenchymal stem cells or endothelial progenitor cells invariably results in the improvement of renal function after various noxious stresses (reviewed in Bussolati et al., 2009). In contrast, there is a continuing debate on the putative mechanisms of this effect. The heart of the matter is that the proportion of endogenous engrafting cells actually substituting for the injured tissue is very small (Lin et al., 2003; Humphreys et al., 2011). The same is true for exogenous adoptively transferred cells, leading to the conclusion that other pathways may be involved in kidney regeneration after the injury. Remarkably, administration of the medium conditioned by cultured mesenchymal stem cells turned out to be sufficient to elicit beneficial effects associated with transplantation of these cells (Bi et al., 2007). There is growing evidence that mesenchymal stem cells exert their therapeutic effect by secreting anti-apoptotic VEGF, HGF, and IGF-1; anti-inflammatory effect by secreting PGE-2, TGF-β, HGF, IL-10, human leucocyte antigen G (HLA-G), leukaemia-inhibitory factor (LIF), and suppress T-cell proliferation; pro-angiogenic effect by releasing bFGF, VEGF, placental growth factor (PlGF), among other factors; and have a chemoattractive and anti-scarring effects. Summing up a body of work, the following mechanisms have been advocated as contributors to the beneficial effects of stem and progenitor cells (Fig 221.11): paracrine signalling by stem cells, microvesicular or tunnelling nanotube-mediated transfer of information from stem to somatic cells have been advocated (Camussi et al., 2011; Tögel and Westenfelder, 2011; Yasuda et al., 2012), but the actual contribution of these pathways to regeneration remains unknown.

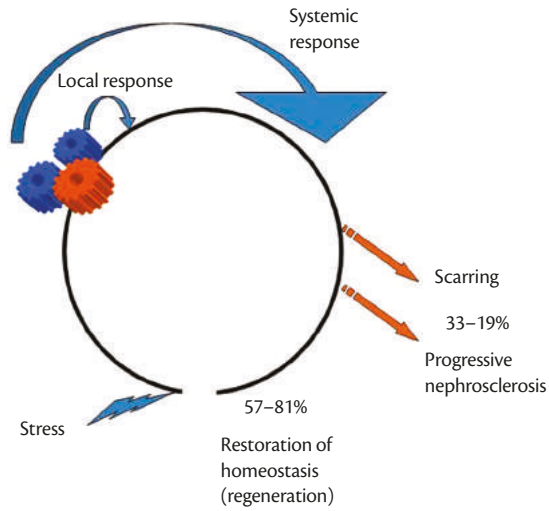

Fig. 221.10 The outcomes of acute kidney injury: from a near-complete functional and structural restoration to scarring and progressive nephrosclerosis. Different sources provide varying figures for chronization viz-a-viz near-complete functional restoration.

The outcome data quoted herein were obtained from Liaño et al. (2007) and Amdur et al. (2009).

Some lessons could be learned, perhaps, from the paradigm of wound repair and regeneration in amphibians. Mature somatic cells surrounding the wound dedifferentiate forming a so-called blastema and eventually acquire stem cell-like pluripotency allowing them to differentiate into multiple cell types (Brockes and Kumar 2002; Gurtner et al., 2008). Classical stages of tissue repair are (1) inflammation occurring within minutes to hours after the injury and manifesting in the egress of neutrophils and later monocytes and lymphocytes to the site; (2) formation of a new tissue characterized by the proliferation and migration of various cells and formation of new blood vessels, as well as formation of myofibroblasts from fibroblasts and production of extracellular matrix, all occurring 2–10 days after injury; and (3) remodelling phase taking place in 2–3 weeks after injury and characterized by apoptosis of multiple cell types (Gurtner et al., 2008). All these stages are in fact recapitulated in mammals with AKI: rapid

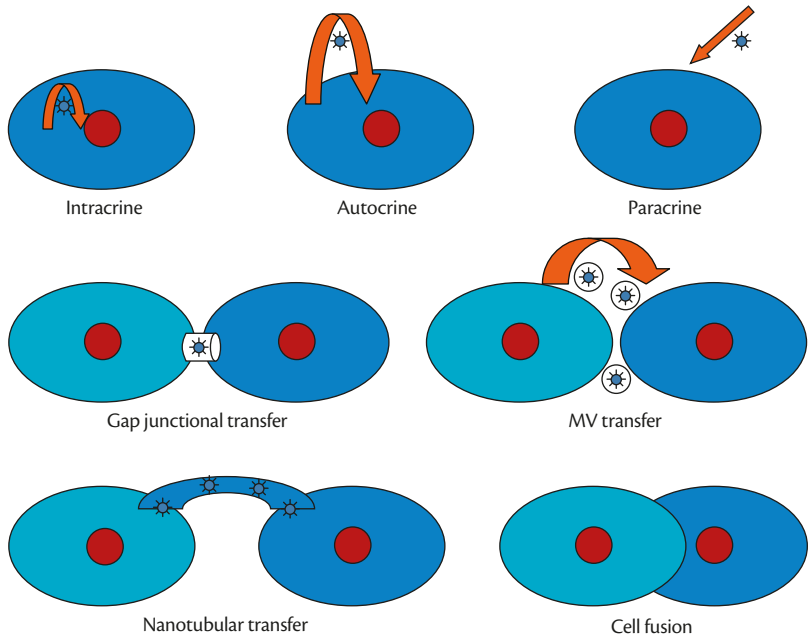

Fig. 221.11 Mechanisms of communication between stem cells and injured somatic cells. MV = microvesicles; Nanotubular = tunnelling nanotubes. Modified from Re and Cook (2010).

inflammatory response, early mitotic figures in non-lethally injured cells, and later remodelling of the tissue. This remodelling stage chronologically coincides with the transition from the oliguric to diuretic phase of AKI, however, the proof of a mechanistic link is lacking at the time of this writing.

Summary

The combination of haemodynamic and tubular dysfunction is responsible for the pathogenesis of the syndrome of AKI. Haemodynamic compromise is in most cases a result of excessive vasoconstriction and defective vasorelaxation, except for the endotoxaemia-induced AKI. Tubulopathy, on the other hand, is manifested by the desquamation of proximal tubular epithelia and obstruction of the distal nephron, leading to the elevation of tubular hydrostatic pressure and equilibration of glomerular filtration pressure, culminating in cessation of glomerular filtration. This latter pathogenetic step represents a feedback link between the haemodynamic and tubular compromise eventuating in oliguric AKI.

Deepening understanding of the pathophysiology of this syndrome leads the targeted search for biomarkers of AKI. Although current tests based on grading the elevation of creatinine concentration in the serum, as detailed in Chapter 220 are insufficiently sensitive, an array of other pathophysiologically relevant biomarkers of AKI is emerging. These biomarkers are beginning to unveil more subtle, hitherto clinically unrecognizable forms of AKI which are not associated with an overt elevation in serum creatinine. It will not be surprising, if the use of these much more sensitive biomarkers will bring about the realization that clinical AKI is a 'tip of the iceberg', whereas an asymptomatic, subclinical response to various insults, including medications, represents an as yet obscure and uninvestigated much larger proportion of cases.

AKI is an ample example of localized and systemic inflammatory disease. While the local inflammatory process has a tendency to resolve itself, the systemic inflammatory response, when sufficiently intense and/or prolonged, may not only exacerbate the local disease, but can also involve other organs (heart, lungs, liver, etc.) accounting for the increased mortality even in cases of a mild AKI. This explains the old dictum that patients die not from AKI but with AKI. This fledgling realization of the importance of the systemic inflammatory response to the localized injury and inflammation has a potential to explain the added severity of concomitant diseases or pre-existing chronic conditions that can 'prime' the systemic response and exacerbate it out of proportion to the actual acute kidney damage. And finally, while therapies for ameliorating AKI per se are limited, an additional potentially powerful strategy that could reap significant benefits in the future is to tackle the intensity of the systemic inflammatory response.

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CHAPTER 222

Clinical approach to the patient with acute kidney injury: diagnosis and differential diagnosis

Norbert Lameire, Raymond Vanholder, and Wim Van Biesen

Introduction

As explained in Chapter 220, acute kidney injury (AKI) is a broad clinical syndrome, defined by an acute fall of glomerular filtration rate (GFR), reflected by an acute rise of serum creatinine (SCr), and/or decline in urine output over a given time interval (Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group, 2012). This definition is independent of the presence of underlying histopathological alterations or of the pattern of functional recovery.

A traditional classification of AKI is based on various aetiologies including prerenal AKI, acute postrenal obstructive nephropathy, and intrinsic acute kidney diseases, that is, acute tubular necrosis (ATN), acute interstitial nephritis (AIN), and acute glomerular and renal vasculitis diseases. Of these, only 'intrinsic' renal AKI represents 'true kidney disease' while prerenal and most cases of postrenal AKI are the consequence of extrarenal conditions, leading to a decreased GFR. If these conditions persist, they will eventually evolve to cellular damage and to intrinsic renal disease.

Recent evidence is accumulating that even mild and transient AKI of any origin has important clinical consequences, including increased risk of death (Lassnigg et al., 2004; Chertow et al., 2005), and evolution to chronic kidney disease (CKD) and end-stage renal disease (ESRD) (Coca et al., 2009, 2012).

Clinical evaluation of the patient with acute kidney injury

This evaluation should at least address six questions:

1. Is there immediate need for therapeutic intervention because of a life-threatening complication? This first question is addressed in the chapter dealing with the therapy of AKI (Chapter 228).

The following questions are discussed in the present chapter.

2. Is the renal dysfunction acute, acute-on-chronic, or chronic?
3. Is there evidence of true hypovolaemia or reduced effective arterial blood volume, that is, is the AKI prerenal or renal and can renal dysfunction be corrected by improving kidney perfusion?
4. Is there a major vascular occlusion?
5. Is there evidence of renal parenchymal disease other than ATN?
6. Is the cause of AKI urinary tract obstruction, that is, 'post-obstructive' AKI?

The answers to these questions can be given by following the steps outlined in Fig. 222.1. This approach will reveal the likely cause of AKI in most patients and enables the clinician to develop a rational therapeutic plan that will facilitate the rapid restoration of renal function in patients with 'transient AKI' or obstructive AKI. It also provides a basis for the differential diagnosis and treatment of patients with intrinsic parenchymal renal diseases.

Evaluation and general management of patients with and at risk for acute kidney injury

The setting of the patient

Before the patient's history is taken, and physical examination and laboratory and technical investigations are performed, knowing the epidemiology of AKI in different settings (community, hospital ward, or intensive care unit (ICU)) can already orientate the differential diagnostic reasoning.

Community-acquired AKI can usually be attributed to a single cause and has in general a better prognosis than hospital-acquired AKI or AKI in critically ill patients.

AKI acquired on a hospital ward frequently occurs in the setting of co-morbidity, is often multifactorial, and is associated with higher mortality. ICU-acquired AKI is almost always multifactorial, often caused by sepsis, or occurs in the setting of multiorgan failure or complex surgery, and is associated with high mortality.

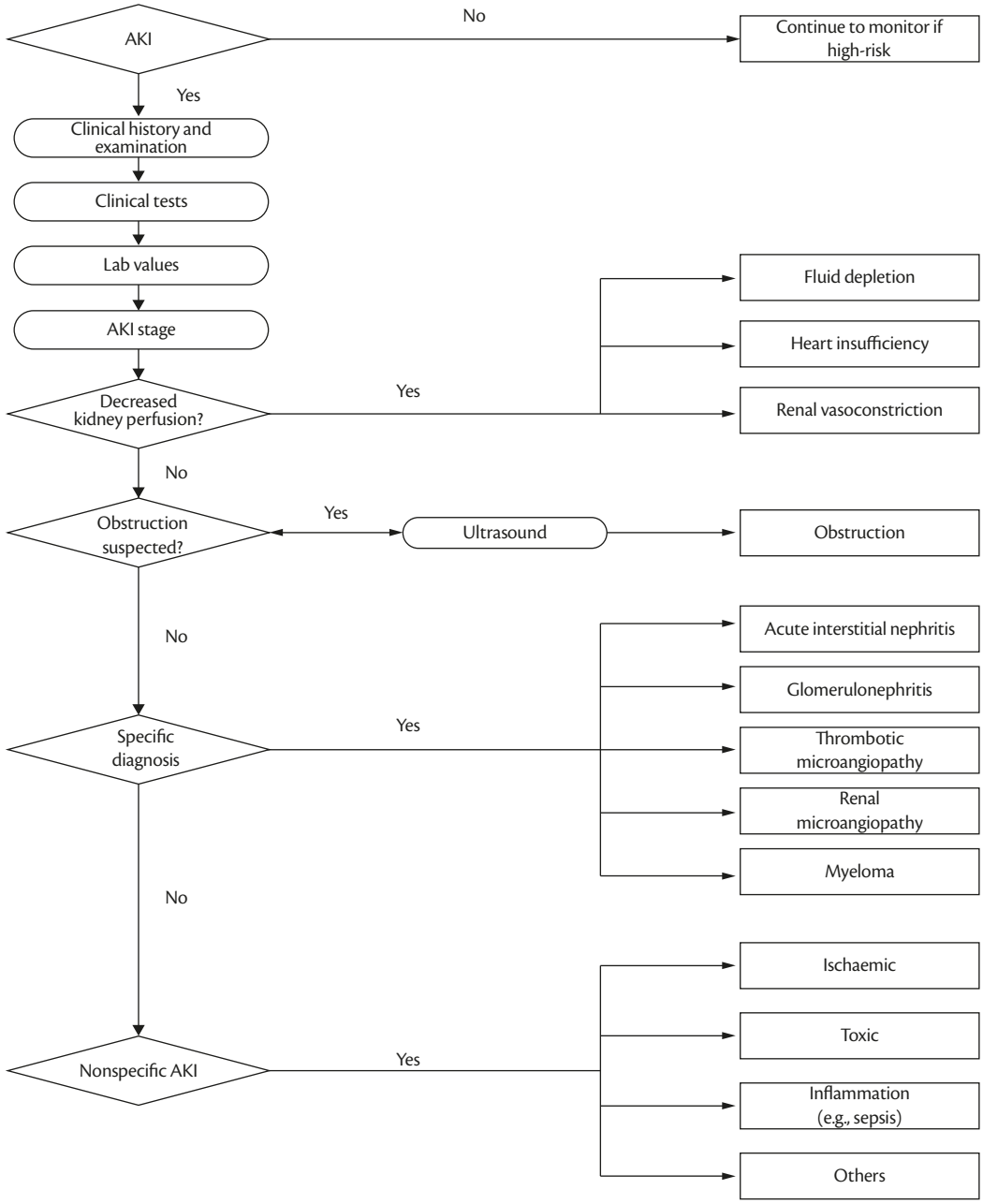

Fig. 222.1 Evaluation and general management of patients with and at risk for AKI.

Reproduced from Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group (2012). KDIGO Clinical Practice Guideline for Acute Kidney Injury. *Kidney Int Suppl*, 2, 1–138.

As recently described (Jha and Parameswaran, 2013; Lameire et al., 2013) the epidemiology and causes of AKI in low-income or tropical countries is dramatically different from high-income countries and the differential diagnostic approach should take these geographical differences into account (see also Chapter 196).

Causes of AKI can also be considered in the context of the underlying disease or process in which it occurs (Fig. 222.2).

Unique causes of AKI can be seen in the setting of malignancy (Chapter 251), immunodeficiency virus (HIV) infection (Chapter 187), pregnancy (Chapter 250), burns (Chapter 253), and the postoperative or intensive care state (Chapters 244 and 245). Four particular populations in which AKI is frequently encountered are the elderly (Chapter 240) and patients with diabetes mellitus, liver disease (Chapter 247), and cardiovascular disease (Chapter 248). The effect of advancing age with decreasing functional renal reserve and the associated co-morbidities increase the risk of AKI, in particular a dramatic (three- to eightfold) increase in the incidence of community-acquired AKI (see Chapter 243). Although elderly individuals are subject to all forms of AKI, 'prerenal' and postrenal causes are especially common. Obstructive uropathy in the elderly is most frequently encountered in community- and hospital-associated AKI and is less common in ICU-related AKI (Liano and Pascual, 1996; Liano et al., 1998).

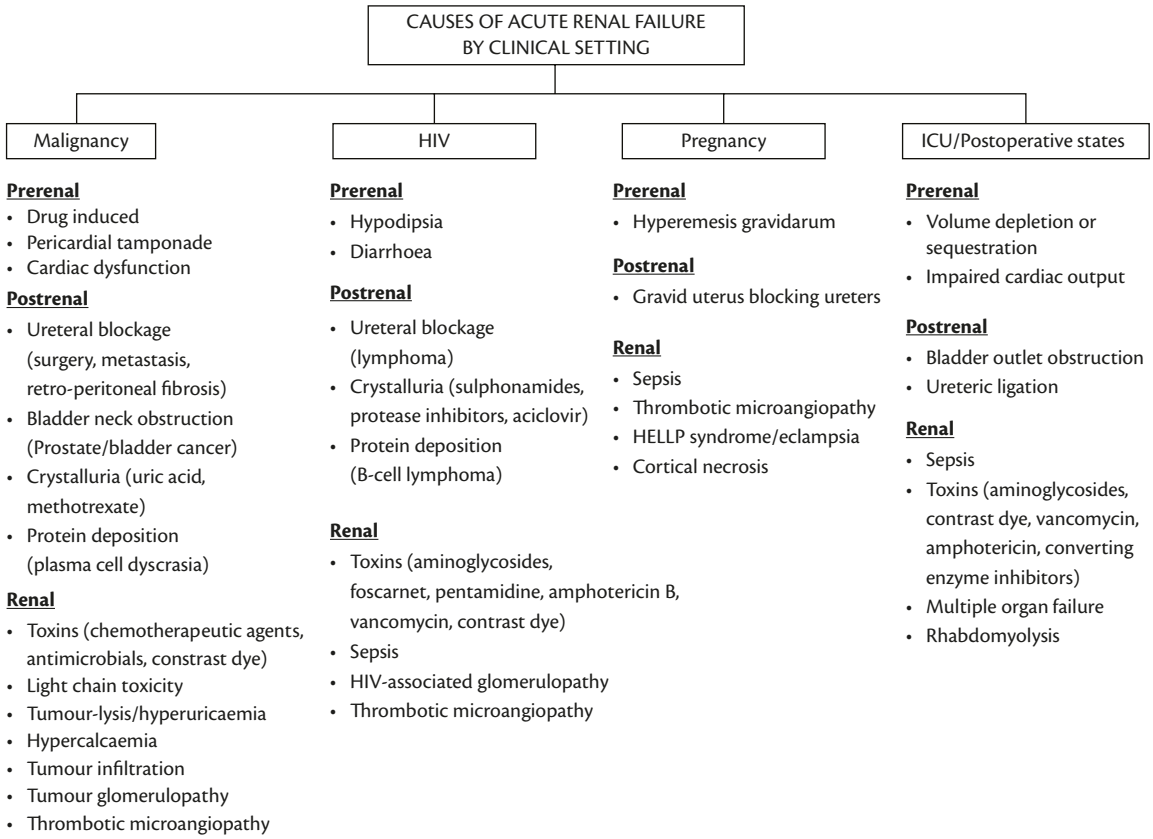

Fig. 222.2 Causes of acute kidney injury by clinical setting.

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Patients with heart and liver disease are susceptible to several renal insults, including those of 'prerenal' AKI (e.g. intensive treatment with diuretics in heart and liver diseases, or large-volume paracentesis, gastrointestinal haemorrhage, in liver disease, etc.) (see Chapters 247 and 248).

The diagnostic approach to any patient with AKI as outlined in Fig. 222.1, involves several steps which should not necessarily all be considered or followed in the order given. The approach encompasses the patient's history, a review of medical records, a thorough and repetitive physical examination, biochemical analysis of serum, urinalysis which may necessitate bladder catheterization, and several subsequent more technical evaluations. The approach should be defined by the acute factors that cause AKI and by those that increase the susceptibility to AKI. It is the interaction between susceptibility and the type and extent of exposure to insults that determines the risk of occurrence of AKI (see Chapter 196) (Table 222.1).

In the hospital setting, the patient's susceptibility can be assessed before certain planned interventions (surgery, administration of potentially nephrotoxic agents) are performed, and some factors may be modified, for example, by correcting hypovolaemia.

In community-acquired AKI, most patients are seen only after having suffered one or another acute exposure (trauma, infection, nephrotoxin).

The patient's history

The past medical history should include previous health checks, systemic conditions (e.g. diabetes, hypertension, ischaemic heart or peripheral artery disease, jaundice, pregnancy, liver disease, congestive heart failure, malignancy), previous urinary symptoms (related to pyelonephritis or urinary tract infection; micro-or macroscopic haematuria), previous blood urea, creatinine, and electrolyte

Table 222.1 A summary of some examples of exposures and susceptibilities of non-specific AKI

Exposure	Susceptibility
Any cause of AKI	Proteinuria, pre-existing CKD
Sepsis	Dehydration, or volume depletion
Critical illness	Advanced age
Burns	Black race
Trauma	CKD
Cardiac surgery (especially cardiopulmonary bypass)	Chronic diseases (heart, lung, liver)
Major non-cardiac surgery	Diabetes mellitus
Nephrotoxic drugs	Cancer
Radiocontrast agents	Anaaemia
Poisonous plants, animals	

Reproduced from Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group (2012). KDIGO Clinical Practice Guideline for Acute Kidney Injury. *Kidney Int Suppl*, 2, 1–138.

results, recent procedures (surgery, angiography, phosphate enemas for bowel cleansing before colonoscopy, other imaging procedures), and infections (e.g. HIV, hepatitis, tropical diseases).

In addition, a complete drug history should be taken, including immunosuppressive therapy (in transplant patients, patients with malignancies, auto-immune disorders), over-the-counter formulations and herbal remedies or recreational drugs, and the intake of drugs such as non-steroidal anti-inflammatory drugs (NSAIDs), angiotensin receptor blockers (ARBs) or angiotensin converting enzyme inhibitors (ACEIs), and antibiotic/antiviral/antimycotic drugs (see Table 222.2).

Events associated with intravascular volume loss, volume sequestration, and impaired cardiac or liver function are important in determining the cause of AKI. A history of thirst, orthostatic lightheadedness or hypotension, and symptoms of congestive heart failure support the diagnosis of 'transient' AKI. The triad of 'three pains of HTVD', headache, orbital, and lumbar pain, are quite typical for hantavirus diseases. The lumbar pain is due to the sometimes impressive swelling of the kidneys in this disease (see Chapter 242).

A history of factors that predispose to vascular disease or pre-existent cardiovascular morbidity, arterial catheterization involving the aorta, and atrial fibrillation are compatible with vascular embolic events leading to AKI, while a history of systemic infection or the presence of systemic symptoms may support a glomerular or vasculitis cause. Medication exposure or a history of acute pyelonephritis and its treatment may point to acute interstitial nephritis. The presence of disorders associated with either rhabdomyolysis, like a major trauma, or intravascular haemolysis suggests the possibility of haem pigment nephropathy (see Chapter 252).

Acute obstructive AKI is common at the extremes of age, especially with a history of changes in the size and force of urine stream; the presence of bladder, prostate, or pelvic cancer; the use of anticholinergic and alpha-adrenergic medications; the presence of anuria, suprapubic pain, or urolithiasis; or exposure to medications known to cause hyperuricosuria or crystalluria.

Patients with either a single kidney or a significant baseline decrease in the function of one kidney should raise the possibility of obstructive AKI, or alternatively of renal artery obstruction, especially in case of anuria, because a single lesion may completely eliminate normal kidney function.

The social history should include recreational activities (exhaustive sports), foreign travel (malaria, schistosomiasis), exposure to waterways or sewage systems (leptospirosis), and exposure to rodents (hantavirus). The professional status of the patient may reveal exposure to environmental toxins, like, for example, trace elements (e.g. cadmium).

Table 222.2 A summary of the most important pathophysiological mechanisms of frequent drugs and toxins causing AKI

Decreased renal perfusion	NSAIDs, ACEIs, ARBs, contrast media, amphotericin B, ciclosporin, tacrolimus
Direct tubular injury	Aminoglycosides, contrast media, amphotericin B, methotrexate, cisplatin, foscarnet, pentamidine, heavy metals, myoglobin, haemoglobin, intravenous immunoglobulin, HIV protease inhibitors
Intratubular obstruction	Contrast media, methotrexate, triamterene, aciclovir, sulphonamides, ethylene glycol, uric acid, cocaine, statins
Immunological-inflammatory	Penicillins, cephalosporins, allopurinol, NSAIDs, sulphonamides, diuretics, rifampicin, quinolones, cimetidine, tetracyclines, phenytoin

Modified from Anderson, R. J. and Barry, D. W. (2004). Clinical and laboratory diagnosis of acute renal failure. *Best Pract Res Clin Anaesthesiol*, 18(1), 1–20.

Differentiating acute from chronic kidney disease

It is useful to determine if a patient's elevated SCr is the result of an acute insult or of a progressive loss of functioning nephrons. Facts that a patient may have been refused insurance or had premiums loaded at some time in the past, or that 'protein in the urine' was noted at a medical examination, or been told that he/she 'had some problem with the kidneys', are likely to indicate long-standing renal disease. An abrupt and unexpected rise in the baseline SCr should prompt an evaluation of superimposed, potentially reversible AKI in patients with CKD. A flow sheet of remote and recent SCr values versus time incorporating changes in drug therapy and other interventions (e.g. radiocontrast investigations or prescription of NSAIDs, ACEIs, or ARBs) is invaluable for differentiation of acute from chronic renal dysfunction and for the identification of the cause of AKI. When past measurements of SCr are not available, the findings of anaemia, hyperphosphataemia, hypocalcaemia, hyperparathyroidism, neuropathy, band keratopathy, and imaging evidence of renal osteodystrophy or of small scarred kidneys are useful pointers to a chronic process. In CKD, the kidneys will usually be small (< 10 cm longitudinally in a person of normal stature) and echogenic; however, normal-sized kidneys on ultrasound do not absolutely exclude CKD. It should be remembered that anaemia, hyperphosphataemia, and hypocalcaemia may also complicate prolonged AKI.

Urine volume in the diagnosis of AKI

Urine volume in AKI can vary from oliguria (i.e. < 500 mL/24 hours or < 20 mL/hour) and even anuria (i.e. < 100 mL/24 hours) to polyuria. The KDIGO workgroup has defined oliguria based on the AKIN and RIFLE classification systems (see Chapter 220). In most AKI patients in the ICU, an indwelling urinary catheter allows accurate measurement of hourly urine output, a parameter useful in monitoring the initial response to fluid resuscitation until the intravascular fluid volume of the patient is adequately restored. Once euvolaemia is reached (see later), hourly urine volumes are less useful in guiding management and an increased urine flow should not be regarded as a primary treatment goal. Once patients are established to be oligo-anuric, the urinary catheter should be removed to reduce the risk of infection. Although severe AKI can exist in the presence of normal urine output (i.e. non-oliguria), changes in urine output can occur before biochemical changes are apparent. Non-oliguric AKI is nowadays more common than oliguric AKI, particularly in ICU patients, because of the more frequent monitoring via daily SCr determinations and/or earlier intervention with fluid administration and diuretics. The 'spontaneous' non-oliguric forms usually have a better prognosis compared to the oliguric forms. This may well relate to a less severe renal insult or a higher incidence of nephrotoxin-induced AKI in the non-oliguric group.

Anuria is seen with cessation of glomerular filtration (e.g., rapidly progressive glomerulonephritis, acute cortical necrosis, or

total renal arterial or venous occlusion) or complete urinary tract obstruction. Brief (< 24–48 hours) episodes of oligo-anuria occur in some cases of ATN. 'Prerenal' forms of AKI nearly always present with oliguria, although non-oliguric prerenal AKI has been reported (Miller et al., 1980). Postrenal and renal forms of AKI can present with any pattern of urine flow. The presence of alternating anuria and polyuria is an uncommon but classic manifestation of urinary tract obstruction, for example, due to a stone that changes its position. In rare cases, unilateral obstruction can lead to anuria and AKI; vascular or ureteral spasm, mediated by autonomic activation, is thought to be responsible for the loss of function in the non-obstructed kidney.

An automated and accurate device in ICU patients was used to determine if changes in urine flow and volume could be a sensitive marker of AKI (Macedo et al., 2011b). The AKIN and RIFLE urine output criteria (see Chapter 220) were assessed by four different definitions of oliguria and compared with SCr criteria, the latter measured at least once per 24 hours. Fifty-five per cent of patients had an episode of oliguria during the ICU stay. There was no significant difference assessing urine output every hour or the total urine volume in a 6-hour period for the detection of episodes of oliguria. Using the SCr criterion, 21 patients (28%) were diagnosed as AKI, whereas an additional 24 (32%) were identified by the urine output criterion. The same authors (Macedo et al., 2011a) subsequently observed that the incidence of AKI increased from 24%, based solely on SCr, to 52% by adding the urine output as a diagnostic criterion, an observation confirmed in more recent studies (Wlodzimirow et al., 2012; Vanmassenhove et al., 2013). Oliguric patients without a change in SCr had an ICU mortality rate (8.8%), similar to oliguric patients with an increase in sSCr (10.4%); in both groups mortality was significantly higher compared to patients without AKI (1.3%) (Macedo et al., 2011a, 2011b). The diagnosis of AKI occurred earlier in oliguric than in non-oliguric patients. Prowle and colleagues (Prowle et al., 2011) demonstrated that transient oliguria is a common event in the ICU and that such incidents are not necessarily associated with development of AKI by SCr criteria. Consequently, the occurrence of short periods (1–6 hours) of oliguria lacks utility in discriminating patients with incipient AKI. In none of these three studies (Macedo et al., 2011a, 2011b; Prowle et al., 2011) are data available on fluid management or volume status of the patients. Neither the impact of fluid therapy on the evolution of the diuresis and renal function, nor the impact of oliguria alone without rise in SCr on the diagnosis of 'transient AKI' or prerenal failure is thus known. Importantly, presence of oliguria is not very helpful in the differential diagnosis between so-called transient AKI and established AKI.

Mandelbaum et al. (2012) using a sophisticated database generated contour plots to investigate various combinations of creatinine/urine output thresholds and observation periods for predicting in-hospital mortality and need of renal replacement therapy (RRT). Mortality risk was high when absolute SCr increase was high regardless of the observation period, and when percentage SCr increase was high and the observation period was long. When the urine output was < 0.5 mL/kg/hour, mortality rate increased rapidly as the urine output decreased. However, when the urine output was > 0.5 mL/kg/hour, there was a minimal reduction in mortality rate as the urine output increased. Furthermore, for urine outputs < 0.3 mL/kg/hour and observation periods < 5 hours, mortality risk was especially sensitive to the degree of oliguria and longer observation time. Mortality risk became independent of the duration of oliguria for observation periods longer than approximately 24 hours and when oliguria was sustained for a long period of time. Similar contour patterns emerged for RRT. This analysis suggest thus that contour plots, including evolution of SCr and urine output may complement the AKIN definition.

Physical examination in the differential diagnosis of intrinsic AKI

Blood pressure

Many patients with AKI may have a low systemic blood pressure and low systemic perfusion, sometimes caused by volume depletion; however the blood pressure may at the moment of assessment not be dramatically low. In the absence of frank hypotension, the clinician may speculate that an unobserved drop in blood pressure must have caused the fall in GFR. This type of AKI has been called 'normotensive', because the patient's blood pressure is—at least temporarily—within the normal range (Abuelo, 2007). Blood pressure readings that were obtained for 3 days prior to the development of AKI and for a similar 3-day period in patients without AKI revealed that relative hypotension is common in hospital patients who develop nosocomial AKI and that finding a 'normal' blood pressure does not exclude that the AKI is the consequence of hypotension (Liu et al., 2009). Alternatively, especially in old age, other conditions inducing vascular stiffness, severe vascular disease, or a prolonged history of inadequately treated hypertension, (micro) vascular damage may be so severe that a higher than normal blood pressure is needed to maintain adequate renal perfusion.

Skin examination may reveal palpable purpura (vasculitis), a fine maculopapular rash (drug-induced interstitial nephritis), or livedo recticularis, purple toes, and other embolic stigmata (atheroemboli). Erysypelas or impetigo may be an indication of acute glomerular disease.

Ophthalmologic examination may show plaques suggestive of atheroemboli (Hollenhorst plaques, i.e. intraluminal retinal cholesterol/fibrin deposits), or findings compatible with bacterial endocarditis, vasculitis, or malignant hypertension. Acute myopia and/or periorbital oedema in an oliguric patient with fever is quite diagnostic for hantavirus infection.

Neck examination for jugular venous pressure and carotid pulses and sounds may be helpful in detecting heart failure, aortic valve disease, or vascular disease.

Cardiovascular examination for heart rate, rhythm, murmurs, gallops, and rubs may be helpful in revealing the presence of heart failure and possible sources of emboli.

Pharyngeal examination may show pharyngitis which in its turn may be linked to acute glomerulonephritis. *Lung examination* can assist in determining the presence of either heart failure, a pneumonia, or a pulmonary-renal syndrome associated with AKI.

Abdominal examination can reveal findings compatible with vascular disease (e.g. bruits, palpable abdominal aortic aneurysm), masses that could be malignant, a distended bladder, possible sources of bacteraemia, or evidence of liver disease.

Examination of the extremities for symmetry and strength of pulses and presence of oedema can be helpful.

If *neurological signs* are present, systemic disorders such as vasculitis, thrombotic microangiopathy, subacute bacterial endocarditis, and malignant hypertension warrant consideration. Peripheral

neuropathy in the presence of AKI raises the possibility of nerve compression caused by rhabdomyolysis, heavy metal intoxication, or plasma cell dyscrasia. *Pelvic examination in females and rectal examination in both females and males* may detect an obstructive cause of AKI. Red, brown, or black urine may point to pigmenturia (rhabdomyolysis, haemolysis) as a source of AKI.

Presence of localized or generalized oedema, and/or ascites may obviously lead to a diagnosis of acute glomerular or vasculitic disease or AKI associated with heart or liver disease.

Abdominal hypertension and/or abdominal compartment syndrome

Intra-abdominal hypertension (IAH) is defined as a sustained or repeated elevation in intra-abdominal pressure (IAP) ≥ 12 mmHg; abdominal compartment syndrome (ACS) is a sustained IAP ≥ 20 mmHg that is associated with new organ dysfunction or failure (Malbrain et al., 2006). Primary acute or subacute ACS usually results from injury or disease in the abdomen or pelvic region and is common in the surgical ICU; better surveillance and early intervention result in a decrease of its incidence (Mohmand and Goldfarb, 2011). Secondary ACS results from extra-abdominal causes and is usually seen in patients in the medical ICU who receive large-volume fluid resuscitation (e.g. patients with septic shock, capillary leak, and major burns) (Cheatham et al., 2007). Developing IAH, even in the absence of full-blown ACS, is associated with higher mortality and an increased risk for developing AKI. At the slightest index of suspicion of IAH, measuring IAP by transduction of the bladder pressure using a urinary catheter is recommended (Mohmand and Goldfarb, 2011). More detailed information on monitoring and management of IAH and ACS was recently published (Mohmand and Goldfarb, 2011).

Assessment of the patient's volume status/the effect of a fluid challenge

It has been proposed (Himmelfarb et al., 2008) that AKI can be characterized by a continuum of volume responsiveness and/or unresponsiveness. In patients with real hypovolaemia, organ perfusion and renal function will improve with volume repletion. In other circumstances, such as presence of congestive heart failure or diastolic dysfunction, renal perfusion is suboptimal despite adequate circulating volume, or even volume overload. In such patients, fluid loading may result in pulmonary oedema and further worsening of cardiac function and not in improvement of kidney perfusion. Patients with sepsis or suffering diseases causing third spacing may already be fluid overloaded, but the intravascular circulating volume is reduced. The effect of volume repletion on the general haemodynamic status and kidney function is mostly a 'retrospective diagnosis' and can only be evaluated by trial and error. Furthermore, in hospital patients, a volume challenge is typically associated with other simultaneous interventions (antibiotics, vasodilators, inotropic drugs), so that the eventual improvement of kidney function or increase in diuresis cannot easily be attributed to intravenous fluids alone.

The general and renal response to a fluid challenge is often an important diagnostic test in differentiating 'transient' AKI from 'established' AKI, mostly ATN. Because fluid loading may provoke dangerous fluid overload, evaluation of the volume status of the patient before administration of a fluid challenge is of great importance. The traditional 'clinical approach' to test whether the patient adequately responds to a volume load by performing repeated fluid challenges may have deleterious effects in the case of reduced right and/or left ventricular function and increased pulmonary permeability (Vincent and Weil, 2006).

The clinical evaluation of the volume status

The history and physical examination of the patient with either hypo- or hypervolaemia has important limits (Peacock and Soto, 2010). Decreased skin turgor, (orthostatic) hypotension and tachycardia, poor capillary refill, core peripheral temperature gradient, and altered mental state are poor and late indicators that detect only overt hypovolaemia (McGee et al., 1999). The jugular venous pressure (JVP) with the patient reclining at 45° should always be assessed. The normal JVP is between 0 and 3 cm above the sternal angle, which corresponds to a right atrial pressure of approximately 8 cm water. Gentle pressure over the liver to increase venous return may be helpful (the hepatojugular reflux). Elevation of JVP does not rule out hypovolaemia, because of the possible confounding effects of underlying heart failure or lung disease.

Recording the patient's daily body weight in conjunction with fluid balance charts and clinical examination can help to estimate the evolution of the fluid balance.

Assessment of some haemodynamic variables during volume administration

More invasive haemodynamic monitoring is often necessary, particularly in ICU patients to predict the general and renal response to fluid administration. As illustrated by the Frank–Starling curve (Fig. 222.3) (Renner et al., 2009), if the heart is operating on the steep part of the Frank–Starling curve, an increase in preload is associated with a relevant increase in stroke volume (preload dependency) and fluid administration can improve renal perfusion. In other words, the patient is then preload dependent and thus fluid responsive (Pinsky and Teboul, 2005; Reuter and Goetz, 2006). In contrast, if the heart is operating on the flat part of the Frank–Starling curve the same increase in preload will not induce a relevant change in stroke volume and renal perfusion and may increase the risk for inducing pulmonary oedema. The importance of these predictive parameters is illustrated by the fact that only about 50% of critically ill patients with suspected hypovolaemia actually show a favourable response to fluid administration (Michard and Teboul, 2002).

There is a consensus that static evaluation of the fluid or haemodynamic status, for example, by measuring the central venous pressure (CVP) or pulmonary artery occlusion pressure (PaOP), provides little information about the likely fluid responsiveness of a particular patient (Vincent et al., 2011; Davison et al., 2012; Vincent and De Backer, 2012).

Unlike the static evaluation, more dynamic entities like variations in stroke volume, arterial pressure, or pulse pressure can better predict volume responsiveness and are being used increasingly in the ICU setting for mechanically ventilated patients (for review, see Davison et al., 2012). Unfortunately, these entities are not valid in patients with arrhythmias, spontaneous ventilation, or low tidal volume, and thus these techniques can only be applied in selected patients (Vincent and De Backer, 2012). The passive leg raising (PLR) test may also be used to predict fluid responsiveness (Cavallaro et al., 2010) but for this test patients must be able

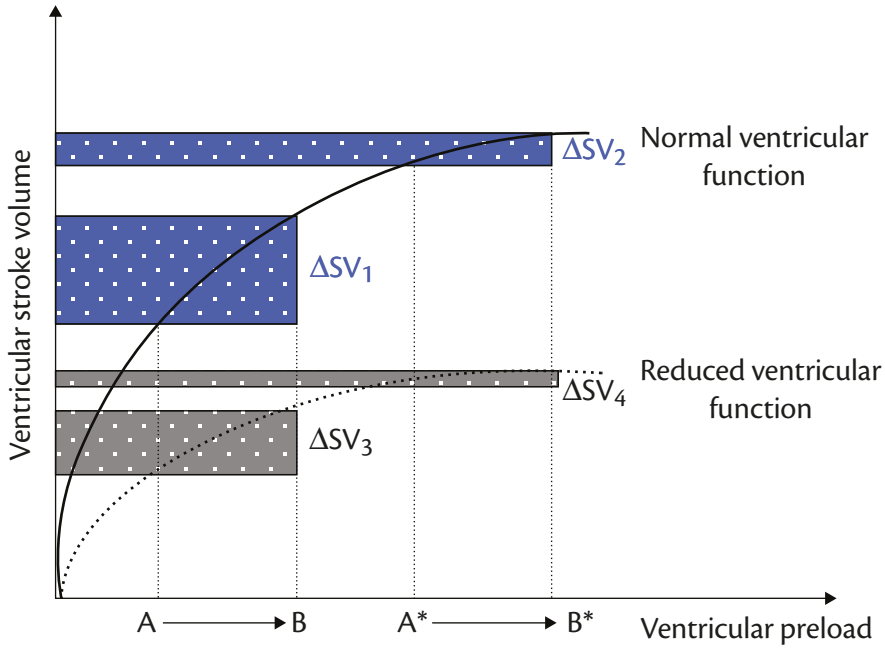

Fig. 222.3 The Frank–Starling curve representing the non-linear relationship between ventricular preload and ventricular stroke volume (straight curve ¼ normal ventricular function; dashed curve ¼ reduced ventricular function). If the heart is operating on the steep part of the Frank–Starling curve, an increase in preload is associated with a relevant increase in stroke volume (preload dependency, DSV1). In contrast, if the heart is operating on the flat part of the Frank–Starling curve the same magnitude of change in preload after volume administration (from A* to B*) does not increase SV (preload independency, DSV2). This relationship is strongly affected by cardiac function. In contrast to a normal ventricular function, the same increase in preload will not induce a relevant change in stroke volume in case of reduced left ventricular function (DSV3 and DSV4).

to tolerate a rapid change in torso position and it requires the use of rapid response cardiac output monitoring. The PLR test can be false-negative in patients with an increased intra-abdominal pressure (IAP) because this impairs venous return and results in false-negative results. Therefore, an IAP measurement seems needed while interpreting the result of a PLR test (Malbrain and Reuter 2010).

As pointed out by Vincent and De Backer (2012) the results of the above mentioned tests are not dichotomic (i.e. no response below a given value, response above that value); there is rather a continuum, with the likelihood of response to fluids increasing when the value increases, so that there remains a 'grey zone' in which there is still some incertitude. Hence, these tests do not negate the need for a 'trial and error' fluid challenge (Vincent and De Backer, 2012), which remains widely used despite all its limitations (Vincent, 2011). When performing a fluid challenge, four items must be defined in advance, which can be summarized by the acronym, TROL:

1. Type of fluid (e.g. Ringer's lactate or isotonic saline)
2. Rate of infusion (e.g. 500 mL in 30 min)
3. Objective (e.g. increase in arterial pressure to 75 mmHg or urine output > 20 mL in 30 min)
4. Limits (e.g. a maximal increase in CVP of 3 mmHg from a baseline of 12 mmHg).

If the target improves but is not reached with the fluid challenge, and the safety limits are not breached, fluid challenges can be repeated until there is no further improvement in the objective or the safety boundaries are exceeded (Vincent and De Backer, 2012).

Confirming that the patient is preload responsive does not always mean that giving fluids is the right approach. In some patients with vasodilatory shock, another treatment option might be more appropriate, such as the administration of low-dose vasoactive drugs, like norepinephrine (noradrenaline).

It is clear that during fluid therapy, haemodynamic monitoring particularly in the critically ill patient needs close cooperation between the ICU specialist and the nephrologist. A more detailed description of this monitoring is beyond the scope of this chapter but can be found in some recent papers (Pinsky et al., 2008; Casserly et al., 2009, 2011).

The laboratory tests for differentiation of acute kidney injury

Urinary chemistries in the differential diagnosis of AKI

The most frequently used urinary parameters in the differential diagnosis between prerenal AKI and ATN are summarized in Table 222.3.

In 'transient' or prerenal AKI, tubular function is presumably intact and augmented activity of the sympathetic nervous system, the renin–angiotensin– aldosterone system, and vasopressin secretion provoke renal vasoconstriction which is associated with a concentrated urine with high urinary osmolality, and enhanced tubular sodium reabsorption with low urinary sodium concentration

Table 222.3 The most important urinary variables in the differential diagnosis between prerenal AKI and ATN

	Prerenal AKI	ATN
Urinalysis	Hyaline casts	RTCs, granular casts
Specific gravity	1020	1010
Osmolality (mOsm/kg)	>500	~300
Sodium (mmol/L)	<20	>40
Fractional excretion sodium (%)	<1	>3
Fractional excretion urea (%)	<35	>35
Fractional excretion uric acid (%)	<7	>15
Fractional excretion lithium (%)	<7	>20
Low molecular weight proteins	Low	High
Brush border enzymes	Low	High
Novel urinary biomarkers[a]	Low	High

[a]For discussion of novel biomarkers, see Chapter 223.

(UNa) and fractional excretion of filtered sodium (FE_{Na} = [(urine sodium × plasma creatinine)/(plasma sodium × urine creatinine)]) below 1%. Values ≥ 3% are seen in ATN (1–3% is the diagnostic 'grey zone' for this test). In the first prospective study examining the validity of FE_{Na} to distinguish prerenal from established ATN in acutely oliguric patients, the FE_{Na} was < 1% in those who had prerenal AKI, as documented by reversal of kidney function secondary to interventions such as fluid resuscitation or improved cardiac output within 24–72 hours. In the patients who did not reverse the elevated SCr, and thus had oliguric ATN, the FE_{Na} was < 1% in only 4% of patients (Miller et al., 1978). Importantly, in this study, the baseline SCr of all included subjects was within the normal range (< 1.4 mg/dL; < 132.6 μmol/L), and diuretic use, mannitol, glucosuria, and bicarbonaturia were not present. Indeed, a paradoxically high FE_{Na} despite the presence of prerenal AKI occurs during diuretic treatment, including mannitol, within the preceding 24 hours, or glycosuria or excretion of alkaline urine. In the latter case, the obligatory excretion of bicarbonate requires the excretion of sodium. In presence of alkalosis and suspicion of 'prerenal AKI', it may be more appropriate to calculate the fractional excretion of chloride ($FE\ Cl^-$). Furthermore, ATN in the setting of rhabdomyolysis and myoglobinuria, haemolysis, cirrhosis, heart failure (Zarich et al., 1985), sepsis (Vaz, 1983), obstruction, acute glomerulonephritis, and radiocontrast nephropathy (Fang et al., 1980) may be associated with a low UNa (e.g. < 10 mmol/L) and FE_{Na} of < 1.0%. In experimental models of rhabdomyolysis, early depletion of the extracellular volume occurs as damaged muscle cells may sequester considerable amounts of volume leading to decreased renal perfusion, and subsequently low FE_{Na}. If left untreated, this low kidney perfusion may evolve into established AKI (ATN) with resulting increases in FE_{Na} (Reineck et al., 1980) (see also Chapter 252).

Finally, renal vasoconstriction in a patient with advanced chronic renal failure may not be expected to be associated with a FE_{Na} of < 1% because of chronic adaptation to an increased single-nephron GFR. Already in 1983, Vaz (1983) had observed low FE_{Na} in two patients with sepsis despite adequate correction of their volume status. Urinary parameters are thus not very useful in differentiating 'prerenal AKI' from ATN in septic AKI (Bagshaw and Bellomo, 2010; Bagshaw et al., 2012). This may result from limited sensitivity of this parameter, or, perhaps more likely, the patient may actually be progressing from a 'transient AKI' state to established ATN, with the urinary status lagging behind on the renal parenchymal status.

In view of the interference of diuretic therapy with the FE_{Na} determination, calculation of the fractional excretion of urea (FE_{urea}) has been proposed as alternative parameter in AKI patients under recent diuretic therapy. Urea reabsorption occurs mainly at the proximal segment of the nephron and is unaffected by diuretic intake, making FE_{urea} potentially more reliable than Fe_{Na} (Kaplan and Kohn, 1992; Carvounis et al., 2002; Pepin et al., 2007) (for a review, see Honoré et al., 2012). However, conflicting results have been published on the use of the FE_{urea}. Prospective small studies in critically ill paediatric (Fahimi et al., 2009) and adult patients (Diskin et al., 2010; Dewitte et al., 2012) found that FE_{urea} < 40% or < 35% was a sensitive and specific index in differentiating 'transient' from persistent AKI patients, especially if diuretics had been administered, By contrast two other prospective studies (Pepin et al., 2007; Darmon et al., 2011b) found that FE_{urea} was of little help for distinguishing 'transient' from persistent AKI, the area under the ROC curve being only 0.59 (95% confidence interval (CI) 0.49–0.70; P = 0.06). In the subgroup of patients receiving diuretics, the results were similar.

A reduced effective circulating volume also stimulates antidiuretic hormone release, resulting in increased distal water and urea reabsorption. A urinary osmolality value > 500mOsm/kg indicates thus an intact tubular function and is to be expected in prerenal AKI. However, maximal urinary concentration capacity is substantially diminished in certain conditions, such as in the elderly, in CKD or during periods of low protein intake; urine osmolality may be low even in prerenal states (Macedo and Mehta, 2009).

Urine dipstick

Routine dipstick and microscopic analysis of urine are often helpful in determining the cause of AKI. Generally, a normal urine analysis in the setting of AKI suggests a prerenal ('transient') or postrenal cause and an abnormal urinalysis a renal cause. However, patients with 'transient' AKI can have a significant number of casts (due to the precipitation of Tamm–Horsfall protein in concentrated, acidic urine) and cellular elements in the urine.

Urinary protein measurement by dipstick is specific for albumin. Small amounts of protein found by dipstick, with larger amounts found by laboratory urinary protein tests, suggest the presence of light chains or other proteins or peptides apart from albumin (haemoglobin, myoglobin, microglobulins, intact immunoglobulins). If the dipstick reaction for protein is moderately or strongly positive in the setting of AKI, quantification is indicated. The presence of > 1–2 g/day of urine protein suggests a glomerular cause of AKI but in many cases of ATN significant proteinuria may be present, due to disturbances of tubular albumin reabsorption.

The urine sediment

Examination of the urine sediment should always be performed in a patient with AKI (Fig. 222.4). Gross or microscopic haematuria, particularly with dysmorphic red cells or red cell casts in the urinary sediment, suggests a glomerular disease. Haematuria can also be associated with a vascular, interstitial, or other structural renal cause of AKI (e.g. stone, tumour, infection, or trauma) and is rarely seen with ATN.

Gross haematuria occurring in patients with underlying glomerular disease has been associated with the development of AKI. Kidney biopsy in such cases often shows distension of many renal tubules by intratubular red cells and tubular cell injury consistent with ATN. This association has most frequently been described in patients with IgA nephropathy, but has also been noted in case reports of patients with thin basement membrane disease and lupus nephritis, who were overanticoagulated with warfarin (Abt et al., 2000; Kabir et al., 2004; Moreno et al., 2012) (see also Chapter 224).

Lack of microscopic urinary erythrocytes despite a positive dipstick reaction for blood is typical of AKI induced by myoglobinuria or haemoglobinuria. Large numbers of white blood cells (WBCs) and in particular of leucocyte casts suggest either pyelonephritis or interstitial nephritis. Eosinophiluria (> 1% of urine WBCs) or eosinophilic casts on Hansel's stain of the urinary sediment is non-specific, but diagnostically valuable when AKI occurs in a setting compatible with either allergic interstitial nephritis (drug exposure, fever, rash, peripheral eosinophiluria), cholesterol embolism, or in some forms of glomerulonephritis (Fletcher, 2008; Kaye and Gagnon, 2008; Perazella and Markowitz, 2010).

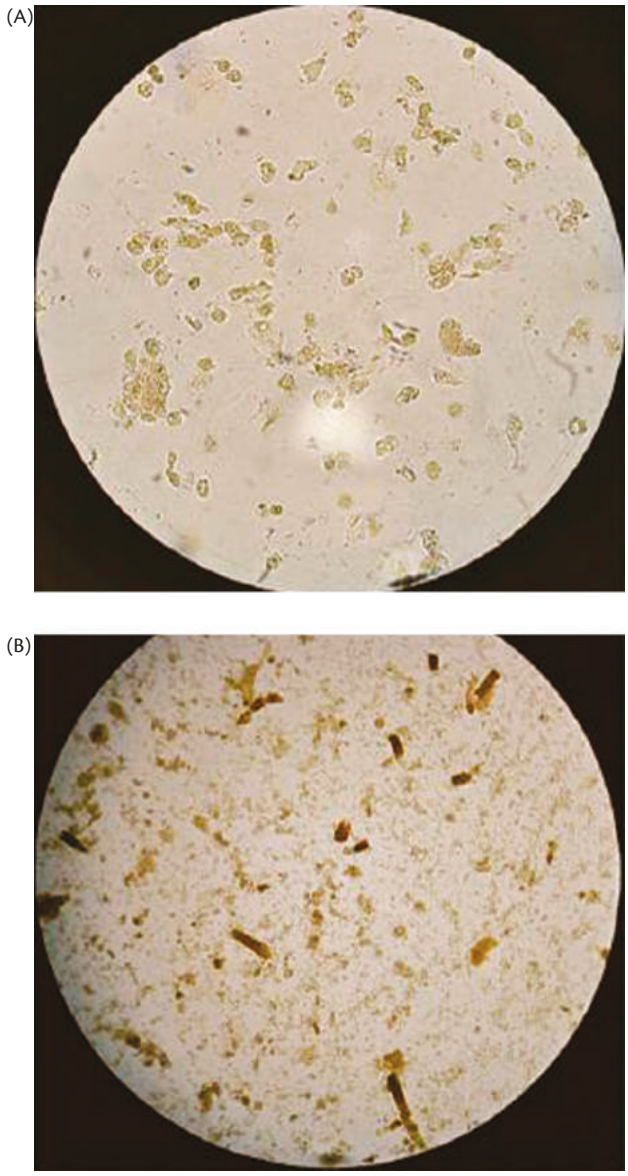

Fig. 222.4 A urine sediment score of 0–4 is used to quantitatively evaluate AKI. A score of 2 is achieved in (A) ≥ 6 renal tubular epithelial cells/high-power field, and a score of 2 is achieved in (B) ≥ 6 granular casts/low-power field.
Reprinted from Perazella, M. A. and Coca, S. G. (2012). Traditional urinary biomarkers in the assessment of hospital-acquired AKI. *Clin J Am Soc Nephrol*, 7(1), 167–74.

Collecting duct cells and total casts in urine detected by cytodiagnostic quantitative assessment are increased in AKI but lack sufficient sensitivity, specificity, and predictive power for routine clinical use. Crystals in the urine sediment should be assessed by an experienced microscopist using fresh warm urine, polarizing microscopy, and knowledge of the urine pH. A large number of uric acid crystals suggests acute uric acid nephropathy, tumour lysis syndrome, or catabolic AKI. Oxalate crystals are compatible with ethylene glycol intoxication, jejunoileal bypass, or massive doses of vitamin C. Drug-induced crystals can result from sulphonamides, indinavir, aciclovir, and triamterene.

The value of the urine sediment has been explored in septic AKI versus non-septic AKI patients (Bagshaw et al., 2012) and its diagnostic performance was compared with other diagnostic parameters, including urine biochemistry. A urine microscopy score (UMS) was derived based on the observed quantification of renal tubular cells and casts in the sediment. Septic AKI was associated with a higher UMS compared with non-septic AKI but there was no correlation between UMS and FE_{Na} or FE_{urea}. A higher UMS score was associated with increased odds of worsening AKI, need for RRT, and in-hospital death; however, this did not persist in multivariable analysis. Urine microscopy may thus have a complementary role for discerning septic from non-septic AKI, and discriminating severity and predicting worsening AKI in critically ill patients.

Apart from taking advantage of the unique ability of the urinary sediment to detect potentially unsuspected diagnoses, its primary purpose in AKI is to distinguish between the bland sediment of 'prerenal AKI' and findings consistent with acute tubular damage, such as 'muddy brown' granular casts, renal tubular epithelial cells (RTECs), and RTEC casts (Fig. 222.4).

Perazella et al. examined the utility of urine microscopy and a urine sediment score (based on RTECs and granular casts) in patients with hospital-acquired AKI due to prerenal AKI or ATN (Perazella et al., 2008). The likelihood ratios for ATN increased in a dose-dependent fashion as the number of granular casts or RTECs increased and declined for prerenal AKI. In patients with an initial diagnosis of ATN (before urine microscopy), the presence of granular casts or urine sediment score ≥ 2 had a positive predictive value of 100% for a final diagnosis of ATN. In patients with an initial diagnosis of prerenal AKI, the lack of granular casts or a urine sediment score of 1 had a negative predictive value of 91% for a final diagnosis of prerenal AKI. Thus, critical performance of urine microscopy appears to be useful to differentiate the most common causes of hospital-acquired AKI.

The same authors subsequently examined the association of urine microscopy with severity and worsening of AKI in hospitalized patients (Perazella et al., 2010) at the time of nephrology consultation for AKI. The scoring system was significantly associated with increased risk for worsening AKI (adjusted relative risk 7.3, 95% CI 4.5–9.7 for worsening with score of ≥ 3 versus score of 0) and was more predictive than AKIN stage at the time of consultation.

These data suggest that a urine sediment score may be useful to predict worsening of AKI as a result of either ATN or 'prerenal AKI' during hospitalization. Kanbay et al. (2010) performed a systematic review of the utility of urine microscopy in the diagnostic evaluation of ATN and 'prerenal AKI'. On the basis of the limited available data for this systematic review, urine microscopy with a sediment scoring system was deemed useful for the differential diagnosis and prognostic stratification of AKI. Finally, a recent clinical review (Perazella and Coca, 2012) concluded that whereas current information on urine diagnostics suggests that urine chemistries have a limited role in differential diagnosis of AKI, urine microscopy and possibly new urine biomarkers (see Chapter 223) may be used together to differentiate prerenal AKI from ATN and predict such outcomes as worsened AKI, acute dialysis, and death.

Although these findings will not surprise practising nephrologists, formal evaluation of the urine sediment is long overdue and welcome; it should also be recognized that a disappointingly low inter-reader agreement in the identification and interpretation of important structures in the urine sediment by nephrologists was found (Wald et al., 2009). To justify the continued use of the urine sediment in the diagnosis of kidney disease, more in particular AKI, measures to standardize its interpretation and to enhance its consistency are needed.

New biomarkers in the differential diagnosis of AKI

As outlined in detail in previous chapters, AKI has mainly been diagnosed by changes in SCr concentration, which reflect mainly changes in GFR. Unfortunately, SCr does not accurately reflect the GFR in patients with AKI because they are not at steady state; furthermore acute changes in SCr lag behind the stage of kidney damage, which presumably precedes the stage of decrease in GFR. In addition, in sepsis, one of the main causes of AKI in critically ill patients, creatinine production may be decreased as has recently been observed in a septic animal model (Doi et al., 2009). Extensive research efforts over the last years have been directed at the discovery and validation of novel AKI biomarkers to detect renal injury prior to the detection of changes in kidney function, to aid potentially in the differential diagnosis of AKI and to predict the short- and long-term prognosis of the patient with AKI (for an extensive review of the current status on novel biomarkers, see Chapter 223).

The furosemide stress test

The furosemide stress test (FST) is based on the tubular handling of furosemide. As an organic acid, furosemide is tightly bound to serum proteins and appears in the tubular lumen by active secretion via the human organic anion transporter system in the proximal convoluted tubule. Once in the tubular lumen, furosemide inhibits luminal active chloride transport throughout the thick ascending limb of Henle. To prevent sodium reabsorption and to increase urine flow, furosemide thus requires two distinct tubular nephron segments to be functioning—making it an interesting physiologic and clinical tool for tubular functional testing (Ho and Power, 2010).

It was recently demonstrated that the 2-hour urine output after a standardized high-dose FST (1 mg/kg of furosemide in naive patients or 1.5 mg/kg in those with prior exposure to furosemide) in clinically euvolaemic patients with early AKI has the predictive capacity to identify those with severe and progressive AKI (Chawla et al., 2013). The area under the receiver-operating characteristic curve (AUC) for the urine output 2 hours after FST to predict progression to AKI Network (AKIN) stage-3 AKI in 77 patients was 0.87 ± 0.09 ($P = 0.001$). The ideal cut-off for predicting progressive AKI during these first 2 hours was a urine volume of 200 mL (100 mL/horr) with a sensitivity of 87.1% and a specificity of 84.1%.

The same group of investigators later showed that in early AKI the 2-hour urine output after FST was significantly better than each of the new proposed urinary biomarkers (see Chapter 223) tested in predicting progression to AKI stage 3 (Koyner et al., 2015).

FST urine output was the only biomarker to significantly predict RRT (0.86 ± 0.08; $P = 0.001$). Regardless of the endpoint, combining FST urine output with individual biomarkers using logistic regression did not significantly improve risk stratification (ΔAUC, $P > 0.10$ for all). When FST urine output was assessed in patients with increased biomarker levels, the AUC for progression to stage 3 improved to 0.90 ± 0.06 and the AUC for receipt of RRT improved to 0.91 ± 0.08. Overall, in the setting of early AKI, FST urine output outperformed biochemical biomarkers for prediction of progressive AKI, need for RRT, and inpatient mortality.

Other laboratory tests to establish the cause of AKI

Various findings in the complete blood count, coagulation assays, changes in serum electrolytes and other parameters, and immunological investigations can suggest specific causes of AKI. These laboratory tests are summarized in Table 222.4.

Imaging procedures

Renal ultrasonography

Ultrasonography (US) is mandatory in patients with AKI if obstructive nephropathy is suspected and often clinicians routinely order a renal ultrasonography (RUS) study. It is however unclear how often this test provides clinically useful information (Licurse et al., 2010). In fact, hydronephrosis (HN), the evidence of obstruction on imaging, is only identified on renal ultrasound in 1–10% of patients with AKI (Liano and Pascual, 1996; Uchino et al., 2005).

Licurse et al. (2010) have developed a stratification system that would help clinicians ascertain the risk of renal obstruction among those with AKI. Multiple risk factors for HN were identified: history of HN; recurrent urinary tract infections; diagnosis consistent with obstruction; non-black race; and absence of the following: exposure to nephrotoxic medications, congestive heart failure, or prerenal AKI. Patients with a history of heart failure, granular casts on urinalysis, elevated leucocyte count, documented hypotension, or exposure to aspirin, diuretics, or vancomycin during hospitalization were less likely to have HN. Among 797 patients in the validation sample, 10.6% had HN and 3.3% had HN requiring urological intervention. By contrast, of 223 patients in the low-risk group, only seven (3.1%) had HN and only one (0.4%) required intervention (223 patients had thus to be screened to find that one case). In adult inpatients with AKI, specific factors can thus identify patients unlikely to have HN or HN requiring intervention on US.

Other sensitive ultrasonographic findings to rule out postrenal AKI are a post–void residual bladder urine < 50 mL and absence of pelvicalyceal dilatation.

Patients with highly distensible collecting systems (e.g. in kidney grafts) or with pyelocaliectasis may be misdiagnosed as having HN. False-negative findings have also been reported in

Table 222.4 Various findings in the complete blood count, coagulation assays, changes in serum electrolytes and other parameters, and immunological investigations as causes in AKI

Laboratory finding	Observed in AKI due to:
Anaemia	Pre-existent chronic renal failure, haemorrhage, haemolysis
Anaemia with rouleaux formation	Plasma cell dyscrasia
Eosinophilia	Atheroemboli, acute interstitial nephritis, eosinophilic granulomatosis with polyangiitis (Churg–Strauss)
Leucopenia	SLE
Thrombocytopenia	SLE, hantavirus infection, DIC, rhabdomyolysis, advanced liver disease with hypersplenism, 'white clot syndrome' due to heparin administration
Thrombocytopenia, reticulocytosis, elevated LDH, schistocytes on peripheral smear, low ADAMTS13 Shiga toxin-PCR, STEC stool culture, STEC O157 IgG/IgM antibodies, Complement status Factor H, I serum levels	Thrombotic microangiopathy HUS
Coagulopathy	Liver disease, DIC, antiphospholipid antibody syndrome
Hyperkalaemia > 5.5 mEq/L Marked hyperkalaemia	Various causes Tumour lysis syndrome, haemolysis, use of NSAIDs, ACEI, or ARB
Marked hyperkalaemia, hyperphosphataemia, hypocalcaemia, elevated serum uric acid and CK, AST, and LDH	Rhabdomyolysis
Marked hyperkalaemia, hyperphosphataemia, hypocalcaemia, very high serum uric acid, normal or marginally elevated CK	Acute uric acid nephropathy, tumour lysis syndrome, heat stroke
Hypercalcaemia	Malignancy, sarcoidosis, vitamin D intoxication, multiple myeloma
Widening of serum anion and osmolal gap[a]	Ethylene glycol or methanol intoxication
Marked acidosis, anion gap > 5–10 mEq/L	Ethylene glycol poisoning, rhabdomyolysis, lactic acidosis in sepsis
Hypergammaglobulinaemia	SLE, bacterial endocarditis, and other chronic infections
M-gradient, hypergammaglobulinaemia	Myeloma
Urine electrophoresis showing free light chains	Myeloma, low-grade plasma cell dyscrasias (even in the absence of serum abnormalities)
Low complement	Glomerular diseases, cholesterol emboli
Elevated serum IgA	IgA nephropathy
Elevated antinuclear antibodies	Autoimmune diseases including SLE, scleroderma, mixed connective tissue disease, Sjögren syndrome.
Elevated anti-double stranded DNA antibodies	SLE
Elevated anti-streptolysin titre and anti-DNAse B titre Complement status (CH50, APH50, C3, C3d, C4, C3 nephritic factor)	Acute glomerulonephritis
Elevated anti-C1Q antibodies	SLE, MPGN, some cases of IgA nephropathy
Elevated ANCA titre	Granulomatosis with polyangiitis (Wegener granulomatosis), microscopic polyangiitis, etc.
Antiglomerular basement membrane antibodies	Anti-GBM nephritis, Goodpasture syndrome
Cryoglobulins	Hepatitis C, lymphoproliferative disorders

ACEI = angiotensin converting enzyme inhibitors; ANCA = antineutrophil cytoplasmic antibody; AST = asparagine aminotransferase; CK = creatinine kinase; DIC = disseminated intravascular coagulation; GBM = glomerular basement membrane; HUS = haemolytic uraemic syndrome; LDH = lactic dehydrogenase; MPGN = membranoproliferative glomerulonephritis; NSAID = non-steroidal anti-inflammatory drugs; SLE = systemic lupus erythematosus.

[a]Mild metabolic acidosis occurs frequently as a consequence of ARF and is often associated with a modest (5–10 mEq/L) increase in the anion gap.

patients with very early (< 8 hours) obstruction. In many other false-negative cases, the patients were of an older age and the obstructing process, usually prostatic carcinoma or retroperitoneal fibrosis, encased the retroperitoneal ureters and renal pelvis, preventing their dilatation. In the elderly, partial obstruction may be obscured by volume depletion and when there is a strong suspicion of obstruction, the examination should be repeated after volume repletion. The renal sonogram can be normal in ATN (Hricak et al., 1982; Jeffrey and Federle, 1983; Paivansalo et al., 1985) but increased cortical echogenicity and cortical expansion have been observed in both animal and human studies (Nomura et al., 1984; Pardes et al., 1983; Rivers et al., 1996),

especially with nephrotoxic ATN (Pardes et al., 1983; Walker et al., 1983) whereas an enlarged hypoechoic cortex may be more typical of ischaemic ATN (Davidson et al., 1999). The cortical enlargement presumably represents oedema whereas increases in cortical echogenicity may be due to cellular and proteinaceous casts and debris within the tubules. The degree of renal enlargement has been shown to inversely correlate with recovery time from ATN (Nomura et al., 1984).

Increased ultrasonographic renal size without HN may occur with acute glomerulonephritis, with infiltration by amyloid or malignancy, in diabetes, and in renal vein thrombosis and may also be present in ATN. The finding of reduced renal size and increased echogenicity points to CKD. Even if the kidneys are reduced in size, the possibility of a prerenal cause of AKI or acute-on-chronic kidney injury must always be considered. US contrast media can improve the diagnostic capabilities in AKI by allowing the visualization of altered renal blood flow and of renal perfusion defects.

In general, US is rarely useful in the workup of AKI when the clinical picture suggests ATN and urinary obstruction is unlikely. However, it may be helpful in identifying underlying CKD in this setting.

Renal Doppler ultrasonography

Renal Doppler ultrasonography studies measuring the renal resistivity index (RRI) have been suggested to differentiate 'transient' AKI from established AKI. Partly as a result of intrarenal vasoconstriction, ischaemic AKI usually produces a reduction in renal blood flow with an increase in intrarenal vascular resistance.

Darmon et al. (2011a) observed in 51 mechanically ventilated patients that 16 had no AKI, 13 had 'transient' AKI, and 22 had persistent AKI. The RRI was 0.71 in the no-AKI group, 0.71 (0.62–0.77) in the 'transient' AKI patients, and 0.82 (0.80–0.89) in the 22 patients with persistent AKI. The RRI was better than urinary indices for diagnosing persistent AKI. In another study of 37 septic shock subjects, an RRI of > 0.74 was the threshold that best predicted AKI on day 5 (Lerolle et al., 2006).

Finally, 18 patients at risk for developing AKI following elective heart surgery with cardiopulmonary bypass developed AKI between days 1 and 4, with six requiring dialysis. The RRI in the postoperative period was significantly increased in AKI patients compared with patients without AKI, and correlated with increasing AKI severity. The RRI predicted delayed AKI with high sensitivity and specificity (0.85 and 0.94, respectively) (Bossard et al., 2011). However the RRI results overlapped between the several types of AKI ('transient' vs persistent AKI); high RRI values are also observed in acute obstruction, which markedly reduces its usefulness to obtain a specific diagnosis. It should further be reminded that increased vascular resistance (by hypocapnic vasoconstriction) and decreased heart rate (decreased end-diastolic Doppler flow velocity) are also raising the RRI and are thus confounding factors in the correct interpretation (Bossard et al., 2011). The measurement of the parameter is also operator dependent.

Intravenous urography and computed tomography scan

Intravenous urography is nowadays largely abandoned in patients with AKI given the need for potentially nephrotoxic contrast media. A plain radiograph of the abdomen is a mandatory investigation in any patient in whom an obstructive cause of AKI is suspected since it can detect even small radio-opaque stones and ureteral stones, not found by US. The presence and site of obstruction is accurately diagnosed by antegrade or retrograde pyelography. A computed tomography (CT) scan performed without contrast is of comparable diagnostic value to the RUS but is more costly and less convenient while it submits the patient to more irradiation. However, CT is superior in the evaluation of ureteral obstruction, since it can delineate the level of obstruction and define retroperitoneal inflammatory tissue (in retroperitoneal fibrosis) or a retroperitoneal malignant mass.

Magnetic resonance imaging

Magnetic resonance imaging (MRI) is usually not applied for evaluation of AKI. An altered corticomedullary relationship is frequently recognized on T-weighted images in patients with AKI but also in other acute renal diseases. When postrenal AKI is suspected, MRI is valuable in assessing HN and detecting the cause and site of obstruction. MR angiography can be useful for detecting abnormalities in the renal artery and vein. The diagnosis of acute renal cortical necrosis in particular becomes more reliable with gadolinium-enhanced MRI. The 'rim sign' is characteristic for this infrequent cause of AKI. In view of the increasingly reported incidence of the syndrome of nephrogenic systemic fibrosis in patients who have been exposed to gadolinium-containing contrast media, and since such cases have also been described in patients with AKI, it is not recommended to use gadolinium-containing compounds unless unavoidable, in patients with a GFR < 30–40 mL/min.

If with any of the above discussed imaging techniques obstruction is present, a ureteral stent or percutaneous nephrostomy can be placed in the same session.

Renal angiography

Renal angiography can be indicated when renal artery occlusion (by embolization, thrombosis, or a dissecting aneurysm) is suspected based on the clinical history (e.g. in patients with atrial fibrillation and acute flank pain) or on duplex scanning. In this setting, MR angiography or spiral CT is superior. Hepatic or renal angiography may also be useful in diagnosing polyarteritis nodosa, by the detection of vascular aneurysms.

Although Doppler ultrasound, MRI, MR angiography, and CT are used more frequently in the evaluation of thromboembolic disease and acute cortical necrosis, renal venography may be indicated to confirm a clinical or duplex ultrasound suspicion of renal vein thrombosis.

When a diagnosis of acute renal artery occlusion is considered, renal angiography should be obtained urgently, as early surgical or thrombolytic therapy may be necessary to salvage the kidney. However, where the complete occlusion occurs in a background of chronic occlusive disease, sufficient collateral blood supply may be provided and even delayed intervention can result in recovery of renal function.

Nuclear imaging in AKI

The functional assessment of the kidney by nuclear medicine procedures is based on the use of radioisotopes bound to non-metabolized molecules with known pharmacokinetics. Renal scintigraphy is usually applied for the assessment of renal function expressed as

GFR, effective renal plasma flow, or more generally kidney perfusion. Newer methods rely on positron emission tomography (PET), which allows the generation of images with higher resolution and absolute quantitation of biological processes such as transport activities, enzyme activities, or angiotensin receptors (Haufe et al., 2006). Study of renal blood flow using ^{99m}Tc-MAG3 scan may be helpful in the setting of AKI, but is not widely used. While the renal uptake in the first 1–2 minutes is normal in 'transient' AKI, it is expected to be reduced in vascular and parenchymal diseases and in ATN (Kalantarinia, 2009). After 20 minutes, the uptake is increased in cases of 'transient' AKI, vascular disease, and ATN and is expected to be reduced in obstructive uropathy and parenchymal renal disease. Excretion of the radioisotope is reduced in AKI irrespective of the cause. Radioisotope investigations are thus not very useful in the differential diagnosis of AKI.

PET provides significantly better spatial resolution than conventional scintigraphy and has in addition the capacity to provide data on the function and molecular composition of an organ. Combination of PET and CT scanning provides an opportunity to combine functional and quantitative data with anatomical and spatial information enabling better localization of lesions. Tracers used for PET scans are either limited to the tissue such as Rb-82, N-13 and Cu-62 PTSM (category II) or can freely diffuse between the blood pool and the tissue, like O-15 (category I). Potential clinical uses for PET scans in the future are based on the results of few studies of kidney imaging including determination of renal blood flow and GFR, diagnosis of renal artery stenosis, determination of the function of tubular peptide, cation and anion transporters, tissue activity of enzymes such as angiotensin-converting enzyme, and regulation of receptors such as angiotensin type 1 receptors within the kidney. In particular, the changes in expression of molecules such as reactive oxygen species that control cell response and repair after injury in the setting of AKI could potentially be determined by PET scanning (Szabo et al., 2006, 2008).

Kidney biopsy

If after careful evaluation the cause of AKI is not clear, kidney biopsy should be considered, especially in patients in whom 'transient' AKI and obstructive causes of AKI have been excluded and the cause of intrinsic renal AKI is unclear. Kidney biopsy is particularly useful when clinical assessment, urinalysis, and laboratory investigation suggest diagnoses that may respond to specific therapy, for example, rapidly progressive glomerulonephritis, vasculitis, and allergic interstitial nephritis. Kidney biopsy should also be considered in AKI when there are symptoms or signs of a systemic illness, such as persistent fever or unexplained anaemia.

Unexpected causes of AKI, such as myeloma, interstitial nephritis, endocarditis or cryoglobulinaemia, or cholesterol emboli may be revealed by kidney biopsy. In almost one-third of elderly patients aged > 80 years (33%) who presented with AKI, pauci-immune glomerulonephritis was found. Myeloma cast nephropathy was the second most common finding within the AKI group but at a much lower incidence (8%). When nephrotic syndrome accompanied AKI, the most common diagnosis was minimal change disease, which was seen in one-quarter of these patients (Stillman et al., 2008; Moutzouris et al., 2009).

In patients diagnosed with AKI and normal-sized kidneys, who do not recover kidney function after 3–4 weeks, a kidney biopsy may be indicated to confirm the cause of AKI, to exclude other treatable causes, and determine the prognosis. Finally, kidney biopsy is a routine diagnostic procedure in patients with AKI after transplantation when it is often essential for distinguishing between ischaemic AKI, acute rejection, and calcineurin inhibitor toxicity.

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CHAPTER 223

The role of novel biomarkers in acute kidney injury

Norbert Lameire

Introduction

As mentioned in Chapter 222, many basic and clinical research efforts have been directed at the discovery and validation of novel acute kidney injury (AKI) biomarkers to detect kidney injury prior to the detection of changes in kidney function, to potentially aid in the differential diagnosis of AKI and to predict the need for renal replacement therapy (RRT) and the short- and long-term prognosis of the patient with AKI. The development of AKI biomarkers is a top research priority by the American Society of Nephrology (Kellum et al., 2008). A recent report from the 10th Acute Dialysis Quality Initiative (ADQI) expert workgroup summarizes the most recent consensus obtained on biomarkers (Murray et al., 2014).

Based on studies in experimental models and in human AKI, a number of biomarkers have been proposed: cystatin C, soluble tumour necrosis factor (TNF) receptors, *N*-acetyl-beta-D-glucosaminidase, kidney injury molecule 1(KIM-1), isoform 3 of the sodium-hydrogen exchanger, interleukin (IL)-16, IL-18, matrix metalloproteinase 9, liver-type fatty acid binding protein (L-FABP), and neutrophil gelatinase-associated lipocalin (NGAL) (Molitoris et al., 2008; Vaidya et al., 2008a, 2008b; Waikar and Bonventre, 2008; Yalavarthy and Edelstein, 2008; Ho and Lucy, 2009; Pickering and Endre, 2009; Rosner, 2009; Soni et al., 2009; Bouman et al., 2010; McIlroy et al., 2010; Moore et al., 2010; Devarajan 2011; Shemin and Dworkin, 2011). These molecules have ranged from constitutive proteins released by the damaged kidney to molecules upregulated in response to injury or non-renal tissue products that are filtered, reabsorbed, or secreted by the kidney (Bonventre et al., 2010). These biomarkers also include proteins or encapsulated molecules in exosomes and more recently microRNAs (Chawla and Kellum, 2012).

The majority of investigations have focused on the ability of biomarkers to detect early either incipient or established AKI. Other studies have prospectively explored their prognostic performance in predicting either need for RRT or intensive care unit (ICU) or hospital mortality or duration of either ICU or hospital stay. A few studies have also investigated their potential in the differential diagnosis between 'transient AKI', 'prerenal AKI', and established intrinsic AKI, mostly acute tubular necrosis (ATN).

An ideal AKI biomarker should be accurate, reliable, easy to measure with a standard assay, non-invasive, reproducible, and sensitive and specific with defined cut-off values (Nguyen and Devarajan, 2008). Urine represents an ideal body fluid for AKI biomarker assessment as it can be obtained non-invasively and repeatedly from a spontaneously voided sample or from an indwelling bladder catheter. The road to AKI biomarker validation spans discovery in pre-clinical studies from bodily fluids, assay development, retrospective study of completed trials and then prospective screening in ongoing trials (Nguyen and Devarajan, 2008). These phases must be completed before a biomarker can be used broadly in clinical practice.

Besides the analytical problems associated with each individual biomarker (for details, see Chapter 7), use of the serum creatinine (SCr) as the gold standard in the evaluation of any novel biomarker is additionally problematic. As pointed out by Waikar et al. (2009), many biomarker studies begin by reciting SCr's imperfections as a biomarker and then judge the performance of the biomarker under study against the same 'gold standard' whose imperfections engendered the need to discover a novel and hopefully superior biomarker! Later on, Waikar et al. (2012) demonstrated that even if a novel tubular injury biomarker would be 100% sensitive and 100% specific, it may appear inaccurate when using SCr as the gold standard. AKI, as defined by SCr may not reflect tubular injury, and the absence of changes in SCr does not assure the absence of tubular injury. In general, the apparent diagnostic performance of a biomarker depends not only on its ability to detect injury, but also on disease prevalence and the sensitivity and specificity of the imperfect gold standard. Assuming that, at a certain cut-off value, SCr is 80% sensitive and 90% specific and disease prevalence is only 10%, a new perfect biomarker with a true 100% sensitivity may seem to have only 47% sensitivity compared with SCr as the gold standard. Minimizing misclassification by using more strict criteria to diagnose AKI will reduce the error when evaluating the performance of a biomarker under investigation. Apparent diagnostic errors using a new biomarker may thus be more a reflection of errors in the imperfect gold standard itself, rather than poor performance of the biomarker. The results of this study suggest that small changes in SCr alone should not be used to define AKI in biomarker or interventional studies. The real gold standard for the AKI biomarkers would be to prove that they can be used to define and risk stratify AKI and related complications, and facilitate early diagnosis and interventions that improve clinical outcomes. If novel AKI biomarkers can be proved superior for these conditions and if they are cost-effective, then they may even replace SCr changes and urine output as the primary clinical tools to diagnose AKI and monitor response to therapy (Murray et al., 2008). Nevertheless, the currently available literature does not suggest that such a 'magic bullet' has been found yet.

During the development of AKI, a number of causes result in biomarkers accumulating in plasma and urine, representing different pathophysiological events during the process of kidney injury and repair (for review, see Martensson et al., 2012). Biomarkers accumulate in urine due to an induced tubular epithelial synthesis in different parts of the nephron (NGAL, IL-18, NAG, KIM-1) and as an effect of impaired reabsorption of the filtered load in the proximal tubule (NGAL, cystatin C). Secretion of biomarkers from activated immune cells migrating into the tubular lumen may also be a source (NGAL, IL-18). Finally, increased synthesis of some biomarkers in extrarenal tissues and immune cells and their secretion into the bloodstream have been shown in animal AKI models (NGAL, IL-18) (Grigoryev et al., 2008). This extrarenal production can increase in response to systemic inflammation, for example, during sepsis and after major surgery or trauma, even in the absence of AKI. This must be taken into account when elevated biomarker levels are evaluated particularly in critically ill and postoperative patients.

Relevant to these considerations are recent findings where in an experimental model of unilateral ischaemic kidney injury, urinary NGAL excretion rate was increased more in the urine coming from the healthy than from the ischaemic kidney (Pedersen et al., 2012). These findings suggest that glomerular filtration of increased plasma NGAL and/or functional changes in the healthy kidney (inflammation?) is an important determinant of urinary NGAL, at least in this model. Increased urinary NGAL levels may thus reflect both increased renal expression as well as increased filtration of NGAL, whether from renal or extrarenal sources, and/or changes in tubular reabsorptive function.

In contrast to conventional markers, such as SCr, blood urea nitrogen (BUN), or serum cystatin C, these novel markers do not reflect kidney function, but instead could signify structural damage to kidney cells. Consequently, these markers are rapidly detectable in response to injury and their increased levels should be independent of a functional deficit. Conversely, a purely functional drop of glomerular filtration rate, as is the case in pure 'transient' or prerenal AKI is not expected to result in an upregulation of these markers. Novel biomarkers to identify subgroups of patients with and without kidney injury could thus theoretically be useful additional criteria for AKI classification.

Neutrophil gelatinase-associated lipocalin

NGAL, also known as human neutrophil lipocalin or lipocalin 2, was first identified as a 25 kDa protein in the secondary granules of human neutrophils (Kjeldsen et al., 1993; Xu et al., 1994). NGAL is released into the bloodstream in response to bacterial infection. Later, NGAL was localized in a number of human tissues, including trachea, lung, stomach, colon, and kidney (Cowland and Borregaard, 1997). NGAL secretion from epithelial cells is induced by several pathological conditions (Xu and Venge, 2000; Cowland et al., 2003). In the search for novel biomarkers of AKI, NGAL was identified as the most rapidly induced protein in murine models of ischaemic and nephrotoxic AKI (Mishra et al., 2003). Concentrations increased several-fold in both serum and urine within hours of the insult. This serendipitous finding shifted the focus on NGAL from a marker of bacterial infection to an early signal for AKI.

Evidence of the biological role of NGAL in different pathological states has recently emerged. By its ability to bind siderophores (small iron-binding molecules) produced by eukaryotic cells, NGAL is involved in iron transport to and from cells. NGAL assists in the delivery of iron to kidney tubular cells and may be involved in the injury-repair process of AKI by inducing differentiation of renal progenitor cells into epithelial tubules (Yang et al., 2002; Mori et al., 2005). Using an NGAL reporter mouse, the NGAL al-Luc2-mC reporter responds to signals that illuminate sites of injury (NGAL expression) *in vivo* and in real time. Following experimental ischaemia-reperfusion as evidenced by a rise in creatinine, the kidneys illuminate indicating NGAL production at the site of injury. By contrast, following manoeuvres that lead to significant prerenal disease associated with hypernatraemia and a rise in SCr, no NGAL illumination occurred, indicating that prerenal disease does not induce NGAL expression, at least in this model. Thus NGAL may potentially be useful in differentiating prerenal disease from intrinsic ATN (Paragas et al., 2011).

A word of caution is needed: as summarized in a review (Martensson et al., 2012) studies have used different platforms for NGAL quantification including Western blotting, radioimmunoassay, enzyme-linked immunosorbent assay, and Triage® device. The antibody configuration has an impact on the clinical performance of the assay and this may explain some of the variability in the results for NGAL as an AKI predictor.

A study (Schinstock et al., 2013) prospectively collected random and 24-hour urine samples from 125 normal volunteers for analytic validation of a urinary enzyme-linked immunosorbent assay for NGAL. For clinical validation of the test, urine from 363 emergency department patients admitted to the hospital was obtained for routine analysis and for NGAL measurement with the same assay and AKI was determined by the use of the AKIN criteria. The results show that NGAL was stable in urine for 7 days when ambient, 4°C, or frozen (−20 or −70°C). The assay was linear between 0.24 and 10,000 ng/mL with a limit of quantitation of 0.24 ng/mL. Intra- and inter-assay precision were excellent; however, urinary white blood cells were associated with increased NGAL levels. The 95th percentile reference value for NGAL in females is ≤ 65.0 and ≤ 23.4 ng/mL in males. Urinary NGAL levels increased with AKI stage but had only fair sensitivity (65%) and specificity (65%) to differentiate no AKI versus Stages 1, 2, or 3 (area under the curve (AUC) 0.70). For the diagnosis of AKI, microscopic analysis was very specific (91%) but not very sensitive (22%) (AUC only 0.57).

NGAL can thus reliably be measured in clinical urine samples, although pyuria is an important potential confounder.

It is now known that different forms of NGAL are secreted by kidney epithelial cells (mainly monomeric NGAL) and neutrophils (mainly dimeric NGAL), respectively (Cai et al., 2010). Monomer-specific assays may improve the early detection of renal cell injury and avoid the confounding effect of leucocyturia (Decavele et al., 2011).

NGAL as predictor of AKI, of need for renal replacement therapy, and of prognosis

The first clinical study evaluating NGAL as an AKI predictor was in children at risk of AKI after cardiopulmonary bypass (CPB). Urinary NGAL increased almost 100-fold and serum NGAL 20-fold within 2 hours post-CPB in children who later (24–48

hours) developed AKI (Mishra et al., 2005). The area under the receiver-operating characteristic curve (AUROC) using the 2-hour urinary NGAL concentration for AKI prediction was almost perfect (0.998). These promising results were confirmed in a second study after cardiac surgery in children (Bennett et al., 2008). In this study, for the 2-hour urine NGAL measurement, the AUROC was 0.95, sensitivity was 0.82, and the specificity was 0.90 for prediction of AKI using a cut-off value of 100 ng/mL. The 2-hour urine NGAL levels correlated with severity and duration of AKI, length of stay, dialysis requirement, and death.

Since these initial impressive results, the predictive and prognostic performances of NGAL have been tested in children and adults in various clinical settings, including cardiac surgery, contrast procedures, intensive care and emergency departments, and transplantation units. In contrast with the results in children, studies in adult patients after cardiac surgery show AUC values for AKI prediction ranging from 0.50 to 0.98 within 48 hours up to 10 days (for review, see Martensson et al., 2012).

Somewhat conflicting results on the performance of serum and urinary NGAL for the early prediction of AKI and the need for RRT were obtained in unselected critically ill ICU patients. In the study by Royakkers et al. (2012) both serum and urinary NGAL were poor predictors of AKI or RRT while plasma NGAL was a good diagnostic marker for AKI development within the next 48 h after admission and for RRT use in the study by Cruz et al. (2010). In the latter population peak plasma NGAL concentrations increased with worsening AKI severity.

A systematic review and meta-analysis of the diagnostic and prognostic value of NGAL in AKI examined data from 19 studies and eight countries involving 2538 patients, of whom 19.2% developed AKI (Haase et al., 2009). Overall, AUC of NGAL to predict AKI was 0.815 (cardiac surgery patients: 0.775; critically ill patients: 0.728; after contrast infusion: 0.894). The diagnostic accuracy of blood NGAL (AUC 0.775) was similar to that of urine NGAL (AUC 0.837). NGAL had better predictive value in children (AUC 0.930) compared with adults (AUC 0.782). It was useful in predicting both RRT (AUC 0.782) and in-hospital mortality (AUC 0.706).

Koyner et al. (2012) used samples from the Translational Research Investigating Biomarker Endpoints in AKI study (TRIBE-AKI), to evaluate whether kidney injury biomarkers measured at the time of first clinical diagnosis of early AKI after cardiac surgery can forecast AKI severity. Biomarkers included urinary IL-18, urinary albumin to creatinine ratio (ACR), and urinary and plasma NGAL. The primary endpoint (progression of AKI defined by worsening AKIN stage) occurred in 45 (11.8%) patients. After adjustment for clinical predictors, compared with biomarker values in the lowest two quintiles, the highest quintiles of three biomarkers remained associated with AKI progression: IL-18 (odds ratio (OR) 3.0; 95% confidence interval (CI) 1.3–7.3), ACR (OR 3.4; 95% CI 0.3–9.1), and plasma NGAL (OR 7.7; 95% CI 2.6–22.5). Each biomarker improved risk classification compared with the clinical model alone, with plasma NGAL performing the best. This study suggests thus that biomarkers measured on the day of AKI diagnosis improve the risk stratification and identify patients at higher risk for progression of AKI and worse patient outcomes.

A comprehensive review of the role of NGAL and other biomarkers in the diagnosis and management of the cardiorenal syndromes, including AKI post cardiac surgery, contrast-induced AKI, and AKI in heart failure is available (Cruz et al., 2012).

Additional general reviews on the potential role of biomarkers in the early detection and prognosis of AKI are available (Ho et al., 2010; Moore and Bellomo 2010; Moore et al., 2010; Belcher et al., 2011; Haase et al., 2011; Siew et al., 2011; Sirota et al., 2011; de Geus et al., 2012) and the reader should consult these reviews for more detailed information.

NGAL in the differential diagnosis of AKI between prerenal, transient, and established AKI

Several biomarkers, such as urinary IL-18, NGAL, and KIM-1, are specific to the kidney and are only released when necrosis or apoptosis of the proximal tubular cells occurs. Some studies have demonstrated that the new biomarkers, including NGAL, are markedly elevated in patients with ATN compared with patients with 'transient' AKI (Coca et al., 2008; Parikh et al., 2010). Taking some of the caveats outlined above into account, if the biomarkers used are specific to kidney tubules, then situations in which SCr levels are increased but levels of biomarkers are not elevated might represent 'transient', almost exclusively, functional AKI. By contrast, AKI episodes in which levels of both biomarkers and SCr are increased would indicate cases of ATN or structural AKI (see Fig. 223.1). The addition of these novel urinary biomarkers to AKI classifications might therefore represent a novel paradigm that could align and improve the clinical practice and clinical research of AKI (Parikh and Coca, 2010).

A single measurement of urinary NGAL was performed in 635 patients admitted to the emergency room to detect and differentiate several forms of AKI: transient AKI, established AKI, chronic kidney disease (CKD), or normal kidney function. Patients with established AKI had a significantly elevated mean urinary NGAL level compared with the other kidney function groups (Nickolas et al., 2008). Whereas the AUC for NGAL (0.948) for predicting established AKI did not significantly differ from that for SCr (0.921), at either of two cut-off values (> 85 micrograms/g creatinine or > 130 micrograms/g creatinine), a positive urinary NGAL level had a stronger correlation with established AKI than levels of SCr or other biomarkers. There remained, however, a disturbing overlap in

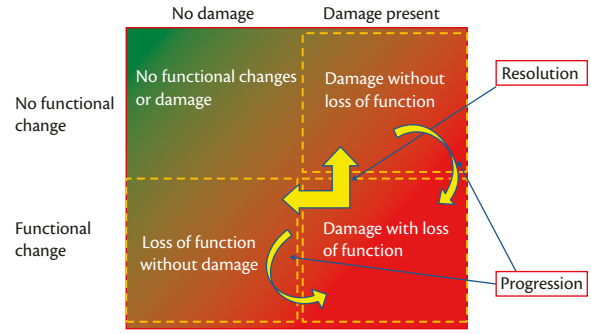

Fig. 223.1 A combination of kidney functional and damage markers simultaneously could provide a simple method to stratify patients with AKI. At initial presentation, patients would be evaluated in terms of these two domains, and then could be assessed over time to monitor their transitions across the domains.
From Murray et al. (2013).

NGAL values between patients with established AKI and 'transient' AKI, but the overlap of the SCr values was more substantial.

Singer et al. (2011) also investigated urinary NGAL to discriminate 'transient' from 'intrinsic' AKI. Urine NGAL was measured in 145 hospitalized patients with elevated SCr levels who met the RIFLE (Risk, Injury, Failure, Loss, and End-stage renal disease) criteria for AKI. Samples were collected at enrolment and 2 days later and patients were followed through their hospital course to ascertain whether they met a composite outcome of death, dialysis, or progression of RIFLE class. Two clinicians reviewed the clinical data and determined whether the patients had 'pre-renal' (or 'transient') AKI (22.1%), intrinsic AKI (51.7%), or were unclassifiable (26.2%). Urine NGAL levels at thresholds > 104 micrograms/L and < 47 micrograms/L identified patients who had intrinsic and 'transient' AKI, respectively, with an overall AUC-ROC of 0.87 and a high specificity and predictive value for meeting a composite outcome when the levels were > 104 micrograms/L. Higher NGAL levels were associated with a greater probability of reaching the composite outcome. However, a major caveat needs to be considered before looking too optimistically at these data (Mehta 2011). The authors (Singer et al., 2011) enrolled patients who all had AKI; however, on adjudication by two experienced clinicians, 26.2% of the patients were labelled as unclassifiable, as their clinical and laboratory measurements did not conform to 'transient' or established AKI criteria. The 'unclassifiable' patients had comorbidities and clinical and laboratory parameters similar to those of the other enrolled patients. While NGAL levels generally tracked the 'transient' and AKI groups, there was considerable overlap of NGAL values in the unclassified group and the NGAL levels did not result in any improvement in classification based on the established thresholds. The incremental value of adding NGAL to creatinine-based logistic regression model only marginally improved the diagnostic accuracy for a composite outcome, from 68.3% to 74.5%. The inability of NGAL to improve the net re-classification of the unclassifiable patients, in whom it would have the most value, highlights the several gaps still present in our knowledge.

The ability of NGAL and CysC in plasma and urine to discriminate between sustained, 'transient', and absent AK, was also prospectively evaluated in a cohort study of ICU patients with normal kidney function on admission (de Geus et al., 2011). Urine NGAL (uNGAL) was the only biomarker significantly differentiating 'sustained' from 'transient AKI' on ICU admission and, individually, uNGAL performed better for the prediction of sustained AKI than the other biomarkers (AUROC = 0.80, 95% CI = 0.72–0.88). The combination of individual markers with a model of clinical characteristics (including MDRD eGFR, bicarbonate levels, and presence of sepsis) did not significantly improve its performance. These results are promising but have been obtained in a very selective population with normal kidney function at admission in the ICU; it is also to be underlined that the clinical characteristics of these patients alone were also able to predict accurately the distinction between sustained and 'transient' AKI.

Nejat et al. (2012) defined prerenal AKI in critically ill patients when the AKI recovered within 48 hours and when the fractional excretion of sodium (FE_{Na}) was < 1%. Urinary biomarker concentrations significantly and progressively increased with the duration of AKI and this increase of at least some biomarkers (KIM-1, cystatin C, and IL-18, but not NGAL and gamma-glutamyl transpeptidase) remained significant in the prerenal group compared with no-AKI patients. The reason why some but not all biomarkers were increased in prerenal AKI is unknown but these results at least could suggest that pre-renal AKI represents a milder form of 'structural' tubular injury. These results were partly confirmed by Doi et al. (2012) who evaluated urinary biomarker levels in an adult mixed ICU cohort of patients with acute prerenal AKI. A number of urinary biomarkers, including NGAL and L-FABP, showed modest but significantly higher urinary concentrations in the 'prerenal' patients than in patients with non-AKI. Besides serum and urine NGAL, some other biomarkers that have been investigated as tools to distinguish between 'transient' and established AKI include urine Na^+/H^+ exchanger isoform 3 (NHE3), and serum and urine cystatin C (du Cheyron et al., 2003; Nickolas et al., 2008; Soto et al., 2010; de Geus et al., 2011; Singer et al., 2011). More recently, urinary calprotectin, a mediator protein of the innate immune system, was found to be quite accurate in the differential diagnosis of AKI (Heller et al., 2011). The median urinary calprotectin was 60.7 times higher in intrinsic AKI (1692 ng/mL) than in prerenal AKI (28 ng/mL, $P < 0.01$), while its concentration in 'prerenal' disease was not significantly different from healthy controls. As mentioned above, the classification of the patients as 'prerenal' or 'renal' was in this study based on predefined clinical and laboratory criteria such as 'rapid response of renal function to volume repletion'. The caveats of these criteria have been discussed above and should be kept in mind in the interpretation of these results.

NGAL as parameter of subclinical AKI?

Some authors (Haase et al., 2012), suggest that incorporation of tubular damage biomarkers into the diagnostic criteria for AKI could lead to the creation of a new category of AKI diagnosed by elevations of tubular damage biomarkers alone, which might or might not evolve into a clinically manifest syndrome characterized by a rise in SCr levels and a decrease in GFR. This condition should be termed 'subclinical AKI', because it is below clinical detection thresholds using the existing methods.

This concept of 'subclinical AKI' is largely based on an analysis of pooled data of serum and urinary NGAL levels from critically ill patients suffering predominantly cardiorenal syndrome (Haase et al., 2011). This analysis used the terms NGAL(−) or NGAL(+) according to study-specific NGAL cut-off values for optimal AKI prediction and the terms SCr(−) or SCr(+) according to consensus diagnostic increases in SCr defining AKI. A priori-defined outcomes included need for RRT, hospital mortality, their combination, and duration of stay in ICU and in hospital. According to the four study groups, there was a stepwise increase in subsequent RRT initiation in the NGAL(−)/SCr(−) group versus NGAL(+)/SCr(−), versus the NGAL(−)/sCREA(+), and the NGAL(+)/sCREA(+) groups. A similar stepwise increase in hospital mortality and a similar and consistent progressive increase in median number of ICU and in-hospital days was observed with increasing biomarker positivity. Urine and plasma NGAL indicated a similar outcome pattern. This study at least suggests that NGAL levels detect patients suffering from 'subclinical AKI' who have an increased risk of adverse outcomes. Patients without increased SCr levels currently have very low rates of referral for nephrological consultation and improved recognition of subclinical AKI as an important disease entity might be expected to increase rates of subspecialty consultation (with nephrology and/or critical care specialists) for patients

in this category. This earlier referral could hopefully improve patient outcomes by allowing more careful avoidance of nephrotoxins, appropriate modification of drug dosing, further attention to fluid status, and possibly therapeutic interventions that have thus far failed to show benefit may be due to late detection through creatinine-based monitoring. In particular, toxin-mediated AKI might be amenable to biomarker detection given the direct tubular injury imparted by various nephrotoxins (Sirota et al., 2011).

For the time being, it is not possible to firmly establish the role of these biomarkers in early management of the patient with AKI, beyond the routine clinical and biochemical evaluation and management of these patients.

Kidney injury molecule 1

KIM-1, a type 1 transmembrane protein with an immunoglobulin and mucin domain, is specific to the kidney and expressed at a low level in normal tissue. Following experimental renal ischaemic injury, it is dramatically upregulated when necrosis or apoptosis in the proximal tubule occurs, and KIM-1 and its soluble ectodomain in urine (90 kDa) are believed to play a role in the regeneration processes after epithelial injury (Bonventre, 2009). The use of KIM-1 as a biomarker of AKI in humans was suggested in a 2002 study where in seven patients with ischaemic ATN, mean KIM-1 levels were significantly higher than in 16 patients with other forms of AKI (Han et al., 2002). In adult patients with post-cardiac surgery AKI, a ROC curve for urinary KIM-1 drawn immediately after surgery had an AUC of 0.68, which was better than the value for NGAL (Han et al., 2009). This study also demonstrated that combining multiple AKI biomarkers improved the overall predictive value. In hospitalized patients with AKI a correlation between urinary KIM-1 levels and Acute Physiologic and Chronic Health Evaluation (APACHE) II scores was demonstrated; in addition, KIM-1 quartiles were shown to correlate with dialysis requirement and hospital mortality (Liangos et al., 2007). In children admitted in the emergency department, KIM-1 levels had an AUROC to predict AKI (paediatric RIFLE criteria I) of 0.73 (Du et al., 2011).

In renal transplantation, urinary KIM-1 levels were correlated with the rate of graft functional decline. In addition, separating the patients into low and high KIM-1 groups, graft survival was significantly worse in the group with high KIM-1 expression (Szeto et al., 2010).

Na^+/H^+ exchanger isoform 3

Urinary levels of this protein, the most abundant apical sodium transporter in the renal tubule, were estimated from semiquantitative immunoblots of urine membrane fraction samples collected from ICU patients and compared with the FE_{Na} and urinary retinol-binding protein (RBP) (du Cheyron et al., 2003). NHE3 was not detected in urine from controls but levels of urinary NHE3 normalized to urinary creatinine level were increased in patients with 'transient' AKI and six times as much in patients with ATN, without overlap. Conversely, urinary NHE3 protein was not detected in patients with intrinsic AKI other than ATN. Normalized NHE3 level correlated positively with SCr level in patients with tubular injury. Values for FE_{Na} and normalized urinary RBP did not discriminate ATN from intrinsic AKI other than ATN and 'transient' AKI, respectively.

Cystatin C

Cystatin C, a 122-amino acid, low-molecular-weight protein is a member of the cysteine proteinase inhibitors and is produced at a constant rate by all nucleated cells. It is freely filtered by the glomerulus, reabsorbed and catabolized, but not secreted by the renal tubules (Laterza et al., 2002). Unlike creatinine, serum cystatin C concentration appears to be independent of age, sex, and muscle mass (Filler et al., 2005).

Cystatin C has been reported to rise faster than sCr after a fall in GFR, enabling earlier identification of AKI (Herget-Rosenthal et al., 2004; Nejat et al., 2010).

Human studies on urinary cystatin C have shown promise as a biomarker of AKI, with cystatin C levels assayed by ELISA. In adult cardiac surgery, urinary cystatin C had AUCs of 0.705 for the immediate postoperative time point and 0.704 for the 6-hour postoperative time point (Koyner et al., 2008). Within 3 days of surgery, the ratio of urinary cystatin C to urine creatinine ratios had increased > 20-fold in patients with AKI, compared to a fivefold increase in non-AKI patients. In an ICU population, urinary cystatin C had an AUC of 0.70 for the diagnosis of AKI and was independently associated with sepsis, AKI, and death (Nejat, 2010). In 91 patients who received deceased donor kidney transplants, urinary cystatin C could predict delayed graft function (AUC of 0.74 for the 6-hour urine cystatin C:creatinine ratio). In addition, the urine cystatin C:creatinine ratio on the first postoperative day was significantly associated with 3-month graft function (Hall et al., 2011).

Soto et al. (2010) examined the discriminative and predictive abilities of serum and urinary cystatin C for the prediction of AKI in a prospective cohort study of a heterogenous group of patients who presented to an emergency department. Both serum cystatin C (sCysC) and sCr were similarly useful for the early diagnosis of AKI: the AUC-ROC was > 0.86 for sCysC and > 0.88 for sCr at all five study points, indicating excellent discriminatory ability for the overall early diagnosis of AKI. There were no differences between the ROC curves for sCysC and sCr at the critical first two time points of the study, (initial patient presentation and 6 hours thereafter, respectively). However, only sCysC attained a significant early predictive power. SCysC could differentiate between AKI and 'prerenal AKI', but not between AKI and CKD. These sobering results suggest that sCysC has no real advantage over sCr for the early diagnosis or differential diagnosis of AKI in the emergency department setting.

Interleukin 18

Like NGAL, IL-18 plays a role in the immune system and is a proinflammatory cytokine of 18 kDa. Animal studies have demonstrated that IL-18 is also a mediator of ischaemic injury in the heart, brain, and kidney and have confirmed that IL-18 plays a key role in ischaemic AKI (for summary, see Sirota et al., 2011).

A first study of its role as biomarker in human AKI, measured urinary IL-18 levels in 72 patients with several forms of acute and chronic renal diseases, patients with a renal transplant, and healthy controls (Parikh et al., 2004). Among the non-transplant patients, those with ATN had significantly higher IL-18 levels than all others. In addition, transplant recipients who developed delayed graft function had significantly higher urine IL-18 levels than those with prompt graft function.

In critically ill patients, the median urine IL-18 was 104 pg/mL at 24 hours in the AKI group versus 0 pg/mL in the group without AKI (Parikh et al., 2005). IL-18 was found to be significantly elevated up to 48 hours before the creatinine-defined occurrence of AKI and IL-18 levels were found to be an independent predictor of death. A study in the critical care setting found a modest AUC of IL-18 for predicting AKI (only 0.62) but elevated urinary IL-18 was independently predictive of a composite outcome of death or acute dialysis within 28 days (OR 1.86) (Siew et al., 2010).

Also in paediatric patients, urine IL-18 levels rose prior to the rise in creatinine in patients with AKI, and elevated levels were independently associated with mortality. Further, the degree of urine IL-18 elevation predicted the severity of AKI (Washburn et al., 2008).

Based on data of the Translational Research Investigating Biomarker Endpoints for Acute Kidney Injury (TRIBE-AKI) study in both paediatric and adult post-cardiac surgery AKI patients, the highest quintiles of urine IL-18 and urine NGAL were strongly associated with AKI risk and elevated urinary biomarkers were associated with longer ICU stay, longer hospitalization, and longer mechanical ventilation. The AUCs for the urine IL-18 ROC curve and the urine NGAL ROC curve were 0.72 and 0.71, respectively in the paediatric group (Parikh et al., 2011). In the adult patients, urine IL-18 and NGAL as well as plasma NGAL measured prior to surgery and for 5 postoperative days showed in multivariate analysis that the highest quintiles of urine IL-18 and plasma NGAL at 6 hours were strongly associated with risk of AKI.

A comparative study of 32 candidate biomarkers in the urine of 95 patients with AKIN stage 1 after cardiac surgery to predict the primary outcome of worsening AKI or death found that IL-18 was the best predictor of both outcomes (AUC of 0.74 and 0.89). L-FABP (AUC of 0.67 and 0.85), NGAL (AUC of 0.72 and 0.83), and KIM-1 (AUC of 0.73 and 0.81) were also good predictors (Arthur et al., 2014) (see below).

Liver-type fatty acid binding protein

L-FABP is expressed in various organs, including liver and kidneys (Noiri et al., 2009). Its function in the kidney is presumed to be the same as that in the liver: cellular uptake of fatty acids from plasma and promotion of intracellular fatty acid metabolism. Through this mechanism, L-FABP may inhibit the accumulation of intracellular FAs, thereby preventing their oxidation (Kamijo-Ikemori et al., 2006). Renal L-FABP may help maintain low levels of free fatty acids in the cytoplasm by facilitating their intracellular metabolism and their excretion in urine. Urine L-FABP appears to be a more sensitive predictor of AKI than SCr and could serve as a clinical predictor of contrast-induced nephropathy (Nakamura et al., 2006). In patients who developed AKI after cardiac surgery univariate logistic regression analyses showed that both bypass time and urinary L-FABP were significant independent risk indicators for AKI. After excluding bypass time from the model urinary L-FABP levels at 4 hours after surgery were an independent risk indicator with an AROC curve of 0.810, sensitivity 0.714, and specificity 0.684 for a 24-fold increase in urinary L-FABP (Portilla et al., 2008). Furthermore, higher urine L-FABP levels differentiated patients with septic shock from those with severe sepsis, AKI, and from healthy controls (Nakamura et al., 2009). Urine L-FABP shows promise as an early accurate biomarker of AKI; however, it appears to rise later than NGAL. The predictive ability of L-FABP for AKI requires further clinical confirmation in different patient populations.

It is widely acknowledged that a single biomarker may be unable to diagnose all aspects of a complex multifactorial process such as AKI, and that a panel of biomarkers may be necessary. Capillary electrophoresis-mass spectrometry was recently used to identify urinary peptides predictive of AKI and a sequence of 20 peptides was significantly associated with AKI. A good diagnostic performance of the marker pattern was found with an AUROC curve of 0.91 and, in comparison to other markers of AKI, discussed in this chapter, the proteomic marker pattern was found to be of superior prognostic value, detecting AKI up to 5 days in advance of the rise in SCr (Metzger et al., 2010).

Since a systematic comparison of the prognostic ability of each biomarker alone or in combination has not been performed, Arthur et al. (2014) recently assessed such a comparison by measuring the concentration of 32 candidate biomarkers in the urine of 95 patients with AKIN stage 1 after cardiac surgery. Urine markers were divided into eight groups based on the putative pathophysiological mechanism they reflect. The ability of the markers alone or in combination to predict the primary outcome of worsening AKI or death and the secondary outcome of AKIN stage 3 or death was then compared. As already mentioned above, IL-18 was the best predictor of both outcomes (AUC of 0.74 and 0.89). L-FABP (AUC of 0.67 and 0.85), NGAL (AUC of 0.72 and 0.83), and KIM-1 (AUC of 0.73 and 0.81) were also good predictors. Correlation between most of the markers was generally related to their predictive ability, but KIM-1 had a relatively weak correlation with other markers. The combination of IL-18 and KIM-1 had a very good predictive value with an AUC of 0.93 to predict AKIN 3 or death. Thus, a combination of IL-18 and KIM-1 would result in improved identification of high-risk patients for enrolment in clinical trials

Siew et al. (2013) examined the ability of urine NGAL, L-FABP, and cystatin C to predict AKI development, death, and dialysis in a nested case–control study of 380 critically ill adults with an eGFR > 60 mL/min/1.73 m^2. One hundred and thirty AKI cases were identified following biomarker measurement and were compared with 250 controls without AKI. AUROCs for discriminating incident AKI from non-AKI were 0.58 (95% CI: 0.52–0.64), 0.59 (0.52–0.65), and 0.50 (0.48–0.57) for urine NGAL, L-FABP, and cystatin C, respectively. The combined AUROC for NGAL and L-FABP was 0.59 (56–0.69). Both urine NGAL and L-FABP independently predicted AKI during multivariate regression; however, risk reclassification indices were mixed. Neither urine biomarker was independently associated with death or acute dialysis (NGAL hazard ratio 1.35 (95% CI: 0.93–1.96), L-FABP 1.15 (0.82–1.61)), although both independently predicted the need for acute dialysis alone (NGAL 3.44 (1.73–6.83), L-FABP 2.36 (1.30–4.25)). Thus, urine NGAL and L-FABP independently associated with the development of incident AKI and receipt of dialysis but exhibited rather poor discrimination for incident AKI using conventional definitions.

Angiotensinogen

Urinary angiotensinogen has been recently described as a novel prognostic biomarker of AKI, although it has not yet been investigated as an early diagnostic biomarker. In patients with AKI after

cardiac surgery and patients with AKI secondary to non-surgical causes, elevated urinary angiotensinogen is associated with progression to higher stages of AKI as well as hard outcomes, such as increased length of hospital stay, need for RRT, and death (Alge et al., 2013a, 2013b).

Activation of the renin–angiotensin system (RAS) has long been recognized as an important contributor to chronic renal injury. Urinary angiotensinogen has been proposed as a marker of intrarenal RAS activity, and it is predictive of progression of CKD. The prognostic significance of urinary angiotensinogen as an AKI biomarker is strongly suggestive of a role for RAS activation in modulating the severity of AKI.

Cell-cycle arrest biomarkers: tissue inhibitor of metalloproteinase-2 and insulin growth factor binding protein 7

As described in Chapter 221, the pathophysiology of AKI involves many different complex cellular and molecular pathways, involving inflammatory, interstitial, endothelial, and epithelial cells. These mechanisms comprise immunity, inflammation, apoptosis, and cell cycle pathways. As discussed in Chapter 238, AKI has been recognized as a major contributor to chronic and end-stage kidney disease and the appearance of tubulointerstitial fibrosis during the repair phase after either ischaemic or toxic injury is a poor prognostic indicator and represents a common final pathway in the progression to end-stage renal disease. It was demonstrated that proximal tubular cells arrested in the G2/M stage of the cell cycle after injury produce profibrogenic growth factors that are capable of stimulating fibroblast proliferation and collagen production (Yang et al., 2010). Renal tubular cells enter a period of G1 cell-cycle arrest after inducing ischaemia (Witzgall et al., 1994) or sepsis (Yang et al., 2009).

Tissue inhibitor of metalloproteinase-2 (TIMP-2) and insulin growth factor binding protein 7 (IGFBP7) are both involved in G1 cell cycle arrest during the early phase of cell injury. The G1 cell cycle arrest may prevent the division of cells with damaged DNA until the DNA damage is repaired (Rodier et al., 2007).

The Sapphire study (Kashani et al., 2013) demonstrated that the AUC values to predict the development of AKI (AKIN stage 2 or 3) in critically ill patients within 12 hours were 0.76 for IGFBP7 and 0.79 for TIMP-2. Multiplication of the two markers ([TIMP- 2] × [IGFBP7]) resulted in an even higher AUC (0.80) and was significantly superior to all previously described markers of AKI. Moreover, [TIMP-2] × [IGFBP7] significantly improved risk prediction when added to clinical scoring systems. A subsequent study in critically ill patients showed the ability of urinary [TIMP-2] × [IGFBP7] to predict moderate to severe AKI within 12 hours after admission in the ICU (Bihorac et al., 2014).

Conclusion

In conclusion it is fair to state that as of today, biomarkers can certainly increase our understanding of the pathophysiology of AKI.

An outstanding recent review (Alge and Arthur, 2015) summarized the actual status of the different biomarkers described in this chapter by pointing out that they can be integrated in one pathophysiological and clinical model of AKI. It seems that these novel AKI biomarkers contribute to the different clinical phases of AKI and progression to chronic renal injury, whereby some are contributing to renal injury and others are more protective. Others like the cell cycle biomarkers and angiotensinogen may play a role in the maladaptive repair process after kidney injury, leading to fibrosis and chronic kidney disease.

For the clinician, it appears, however, that the promising results with new biomarkers for early detection and differential diagnosis of AKI in clinical practice has only been confirmed in the setting of children without co-morbidities and with a well-defined timing of renal injury. Results are far less robust when validation is searched for in adult heterogenic populations, including patients with co-morbid conditions such as diabetes mellitus, vascular disease and CKD. Whereas AUROC values sometimes look impressive, applying levels of urinary or serum biomarkers for discrimination in individual patients is hampered by wide overlap between groups, which might result in many false positives. Biomarkers reflect a general degree of severity of disease, rather than being specific for kidney injury. However, as pointed out at the beginning of this chapter, it is possible that the persistent use of a very imperfect gold standard like the SCr for the definition of AKI is seriously troubling the objective evaluation of many of the novel biomarkers.

Before biomarkers can be advocated to diagnose AKI at the bedside, further research on the implications of 'subclinical' AKI, that is, diagnosed by the biomarker but not by an increase in creatinine or decrease of diuresis, should be performed. More prospective studies with biomarkers are needed (Vanmassenhove et al., 2013).

The recent ADQI expert group suggests that in the near future the combined use of biomarkers of kidney dysfunction (SCr and/or urine output) and damage (biomarkers, including urinary sediment changes) may facilitate an earlier diagnosis of AKI, along with more accurate differential diagnosis and prognostic assessment, particularly when such markers are monitored serially over time and are combined with clinical parameters (Murray et al., 2014).

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CHAPTER 224

Prevention of acute kidney injury: overview

Norbert Lameire

Introduction

This chapter focuses on the primary and secondary prevention of clinical acute kidney injury (AKI), that is, on the clinical strategies which reduce the occurrence of AKI in patients with or without underlying chronic renal disease who either do not yet exhibit evidence of acute renal dysfunction or injury, or where injury has been identified but where the functional outcome has not yet evolved to completion. Primary prevention follows identification of risk, while secondary prevention is a form of early intervention, which aims to attenuate and prevent progression of injury. Ideally secondary intervention is initiated during the injury evolution time between insult and the detected decrease in glomerular filtration rate (GFR) (early secondary prevention; Fig. 224.1) (Pickering and Endre, 2009).

Since the diagnosis of AKI is dependent on the finding of a decline in GFR (increase in serum creatinine (SCr), cystatin C, or other parameters of GFR), or of a fall in diuresis, many of the prevention measures that clinically are employed are in fact secondary interventions with the aim of either stabilizing renal function or improving it towards normal.

The prevention of AKI should start with an assessment of the risk to develop AKI, identification of comorbidities, use of potentially nephrotoxic medications, and early recognition of acute reversible risk factors associated with AKI (Table 224.1).

Identification of high-risk individuals

General risk factors that are consistent across multiple causes of AKI include age; pre-existing renal, hepatic, or cardiac dysfunction; hypovolaemia; hypotension; sepsis; diabetes mellitus; and exposure to nephrotoxins (e.g. aminoglycosides, amphotericin, immunosuppressive anticancer and antiviral drugs, statins, non-steroidal anti-inflammatory drugs (NSAIDs), angiotensin converting enzyme inhibitors (ACEIs), and/or angiotensin receptor blockers (ARBs), intravenous contrast media, and phosphate enemas). A surveillance approach, applying close monitoring in patients at risk of developing AKI, is a fundamental key to AKI prevention (Molitoris et al., 2008) with electronic notification of clinicians to attenuate nephrotoxin-induced AKI (Rind et al., 1994). In the latter study, email messages were sent to notify clinicians whenever mild increases in SCr occurred in patients receiving a nephrotoxic drug (Rind et al., 1994). This notification led to earlier discontinuation of the offending agent compared to when clinicians were not notified and decreased the frequency of development of severe AKI from 7.5% to 3.4%.

Others evaluated whether a real-time electronic alert system (using the RIFLE (Risk, Injury, Failure, Loss, and End-stage renal disease) criteria), called an 'AKI sniffer', would have an effect on therapeutic interventions and the course of AKI patients in a mixed surgical/medical intensive care unit (ICU) (Colpaert et al., 2012). The study was divided in three phases: a 2.5-month pre-alert control phase (during which physicians were blinded to the electronic alert system), a 3-month alert phase (during which physicians received real-time alerting of worsening RIFLE class as an electronic alert on a cordless telephone system), and a 1.5-month post-alert control phase. A higher percentage of patients in the alert group received a therapeutic intervention (fluid therapy, diuretics, or vasopressors) within 60 minutes after the AKI alert (28.7% in the alert group vs 7.9% and 10.4% in the pre-alert and post-alert control groups, respectively). During the alert period, a greater proportion of individuals who experienced RIFLE-R AKI had a decrease in RIFLE class within 8 hours (e.g. to normal) compared with the pre-alert and post-alert groups, although the absolute differences were modest. The study has several limitations, including a single-centre design, being underpowered to assess any effect of the AKI alert intervention on significant clinical outcomes, and the fact that most of the alerts (92.3%) were for AKI defined by low urine output criteria.

Several profiling models have examined the clinical risk factors for the development of AKI among ICU populations or hospitalized patients (Coritsidis et al., 2000; Mehran et al., 2004; Thakar et al., 2005; Kheterpal et al., 2009) (see also Chapter 236). To the list of general risk factors, more specific factors should be added depending on the particular patient category.

Some of these risk factors will be described in more detail below. For example, in AKI post cardiac surgery, procedure-related risk factors include cross-clamp time, the duration of cardiopulmonary bypass (CPB) (especially if > 70 minutes), pulsatile versus non-pulsatile bypass flow, normothermic versus hypothermic bypass, and haemodilution and on-pump versus off-pump coronary artery bypass (OPCAB) surgery. It is now appreciated that patients undergoing complex, on-pump surgery (i.e. anything more than primary coronary artery bypass grafting (CABG)) have a significantly greater risk of postoperative, often dialysis needing AKI. In most cases of cardiac surgery, postoperative serum creatinine (SCr) decreases by about 0.1–0.2 mg/dL (8.9–17.8 μmol/L) due

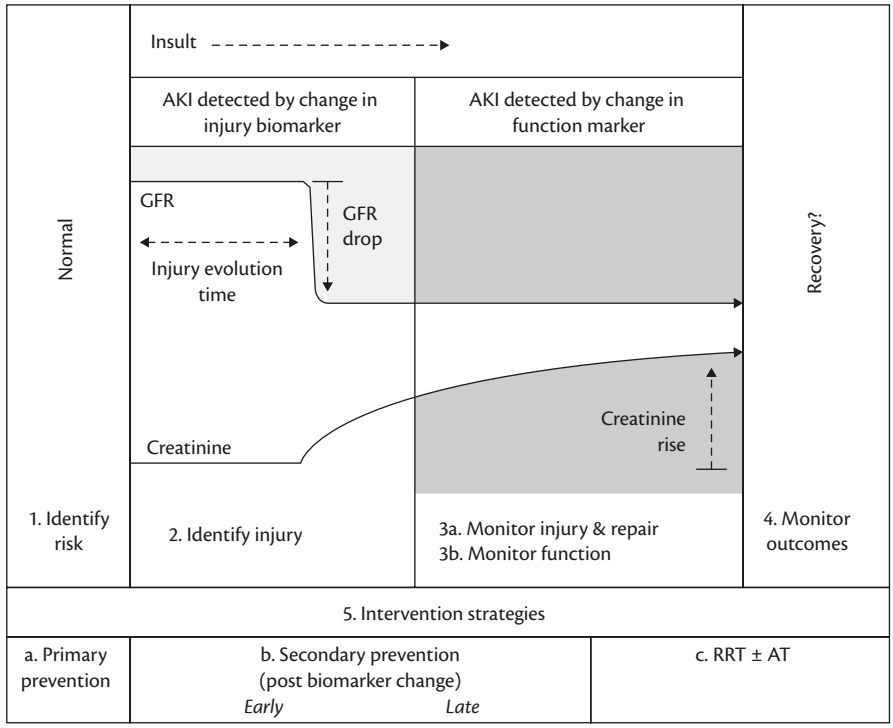

Fig. 224.1 Paradigm of the prevention of AKI with the presumption that phase-specific biomarkers will lead to phase-specific treatment. Late secondary prevention can only start after the rise of SCr is detected. AT = adjunct therapy; RRT = renal replacement therapy.
Modified from Pickering and Endre (2009).

to haemodilution (Haase-Fielitz et al., 2009). When this decrease does not occur, the possibility of masked decreased renal function should be kept in mind. The utility of obtaining a postoperative SCr level within 6 hours of completion of cardiovascular surgery and then daily for early diagnosis of AKI was also recently demonstrated by Ho et al. (2012). The immediate (i.e. < 6 hours) postoperative SCr level change (DeltaSCr), was categorized as within 10%, decrease > 10%, or increase > 10% relative to a preoperative baseline SCr. AKI was defined according to the new KDIGO consensus definition as an increase in SCr level > 0.3 mg/dL within 48 hours or > 1.5 times baseline within 1 week. After surgery, 176 patients (52%) experienced a decrease > 10% in SCr level, 26 (7.4%) experienced an increase > 10%, and 143 had DeltaSCr within ± 10% of baseline. During hospitalization, 53 (14%) developed AKI. Bypass pump time, baseline estimated glomerular filtration rate (eGFR), and European System for Cardiac Operative Risk Evaluation Score (euroSCORE) were associated with AKI in a parsimonious base logistic model. Added to the base model, immediate postoperative DeltaSCr was associated strongly with subsequent AKI and significantly improved model discrimination over the base model. A ≥ 10% SCr level decrease predicted significantly lower AKI risk (odds ratio (OR) 0.37; 95% CI 0.18–0.76), whereas a ≥ 10% SCr level increase predicted significantly higher AKI risk (OR 6.38; 95% CI 2.37–17.2) compared with the reference category. In elective cardiac surgery patients, an immediate postoperative DeltaSCr evolution improves thus the early prediction of AKI (Ho et al., 2012). A recent paper (Tolpin et al., 2012) has retrospectively explored if even smaller increases in SCr that do not meet the Acute Kidney Injury Network (AKIN)/RIFLE criteria, were independently associated with mortality in patients with normal renal function or with preoperative renal insufficiency undergoing CABG. A stepwise increase in 30-day all-cause mortality was observed when SCr increased in steps of 0.1 mg/dL (8.9 μmol/L) from 0 to 0.4 mg/dL (0 to 35.6 μmol/L). It is conceivable that these small changes in SCr reflect more underlying comorbidities and presence of subclinical chronic (vascular or microvascular) kidney disease rather than true kidney damage, and that the 'AKI' detected by these minimal increases in SCr is more a marker of risk rather than a causal factor. Haase et al. (2012) investigated whether intraoperative hypotension, anaemia, or their combination, red blood cell transfusion, or vasopressor use are independent risk factors for postoperative AKI defined by the RIFLE classification and other thresholds in 920 consecutive on-pump cardiac surgery patients using a mixed logistic multivariate model. Overall, 19.5% developed AKI which was associated with an 8.2-fold increase in in-hospital mortality. Haemoglobin concentration was an independent risk factor for AKI (OR 1.16 per g/dL decrease; 95% CI 1.05–1.31; P = 0.018) with systemic arterial oxygen saturation and pressure values not adding further strength to such an association. Mean arterial pressure (MAP) alone or vasopressor administration was not independently associated with AKI but volume of red blood cell transfusion was, with its effect being apparent at a haemoglobin level of > 8 g/dL (> 5 mmol/L). In patients with severe anaemia (< 25th percentile of lowest haemoglobin), the independent effect of hypotension (> 75th percentile of area under the curve MAP < 50 mmHg) on AKI was more pronounced (OR 3.36; 95% CI 1.34–8.41; P = 0.010). Based on this analysis, intraoperative avoidance of the extremes of anaemia, especially during severe hypotension and avoidance of transfusion in patients with haemoglobin levels > 8 g/dL (> 5 mmol/L) may help decrease AKI in post-cardiac surgery patients.

Table 224.1 A summary of major risk factors for AKI in common clinical situations

Postoperative (general)	Cardiac surgery	Critically ill	Sepsis	Contrast -AKI	Nephrotoxic agents
Cardiac	Female gender	Active cancer	Serum bilirubin > 1.5 mg/dL	Systolic BP < 80 mmHg for > 1 hour and need for inotropic support or IABP 24 hour after procedure	*Amphotericin*
Haemodynamic instability	ACEI or ARB therapy	Low serum albumin	Age	Use of IABP	Volume depletion
Congestive heart failure	Heart failure	A–a gradient[a]	SCr > 1.3 mg/dL	Heart failure (NYHA class 3-4), history of pulmonary oedema, or both	Concurrent other nephrotoxins
Aortic cross clamping	LV ejection fraction	Type of fluid substitution	Prolonged hypotension	Age > 75 years	*Aminoglycosides*
Major vascular surgery	< 35%		Multiorgan dysfunction	Hct: < 39% for ♂; <36% for ♀	Duration of > 7 days
Hypertension	Preoperative IABP		Elevated CVP > 8 cm H_2O under fluid substitution for haemodynamic instability	Diabetes mellitus	Volume depletion
Infection	COPD		Type of fluid substitution	Volume of contrast > 100 mL	Divided dose regimens
Sepsis	Insulin-requiring diabetes			Type of contrast medium	Sepsis
Multiorgan failure	Previous cardiac surgery			SCr > 1.5 mg/dL or eGFR < 60 mL/min/1.73 m²	Liver disease
Gastrointestinal and endocrine	Emergency surgery			Intra-arterial injection	Old age
Cirrhosis	Valve surgery only				Pre-existing CKD
Biliary surgery	Combination of CABG + valve surgery				
Obstructive jaundice	Other cardiac surgery				
Diabetes mellitus	Preoperative SCr >2.1 mg/dL				
Renal	Off vs on-pump surgery				
Transplantation					
Oliguria < 400 mL/day					
SCr > 2 mg/dL					
Miscellaneous					
Age > 70 years					
Trauma					
Massive blood transfusion					
Type of fluid substitution					

BP = blood pressure; CABG = coronary arterial bypass graft; CKD = chronic kidney disease; COPD = chronic obstructive pulmonary disease; CVP = central venous pressure; Hct = haematocrit; IABP = intra-aortic balloon pump; LV = left ventricular; NYHA = New York Heart Association; SCr = serum creatinine.

[a]A–a gradient: alveolar–arterial oxygen gradient calculated using the sea level standard formula [(713 × F_IO_2) – (PCO_2/0.8) – P_aO_2], where F_IO_2 = fractional inspired oxygen concentration; P_aO_2 = arterial partial oxygen pressure; PCO_2 = partial CO_2 pressure. The normal A–a gradient varies with age and ranges from 7 to 14 mmHg when breathing room air.

Modified from Lameire et al. (2007)

Common drugs as risk factors for acute kidney injury

Non-steroidal anti-inflammatory drugs

Non-steroidal anti-inflammatory drugs (NSAIDs) cause acute inhibition of cyclooxygenase (COX, type I or II), and can reduce GFR and renal blood flow. In critically ill patients, renal hypoperfusion due to decreased effective arterial volume is relatively common, and inhibition of prostaglandin-induced vasodilation by these agents may further compromise renal blood flow and exacerbate eventual ischaemic injury. The contributing factors for haemodynamic (prerenal) AKI induced by NSAID are well known and include intravascular volume depletion, hypoalbuminaemia, oedematous disorders, particularly severe heart failure, advancing age, atherosclerotic cardiovascular diseases, underlying chronic kidney disease (CKD) with renal failure, liver disease, or recent diuretic use (Murray and Brater, 1997).

However, the risk for this type of AKI in the general, including healthy aged population, is low. Although the incidence increases in the impoverished and/or medicated aged, these individuals still have a < 1 in a 100 chance of developing a decrease in renal function after NSAID; many (~ 50%) of these are prerenal and thus readily reversible on fluid repletion and cessation of NSAID (Adam, 2011).

ACEIs and ARBs

A similar reversible form of AKI can complicate ACEI and/or ARB therapy in the presence of decreased renal blood flow from severe bilateral renal artery stenosis, renal artery stenosis in a solitary kidney, and other high-renin, high-angiotensin II states (i.e. oedematous states and volume depletion disorders). In these situations, ACEIs or ARBs, by their resultant decrease in both renal perfusion pressure and efferent arteriolar constriction, can precipitously decrease GFR. About one-third of patients with severe congestive heart failure experience an abrupt rise in SCr concentration following ACEI therapy (Packer, 1987). In the setting of heart failure, this increase in SCr following ACE inhibition tends to be mild and readily reversible on discontinuation of the drug. However, in patients with an increase in SCr > 30% after the initiation of ACEI and ARB treatment, underlying bilateral renal artery stenosis, stenosis of the renal artery in a solitary kidney, or diffuse intrarenal small vessel disease should be suspected and these drugs should be discontinued. Although there is limited information on this topic it is generally advisable to discontinue ACEIs/ARBs during an AKI episode. However, these decisions need to be individualized and ACEIs/ARBs may be restarted when there is recovery of renal function in order to support other organ function (e.g. heart failure).

For example, a retrospective cohort study, including 487,372 users of antihypertensive drugs used nested case–control analysis in general practices in the United Kingdom (Lapi et al., 2013). During a mean follow-up of almost 6 years, 2215 cases of AKI were identified (incidence rate 7/10,000 person-years). Current use of a double therapy combination containing either diuretics or ACEIs or ARBs with NSAIDs was not associated with an increased rate of AKI but use of triple therapy combinations was associated with a significantly increased rate (rate ratio 1.31; 95% CI 1.12–1.53). The highest risk was observed in the first 30 days of use of this triple combination (rate ratio 1.82; CI 1.35–2.46). Given that NSAIDs are widely used and that a greater incidence rate of AKI was estimated among antihypertensive drugs users than in the general population, increased vigilance may be warranted when diuretics and ACEIs/ARBs are used concurrently with NSAIDs.

The use of ACEIs and ARBs in the pre- and perioperative periods of cardiac surgery remains controversial. A retrospective cohort study of 1358 adult patients found that preoperative use of ACEIs/ARBs was associated with a 27.6% higher risk for postoperative AKI and suggested that stopping ACEIs or ARBs before cardiac surgery may reduce the incidence of AKI (Arora et al., 2008). Raja and Fida (2008) conducted a systematic review on the topic of the use of ACEIs/ARBs and cardiac surgery and selected 11 articles (including three randomized controlled trials (RCTs)) to determine whether these drugs should be held before cardiac surgery to avoid postoperative vasodilatory hypotension that might necessitate vasopressor use. It was concluded that low-quality evidence supported a recommendation to stop ACEIs or ARBs before cardiac surgery since there was no increased incidence of AKI or other clinical sequelae of hypotension. However, a more recent propensity score-based analysis of patients undergoing CABG on CPB (Benedetto et al., 2008), not included in the systematic review of Raja and Fida (2008), found an incidence of AKI in 6.4% patients who received preoperative ACEIs and 12.2% in patients who did not ($P < 0.02$). The incidence of AKI requiring dialysis was 2.4% in the treatment group and 6.3% in controls ($P < 0.03$). After adjusting for propensity score and covariates, preoperative ACEIs were thus found to reduce the incidence of postoperative AKI (OR 0.48; 95% CI 0.23–0.77; $P < 0.04$). Also other studies reported that the chronic preoperative use of renin–angiotensin system inhibitors did not affect postoperative renal function or increase the risk of postoperative AKI after off-pump CABG (Yoo et al., 2010). Moreover, in a recent prospective observational study, treatment with an ACEI before and early after surgery was associated with a significantly lower risk of cardiovascular and overall composite events; *de novo* addition of ACEI therapy postoperatively was related to a lowering of odds in overall composite outcomes by nearly one half; and notably, withdrawal of ACEI treatment after surgery was associated with significant rise in odds of cardiac and renal ischaemic events (Drenger et al., 2012).

In the absence of more definitive evidence, discontinuing these drugs the day before surgery may be prudent. Overall, there is, however, insufficient evidence to guide the decision regarding whether to continue ACEIs or ARBs during and immediately after cardiac surgery. Such treatment decisions must be individualized, which may include holding these agents if the patient has postoperative vasoplegia and vasopressor-requiring shock and/or postoperative AKI or hyperkalaemia.

Statins

Statin use could lead to unintended adverse renal effects (Wolfe, 2004; Kiortsis et al., 2007; Hippisley-Cox and Coupland, 2010). A large-scale RCT compared high-dose (20 mg) rosuvastatin with placebo in almost 18,000 patients (Ridker et al., 2008). Data subsequently reported to the United States Food and Drug Administration showed a non-significant increase of 19% in AKI (risk ratio 1.19; 95% CI 0.61–2.31) (Roberts, 2009). The non-significant risk increased further to 35% (OR 1.35; CI 0.81–2.23) when the endpoint also included doubling of SCr.

A recent multicentre, retrospective, observational analysis revealed that the prescription of high-potency statins (≥ 10 mg rosuvastatin, ≥ 20 mg atorvastatin, ≥ 40 mg simvastatin), compared with the prescription of lower-potency statins, is associated with an increased rate of hospital admission for AKI. The increased risk of AKI occurs early after start of statin treatment and remains elevated for at least 2 years (Dormuth et al., 2013). The effect seems to be strongest in the first 120 days after initiation of statin treatment. It was further estimated that 1700 patients with non-chronic kidney disease need to be treated with a high potency statin instead of a low potency statin for 120 days to cause one additional hospitalization for AKI. The results of this impressive study are in line with another multicentre study of statin use and AKI in patients with community-acquired pneumonia (CAP) that reported an odds ratio of 1.32 for AKI in patients with CAP who received statins compared with statin naïve patients (Murugan et al., 2012). By contrast, a meta-analysis of four observational studies of rosuvastatin, designed to study multiple outcomes but which included renal failure, reported no difference between rosuvastatin and other statins (Garcia Rodriguez et al., 2010). Other studies in post-aortic surgery patients either did not find a deleterious effect on kidney function of preoperative statin use or even some protection of renal function (Moulakakis et al., 2010; Argalious et al., 2012).

Despite their role as possible risk factors for the development of AKI, statins have also been recommended as drugs in the prevention of AKI (see Chapter 226).

Warfarin

A growing body of literature has suggested an association between anticoagulation with warfarin and an international normalizated ratio (INR) > 3.0 IU and worsening renal function. Patients receiving warfarin are at increased risk for AKI for a number of reasons, including comorbidities, an increased risk of haemorrhage and renal ischaemic insult, and rare syndromes such as atheroembolism or allergic acute interstitial nephritis (Kapoor and Bekaii-Saab, 2008). An entity called warfarin-related nephropathy (WRN) has been described as a cause of AKI (and accelerated CKD progression) in patients with haematuria while on warfarin therapy. In 2000 and 2004, groups at two centres reported single cases of severe AKI with macroscopic haematuria in warfarin-treated patients with elevated INR values (3.6 and 8, respectively), and proposed that renal tubular obstruction by erythrocyte casts was responsible for AKI in each case (Abt et al., 2000; Kabir et al., 2004). In both cases, there was widespread occlusion of renal tubules with erythrocyte casts on renal biopsy, associated with acute tubular necrosis and many erythrocytes in Bowman's capsules, but not the interstitium.

Brodsky and colleagues published series of patients who received renal biopsies over a 5-year period for otherwise unexplained AKI and haematuria during warfarin therapy (Brodsky et al., 2009). All biopsies had findings of extensive erythrocytes in Bowman's spaces and tubules, including occlusive erythrocyte casts in 11.5% ± 2.3% of tubules. They further noted that most of the occlusive erythrocyte casts were in distal nephron segments, and did not contain Tamm–Horsfall protein. Finally, although they found underlying, inactive renal lesions in all cases, but without active glomerulonephritis, it was proposed that CKD patients under warfarin therapy and with abnormal glomeruli might be susceptible to glomerular haemorrhage/haematuria resulting in AKI caused by tubular obstruction and injury by occlusive erythrocyte casts. In 2011, the same group proposed the term of 'warfarin-related nephropathy' (WRN) to describe the syndrome of 'an unexplained increase' in SCr associated with INR > 3.0 IU and the prevalence, risk factors, and outcomes of this phenomenon were analysed (Brodsky et al., 2011). The diagnosis of 'presumptive WRN', defined by an increase in SCr > 0.3 mg/dL (> 26.4 μmol/L), occurred within 1 week of an INR > 3.0 IU (without evidence of haemorrhage based on administrative coding data). The incidence of WRN was higher in the CKD subset (33%) than in the non-CKD group (16.5%). In the overall cohort and the non-CKD subgroup, SCr values were significantly higher at the onset of INR > 3.0 IU in the group that developed WRN, and remained higher than the non-WRN group through 3 months of follow-up. In the CKD cohort, SCr values were similarly elevated in both the WRN and non-WRN groups before the index INR elevation, increasing further in WRN patients, and remaining higher through 3 months. The risk of WRN was higher in elderly individuals, and patients with hypertension, heart failure, diabetes mellitus, CKD, or diabetic nephropathy. The WRN cohort had a lower 5-year survival rate than the non-WRN cohort (58% vs 73%, respectively; $P < 0.001$), with similar trends in the CKD and non-CKD strata. Although clearly limited by several features (retrospective design using administrative data, single centre), this study provided additional support for the hypothesis that warfarin anticoagulation can cause AKI and perhaps accelerate CKD progression. This complication is not restricted to patients with clinically apparent underlying CKD. Taken together, the available data also suggest that the potential diagnosis of WRN might prompt consideration of a renal biopsy (balancing the risk of anticoagulation reversal) in patients with AKI that is sustained, otherwise unexplained, and occurred during warfarin therapy with a supratherapeutic INR, particularly if associated with haematuria. It will also be of interest to learn whether supratherapeutic anticoagulation with other drugs is associated with a similar form of haematuria-associated AKI.

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CHAPTER 225

Prevention of acute kidney injury: non-pharmacological strategies

Norbert Lameire

Introduction

Prevention of acute kidney injury (AKI) in patients at increased risk, or in the phase of incipient AKI, should first emphasize non-pharmacologic interventions, such as ensuring adequate renal perfusion pressure by optimizing general volume status by fluid therapy and, in case of necessity, maintaining adequate haemodynamic status by the use of vasopressors, and by avoidance of further injury by removing or decreasing the effect of any nephrotoxic substances, including contrast media and other potentially nephrotoxic drugs. This chapter describes the non-pharmacological prevention interventions, while Chapters 226 and 227 will discuss the role of pharmacologic interventions and prevention of nephrotoxin induced AKI.

On- versus off-pump surgery in coronary artery bypass grafting

Although most coronary artery bypass grafting (CABG) procedures are still performed on the arrested heart with the support of cardiopulmonary bypass (CPB), it is possible to perform CABG surgery (but not valve replacement) without CPB, a technique known as 'off-pump' CABG (OP-CAB), performed on the beating heart. Peri- and postoperative AKI in patients undergoing CABG surgery could at least in part be caused by renal hypoperfusion and ischaemic insults as well as inflammation and oxidant stress induced by the CPB pump. Potential benefits of OP-CAB (compared with on-pump procedures) are reduction of AKI risk, reduced risk of cerebral dysfunction (due to stroke and neurocognitive deficits), reduction in intensive care unit (ICU) and hospital stays, and reduced mortality. However, although OP-CAB obviously removes the bypass circuit, it can be associated with greater haemodynamic instability secondary to ventricular compression as the heart is manipulated to access the coronary arteries. Surgeon experience and expertise are particularly critical to success in this procedure. A comprehensive meta-analysis examining off-pump versus conventional CABG surgery found that the off-pump technique was associated with a statistically significant 40% lower odds of postoperative AKI and a non-significant 33% lower odds for dialysis requirement (Seabra et al., 2010). Within the selected trials, OP-CABG surgery was not associated with a significant decrease in mortality. However, the trials were clinically heterogeneous, particularly with regard to their definitions of kidney outcomes, and mostly were of poor to fair quality (based on the Jadad score). The very low event rates (often zero or one patient) make the estimates suspect and highly imprecise. There is also a possibility of publication bias. A more recent meta-analysis, incorporating recent larger trials, and adjusting for differences in trials using a technique known as meta-regression, found a significant 30% reduction in the occurrence of postoperative stroke with OP-CAB without a significant difference in mortality or myocardial infarction (Afilalo et al., 2012). Unfortunately renal outcomes were not analysed. Recently, the 30-day results of the CABG Off- or On- Pump Revascularization Study (CORONARY) were reported (Lamy et al., 2012). No significant difference between off- and on-pump surgery was observed in the primary outcome of death, myocardial infarction, stroke, or new dialysis at 30 days (9.8% vs 10.3%; P = 0.59). There was, however, a lower rate of transfusion and a higher rate of repeat revascularization with off-pump surgery. A 1-year follow-up of the CORONARY study (Lamy et al., 2013) reported that, consistent with the 30-day findings, there was no significant difference between off- and on-pump CABG in the composite outcome of death, myocardial infarction, stroke, or new dialysis at 1 year (12.1% vs 13.3%; P = 0.24). Repeat revascularization remained more common in the off-pump group (1.4% vs 0.8%; P = 0.07), and quality-of-life and neurocognitive outcomes were similar in the two groups. The German Off-Pump Coronary Artery Bypass Grafting in Elderly Patients (GOPCABE) randomized 2539 patients 75 years of age or older from 12 German centres to off-pump or on-pump CABG (Diegeler et al., 2013). Again, no significant difference between groups was observed in the primary outcome of death, myocardial infarction, stroke, repeat revascularization, or new renal replacement therapy (RRT) at 30 days (7.8% vs 8.2%; P = 0.74) or at 1 year (13.1% vs 14.0%; P = 0.48). Similar to the results of prior studies, there were fewer transfusions and more repeat revascularizations with off-pump surgery. Finally, Chawla et al. (2012), using a non-randomized cohort of 742,909 non-emergent, isolated CABG cases, which included 158,561 off-pump cases, found in a propensity-weighted analysis, that OP-CABG was associated with a reduction in the composite in-hospital death or RRT, with patients having lower preoperative renal function exhibiting greater benefit. The risk difference (on-pump minus off-pump) ranged from 0.05 (95% confidence interval (CI) 20.06–0.16) per 100 patients for estimated glomerular filtration rate (eGFR) ≥ 90 mL/min/1.73 m^2 to 3.66 (95% CI 2.14–5.18) per 100 patients for eGFR 15–29 mL/min/1.73 m^2. These data suggest that chronic kidney disease (CKD) patients experience less death or incident RRT when treated with off-pump compared with on-pump CABG. The reduction in

incident RRT, not death, drove this effect on the composite among patients with low eGFR. Since many of the recent trials were not yet published at time of writing the guidelines, the KDIGO Work Group concluded that there was not enough evidence to recommend off -pump coronary artery bypass for reducing AKI or the need for RRT (Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group, 2012). Based on the most recent results and in the light of the study by Chawla et al. (2012) and an older study by Sajja et al. (2007), this opinion should probably be modified for patients with advanced CKD. These most recent trials suggest that preoperative CKD should be a consideration in the selection of CPB versus OP-CAB surgery, but they suggest even more that randomized clinical trials in this patient subset are warranted.

Fluid therapy

Volume expansion and haemodynamic stabilization with optimization of cardiac output and blood pressure to ensure renal perfusion are key factors in preventing the initiation or worsening of AKI, regardless of the nature of the insult. However, once kidney injury has been initiated, the impact of volume expansion on clinical outcomes has not been well described and needs to be balanced with the unwanted consequence of fluid accumulation and fluid overload. Volume expansion should be avoided in patients with high intra-abdominal pressure, significant difficulties with oxygenation, or considerable peripheral oedema that may hinder wound healing after surgery. Fluid administration should be assessed at regular intervals by clinical and non-clinical investigations (see Chapter 222). (See Box 225.1.)

Hypovolaemia with or without a prerenal component of AKI

The goals of treatment of extracellular fluid (ECF) volume depletion are to replace the fluid deficit in general, with a fluid of the same composition of the lost fluid. The first step is an estimation of the magnitude of volume loss. The clinical and haemodynamic assessment of the volume status of a patient with risk for AKI or incipient AKI is described in Chapter 222.

In general, mild volume contraction can usually be corrected through the oral route but in cases of more severe volume contraction or hypovolaemic shock with evidence of life-threatening circulatory collapse or organ dysfunction, intravenous (IV) fluid must be administered as rapidly as possible until clinical parameters improve. However, in most cases, a slow, more careful approach is warranted, particularly in the elderly and in patients with an underlying cardiac condition, to avoid overcorrection with subsequent pulmonary or peripheral oedema.

Box 225.1 Settings where fluid administration has successfully prevented AKI

- Pre-renal AKI due to hypovolaemia: administration of potential nephrotoxins, such as aminoglycosides, amphotericin B, cisplatin, and IV aciclovir
- Administration of radiocontrast media
- Tumour lysis syndrome
- Surgical procedures, in which there is a reduction in the intravascular volume during either the intraoperative or postoperative period. Most preventive studies have been performed in the setting of cardiac surgery, abdominal aortic aneurysm surgery, surgery to correct obstructive jaundice, and renal transplantation
- Burns
- Haemoglobinuria and myoglobinuria
- Sepsis and septic shock.

Selection of the fluid

Colloids versus crystalloids

Insofar as volume depletion is the result of an intravascular deficit, colloid solutions, which contain large molecules such as albumin, hydroxyethyl starch (HES) or gelatine, should, at least theoretically, enable faster and more effective intravascular expansion with less total volume than crystalloids, and in addition with less risk of oedema (Schneider and Bellomo, 2013; Shaw and Kellum, 2013).

HES solutions have been used for many years for fluid resuscitation of hypovolaemic critically ill patients. In recent years, there has been increasing use of HES perioperatively as part of a goal-directed strategy (Grocott et al., 2012). Perceived advantages for HES over crystalloid have included more rapid restoration of intravascular volume, more prolonged intravascular retention, and less oedema. However, in hypovolaemic patients, intravascular volume expansion by crystalloids is much greater than that achieved in euvolaemic healthy volunteers and, if the endothelial glycocalyx is damaged (such as in septic shock), intravascular retention of colloids may not be substantially better than crystalloids (Doherty and Buggy, 2012; Woodcock and Woodcock, 2012). The vascular endothelial glycocalyx is often damaged in sick patients, leading to a 'leakier' capillary barrier for fluid (Chappell et al., 2009). When colloidal solutions diffuse into the interstitium, they affect the Starling equation by reducing the oncotic pressure gradient across the capillary barrier making extravasation more likely (Chappell et al., 2009).

The European Medicines Agency's (EMA's) Pharmacovigilance Risk Assessment Committee (PRAC) has recently recommended the suspension of hydroxyethyl starch (HES) products (PRAC, 2013). This decision is based mainly on three randomized trials in critically ill patients comparing HES with crystalloids, which showed greater risk of kidney injury requiring dialysis in the HES group (Brunkhorst et al., 2008; Myburgh et al., 2012; Perner et al., 2012). Two of these studies also showed significantly higher mortality in those treated with HES (Brunkhorst et al., 2008; Perner et al., 2012). The two most recently performed randomized controlled trials (RCTs) comparing HES and crystalloid fluids were performed in 2012: the 6S (Scandinavian Starch for Severe Sepsis/Septic Shock Trial) (Perner et al., 2012) trial in 26 centres in Scandinavia and CHEST (Crystalloid versus Hydroxyethyl Starch Trial) (Myburgh et al., 2012) in 32 centres in Australia and New Zealand. Together, both trials analysed 7798 patients with an AKI event rate of 50% and an RRT rate of 7.5%.

In the 6S trial, critically ill septic patients allocated to receive 6% HES (130/0.4) did not require a decreased volume of fluids

Table 225.1 A comparison of the most pertinent results between the 6S and the CHEST trials

Characteristic	6S	CHEST
Total patients (N)	798	7000
Patients with sepsis (N)	798	1937
Time from ICU admission to enrolment (hours)	4	11
Ratio of HES to crystalloid first 24 hours	1:1	1:1.2
Differences in CVP response	No	Yes
Carrier solution	Ringer's acetate	0.9% saline
Starch origin	Potato	Corn
Results (HES vs comparator) RR for AKI RR for use of RRT (95% CI) RR for death by 90 days (95% CI)	1.03 (0.90–1.17); P = 0.7 1.35 (1.01–1.80); P = 0.04 1.17 (1.01–1.36); P = 0.03	0.94 (0.90–0.98); P = 0.007 1.21 (1.00–1.45); P = 0.04 1.06 (0.96–1.18); P = 0.26

CI = confidence interval; CVP = central venous pressure; HES = hydroxyethyl starch; ICU = intensive care unit; RR = relative risk; RRT = renal replacement therapy.

From Shaw and Kellum (2013).

to achieve resuscitation targets compared with patients assigned to Ringer's acetate (control solution). In addition, patients assigned to HES had an increased in-hospital mortality rate at 90 days (relative risk (RR) 1.17 versus Ringer's acetate group; P = 0.03) as well as an increased use of RRT (RR 1.35; P = 0.04) (Table 225.1). However, because patients in this study were a unique cohort of patients with severe sepsis or septic shock, it was unclear whether these findings could be translated to other critically ill patients.

The CHEST study compared 6% HES (130/0.4) with 0.9% saline in 7000 critically ill patients. The overall in-hospital mortality (17.5%) was lower than expected and no difference was detected between the two groups in 90-day mortality. However, similar to the findings of the 6S trial, more patients allocated to receive HES required RRT (RR 1.21; P = 0.04). In addition, HES-treated patients experienced a higher rate of adverse events (5.3% vs 2.8%, P = 0.001) (Table 225.1). Post hoc analysis showed that, during the first 7 days after randomization, serum creatinine (SCr) levels were increased and urine output was decreased in the HES group, as compared with the saline group. Other earlier studies have also shown that use of HES is associated with renal impairment (Cittanova et al., 1996; Schortgen et al., 2001). Recent meta-analyses have concluded that use of HES solutions is associated with increased mortality and/or increased need for renal replacement therapy (Gattas et al., 2012; Haase et al., 2013; Patel et al., 2013; Perel et al., 2013; Zarychanski et al., 2013). In addition, colloids are associated with higher cost and those based on starch may accumulate in the tissue (Gattas et al., 2012).

As HES fluids also have higher associated costs than crystalloids, the decision of the EMA to suspend these solutions in critically ill patients, in particular patients suffering from sepsis, burns, severe trauma and major surgery, therefore seems reasonable. Whether the use of starch outside these patient groups has any benefit, particularly in patients in whom the endothelial glycocalyx is probably better preserved (e.g. in routine surgery), is a question that remains to be answered (Schneider and Bellomo, 2013; Shaw and Kellum, 2013).

Role of albumin versus crystalloids as resuscitation fluid in sepsis, cerebral trauma, and severe liver disease

Clinicians who prefer to include colloids for fluid resuscitation and who have, until now, been using HES, may choose to use a gelatin solution instead. But there are only few, low-quality data showing that fluid resuscitation with gelatin is achieved with a lower volume than with crystalloid and a recent observational study shows that gelatin may be associated with AKI (Bayer et al., 2012). Intravenous colloids cause approximately 4% of all perioperative anaphylactic reactions and the vast majority of these are caused by gelatin (Harper et al., 2009).

For patients with severe sepsis and septic shock, the international Surviving Sepsis Campaign recommends the use of crystalloids as the initial fluid of choice; it also recommends against the use of hydroxyethyl starches and suggests use of 4.5% human albumin solution in patients with septic shock who require large volumes of crystalloid (Dellinger et al., 2013). A pre-defined subgroup analysis of a RCT showed that use of albumin compared with saline in sepsis does not impair renal function (Finfer et al., 2011). A meta-analysis of clinical trials of fluid resuscitation with albumin-containing fluids compared with other fluid resuscitation strategies in patients with sepsis documented a lower mortality among those receiving albumin (Delaney et al., 2011). This study differed from previous systematic reviews on the topic by including only studies with a definable subgroup of patients with sepsis. However, the observed beneficial effect lost statistical significance in random effects modelling. It remains uncertain whether the results of this meta-analysis are due to underpowered studies, or whether albumin truly possesses no unique benefit as a resuscitation fluid in sepsis. It is worth noting that the largest RCT on the topic to date, the SAFE study (Finfer et al., 2004), demonstrated no adverse effects of albumin on organ failure compared with isotonic saline, but did suggest a potential mortality benefit in the subgroup of patients with sepsis (Finfer et al., 2011). Combined, these data suggest that albumin should at least be considered alongside crystalloids as potential first-line agents during the initial phase of sepsis resuscitation, although ongoing and recently completed clinical trials may help to provide more definitive guidance on the topic (NCT00707122 and NCT00327704).

The question of whether or not colloids per se may be harmful in patients with traumatic brain injury (TBI) was triggered by the results of the SAFE study (Finfer et al., 2004) and the subsequent post hoc analysis (Myburgh et al., 2007), suggesting that in TBI, fluid resuscitation with human albumin is associated with a higher mortality rate as compared with sodium chloride 0.9%. This fact led to the recent recommendation that no colloids should be used in patients with TBI (Reinhart et al., 2012). Hypo-osmolar solutions increase brain volume and intracerebral pressure, especially in the presence of an injured blood–brain barrier, and therefore may exert potentially harmful effects in patients with TBI, irrespective of the colloid composition. It should be noted that the colloid Albumex 4% solution used in the SAFE trial, is hypo-osmolar, because it has a theoretical osmolarity of 274.4 mOsm/L, resulting in a nominal

osmolality of only 250 mOsm/kg (for review, see Van Aken et al., 2012). Because the used human albumin solution, just like other clinically used colloid solutions like gelatin and Hartmann's solution, is hypo-osmolar compared to human plasma it may increase the risk of brain oedema irrespective of the colloid preparation itself (Van Aken et al., 2012). A recent study from the SAFE study group (Cooper et al., 2013) indeed demonstrated that resuscitation with albumin was associated with increased intracerebral pressure (ICP) during the first week after injury. During the same week, more patients who received albumin died compared with those who received saline. These data suggest that increased cerebral oedema leading to increased ICP is the most likely mechanism for increased death observed in TBI patients in the ICU resuscitated with albumin compared with those treated with saline. However, there exist specific settings in which albumin is appropriate for initial management of expansion of intravascular volume. Recent studies in liver failure have shown that not only albumin concentration but also albumin function is reduced. Indeed, in liver disease, albumin function is several times less than its concentration. In patients with cirrhosis, IV albumin infusion (1.5 g/kg at diagnosis followed by 1 g/kg on day 3) reduces mortality and prevents renal failure in patients with spontaneous bacterial peritonitis and improves outcome following large-volume paracentesis (Sort et al., 1999) (see also Chapter 247). In combination with vasoconstrictors, albumin is useful in the management of patients with hepatorenal syndrome (for a recent review, see Garcia-Martinez et al., 2013). Along the same lines, the most recent diagnostic criteria for hepatorenal syndrome include a lack of improvement in renal function after volume expansion with albumin (1 g/kg/day up to 100 g/day) for at least 2 days and withdrawal of diuretic therapy (Salerno et al., 2007).

Crystalloid solutions with sodium as the principal cation are effective as they distribute primarily in the ECF compartment. A third of an infusate of isotonic saline remains in and expands the intravascular compartment; two-thirds distributes into the interstitial compartment. Isotonic saline (0.9% NaCl) is usually the initial choice in volume-depleted patients with normal serum sodium concentration and in most of the patients with low serum sodium concentration. Isotonic saline is also the preferred fluid to restore ECF volume in hypovolaemic patients with hypernatremia. Once euvolaemia is established, further fluid therapy should then be delivered to gradually correct tonicity in the form of hypotonic (0.45%) saline. Administration of large volumes of isotonic saline may result in elevation of serum sodium above the normal range because it is slightly hypertonic (155 mmol/L) compared with plasma. If that happens, hypotonic saline can be continued instead, until volume is replete.

Balanced crystalloid solutions (Hartmann's, Ringer's lactate, Plasma-Lyte®)

Fluid preparations may be based on a simple non-buffered salt solution, such as normal saline, or may be modified with bicarbonate or bicarbonate precursor buffers, such as maleate, gluconate, lactate, or acetate, to better reflect the physiological state. These latter fluids have theoretical advantages over hyperchloraemic solutions, such as 0.9% saline which induce hyperchloraemic acidosis (Kellum et al., 1998; Scheingraber et al., 1999). This acidosis can induce inflammation (Kellum et al., 2006) and haemodynamic instability (Kellum et al., 2004), at least in animal experiments. A recent Cochrane systematic review, covering studies published between 1983 and 2011, compared the safety and efficacy of perioperative administration of buffered versus non-buffered fluids for plasma volume expansion or maintenance in adult patients undergoing surgery (Burdett et al., 2013). Buffered fluids were not only equally safe and effective as non-buffered saline-based fluids, but were associated with less hyperchloraemia and less metabolic acidosis.

An analysis of a large database, not covered in the Cochrane review and containing > 30,000 patients undergoing abdominal surgery compared patients receiving 0.9% saline as the only IV fluid on the day of the procedure to patients receiving only Plasma-Lyte®, a balanced crystalloid (Shaw et al., 2012). For the entire cohort, the in-hospital mortality was 5.6% in the saline group and 2.9% in the balanced group ($P < 0.001$). After adjustment for baseline imbalances performed with several statistical models including a propensity score, no difference was observed between the two groups in terms of in-hospital mortality (except in the emergency surgery subgroup (odds ratio (OR) 0.51; 95% CI 0.28–0.95) in favour of Plasma-Lyte®)) or major complications. The latter occurred in 33.7% of the saline group and 23% of the balanced group ($P < 0.001$). In patients with abdominal aortic reconstruction, an intraoperative comparison of 0.9% saline and lactated Ringer's solution demonstrated that hyperchloraemic metabolic acidosis occurred not only much more frequently with saline than with lactated Ringer but the saline resuscitated patients required also greater amounts of blood components (Waters et al., 2001). However, no differences in renal function were identified. A second small study randomized patients undergoing kidney transplantation to receive either isotonic saline or lactated Ringer with as primary outcome the SCr at day 3 post-transplant (O'Malley et al., 2005). A markedly increased incidence of hyperkalaemia (> 6 meq/L) was found in the saline group, presumably due to the higher incidence of acidosis. Due to these significant differences between the groups, the trial was halted early for safety reasons. A reduced incidence of renal morbidity (RRT and RIFLE (Risk, Injury, Failure, Loss, and End-stage renal disease) criteria I and F) was recently reported (Yunos et al., 2012) when chloride-rich solutions were replaced with chloride-restrictive solutions in the ICU. The mechanisms whereby saline exacerbates AKI are not well understood. Animal studies suggest that high chloride concentrations reduce GFR via tubuloglomerular feedback (Wilcox, 1983). Preliminary data in an animal sepsis model suggest that saline injures the kidney, as measured by urine neutrophil gelatinase-associated lipocalin (NGAL) levels and histology. Also inflammation (plasma interleukin 6) was increased with saline compared with balanced crystalloid (Shaw and Kellum, 2013). Collectively, this evidence strongly suggests that the type of crystalloid used for comparator in all the studies on colloids versus crystalloids is at least as important as the type of colloid examined.

Early goal-directed protocols in the prevention of acute kidney injury

Sepsis-induced AKI

The epidemiology, pathophysiology, and general management of patients with septic AKI is discussed in Chapter 244 and in a number of recent reviews (Daniels, 2011; Ricci et al., 2011; Zarjou and Agarwal, 2011; Namas et al., 2012; Romanovsky et al., 2014).

Prevention strategies for septic AKI include the optimization of haemodynamic and fluid management of patients with shock, appropriate use of antibiotics along with avoidance of potentially nephrotoxic drugs, and the careful management of all other risk factors for AKI as described in Chapter 224 (Ricci et al., 2011). In other words, kidney perfusion should ideally be optimized by restoration of arterial filling, cardiac output, and mean arterial pressure (MAP). For critically ill septic patients, this will likely encompass some combination of fluid therapy, vasoactive support (i.e. inotropic, vasopressor, and/or vasodilator therapy where indicated), evaluation for relative adrenal insufficiency, and, in circumstances of persistent catecholamine-resistant shock, referral for extracorporeal support (i.e. extracorporeal membrane oxygenation). Numerous implementation studies have demonstrated the benefit of this 'bundled care' in the initial treatment of patients with severe sepsis and septic shock, but the relative value of each component of these bundles remains uncertain (Puskarich, 2012). A meta-analysis found that implementation of sepsis bundles was consistently associated with improved survival (Barochia et al., 2010). Sepsis resuscitation is based upon the hypothesis that the fundamental flaw in septic shock is a deficiency in oxygen supply compared with demand. A graduated, stepwise resuscitation strategy involving serial assessments and interventions targeting cardiac preload, perfusion pressure, and oxygen delivery form the scaffold of current quantitative resuscitative protocols in the critically ill septic patient (Puskarich, 2012).

The Surviving Sepsis Campaign guidelines for the management of severe sepsis and septic shock were published in 2004 and subsequently updated in 2008 (Dellinger et al., 2004, 2008). Care bundles were created and the first (the 'Resuscitation Bundle') comprised a set of tasks to complete within the first 6 hours following the identification of sepsis (Box 225.2) (Daniels. 2011).

Box 225.2 The Surviving Sepsis Campaign Resuscitation Bundle

- Measure serum lactate
- Obtain blood cultures prior to antibiotic administration
- From the time of presentation, broad-spectrum antibiotics to be given within 1 hour
- Source of infection to be identified and drained within 6 hours
- In the event of hypotension and/or lactate > 4 mmol/L (36 mg/dL):
  - deliver an initial minimum of 20 mL/kg of crystalloid (or colloid equivalent)
  - give vasopressors for hypotension not responding to initial fluid resuscitation to maintain mean arterial pressure ≥ 65 mmHg
- In the event of persistent arterial hypotension despite volume resuscitation (septic shock) and/or initial lactate > 4 mmol/L (36 mg/dL):
  - achieve central venous pressure of ≥ 8 mmHg
  - achieve central venous oxygen saturation of ≥ 70%.

The Surviving Sepsis Campaign recommends thus that extracellular volume and cardiac output be assessed and supported with adequate and early goal-directed therapy (EGDT) (see below) (Dellinger et al., 2004, 2008). Many of these recommendations are based on the results of Rivers et al. (2001, 2005) who demonstrated in a single-centre study that early (within the first 6 hours in the emergency department) versus delayed administration of fluid, vasopressors, blood products, and inotropes to maintain some of these targets showed benefits in terms of mortality and multiorgan failure in septic patients. The early timing of the fluid administration and the physiologic endpoints to be monitored have emerged as EGDT. The predefined physiologic goals of EGDT within 6 hours of diagnosis are MAP ≥ 65 mmHg, central venous pressure (CVP) between 8 and 12 mmHg, improvement of blood lactate levels, central venous oxygen saturation > 70%, and urine output ≥ 0.5 mL/kg/hour. It should be noted that renal outcomes were not assessed in the original RCT on EGDT (Rivers et al., 2001). A later, slightly modified goal-directed study randomized patients with septic shock to therapy with or without a written protocol using CVP, MAP, and urine output as therapeutic goals (Lin et al., 2006). Implementation of this goal-directed therapy (GDT) caused a more rapid reversal of persistent shock, reduced mortality rates, and lowered incidence of renal failure and central nervous system complications, compared with non-GDT. Most studies with early interventions (defined as before the occurrence of organ failure, within 24 hours of trauma, or within 12 hours after surgery) showed lower mortality rates (Durairay and Schmidt, 2008) but targeting supra-normal cardiac index and oxygen delivery, for example, later in the course of sepsis conferred no benefit (Gattinoni et al., 1995). This point therefore emphasizes that what is beneficial early is not necessarily beneficial later in the course of critical illness. Data from the Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network indicate that after initial resuscitation, a conservative approach to fluid administration was associated with faster weaning from mechanical ventilation and decreased length of ICU stay, without any deterioration of kidney function or worse kidney outcomes (Wiedemann et al., 2006). A liberal fluid approach as part of EGDT appears to be beneficial during the first 6 hours of shock, but a conservative fluid approach should be followed after shock resolution.

It is noted that the recommendation for early EGDT in septic shock is based primarily on single-centre randomized clinical trials (Rivers et al., 2001; Lin et al., 2006) and observational studies (Rhodes and Bennett, 2004; Nguyen et al., 2006; Jones et al., 2007, 2008; Crowe et al., 2010). Furthermore, it has been suggested that the protocol must be specified (Palevsky et al., 2013), meaning that any protocol that is instituted based on the EGDT principle should be one that has been previously studied and validated. For example, previous studies of increasing oxygen transport have demonstrated that the use of dobutamine to increase oxygen transport can worsen mortality (Rudis et al., 1996) although the Rivers et al. (2001) study of EGDT suggests that dobutamine in an appropriate clinical context may not be harmful and may have benefit. Thus, medical centres adopting protocolized care should only adopt protocols that have been previously shown to be helpful and demonstrated no harm. If *de novo* protocols are developed for use, they should be used in the confines of a clinical trial to ensure no harm. Three large multicentre RCTs are currently enrolling patients: ProCESS (NCT00510835), ARISE (NCT00975793),

and ProMISE (ISRCTN36307479) comparing standard care with bundled care in septic patients. Although the shift in the standard of care in early septic shock over the past 10 years may impact the interpretation of these studies, the varied study locations and large number of patients will provide a wealth of data that will certainly influence the care of patients with sepsis in the coming decade (Puskarich, 2012).

Postoperative AKI

The same basic strategy of GDT including the same haemodynamic and metabolic targets has also been advocated in the perioperative period to prevent post- surgery AKI. While the risks and benefits of this strategy are unclear, a meta-analysis provides some evidence that such protocolized resuscitation may be better than standard care (Brienza et al., 2009). A heterogeneous collection of study populations, types of surgical procedures, monitoring methods, and treatment strategies make the interpretation of this meta-analysis difficult (Brienza et al., 2009). A follow-up meta-analysis, focused on cardiac and vascular surgery showed that compared with routine haemodynamic monitoring, perioperative GDT did not reduce mortality in both types of surgeries. GDT however significantly reduced the number of cardiac patients with complications but had no effect in vascular patients. The different characteristics and comorbidities of the enrolled study population could probably explain these conflicting results (Giglio et al., 2012).

A recent systematic literature review and meta-analysis of controlled trials of goal-directed resuscitation protocols in the settings of surgery focused on AKI and the quantity of fluid administered (Prowle et al., 2012). It was hypothesized that the beneficial effects of GDT on subsequent renal function are related to the amount of additional fluid given during GDT compared with control patients, treated according to the standard of care. In 24 perioperative studies, GDT was associated with decreased risk of postoperative AKI (OR 0.59; 95% CI 0.39–0.89) but additional fluid given was limited (median: 555 mL). Moreover, the decrease in AKI was greatest (OR 0.47; 95% C: 0.29–0.76) in the 10 studies where fluid resuscitation was the same between GDT and control groups. Inotropic drug use in GDT patients was associated with decreased AKI, whereas studies not involving inotropic drugs found no effect. The greatest protection from AKI occurred in patients with no difference in total fluid delivery and with use of inotropes (OR = 0.46, 95% CI = 0.27–0.76, P = 0.0036). GDT-based fluid resuscitation may thus decrease AKI in surgical patients but this effect requires little overall fluid resuscitation and appears most effective when supported by inotropic drugs. From this evidence, it is thus difficult to ascribe benefits of GDT simply to the provision of greater volumes of IV fluids to hypovolaemic patients, suggesting that any beneficial effect is actually derived from other aspects of care, in particular administration of vasopressor agents.

It is clear that more trials conforming to the characteristics of low-risk-of-bias studies and enrolling a larger and well-defined population of patients are needed to better clarify the effect of GDT in the specific setting of cardiovascular surgery. Given the limitations of the current studies and the lack of comparative effectiveness studies of individual protocols, one can only conclude that protocols for resuscitation in the setting of septic shock and high-risk surgery appear to be superior to no protocol (Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group, 2012).

Dangers of excessive fluid therapy

Once apparent optimization of haemodynamics and intravascular volume status has been achieved, as assessed either by direct measures of cardiac output or by pulse-pressure variation or by monitoring urine output (see Chapter 229), fluid administration should stop as there is little evidence to support continued aggressive fluid resuscitation to improve kidney function. On the contrary, there is evidence that such continued fluid administration and the resulting positive cumulative fluid balance can contribute to notable deteriorations in both non-renal and renal organ functions (for review, see Prowle et al., 2010). Organ dysfunction is thought to be at least partially mediated by organ oedema, which distorts tissue architecture, impairs oxygen and metabolite diffusion, and obstructs capillary flow and lymphatic drainage (Butcher and Liu, 2012). These effects are particularly pronounced in encapsulated organs such as the kidney, which cannot accommodate additional volume without significant increases in interstitial pressure and compromised blood flow. Also abdominal compartment syndrome with excessive abdominal fluid accumulation leads to impaired renal function (Shibagaki et al., 2006). The deleterious effects of organ oedema have been best demonstrated in the lung, where restrictive fluid management strategies have been associated with improved oxygenation and shortened duration of mechanical ventilation (for review, see Butcher and Liu, 2012). Whether the association of fluid overload with adverse outcomes is due to a direct effect of fluid overload itself or is due to indirect associations between fluid overload and other disease states remains unknown, however. The Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network has completed the largest randomized trial assessing fluid therapy in patients with lung injury (Wiedemann et al., 2006). This trial compared restrictive and liberal strategies for fluid management in 1000 critically ill patients, mostly suffering from pneumonia or sepsis, and with evidence of acute lung injury (ALI). Those receiving a restrictive fluid strategy had a near neutral fluid balance at 72 hours, whereas those in the liberal strategy were positive by > 5 L. Although the study failed to show a difference in mortality between the strategies, a restrictive strategy improved lung function, increased in ventilator-free days, and reduced ICU length of stay. Moreover, those in the restrictive group had a trend towards a reduced need for RRT. A post hoc analysis (Grams et al., 2011) of the relationship between fluid balance, diuretic use, and outcome in patients included in the ARDS trial who developed AKI shows that there were 137 in the fluid-liberal arm and 169 AKI patients in the fluid-conservative arm (P = 0.04). Baseline characteristics were similar between both groups. Post-AKI fluid balance was significantly associated with mortality in both crude and adjusted analysis. The mortality at 60 days was higher in patients in the fluid-liberal management arm than in patients in the fluid-conservative arm of the study (40.9% vs 37.9%). More patients in the liberal arm required dialysis (32.1% vs 26.6%), although these differences failed to reach significance. Higher post-AKI furosemide doses had a protective effect on mortality but no significant effect after adjustment for post-AKI fluid balance. There was no threshold dose of furosemide above which mortality increased. In addition, a positive fluid balance after the development of AKI is also associated with progression to more severe grades of AKI and increased requirement for renal support. These data also suggest that diuretics are at least safe to use during critical illness and may have a beneficial survival

effect through the achievement of a more negative fluid balance. Although a number of critical remarks on this post hoc analysis can be formulated, it shows that the role of fluid therapy in patients with AKI needs to be closely examined and reassessed and that formal investigations into the potentially beneficial effects of furosemide on fluid balance are required (Glassford and Bellomo, 2011).

Several observational studies have demonstrated a correlation between fluid overload and mortality in both critically ill adults and children with AKI (Brandstrup et al., 2003; Foland et al., 2004; Van Biesen et al., 2005).

In critically ill children with AKI requiring RRT, the percentage fluid overload, from ICU admission to RRT initiation was calculated by increase in body weight and using fluid intake and output data (Sutherland et al., 2010). Patients were divided into three strata based on these percentages: < 10%, 10–20%, and at least 20%. In univariate analyses, patients with at least 20% fluid overload had higher mortality than patients with either 10–20% fluid overload or < 10% fluid overload ($P < 0.001$). In a multivariate logistic regression model controlling for severity of illness, fluid overload remained independently associated with mortality.

In adult patients, using data extracted from the Sepsis Occurrence in Acutely Ill Patients (SOAP) study, independent risk factors for 60-day mortality in AKI patients were age, Simplified Acute Physiology Score II (SAPS II), heart failure, liver cirrhosis, medical admission, a positive fluid balance, and need for mechanical ventilation (Payen et al., 2008). Bouchard et al. (2009) subsequently examined the association of fluid overload and outcomes in adults using the Program to Improve Care in Acute Renal Disease (PICARD) cohort of 618 critically ill patients with AKI requiring nephrology consultation. Fluid balance in the 3 days preceding nephrology consultation was expressed as a percentage relative to the hospital admission weight, with fluid overload defined as an increase of > 10%. Mortality at 30 days, 60 days, and hospital discharge, as well as Acute Physiology, Age, Chronic Health Evaluation (APACHE) III score, number of failed organ systems, need for mechanical ventilation, and incidence of sepsis, were all significantly higher in patients with fluid overload. In patients requiring RRT, the odds ratio for death associated with fluid overload was 2.07 and 2.52 at dialysis initiation and cessation, respectively, after adjusting for initial dialysis modality and for APACHE III score. In non-dialysed patients, the adjusted OR for death associated with fluid overload at AKI diagnosis was 3.14 after adjusting for APACHE III score only. Mortality was proportional to both the degree and duration of fluid overload. The most recent study in the literature is a retrospective analysis of data from patients enrolled in Australian and New Zealand Intensive Care Society Randomized Evaluation of Normal vs Augmented Level Renal Replacement Therapy in ICU, a large RCT of dose of dialysis in patients with AKI (Bellomo et al., 2012). In this study, positive fluid balance during ICU admission was again associated with an increased risk of death, even after adjustment for severity of illness and other clinical factors associated with an increased risk of death (OR 3.14; $P < 0.0001$). Positive fluid balance was also associated with a decreased number of RRT-free days, ICU-free days, and hospital-free days. Of note, the mean Sequential Organ Failure Assessment cardiovascular score was higher in those with positive fluid balance, suggesting that there may be important haemodynamic differences between patients who are able to achieve negative fluid balance and those patients who remain in positive fluid balance. Furthermore, this finding highlights the importance of future studies to better characterize the impact of extracorporeal fluid removal on haemodynamics and haemodynamic stability; such studies will be critical for the design of clinical trials to test the impact of fluid removal and fluid balance on patient outcomes.

Lung-protective mechanical ventilation

ALI and AKI are complications often encountered in similar settings of systemic inflammatory response syndrome (SIRS), shock, and evolving multiple organ dysfunction. Both diseases have deleterious bidirectional interrelations including the renal effects of ALI and mechanical ventilation, and the pulmonary sequelae of AKI. Chapter 249 discusses in more detail the many basic and clinical interrelations between lungs and kidneys. This part is limited to the effects of mechanical ventilation on kidney function and its impact on prevention of AKI.

ALI and the associated need for mechanical ventilation has important effects on renal function and the implementation of lung-protective ventilatory strategies has disclosed the role of inflammatory mediators of ALI and more specifically ventilator-induced lung injury on the pathogenesis of AKI (for reviews see Pannu and Mehta, 2004; Koyner and Murray, 2010; Murray, 2010).

Mechanical ventilation may induce AKI by three proposed mechanisms: (1) through effects on arterial blood gases, (2) through an effect on systemic and renal blood flow, and (3) by triggering a pulmonary inflammatory reaction—biotrauma—followed by the systemic release of mediators generated during this pulmonary biotrauma (Kuiper et al., 2005). The development of AKI in ventilated patients is a major complication which independently increases morbidity and mortality (Joannidis and Metnitz, 2005; Hoste and Schurgers, 2008) and the mortality of ALI combined with AKI may approach 80% (Mehta et al., 2002).

In most mechanically ventilated patients, normal gas exchange is targeted; that is, a normal arterial oxygen pressure (PaO_2) and carbon dioxide pressure ($PaCO_2$. In many patients with ALI or ARDS, maintenance of a normal gas exchange may require ventilatory settings that may further injure the lungs. Such settings of mechanical ventilation and lung-injurious ventilator strategies include higher tidal volumes and lower positive end-expiratory pressure (PEEP) (Koyner and Murray, 2008).

In protective mechanical ventilation, a lower than normal PaO_2 or a higher $PaCO_2$ is accepted and this is realized mainly by applying lower tidal volume ventilation.

The literature data are somewhat contradictory whether the resulting 'permissive' hypercapnia may be beneficial (for detailed discussion, see Kuiper et al., 2005; Koyner and Murray, 2008, 2010).

A follow-up report on a previous RCT comparing conventional versus low tidal volume (Ranieri et al., 1999) was able to show a dramatic reduction in AKI in the low tidal volume-ventilated group (Ranieri et al., 2000). The most convincing results were obtained in the ARDS Network trial (The Acute Respiratory Distress Syndrome Network, 2000). Two groups of a total of 861 ventilated ALI/ARDS patients were randomized to tidal volumes of either 12 or 6 mL/kg of ideal body weight. The trial was stopped early when mortality was found to be lower in the low tidal volume group (31 vs 39.8%). In this trial the investigators crudely defined AKI as a SCr of > 2 mg/dL (176 μmol/L) and were able to demonstrate that those treated

with low tidal volume incurred fewer days with AKI compared to those treated with the higher tidal volume (18 ± 11 vs 20 ± 11 days).

Mechanical ventilation with conventional tidal volumes also contributes to the development of lung injury in patients without ALI at the onset of mechanical ventilation (Determann et al., 2010). A more recent secondary analysis of this RCT showed that of the 86 patients without AKI at inclusion, 18 patients (21%) subsequently developed AKI. However, there was no significant difference between the ventilation strategies (Cortjens et al., 2012).

The other strategy to prevent AKI in mechanically ventilated patients is related to the fluid and volume management of these patients.

As discussed earlier in this chapter in the section on fluid management, the ARDS Network group performed the Fluids and Catheters Treatment Trial (FACCT) using a 2 × 2 design to combine two trials in 1000 patients with ALI and receiving low tidal volume mechanical ventilation (Wiedemann et al., 2006). The major positive finding was the improvement in ventilator-free survival with the fluid-conservative management; however, this underpowered study was not able to demonstrate a difference in 60-day mortality, nor was there a difference in the occurrence of AKI. There was, however, a trend towards higher SCr levels in the fluid-restricted group (P = 0.07) with a similar trend towards an increased need for RRT in the fluid-liberal group (14%) compared to the fluid-conservative group (10%; P = 0.06).

It is clear that further investigations on the roles of fluid management and mechanical ventilation modalities with more precise definitions of AKI in critically ill patients are needed.

Blood glucose control

Stress hyperglycaemia is a distinctive clinical feature of critical illness (Van Cromphaut, 2009). Stress mediators and central and peripheral insulin resistance appear pivotal to the occurrence of stress hyperglycaemia. Inflammatory mediators and counter-regulatory hormones impede crucial elements of the insulin signalling pathway. Still, exogenous insulin administration normalizes blood glucose levels in this setting because it may counteract hepatic insulin resistance during acute critical illness. Extensive observational data have shown a consistent, almost linear relationship between blood glucose levels in patients hospitalized with myocardial infarction and adverse clinical outcomes, even in patients without established diabetes (Kosiborod et al., 2005, 2009). As discussed in Chapter 228 and in a comprehensive review (Gunst and Schetz, 2009), this 'stress-induced hyperglycaemia', is also directly associated with acute kidney dysfunction; several studies have highlighted the importance of correcting hyperglycaemia and have proposed algorithms for glycaemia control in critically ill patients.

The first landmark prospective RCT involved mechanically ventilated adults admitted to a surgical ICU (Van den Berghe et al., 2001). The patients were randomly assigned to receive intensive insulin therapy (maintenance of blood glucose at a level between 80 and 110 mg/dL (4.4 and 6.1 mmol/L)) or conventional treatment (infusion of insulin only if the blood glucose level exceeded 215 mg/dL (11.9 mmol/L) and maintenance of glucose at a level between 180 and 200 mg/dL (10.0 and 11.1 mmol/L)). Remarkably, intensive insulin therapy reduced overall in-hospital mortality by 34%, bloodstream infections by 46%, and importantly, AKI requiring dialysis or haemofiltration by 41%. Whereas the lowered blood glucose level was related to reduced mortality and other complications, the insulin dosage was an independent determinant for prevention of AKI (Van den Berghe et al., 2003). Whether these associations are simply a consequence of the deranged metabolic milieu that accompanies critical illness or there is a direct effect of hyperglycaemia and insulin resistance on the kidney still needs more evaluation. Pooled analyses of early multicentre studies have, however, failed to confirm the earlier observations of beneficial effects of intensive insulin therapy on renal function; the risk of hypoglycaemia with this approach is significant, and the survival benefits of intensive insulin therapy are in doubt (Wiener et al., 2008; Griesdale et al., 2009). The international Normoglycemia in Intensive Care Evaluation and Survival Using Glucose Algorithm Regulation study (NICE trial) found a 90-day mortality of 27.5% in the intensive insulin therapy group (target blood glucose range 81–108 mg/dL (4.5–6.0 mmol/L)) and a 90-day mortality of 24.9% in the conventional glucose control (target ≤ 180 mg/dL (≤ 10.0 mmol/L)) (OR for intensive control = 1.14; 95% CI 1.02–1.28; P = 0.02) (Finfer et al., 2009). The treatment effect did not differ significantly between surgical patients and medical patients. There was no significant difference between the two treatment groups in incidence of new RRT (15.4% vs 14.5%). Severe hypoglycaemia (blood glucose level ≤ 40 mg/dL (≤ 2.2 mmol/L)) was reported in 6.8% in the intensive-control group and in only 0.5% in the conventional-control group (P < 0.001).

A follow-up study of the NICE trial confirmed that in critically ill patients, intensive glucose control leads to moderate and severe hypoglycaemia, both of which are associated with an increased risk of death (Finfer et al., 2012). The association exhibits a dose–response relationship and is strongest for death in patients with distributive shock. It was, however, recognized that the data of this study cannot prove a causal relationship.

Considering the balance between potential benefits and harm, the KDIGO AKI Work Group suggests using insulin for preventing severe hyperglycaemia: the average blood glucose should not exceed 150 mg/dL (8.3 mmol/L), in critically ill patients but in view of the danger of potentially serious hypoglycaemia it is also recommended that insulin therapy should not be used to lower blood glucose to < 110 mg/dL (6.1 mmol/L) (Kellum and Lameire, 2013).

A practical algorithm for monitoring glucose levels and managing insulin therapy in the ICU is represented in Fig. 225.1 (Kavanagh and McCowen, 2010).

Remote ischaemic preconditioning

Remote ischaemic preconditioning (RIPC) is a method by which the deliberate induction of transient non-lethal ischaemia of an organ protects against subsequent ischaemic injury of another organ. The precise mechanisms of benefit for ischaemic preconditioning remain poorly characterized (for review, see Kharbanda et al., 2009). Molecules that have been implicated include adenosine, bradykinin, calcitonin gene-related peptide, and nitric oxide. It has been demonstrated that ischaemic preconditioning decreases pro-inflammatory gene expression in circulating leucocytes in healthy volunteers and decreases neutrophil adhesion. In studies of preconditioning in the kidney, reactive oxygen species, inducible nitric oxide synthase, hypoxia induced factor 1, and ecto-59-nucleotidase (CD73) which promotes extracellular adenosine generation, have

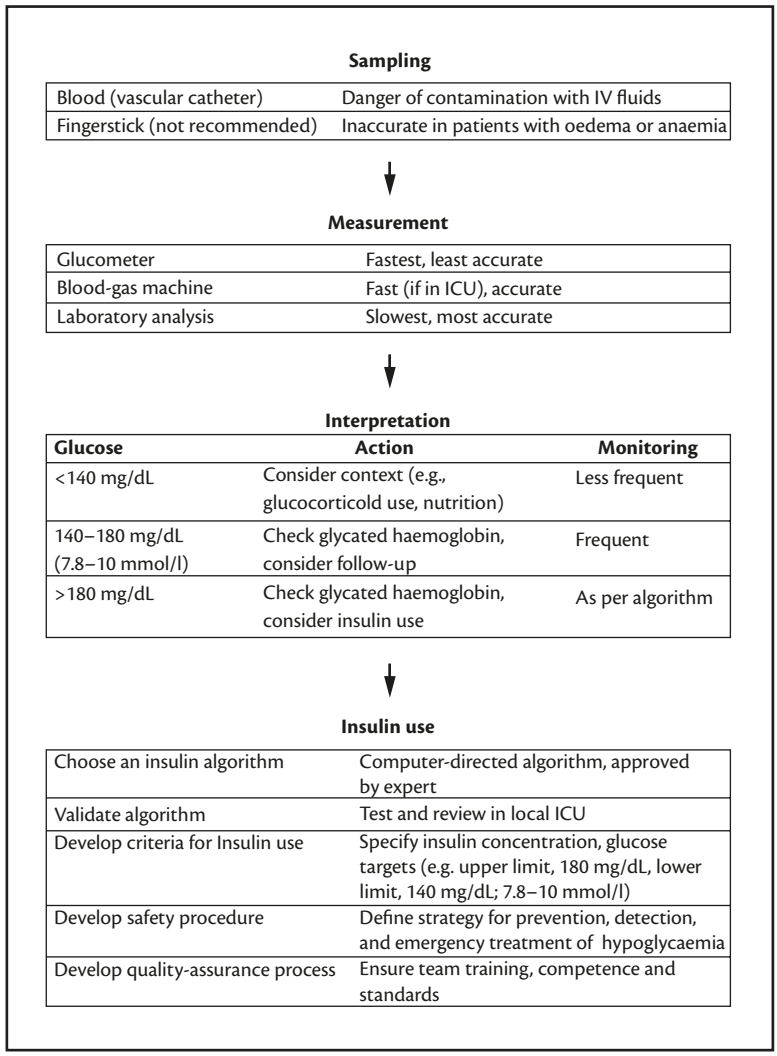

Fig. 225.1 Algorithm for monitoring blood glucose levels and managing insulin therapy in the ICU.
From Kavanagh and McCowen (2010).

all been implicated. Finally, preconditioning has been shown to affect mitochondrial function and in particular the mitochondrial permeability transition pore, which under conditions of cellular stress may open, resulting in mitochondrial swelling and cell death. However, not surprisingly, the mechanisms described again seem to vary based on the type of preconditioning (local vs remote) and the timing of preconditioning relative to the actual injury (early vs late).

Some (Ali et al., 2007; Venugopal et al., 2010; Zimmerman et al., 2011), but not all studies have suggested that RIPC protects against AKI (Choi et al., 2011). Transient limb ischaemia is the most frequent insult applied to generate protection against distant organ injury. The protocols used vary with regard to the duration of the preconditioning regimen and the timing of the preconditioning regimen relative to the actual injury, and results in human trials to prevent AKI and other ischaemic insults have been similarly variable.

The best data are from a single-blind randomized trial in which RIPC was induced by three 5-minute cycles of thigh ischaemia in 120 patients prior to elective cardiac surgery (Zimmerman et al., 2011). Postoperative AKI (defined as an elevation of SCr ≥ 0.3 mg/dL (26 μmol/L) or ≥ 50% within 48 hours of surgery) was reduced among patients randomized to RIPC compared with controls (20 vs 47%, respectively). Post hoc analysis showed that kidney injury that was sustained for at least 2 days was also reduced in the RIPC group (17 vs 36%). There were reductions in both stage 1 and stage 2 cases of AKI in the RIPC group. There were no stage 3 cases in the trial. Although the incidence of sustained AKI was reduced, ICU length of stay was unchanged. Secondary renal endpoints (plasma NGAL, urine output) did not differ between groups.

By contrast, in a second randomized study involving 76 patients undergoing 'complex' valvular heart surgery, there was no difference in the incidence of AKI, nor of biomarkers of renal injury, between those receiving RIPC and controls (Choi et al., 2011). Young and colleagues randomized 96 patients undergoing cardiac surgery to RIPC or placebo, to assess cardiac and renal protective effects (Young et al., 2012). Their three component primary endpoints included the maximum stage of the RIFLE AKI classification system in the perioperative period. AKI developed in 27.1% of the RIPC group versus 29.2% in controls.

RIPC failed to reduce the duration of AKI incidence, postoperative pressor support, or high-sensitivity troponin levels at 6 and 12 hours postoperatively.

Finally, Pedersen et al. (2012) randomized 113 children undergoing surgery to repair complex congenital cardiac disease to RIPC versus control, and found no difference in the incidence of AKI (using the RIFLE system definition) or acute dialysis. There was also no difference in the postoperative increases in SCr, serum cystatin C, or NGAL in plasma and urine, which occurred in both groups, along with a similar decrease in urine output on the first postoperative day. Recently, a systematic review and meta-analysis on the role of RIPC on postoperative AKI after cardiac and vascular interventions was published by Li et al. (2013). The authors identified 10 studies with a total of 924 patients undergoing cardiac and vascular interventions with or without RIPC. There was a significantly lower incidence of AKI in the RIPC group compared with control group using the fixed effect model (RR 0.69; 95% CI 0.53–0.90; P = 0.007), but not with the random effects model (RR 0.73; 95% CI 0.50–1.06; P = 0.10). There was no difference in the levels of renal biomarkers, incidence of RRT, mortality, hospital stay, and ICU stay between two groups. This meta-analysis concluded that at present there is not enough evidence that RIPC provides renal protection in patients undergoing cardiac and vascular interventions.

Summarizing, despite convincing preclinical data and some evidence from early-phase clinical trials of cardiorenal protection from ischaemic insults in high-risk cardiovascular patients, it remains unclear whether this non-pharmacologic approach to AKI prevention is effective. Multicentre clinical trials with primary and secondary renal endpoints including clinical outcomes and markers of kidney function and damage, along with assessments of cardiac injury and associated cardiorenal clinical endpoints, are needed to definitively answer this question (Endre, 2011).

RIPC has also been investigated in the prevention of contrast-induced (CI)-AKI (Er et al., 2012). The RenPro trial randomized patients with impaired renal function (SCr > 1.4 mg/dL (124 μmol/L) or eGFR < 60 mL/min/1.73 m^2) undergoing elective coronary angiography in a 1:1 ratio to standard care with (N = 50) or without ischaemic preconditioning (N = 50; intermittent arm ischaemia through four cycles of 5-minute inflation and 5-minute deflation of a blood pressure cuff). Overall, both study groups were at high risk of developing CI-AKI. The primary endpoint was the incidence of CI-AKI, defined as an increase in SCr ≥ 25% or ≥ 0.5 mg/dL above baseline at 48 hours after contrast medium exposure, occurred in 26 patients (26%), 20 (40%) in the control group and 6 (12%) in the remote ischaemic preconditioning group (OR 0.21; 95% CI 0.07–0.57; P = 0.002). No major adverse events were related to remote ischaemic preconditioning. The consistent signal of benefit with multiple markers of acute renal dysfunction (SCr or cystatin C) and kidney damage (urinary NGAL), along with favourable clinical outcome trends, does suggest a compelling need for further trials of RIPC for this indication.

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CHAPTER 226

Prevention of acute kidney injury: pharmacological strategies

Norbert Lameire

Role of vasopressors

As mentioned in Chapter 225, avoiding hypotension is a mainstay of haemodynamic optimization. In patients with persistent hypotension despite volume loading, vasopressors should be employed to increase mean arterial pressure (MAP) with the goal of ensuring optimal renal perfusion. In septic patients, norepinephrine (noradrenaline) has traditionally been used to increase blood pressure with improvement of creatinine clearance (Albanese et al., 2005). A randomized controlled trial (RCT) comparing dopamine with norepinephrine as initial vasopressor in septic shock showed no significant differences between groups with regard to renal function or mortality, even if the use of norepinephrine was associated with lower incidence of arrhythmias (De Backer et al., 2010, 2012). More importantly, a meta-analysis found that patients with septic shock assigned to dopamine compared with norepinephrine in RCTs demonstrated significantly higher mortality (De Backer et al., 2012). These data suggest that norepinephrine is superior to dopamine in the routine care of patients with septic shock.

Vasopressin

Vasopressin is gaining popularity in the treatment of shock refractory to norepinephrine (Delmas et al., 2005). The results of the Vasopressin and Septic Shock Trial (VASST) (Russell et al., 2008) suggest that, compared with norepinephrine, vasopressin may offer some advantage in patients with less severe septic shock. Septic patients were randomized to receive a blinded infusion of either low-dose vasopressin (0.01–0.03 U/min) or norepinephrine infusion (5–15 micrograms/min) in addition to open-label vasopressors. There was no significant difference between both groups in either the 28-day or in 90-day mortality rates. In the prospectively defined stratum of less severe septic shock, the mortality rate was, however, lower in the vasopressin group at 28 days (26.5% vs 35.7%, P = 0.05); there was no significant difference in 28-day mortality in the stratum of more severe septic shock.

In a post hoc analysis of the VASST trial, Gordon et al. (2010) compared the effects of vasopressin versus norepinephrine infusion on the outcome of acute kidney injury (AKI) in septic shock using the RIFLE (Risk, Injury, Failure, Loss, and End-stage renal disease) criteria for AKI. Kidney injury was present in 464 patients (59.6%) at study entry. In patients in the RIFLE 'Risk' category, vasopressin was associated with a trend to a lower rate of progression to renal 'Failure' or 'Loss' categories, and a lower rate of use of renal replacement therapy (RRT) (17.0 vs 37.7%, P = 0.02). Mortality rates in the 'Risk' category showed a tendency for lower mortality on the vasopressin group. This study suggests thus that vasopressin may reduce progression to renal failure and mortality in septic shock patients at risk of kidney injury. Finally, a systematic review on the use of vasopressin or terlipressin in vasodilatory shock demonstrated that these drugs do not produce any survival benefit in the short term in patients with vasodilatory shock (Polito et al., 2012). Physicians may, however, value the sparing effects of vasopressin/terlipressin on norepinephrine requirement given its apparent safe profile.

In conclusion, current clinical data are insufficient to recommend one vasoactive agent over another in preventing AKI, but it should be emphasized that vasoactive agents should not be withheld from patients with vasomotor shock over concern for kidney perfusion. Indeed, appropriate use of vasoactive agents can improve kidney perfusion in volume-resuscitated patients with vasomotor shock (Kellum and Lameire, 2013).The use of norepinephrine to improve renal oxygen delivery and renal oxygenation has been tested in postcardiac surgery, aiming at different targets of MAP (between 60 and 90 mmHg) (Redfors et al., 2011). In 12 post-cardiac surgery AKI patients with norepinephrine-dependent vasodilatory shock and AKI, norepinephrine infusion rate was randomly and sequentially titrated to target MAPs of 60, 75, and 90 mmHg. At a target MAP of 75 mmHg, oxygen delivery (13%), glomerular filtration rate (GFR) (27%), and urine flow were higher and renal oxygen extraction was lower (−7.4%) compared with at a target MAP of 60 mmHg. However, the renal variables did not differ when compared at target MAPs of 75 and 90 mmHg. It seems thus that restoration of MAP from 60 to 75 mmHg improves renal oxygen delivery, but no further benefit is obtained at higher levels of MAP. In 217 patients with sustained hypotension, the evolution of MAP during the first 24 hours has been compared between patients who developed AKI 72 hours after inclusion and patients who did not (Badin et al., 2011). Results of the study showed that patients with initial hypotension-induced renal impairment may need higher levels of MAP (72–82 mmHg) than the usually recommended 65 mmHg.

Loop diuretics/mannitol

The development of oliguria in AKI complicates the clinical management, in particular the fluid balance of the patients. It is therefore not surprising that diuretic agents are used frequently by clinicians to improve urine output or as an attempt to convert an oliguric state to a non-oliguric state. A number of diuretics with varying pharmacologic properties (loop diuretics (furosemide, bumetanide, torasemide), thiazide diuretics (metolazone, hydrochlorothiazide, often given in combination with loop diuretics), and osmotic diuretics such as mannitol) have been studied and are administered in the setting of AKI. There are a number of mechanistic studies and preclinical data providing physiological and pharmacological arguments for using diuretics, in particular loop diuretics, in the primary and secondary prevention of AKI; these arguments have been summarized in recent comprehensive reviews (Nigwekar and Waikar, 2011; Labib et al., 2013). Kellum and Lameire have recently summarized the recommendations of the KDIGO Workgroup on guidelines in AKI related to the role of diuretics in AKI (Kellum and Lameire, 2013).

Targeted patient populations have included patients undergoing cardiovascular surgery and those at risk for contrast-induced AKI (CI-AKI) (for review, see Nigwekar and Waikar, 2011). Specifically, prophylactic furosemide was found to be ineffective or harmful when used to prevent AKI after cardiac surgery, and to increase the risk of AKI when given to prevent CI-AKI (Solomon et al., 1994; Lassnigg et al., 2000; Lombardi et al., 2003). Epidemiologic data suggest that the use of loop diuretics may increase mortality in patients with critical illness and AKI (Mehta et al., 2002b), along with conflicting data that suggest no harm in AKI (Uchino et al., 2004). Finally, furosemide therapy was also ineffective and possibly harmful when used to treat AKI (Cantarovich et al., 2004; Ho and Sheridan, 2006). A systematic review and meta-analysis by Ho and Power also included six studies that used furosemide to treat AKI, with doses ranging from 600 to 3400 mg/day (Ho and Power, 2010). No significant reduction was found for in-hospital mortality or for RRT requirement. Furosemide may, however, be useful in achieving fluid balance to facilitate mechanical ventilation according to the lung-protective ventilation strategy in haemodynamically stable patients with acute lung injury (see below).

Gulbis and Spencer (2006) published a systematic review of eight studies, including seven RCTs and one observational study, and concluded that a more consistent and sustained diuresis is produced by a continuous infusion of furosemide compared with intermittent bolus doses of furosemide. However, there does not appear to be a significant difference in the total urine output or a change in serum electrolyte levels with continuous administration compared with intermittent bolus doses. A recent review in cardiac surgery patients (Gandhi et al., 2012) found that two of the five RCTS showed that continuous furosemide infusion was associated with a reduced need for RRT, while two RCTs failed to show any benefit; one trial reported an increased incidence of renal impairment. The conclusion of this review is that continuous furosemide infusion in the perioperative period promotes a gentle and sustained diuresis in cardiac surgery patients but that the evidence supporting this strategy in terms of reducing the need for RRT is weak. If considered, an appropriate dose is between 2 and 15 mg/hour in adult patients; the infusion duration should not exceed 72 hours (Gandhi et al., 2012). One setting where diuretics together with controlled crystalloid administration should be further explored is the Forced Euvolemic Diuresis Using the RenalGuard Device for Prevention of CI-AKI protocol.

The concept of using forced diuresis (combining diuretics to augment and maintain increased urine output, along with crystalloid administration to maintain euvolaemia) to prevent CI-AKI is theoretically attractive for a variety of mechanistic reasons: rapid transit in dilute urine might decrease renal tubular exposure to nephrotoxic contrast, furosemide also might diminish oxygen consumption in the vulnerable thick ascending loop of Henle, and mannitol might prevent tubular obstruction with casts and exert antioxidant effects. The Prevention of Radiocontrast Induced Nephropathy Clinical Evaluation (PRINCE) trial, randomized 98 patients to forced diuresis with furosemide, mannitol, and dopamine versus placebo (crystalloid alone, with volume status and perfusion monitored with pulmonary artery catheters). In the PRINCE trial, there was less CI-AKI (and dialysis) in the subset of patients who achieved a urine output of > 150 mL/hour (Stevens et al., 1999). However, there were several methodological limitations with this trial and other studies found that diuretic therapy increased the incidence of CI-AKI (Solomon et al., 1994; Dussol et al., 2006), perhaps by causing negative fluid balance. A randomized trial by Majumdar and colleagues of protocolized fluid and diuretic-driven, forced diuresis to prevent CI-AKI in CKD patients (Majumdar et al., 2009) also found increased AKI incidence in the intervention group, despite apparent efficacy of volume replacement in preventing negative fluid balance and hypovolaemia, unlike the prior, negative diuretic trials (Solomon et al., 1994; Dussol et al., 2006).

It was concluded that forced euvolaemic diuresis significantly increased the risk of CI-AKI and was not recommended; the KDIGO AKI guideline similarly recommends that diuretics should not be used to prevent any form of AKI, including CI-AKI (Lameire and Kellum, 2013). However, this approach remains an area of clinical trial activity, and a recent trial continues to suggest potential utility of forced diuresis to prevent CI-AKI, using a novel device to control fluid balance and prevent unintended hypovolaemia (Briguori et al., 2011). The RenalGuard device incorporates a closed-loop fluid management system, with a high-volume fluid pump, and a high-accuracy dual-weight measuring system, among other features. It is used to facilitate maintenance of a high urine output for forced diuresis with accurate fluid balancing to prevent iatrogenic fluid balance complications (hypovolaemia or pulmonary oedema). Briguori and colleagues conducted the Renal Insufficiency after Contrast Media Administration Trial II (REMEDIAL II) trial in four interventional cardiology centres in Italy (Briguori et al., 2011) and randomized patients with an estimated GFR (eGFR) ≤ 30 mL/min/1.73 m^2 and/or a Mehran CI-AKI risk score ≥ 11 (Mehran et al., 2004) to receive intravenous (IV) sodium bicarbonate solution (3 mL/kg load, followed by 1 mL/kg per hour until 6 hours post angiography) and *N*-acetylcysteine (NAC) (control group) or NAC and furosemide plus hydration with IV normal saline controlled by the RenalGuard System (Renal-Guard group). In the RenalGuard group, furosemide (0.25 mg/kg) was administered to achieve the desired urinary flow rate of ≥ 300 mL/hour, and saline infusion was adjusted to maintain fluid balance, with additional furosemide doses as required to maintain the target urine output during and for 4 hours post angiography. The primary endpoint was an increase in the serum creatinine (SCr) concentration of ≥ 0.3 mg/dL (26.4 μmol/L) 48 hours

after the procedure. Secondary endpoints included serum cystatin C changes and rate of in-hospital acute dialysis. There were no significant baseline differences between the groups, who were at high risk for CI-AKI with a median SCr of 1.8 mg/dL and a mean eGFR of 32 mL/min/1.73 m^2 and who received a mean contrast volume of 140 mL. Seventy per cent of the cohort was diabetic. CI-AKI occurred in 16 of 146 patients in the RenalGuard group (11%) and in 30 of 146 patients in the control group (20.5%; odds ratio (OR) 0.47; 95% CI 0.24–0.92). Subgroup analysis showed a similarly lower risk of adverse events in those with eGFR ≤ 30 mL/min/1.73 m^2 or Mehran risk score ≥ 11. The rate of in-hospital dialysis was higher in the control group (4.1% vs 0.7%; $P < 0.06$), with borderline statistical significance. There was no significant difference between the groups in other adverse event rates. The authors concluded that RenalGuard therapy is superior to sodium bicarbonate and NAC in preventing CI-AKI in high-risk patients. Unfortunately, there are a number of limitations in the trial design. First, this was an unblinded trial. Second, although both groups received NAC, the control group received a combination of oral and IV NAC, and the RenalGuard group only received IV NAC, with different total doses. Furthermore, the groups differed in the type crystalloid administered (bicarbonate in the control group, saline in the RenalGuard group). Nonetheless, the results are interesting, and should prompt the conduct of a larger, multicentre confirmatory trial that includes clinical endpoints, and uses isotonic saline and otherwise similar protocols in both arms.

A beneficial role for loop diuretics in facilitating discontinuation of RRT in AKI is also not evident from clinical studies (Uchino et al., 2009; Van Der Voort et al., 2009).

In summary, the 2012 KDIGO guidelines suggest that diuretics should not be used to treat AKI except in the management of volume overload (Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group, 2012). They can be given for a short length of time for volume control, but such use should not postpone the initiation of dialysis (if required) (Lameire et al., 2002).

The often retrospective and/or underpowered studies using prophylactic mannitol did not meet the criteria of the KDIGO Work Group on AKI to be included in recommendations (Kellum and Lameire, 2013). Mannitol is often added to the priming fluid of the cardiopulmonary bypass system to reduce the incidence of renal dysfunction, but the results of these studies are not very convincing (Schetz, 2004). Two small randomized trials—one in patients with pre-existing normal renal function (Yallop et al., 2008), the second in patients with established renal dysfunction (Smith et al., 2008)—did not find differences for any measured variable of renal function. More convincing are the results obtained with the preventive administration of mannitol, just before clamp release, during renal transplantation (van Valenberg et al., 1987; Schnuelle and van der Woude, 2006). The sparse controlled data available have shown that 250 mL of 20% mannitol given immediately before vessel clamp removal reduces the incidence of post-transplant AKI, as indicated by a lower requirement of post-transplant dialysis. However, 3 months after transplantation, no difference is found in kidney function compared with patients who did not receive mannitol (Weimar et al., 1983).

Finally, it has been suggested that mannitol is beneficial in rhabdomyolysis by stimulating osmotic diuresis and by lowering the intracompartmental pressure in the affected crushed limbs (Better and Abassi, 2011) (see Chapter 252); again, these studies were either not randomized or were underpowered.

Vasodilating drugs

Dopamine

In experimental animals and healthy human volunteers, renal dose dopamine (< 5 micrograms/kg of body weight per minute) increases renal blood flow and, to a lesser extent, GFR. A number of systematic reviews and meta-analysis have reached identical conclusions: dopamine does not provide any benefit for prevention or early treatment of ischaemic or nephrotoxic AKI (Denton et al., 1996; Bellomo et al., 2000; Kellum and Decker, 2001; Friedrich et al., 2005; Lauschke et al., 2006). Furthermore, dopamine, even at low doses, can induce tachyarrhythmias, myocardial ischaemia, and intestinal ischaemia (due to precapillary vasoconstriction), which might promote bacterial translocation from the intestinal lumen into the systemic circulation and extravasation necrosis, among other complications (Lauschke et al., 2006). Finally it causes hypopituitarism (Van den Berghe, 2006), and suppresses T-cell function (Murray, 2003).

Atrial natriuretic peptide

Natriuretic peptides are hormones secreted by the heart in response to volume overload with increased cardiac stretch and other stimuli. Atrial natriuretic peptide (ANP) is a 28-amino acid peptide synthesized by atrial myocytes. Brain natriuretic peptide (BNP) is a 32-amino acid peptide synthesized in the brain and in the heart. ANP and BNP are systemic and renal vasodilators which inhibit renal tubular sodium reabsorption, activate the renin–angiotensin–aldosterone system, and lower oxygen requirements in several nephron segments (for recent overviews and reviews see Martinez-Rumayor et al., 2008; Rubattu et al., 2008). Nigwekar and colleagues recently conducted a systematic review and meta-analysis of ANP for management of AKI (Nigwekar et al., 2009). They found 19 relevant studies, among which 11 studies were for prevention and eight were for treatment of AKI. Pooled analysis of prevention trials showed a trend toward reduction in RRT in the ANP group (OR = 0.45; 95% CI 0.21–0.99) and good safety profile, but no improvement in mortality. The analysis of the treatment studies did not show significant difference for either RRT requirement or mortality between the ANP and control groups. However, low-dose ANP preparations were associated with significant reduction in RRT requirement. The incidence of hypotension was not different between the ANP and control groups for low-dose studies, whereas it was significantly higher in the ANP group in the high-dose ANP studies (OR = 4.13; 95% CI = 1.38–12.41; $P < 0.01$). Finally, a pooled analysis of studies that examined oliguric AKI did not show any significant benefit from ANP for RRT requirement or mortality. Only two of the treatment studies included in Nigwekar and colleagues' analysis (Allgren et al., 1997; Lewis et al., 2000) were of adequate size and quality. It should be recognized that some recent more positive studies (Sezai et al., 2010; Sezai et al., 2011) were not included in the Nigwekar et al. analysis. For example, in the trial by Sezai et al. (2011), 303 patients with preoperative chronic kidney disease (CKD) (eGFR < 60 mL/min/1.73 m^2) who underwent coronary artery bypass grafting (CABG) were randomized to receive carperitide (synthetic human ANP (hANP)) by IV infusion (0.02 mg/kg/min) versus saline from the start of

cardiopulmonary bypass (CPB) until 12 hours after oral medications recommenced postoperatively. The (rather unorthodox) primary endpoints were the dialysis-free rate at 1 year postoperatively and SCr and eGFR at 0, 1, and 3 days, 1 week, and 1 month postoperatively. Secondary endpoints included early postoperative outcomes (survival and complications), overall and cardiac event-free survival rates at 1 year postoperatively, a variety of postoperative absolute and fractional SCr increments, and circulating ANP and cyclic-guanosine monophosphate (a downstream mediator of ANP effects) levels. There were no significant differences in preoperative baseline patient characteristics or operative details between the groups. Study drug infusions were administered for approximately 2.4 days in the hANP group, and approximately 3 days in the placebo group. Circulating ANP and cyclic-guanosine monophosphate levels were similar in the groups at baseline, and both were consistently higher in the hANP group throughout the perioperative period. The incidence of acute/early dialysis (period unspecified, probably up until hospital discharge) was higher in the placebo group (5.5%) than the hANP group (0.7%; P = 0.04). Five additional patients in the placebo group and one patient in the hANP group received dialysis in the follow-up period after hospital discharge. Thus, the dialysis incidence rate through 1 year postoperatively (one of the primary study endpoints) was 9% in the placebo group versus 1.4% in the hANP group (P = 0.01). There was no significant difference in mortality rate (a competing risk for dialysis initiation, and a secondary endpoint of this trial) in the first year postoperatively, although death rates were low, and the study was likely underpowered for this endpoint (death rate 0.71% in the hANP group versus 4.2% in the placebo group; P = 0.06). Although preoperative creatinine (and eGFR) was similar in the two groups, SCr was consistently higher in the placebo group from the first postoperative day through 1 year (with associated lower eGFR), although it is unclear how the individuals who required dialysis were handled in the analysis of mean creatinine. However, a variety of secondary endpoint analyses of absolute and fractional SCr increments also significantly favoured the hANP group. In summary, these data (despite some trial methodology and reporting problems) suggest that perioperative infusion of hANP has a sustained protective effect against kidney injury superimposed on stage 3 or 4 CKD after cardiac surgery with CPB. Taken together with the previous trials of these authors (Sezai et al., 2009, 2010), such data continue to suggest that therapy with hANP may protect the kidneys of patients undergoing CPB, including those with preoperative CKD. However, the endpoints chosen for most of these trials continue to be efficacy markers (e.g. SCr changes), rather than clinically significant outcomes (e.g. dialysis-free survival) given the modest event rates for dialysis post CPB even in these high-risk populations, and none of the trials performed with hANP or any natriuretic peptide has convincingly demonstrated such evidence of effectiveness. Therefore, although subset analyses separating low-dose from high-dose ANP trials suggest potential benefits, the preponderance of the literature according to the KDIGO Workgroup, suggests no benefit of ANP therapy for AKI (Kellum and Lameire, 2013). Consequently, the KDIGO AKI guideline states: 'We suggest not using atrial natriuretic peptide (ANP) to prevent (level 2C) or treat (level 2B) AKI.' (Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group, 2012).

Despite the continuing emergence of positive studies of ANP in cardiac surgery patients, it is unlikely that such guidelines will change until larger trials with more significant clinical endpoints are conducted in this high-risk population.

Nesiritide

Recombinant BNP (nesiritide) has the same amino acid sequence as human BNP, and is currently approved by the US Food and Drug Administration (FDA) for treatment of symptomatic acute decompensated heart failure. Nesiritide induces vasodilation and indirectly increases cardiac output, having no inotropic or heart rate effect. In some individuals, a resultant decrease in the neurohormonal activation can result in natriuresis and diuresis. In adults with acute decompensated heart failure, nesiritide reduces pulmonary capillary wedge pressure, reduces right atrial pressure and systemic vascular resistance, decreases symptoms of heart failure, and enhances clinical status. However, questions regarding the risks of nesiritide therapy have recently been raised. The most frequently reported adverse effect is dose-related hypotension and an acute increase in SCr concentration. This effect on kidney function has not been shown to negatively affect mortality and reviews of large, observational, registry databases do not suggest an adverse inpatient mortality effect compared with other vasodilator therapies (Yancy, 2007). Meta-analysis of outcome data from nesiritide congestive heart failure trials has generated some controversy (Sackner-Bernstein et al., 2005a, 2005b; Topol, 2005). Sackner-Bernstein and colleagues analysed mortality data from 12 RCTs; three trials provided 30-day mortality data, and found a trend towards an increased risk of death in nesiritide-treated subjects, while in another meta-analysis of five randomized trials that included 1269 subjects, the same investigators found that there was a relationship between nesiritide use and worsening renal function, defined as a SCr increase > 0.5 mg/dL (> 44.2 μmol/L) (Sackner-Bernstein et al., 2005a, 2005b). Nesiritide doses ≤ 0.03 micrograms/kg/min and even at doses ≤ 0.015 micrograms/kg/min significantly increased the risk of renal dysfunction compared with non-inotrope-based controls or compared with all control groups (including inotropes). There was no difference in dialysis rates between the groups. The role of nesiritide in patients with left ventricular dysfunction (ejection fraction ≤ 40%) undergoing CABG was investigated by Mentzer et al. (2007). The drug was administered as a 24- to 96-hour infusion of 0.01 micrograms/kg/min. Compared with placebo, nesiritide was associated with a significantly attenuated peak increase in SCr and a smaller fall in eGFR during hospital stay or by study day 14, and a greater urine output during the initial 24 hours after surgery. In addition, nesiritide-treated patients had a shorter hospital stay and lower 180-day mortality. Although SCr increased in both groups, it returned to baseline within 12 hours in those treated with nesiritide and remained elevated in the placebo group throughout hospitalization. Renal protection was greatest in patients with pre-existing renal dysfunction. Another RCT (Witteles et al., 2007) evaluated the impact of nesiritide on renal function in patients with acute decompensated heart failure and baseline renal dysfunction. Subjects received either nesiritide (0.01 micrograms/kg/min with or without a 2-microgram/kg bolus) or placebo (5% dextrose in water) for 48 hours in addition to their usual care. Both groups had similar baseline parameters like age, blood pressure, and SCr (1.82 vs 1.86 mg/dL). There were no significant differences in the incidence of a 20% creatinine rise or in the change in SCr. There were no significant differences in the secondary endpoints of change in body weight, dose of IV furosemide

administered, discontinuation of the infusion of nesiritide due to hypotension, or 30-day death/hospital readmission. Another retrospective study determined independent risk factors for 60-day mortality by multivariate analysis in a cohort of 682 older heart-failure patients treated with nesiritide versus those who were not (Iglesias et al., 2008). When patients were stratified according to nesiritide usage, AKI emerged as an independent risk factor for mortality only among patients who received the drug. In a 7000-patient multicentre RCT in acute decompensated heart failure, patients were randomly assigned to nesiritide, as compared with placebo (O'Connor et al., 2011). The nesiritide group more frequently reported markedly or moderately improved dyspnoea at 6 hours (44.5% vs 42.1%; P = 0.03) and 24 hours (68.2% vs 66.1%; P = 0.007), but the prespecified level for significance (P ≤ 0.005 for both assessments or P ≤ 0.0025 for either) was not met. The rate of rehospitalization for heart failure or death from any cause within 30 days was 9.4% in the nesiritide group versus 10.1% in the placebo group (P = 0.31). There were no significant differences in death rates from any cause at 30 days or rates of worsening renal function, defined by a > 25% decrease in the eGFR. Nesiritide was not associated with a worsening of renal function, but it was associated with an increase in rates of hypotension. On the basis of these results, nesiritide cannot be recommended for routine use in the broad population of patients with acute heart failure. A prospective RCT (the Nesiritide Study) in patients undergoing high-risk cardiovascular surgery found no benefit of nesiritide for 21-day dialysis and/or death (Ejaz et al., 2009). However, this study did demonstrate that the prophylactic use of nesiritide was associated with reduced incidence of AKI in the immediate postoperative period (nesiritide 6.6% vs placebo 28.5%; P = 0.004). Lingegowda and colleagues investigated whether the observed renal benefits of nesiritide had any long-term impact on cumulative patient survival and renal outcomes (Lingegowda et al., 2010). With a mean follow-up period of 20.8 ± 10.4 months, no differences in cumulative survival were noted, but patients with in-hospital incidence of AKI had a higher rate of mortality than those with no AKI (41.4% vs 10.7%; P = 0.002). The possible renoprotection provided by nesiritide in the immediate postoperative period was not associated with improved long-term survival in patients undergoing high-risk cardiovascular surgery. Although currently approved by the FDA only for the treatment of heart failure, nesiritide may in the future also play a role in the prevention of AKI in heart failure and cardiac surgery.

Fenoldopam

Fenoldopam mesylate is a pure dopamine type 1 receptor agonist that has similar haemodynamic renal effects as low-dose dopamine, but without systemic α-adrenergic or β-adrenergic stimulation (Murray, 2006). A meta-analysis found that fenoldopam reduces the need for RRT and in-hospital death in cardiovascular surgery patients (Landoni et al., 2008). However, the pooled studies included both prophylactic and early therapeutic studies, as well as propensity adjusted case-matched studies (rather than purely RCTs). A 1000-patient RCT of fenoldopam to prevent the need for RRT after cardiac surgery is currently underway (ClinicalTrials.gov: NCT00621790); meanwhile, this remains an unproven indication for fenoldopam therapy. A recent meta-analysis (Zangrillo et al., 2012) including 440 patients from six studies explored the ability of fenoldopam to reduce AKI in the perioperative period when compared with placebo. The analysis revealed that fenoldopam consistently and significantly reduced the risk of AKI but with a higher rate of hypotensive episodes and/or use of vasopressors and no effect on RRT, survival, and length of intensive care unit (ICU) or hospital stay. Only one study reported mortality (8-day) in sepsis patients randomized to fenoldopam (35%, N = 150) versus placebo (44%, N = 150), with a RR of 0.79 (95% CI = 0.59–1.05; P = 0.1) (Morelli et al., 2005). As therapy for AKI, only one study reported (21-day) mortality in critically ill patients with early AKI who were randomized to fenoldopam (11/80, 13.8%) versus placebo (N = 19/75, 25.3%; P = 0.068) (Tumlin et al., 2005). Another study reported the change in renal function in AKI patients randomized to fenoldopam (N = 50) versus dopamine (N = 50). The absolute SCr change between the beginning and end of the study drug infusion and the maximum decrease from study entry, were significantly larger in the fenoldopam group (−0.53 ± 0.47) vs dopamine (−0.34 ± 0.38 md/dL) (P = 0.027). Overall, therefore, no data from adequately powered multicentre trials with clinically significant endpoints and adequate safety are available to recommend fenoldopam to either prevent or treat AKI. Finally, the protective action of fenoldopam on the postoperative GFR and SCr after partial nephrectomy in patients with a solitary kidney was explored in a double-blind protocol (O'Hara et al., 2013). Fenoldopam (vs placebo) did not reduce the mean percentage of change in the GFR from baseline to the third postoperative day (P = 0.15), with an estimated ratio of means of 0.89 (95% CI 0.69–1.09) for fenoldopam versus placebo. There was also no difference in the mean SCr over time (P = 0.78). The recommendation against using fenoldopam places a high value on the low value of potential benefit but mainly on avoiding potential hypotension and harm associated with the use of this vasodilator in high-risk perioperative and ICU patients (Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group, 2012).

Adenosine antagonists (theophylline)

Animal studies using theophylline pretreatment have demonstrated attenuation of the intrarenal vasoconstriction after the administration of radiocontrast media. The acute reduction in GFR induced may therefore be theoretically minimized or prevented in some patients by theophylline or aminophylline (presumably via inhibition of the effect of adenosine). A recent review discusses renal adenosine receptor biology and potential clinical therapies for AKI (Yap and Lee, 2012). A 2005 meta-analysis of nine controlled trials of 585 patients (Bagshaw and Ghali, 2005) (theophylline vs controls) concluded that theophylline may reduce the incidence of CI-AKI, although the absolute benefit was small and patients studied were at relatively low risk (only one case required dialysis). This meta-analysis found that findings are inconsistent across studies. A more recent meta-analysis of RCTs between 1966 and July 2011 included studies of adenosine antagonists with or without NAC versus controls with or without NAC in CI-AKI (Dai et al., 2012).Theophylline significantly decreased the risk of CI-AKI and had a protective effect on the absolute change in SCr concentration. Meta-regression showed a significant relation between the relative risk of CI-AKI and baseline SCr level or Jadad score. No clear effects of treatment on risk of dialysis and in-hospital mortality were identified. However, the beneficial effects of theophylline were not observed in patients with high baseline SCr values (SCr > 1.5 mg/dL (132μmol/L)). In addition, the long-term effect of this agent on more clinically important outcomes was not established.

It seems therefore that large-scale, high-quality multicentre trials in participants with different underlying risks of CI-AKI are needed wherein evaluation of clinically relevant outcomes should be incorporated (Dai et al., 2012). By contrast, concurrent administration of the antiplatelet agent dipyridamole may increase contrast toxicity by enhancing the action of adenosine (Katholi et al., 1995). There is at present little evidence to recommend theophylline for the prevention of CI-AKI.

Similarly, adenosine antagonism is not beneficial in the cardiorenal syndrome. Three pivotal phase 3 trials in a total of 2500 patients were recently completed, aiming to corroborate the renoprotective effects of rolofylline in patients with cardiorenal syndrome, and to establish drug safety. The final results of the PROTECT trial have been published (Massie et al., 2010). Rolofylline, as compared with placebo, did not provide a benefit with respect to the three primary endpoints: survival, heart-failure status, and changes in renal function. Persistent renal impairment developed in 15.0% of patients in the rolofylline group and in 13.7% of patients in the placebo group (P = 0.44). By 60 days, death or readmission for cardiovascular or renal causes had occurred in similar proportions of both groups of patients. Adverse-event rates were similar overall; however, only patients in the rolofylline group had seizures, a known potential adverse effect of A_1-receptor antagonists. Rolofylline therefore does not appear to be effective for treatment of cardiorenal AKI.

The role of theophylline in the prevention of neonatal AKI is described in Chapter 239.

N-acetylcysteine

NAC is a modified form of L-cysteine, an amino acid that is a precursor to reduced glutathione that can regenerate glutathione stores. It is known to be a potent antioxidant that scavenges oxygen free radicals in the body. It also has vasodilatory properties derived from enhanced nitric oxide (NO) availability (Efrati et al., 2003).

NAC has been most frequently applied in the prevention of CI-AKI, and this topic is discussed in more detail in Chapter 246. As discussed in that chapter and in an editorial (McCullough et al., 2011), based on the ACT (Acetylcysteine for Contrast-induced nephropathy Trial) study (ACT Investigators, 2011), the short-term use of NAC for the prevention of CI-AKI should be abandoned. For researchers, this trial should invoke a rethink on all the reasons for neutral findings, including reconsideration of the therapeutic agent, dose, duration, and measurement of endpoints. NAC has favourable renal haemodynamic effects, acts as a relatively weak antioxidant, and therefore remains an attractive therapeutic target (Briguori et al., 2011). Future CI-AKI trials should consider longer treatment periods, more extensive collection of biomarkers, and relevant clinical endpoints.

Besides the prevention of CI-AKI, NAC has also been tested in the setting of cardiothoracic surgery and liver transplantation, and in hypotensive critically ill patients. Ho and Morgan (2009) performed a meta-analysis on RCTs involving adult patients undergoing major surgery, comparing NAC with a placebo perioperatively on the effects on mortality and AKI requiring dialysis. Additional outcome measures included an incremental increase in SCr > 25% above baseline, surgical re-exploration for bleeding, amount of allogeneic blood transfusion, and length of ICU stay. This meta-analysis found no current evidence that perioperative NAC can alter mortality or renal outcomes in major surgery, when contrast is not used.

A recent in-depth review on the role of NAC in the prevention of postcardiac surgery AKI included two meta-analyses and several RCTs. The RCTs investigated the preventive use of NAC in low-risk, high-risk, and high-risk patients with pre-existing CKD. The prophylactic administration of NAC did not reduce the incidence of AKI, postoperative complications, postoperative interventions, mortality, or length of ICU stay (Ashworth and Webb, 2010).

A clinical review (Sisillo and Marenzi, 2011) also concluded that the potential benefit of perioperative NAC administration in reducing the risk of AKI after cardiac surgery remains uncertain. IV administration of NAC was also not effective in reducing renal or hepatic injury in the setting of liver transplantation (Hilmi et al., 2010).

After a thorough analysis of the available literature, including a number of meta-analysis, the KDIGO guidelines workgroup on AKI also concluded that none of the studies found either a meaningful difference in need for RRT, or in AKI defined as variable changes in SCr after surgery with NAC compared with placebo (Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group, 2012).

Only one single study has compared NAC to placebo in critically ill patients (Komisarof et al., 2007). Patients receiving NAC had an incidence of AKI of 15.5%, compared to 16.9% in those receiving placebo (NS). There were no significant differences between treatment arms in any of the secondary outcomes examined, including incidence of a 50% increase in SCr, maximal rise in SCr recovery of renal function, length of ICU and hospital stay, and requirement for RRT. Mortality in both arms was 10%. Based on this single study, which is underpowered but did not show any beneficial effect on incidence of AKI, NAC cannot be recommended to prevent AKI in critically ill patients with hypotension.

Statins

The role of statin therapy as a possible risk factor for developing AKI is discussed in Chapter 224. Statins induce downregulation of angiotensin receptors, decrease endothelin synthesis, decrease inflammation and improve endothelial function by inhibiting nuclear factor kappa B, decrease expression of endothelial adhesion molecules, increase NO bioavailability, attenuate production of reactive oxygen species, and protect against complement-mediated injury (Mihos et al., 2010; Zhou and Liao, 2010).

All these mechanisms may be involved in the protective effect against CI-AKI and post cardiovascular surgery, the two clinical situations where statins have been applied. The possible role of statins in the prevention of CI-AKI is described in Chapter 246.

Hilmi et al. (2010) tested the hypothesis that in patients undergoing endovascular aortic repair, the postoperative GFR decreases less in patients taking preoperative statins than in those who do not. A decrease in the GFR of ≥ 25% (the threshold to diagnose CI-AKI) developed in 13.5% of patients given statins before operation compared with 12.2% in those who were not taking statins.

In another study (Moulakakis et al., 2010), patients receiving an infrarenal fixation of their abdominal aortic aneurysm or aortoiliac aneurysm graft had no change in renal function, regardless of whether they were on statins or not. In patients with suprarenal fixation not receiving statins, a small but significant deterioration

in renal function was observed in the early postoperative period, whereas patients on statins experienced no change in renal function. However, during follow-up, a constant worsening of renal function at 6 and 12 months was observed, irrespective of the medication with statins.

A similar study (Argalious et al., 2012) found that statin therapy is not associated with a statistically significant change in the mean postoperative GFR in patients undergoing endovascular aortic surgery.

Previous studies suggested that statin pretreatment reduces cardiac events in patients undergoing percutaneous coronary intervention. However, most data were observational, and single randomized trials included limited numbers of patients.

A careful analysis of a large dataset by Molnar et al. (2011) suggesting an association between statin use and lower risk for postoperative AKI was insufficiently persuasive because of limitations related to confounding by indication and differential misclassification of exposure and outcome status (Waikar and Brunelli, 2011).

However, Brunelli et al. (2012) assembled a retrospective cohort of 98,939 patients who underwent a major open abdominal, cardiac, thoracic, or vascular procedure between 2000 and 2010. Users of statins were pair-matched to non-users on the basis of several valid parameters. AKI was defined according Acute Kidney Injury Network or the RIFLE staging systems, and on the need for RRT. Across various AKI definitions, statin use was consistently associated with a decreased risk. Associations were similar among diabetics and non-diabetics, and across strata of baseline kidney function. The protective association of statins was most pronounced among patients undergoing vascular surgery and least among patients undergoing cardiac surgery. A recent double-blind RCT in 100 cardiac surgical patients at increased risk of postoperative AKI showed that in patients who received atorvastatin (40 mg once daily for 4 days starting preoperatively) the maximal increase in SCr during the 5 days after surgery was the same as in control patients without statin. RIFLE R or greater occurred in 26% of patients with atorvastatin and 32% with placebo (P = 0.65). Postoperatively, urinary neutrophil gelatinase-associated lipocalin (NGAL) changes were similar in both groups. This small but well-performed RCT demonstrated therefore that short-term perioperative atorvastatin use is not associated with a reduced incidence of postoperative AKI or smaller increases in urinary NGAL (Prowle et al., 2012).

Finally, a RCT randomized patients with CKD to (1) the atorvastatin group (80 mg within 24 hours before contrast media exposure (N = 202)), or (2) the control group (N = 208) (Quintavalle et al., 2012). All patients received a high dose of NAC and sodium bicarbonate solution. CI-AKI (i.e. an increase >10% of serum cystatin C concentration within 24 hours after contrast media exposure) occurred in 4.5% in the atorvastatin group and in 17.8% in the control group (OR = 0.22; 95% CI: 0.07–0.69; P = 0.005). CI-AKI rate was lower in the atorvastatin group in both diabetics and non-diabetics and in patients with moderate CKD (eGFR 31–60 mL/min/1.73 m^2). These results should be confirmed by future trials. Currently, there is no basis to recommend the initiation of statin therapy specifically for the pericontrast period to prevent CI-AKI. In patients undergoing cardiovascular surgery, and who are already on statin therapy, or need it for other indications, statins should be maintained through the peri- and postoperative period, but careful monitoring of renal function should be performed.

Insulin-like growth factor and erythropoietin

Based on an analysis of the three RCTs with insulin-like growth factor-1 that are currently available (Franklin et al., 1997; Hirschberg et al., 1999; Hladunewich et al., 2003) and which were overall negative or at least equivocal, one cannot recommend its use in patients with AKI. Recent animal studies suggest a potential clinical benefit of erythropoietin (EPO) in AKI. In various rodent models of AKI, EPO consistently improved functional recovery. The renoprotective action of EPO may be related to pleomorphic properties including antiapoptotic and antioxidative effects, stimulation of cell proliferation, and stem-cell mobilization (for review, see Moore and Bellomo, 2011).

In human AKI, a small pilot trial evaluated the effectiveness of EPO in the prevention of AKI after elective CABG (Song et al., 2009). AKI was defined as a 50% increase in SCr levels over baseline within the first five postoperative days. Of 71 patients, 13 developed postoperative AKI: 8% of the patients in the EPO group compared to 29% in the placebo group. A recently published, long-term follow-up study of the patients in this trial (Oh et al., 2012) demonstrated that EPO pretreatment reduced mortality or end-stage renal disease (ESRD) incidence in patients with AKI, but did not reduce mortality or ESRD in patients without AKI. It was presumed that the lower mortality in the EPO group might be due to a beneficial effect of EPO on recovery after AKI.

By contrast, a RCT reported no benefit of EPO on the outcome of AKI in a heterogenous group of ICU patients with two elevated urinary markers of tubular damage (Endre et al., 2010). Although the two urine biomarkers facilitated the early intervention, their transient increase compromised effective triaging. In addition, another RCT also found that administration of α-EPO after cardiac surgery, although safe, was not associated with either nephroprotective or anti-inflammatory properties (De Seigneux et al., 2012).

Finally, a study evaluated potential benefits of EPO-α given intra-arterially at the time of reperfusion of renal allograft on the degree of allograft function, as well as tubular cell injury, measured by urinary biomarkers in the early post-transplant period (Sureshkumar et al., 2012). No demonstrable beneficial effects of EPO in terms of reducing the incidence of delayed graft function or improving short-term allograft function could be observed.

It is hoped that the results of the EPO-AKI and EPO-Biomarkers, both two components of the renal substudy of the EPO-TBI trial (NCT00987454) will bring more clarity in this field. EPO-TBI is a trial of EPO as cerebral protection after traumatic brain injury, and the renal substudy assesses the effect of EPO on the development of AKI and the response to treatment using multiple renal biomarkers with different time profiles in patients with traumatic brain injury.

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CHAPTER 227

Prevention of acute kidney injury: drug- and nephrotoxin-induced acute kidney injury

Norbert Lameire

Introduction

The medications implicated in causing drug-induced acute kidney injury (AKI) can be classified based on their mechanism of renal injury (Table 227.1) (Bentley et al., 2010), such as prerenal, intrinsic renal, and postrenal (obstructive), as well as their histopathologic findings (i.e. osmotic nephrosis).

Only a few drugs can be discussed here; more comprehensive and detailed discussions can be found in Chapter 362 or a textbook devoted to nephrotoxicity of drugs and chemicals (De Broe et al., 2008).

Aminoglycosides

AKI due to acute tubular necrosis (ATN) is a relatively common complication of aminoglycoside therapy, with a rise in the serum creatinine (SCr) concentration of > 0.5–1 mg/dL (44–88 μmol/L) or a 50% increase in SCr concentration from baseline occurring in 10–20% of patients. Important risk factors for aminoglycoside nephrotoxicity include use of high or repeated doses or prolonged therapy, pre-existing renal insufficiency, advanced age, volume depletion, and the coexistence of renal ischaemia or other nephrotoxins (Moore et al., 1984; Humes, 1988). Hypomagnesaemia is a relatively common additional finding in patients with aminoglycoside-induced ATN and suggests coexistent injury to the thick ascending limb of the loop of Henle, the major site of Mg^{2+} reabsorption. AKI is usually detected during the second week of therapy, probably reflecting a requirement for accumulation within epithelial cells, but may be manifest earlier in the presence of ischaemia or other nephrotoxins. Aminoglycosides are polycations and are freely filtered across the glomerular filtration barrier but the central aspect of gentamicin nephrotoxicity is triggered by drug accumulation in epithelial tubular cells. The pathological tubular lesion may range from a mere loss of the brush border in epithelial cells to an overt tubular necrosis. Aminoglycoside molecules readily bind to anionic phospholipids within the plasma membrane of the proximal tubule cell in a saturable, electrostatic manner. Tubular cell accumulation results from the presence of the endocytic receptor complex formed by megalin and cubulin, an endocytic receptor in the clathrin-coated pits of the apical cell membrane, which transports proteins and organic cations inside the cells. Gentamicin then accesses and accumulates in the endosomal compartment, the Golgi and endoplasmic reticulum (ER), causes ER stress, and unleashes the unfolded protein response. An excessive concentration of the drug over an undetermined threshold destabilizes intracellular membranes and the drug redistributes through the cytosol. It then acts on mitochondria to unleash the intrinsic pathway of apoptosis. In addition, lysosomal cathepsins lose confinement and, depending on their new cytosolic concentration, they contribute to the activation of apoptosis or produce a massive proteolysis. However, other effects of gentamicin have also been linked to cell death, such as phospholipidosis, oxidative stress, extracellular calcium-sensing receptor stimulation, and energetic catastrophe (for detailed reviews see Lopez-Novoa et al., 2011; Quiros et al., 2011).

The risk of toxicity is most likely multifactorial and includes prerenal states (i.e. volume depletion), pre-existing renal or liver disease, concomitant nephrotoxic drug administration, advanced age, more frequent use of iodinated contrast agents, and diabetes (Oliveira et al., 2009). Cumulative dose (especially when associated with persistent elevated trough concentrations) may also be associated with an increased risk of toxicity. In addition, the type of aminoglycoside may play a role. The degree of toxicity associated with each drug may depend on the number of cationic groups on an aminoglycoside molecule (Humes et al., 1982; Bennett et al., 1986; Humes, 1988). Gentamicin is considered one of the most nephrotoxic followed in decreasing order of nephrotoxicity by tobramycin, amikacin, netilmicin, and streptomycin (Humes, 1988).

Strategies to minimize toxicity include adequate hydration, avoidance of concomitant nephrotoxic medications, serial monitoring of renal function, therapeutic drug monitoring, and, potentially, extended interval of dosing (i.e. once daily). For traditional dosing, and in patients with normal renal function, 1–2 mg/kg (gentamicin or tobramycin) is administered every 8 hours. In patients receiving extended-interval therapy, the dose is administered at either 5 or 7 mg/kg (gentamicin or tobramycin), once daily. The resultant concentration exceeds the minimal inhibitory concentration of most Gram-negative organisms by at least 10 times. This maximizes the area under the curve to minimal inhibitory concentration and the peak-to-minimal inhibitory concentration ratios. An interesting pharmacodynamic property of the aminoglycosides relies on their post-antibiotic effect, that is, continued killing of

Table 227.1 Classification of medications implicated in causing drug-induced AKI based on their mechanism of renal injury

Aetiology	Agents
Prerenal	NSAIDs, cyclooxygenase inhibitor-2, angiotensin-converting enzyme inhibitors, angiotensin receptor-blocking agents, ciclosporin, tacrolimus, radiocontrast agents, interleukin-2, diuretics
Intrinsic	
Acute tubular necrosis	Aminoglycosides, amphotericin B, radiocontrast agents, antiretrovirals (adefovir, cidofovir, tenofovir, and foscarnet), cisplatin, zoledronate, cisplatin, cocaine
Acute allergic interstitial nephritis	Antimicrobials (penicillins, cephalosporins, sulphonamides, ciprofloxacin, vancomycin, macrolides, tetracyclines and rifampin), NSAIDs, cyclooxygenase inhibitor-2 inhibitors, proton pump inhibitors (omeprazole and lansoprazole), anticonvulsants (phenytoin and valproic acid), cimetidine and ranitidine, diuretics, cocaine
Glomerulonephritis	NSAIDs, ampicillin, rifampin, lithium, penicillamine, hydralazine, gold, mercury, heroin
Postrenal	Aciclovir, methotrexate, sulfadiazine, foscarnet, indinavir, tenofovir, sulphonamides, triamterene, large-dose vitamin C (because of oxalate crystals), guaifenesin, and ephedrine (nephrolithiasis)
Other	
Osmotic nephrosis	Intravenous immunoglobulins, starches, mannitol, radiocontrast agents (in addition to acute tubular necrosis)

From Bentley et al. (2010).

the organism once the drug concentration falls below the minimal inhibitory concentration (Turnidge, 2003). Favourable pharmacodynamic properties and the potential of less nephrotoxicity (lower trough concentrations) have made this single-daily dosing strategy common in clinical practice. Extended-interval amikacin (15–20 mg/kg) dosing is also used clinically, and the same pharmacodynamic principles apply.

Clinical strategies that may minimize the potential for nephrotoxicity include first of all a selection of the least toxic aminoglycoside, when possible. In addition, hypokalaemia and hypomagnesaemia prior to administering an aminoglycoside should be corrected.

Numerous meta-analyses, summarized in the KDIGO guidelines for AKI (Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group, 2012) indicate that once-daily dosing strategies generally tend to result in less AKI when compared to multiple-dose dosing strategies, although the benefit accrued by the single-daily dose strategy is modest and inconsistent across a number of these studies. It should be noted that multiple-daily dosing strategies continue to be the standard of care for enterococcal endocarditis; no detailed, randomized trials have been reported comparing single-daily versus multiple-daily regimens for enterococcal endocarditis. Other effective clinical strategies include avoiding aminoglycosides in patients with reduced effective arterial volume, adjusting the dose for renal function, limiting the duration of therapy to 7–10 days, and minimizing concomitant nephrotoxic medications (Guo and Nzerue, 2002).

The use of single-daily dosing of aminoglycosides is generally well tolerated but bolus infusions of aminoglycosides should be avoided. The high-dose, once-daily aminoglycoside regimens should be administered over 60 minutes to avoid untoward events such as neuromuscular blockade. This recommendation is particularly important when patients are receiving other potential neuromuscular blocking agents, or have underlying disorders affecting neuromuscular transmission (e.g. myasthenia gravis).

For many years, therapeutic drug monitoring has been the standard of care when administering aminoglycosides. Aminoglycoside levels are variable among individuals, and subtle changes in the volume distribution, renal blood flow, and filtration rate can affect renal handling of aminoglycosides and alter the risk of nephrotoxicity. For these reasons, therapeutic drug monitoring, in combination with or independent from, single-dose daily treatment regimens is recommended (Beauchamp and Labrecque, 2001; Streetman et al., 2001; Kim et al., 2004). More details on drug monitoring in single and multiple daily aminoglycoside administration are available in the KDIGO guidelines on AKI (Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group, 2012).

Amphotericin B (AmB)

This polyene antifungal agent is insoluble in water and needs to be solubilized with deoxycholate and given intravenously in the absence of electrolyte solutions to maintain solubility. Despite its broad-spectrum fungicidal activity against a large number of invasive systemic mycoses, drug-induced nephrotoxicity is common and remains the principal dose-limiting toxicity of AmB (Wingard et al., 1999; Harbarth et al., 2002; Ullmann 2008). AmB-induced nephrotoxicity is related to multiple mechanisms, including ischaemic injury and direct tubular- and glomerular-cell membrane toxicity. Besides vasoconstriction of the afferent renal arteriole that may reduce renal blood flow, the drug also directly inserts into human cellular membranes, where it disrupts membrane permeability and physiology (Varlam et al., 2001; Pai et al., 2005). The end result is enzymuria, loss of renal tubular concentrating ability (polyuria), distal renal tubular acidosis, increasing urinary losses of potassium and magnesium (hypokalaemia and hypomagnesaemia), decreased glomerular function, and decreased synthesis of erythropoietin. AmB deoxycholate-induced nephrotoxicity is often accompanied by concomitant administration of other potentially nephrotoxic agents such as ciclosporin, aminoglycosides, chemotherapeutic agents, and a number of other potentially nephrotoxic agents (Harbarth et al., 2002; Ullmann, 2008). AKI, defined as a 50% increase in baseline SCr with a peak ≥ 2.0 mg/dL, and associated with AmB occurred in as many as one-third of treated patients, with progressive increase in the risk of AKI with increases in cumulative dose (Bates et al., 2001).

Considerable efforts have been undertaken to try to limit nephrotoxicity and permit the continued use of AmB deoxycholate for the management of systemic mycoses. Simple manoeuvres, such as salt repletion and provision of adequate amounts of potassium, which are beneficial in animal models in the prevention of its nephrotoxicity, have a mixed record in clinical practice, and their capacity to prevent AKI when treating severe fungal infections remains unclear (Kidney Disease: Improving Global Outcomes (KDIGO)

Acute Kidney Injury Work Group, 2012). Various dosing strategies such as giving AmB as a continuous infusion rather than a 2- to 4-hour infusion or administration of alternate-day doses of AmB, rather than daily doses to limit nephrotoxicity have not convincingly shown a reduced nephrotoxicity (de Rosa et al., 2006; Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group, 2012).

Lipid formulations of AmB have the same spectrum of activity but generally cause fewer adverse effects. Three lipid formulations are available, including AmB colloidal dispersion, AmB lipid complex, and liposomal AmB. Other formulations that might further reduce the risk of AKI from AmB include nanoparticle packaging in micelles with polyaspartic acid. The safety and efficacy (in incidence of nephrotoxicity) of lipid formulations of AmB have been studied in numerous experimental and clinical trials with conventional AmB deoxycholate as the comparator (for review, see Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group, 2012). Detailed analysis of various trials, and a number of meta-analyses indeed concluded that the lipid formulations are less nephrotoxic than AmB deoxycholate (Girois et al., 2005; Johansen and Gotzsche 2000). When feasible, lipid formulations should thus supplant the use of conventional AmB to reduce the risk of nephrotoxicity, particularly in high-risk patients. The use of these formulations can help to preserve renal function in patients with systemic fungal infections but they are significantly more expensive. However, the existing evidence would suggest that the overall risk:benefit ratio and cost-effectiveness with these lipid formulations is essentially cost-neutral with AmB deoxycholate (Kleinberg, 2006; Ullmann et al., 2006). A meta-analysis found that nephrotoxicity is generally similar between AmB lipid complex and liposomal AmB in patients receiving antifungal therapy and prophylaxis (Safdar et al., 2010).

Another approach to prevent AmB nephrotoxicity is to use alternative agents, such as the azoles and echinocandins. Both the azole compounds (voriconazole, fluconazole, itraconazole, and posaconazole) and the echinocandins (caspofungin, anidulafungin, and micafungin) compare favourably to AmB with respect to their efficacy against a variety of the systemic mycoses and both classes of antifungal agents lack the intrinsic nephrotoxicity associated with AmB deoxycholate. Both the azole compounds and echinocandins have proven to be less nephrotoxic than conventional AmB deoxycholate in observational studies, historical control studies, and in small comparative trials (Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group, 2012).

Crystal-induced acute kidney injury

Tubular precipitation of insoluble crystals (phosphate, methotrexate, aciclovir, sulphonamides, indinavir, uric acid, triamterene, oxalic acid) or protein (haemoglobin, myoglobin, paraprotein) can increase intratubular pressure. If it is sufficiently high, this opposes glomerular filtration pressure and can decrease glomerular filtration rate (GFR) (Perazella, 1999; Yarlagadda and Perazella, 2008).

Obstruction from the active drug and/or its metabolites can occur in the renal tubules or lower urinary tract, or can result in nephrolithiasis. Risk factors may be specific to the offending agent; however, pre-existing renal dysfunction and poor hydration are common.

Patients with drug-related crystal-induced AKI are usually asymptomatic and kidney injury is detected by an increased SCr (Sawyer et al., 1988). Occasionally patients present within 1–7 days after initiation of the offending drug with renal colic symptoms such as flank or abdominal pain, nausea, or vomiting. Urinalysis often reveals haematuria, pyuria, and crystalluria (Perazella, 1999). Significant proteinuria (i.e. > 500 mg/day) is not commonly observed unless the patient has underlying proteinuric kidney disease and subsequently develops crystal-induced AKI. The diagnosis is suggested by the appearance of crystals in the urine, the morphology of which depends upon the specific causative drug. However crystalluria may also be observed in patients who have no evidence of AKI (Berns et al., 1991).

Acute phosphate nephropathy

Acute phosphate nephropathy (APhN) is a clinical pathological entity characterized by acute and subsequent chronic renal failure following exposure to oral sodium phosphate (OSP) bowel purgatives. Several case reports and a comprehensive editorial have described this entity (Markowitz and Perazella, 2009). Risk factors for APhN include older age, female gender, hypertension, chronic kidney disease (CKD), and treatment with angiotensin-converting enzyme inhibitors and angiotensin receptor blockers, and diuretics. The pathomechanism of APhN involves hypovolaemia-induced avid proximal salt and water reabsorption, delivery of a large phosphate load to the distal nephron, and precipitation of calcium phosphate in the distal tubule and collecting duct. OSP solution was withdrawn from the market at the end of December of 2008, but OSP tablets, offered by prescription only, remain available. Prevention of APhN is best achieved by avoiding OSP in high-risk patients, aggressive hydration before, during, and after OSP administration, minimizing the dose of OSP, and maintaining a minimum of a 12-hour interval between OSP administrations. Although case reports and case series provide strong support for an aetiological relationship between OSP and the development of APhN, epidemiological studies have produced less consistent results and a systematic review and meta-analysis did not support an association between OSP and AKI (Brunelli, 2009).

Other crystal-induced nephrotoxic AKI

Aciclovir nephrotoxicity is typically seen after intravenous administration and may be due to direct tubular cell toxicity and the formation of intratubular aciclovir crystals, which appear as birefringent needle-shaped crystals on urine microscopy. However, crystals may also be seen in non-AKI patients, and renal biopsy data suggest that acute interstitial nephritis may be the predominant mechanism of toxicity. Ceftriaxone appears to increase the risk for nephrotoxicity. By contrast, ganciclovir has little nephrotoxicity.

Oliguric AKI typically occurs within a few days of treatment and may be associated with abdominal or loin pain. High serum levels of aciclovir due to decreased renal clearance may produce neurologic toxicity. The AKI is usually mild and recovers on stopping of the drug.

Foscarnet is a phosphate analogue used in the treatment of severe cytomegalovirus infection but also inhibits proximal tubule sodium-phosphate cotransport. AKI occurs in 10–20% of treated patients and may be due to ATN or intratubular crystal obstruction and acute interstitial nephritis. The AKI is usually non-oliguric and associated with mild proteinuria (<1 g) and a benign urine sediment.

Hypocalcaemia due to chelation of calcium may be present. The renal failure is usually reversible, although recovery may take several months. Pre-hydration markedly decreases the incidence of AKI.

Cidofovir and adefovir are nucleotide analogues that have been associated with AKI secondary to proximal tubular injury in 12–24% of cases. They are transported into the proximal tubule by the human organic anion transporter (hOAT), and nephrotoxicity may be reduced by concurrent use of probenecid, which blocks hOAT and volume expansion.

Triamterene spherical birefringent crystals can induce AKI particularly when an overdose is administered to hypovolaemic patients with impaired kidney function. Acidic urine is a risk factor. Prevention consists in adapting the dose to renal function and to alkalinize the urine to a pH > 7.5. Treatment of triamterene-induced established AKI involves volume resuscitation, alkalinizing the urine, and either stopping or reducing the dose.

Most other antiviral agents are not nephrotoxic. In the treatment of hepatitis C, there have been rare reports of ATN secondary to interferon alfa.

Methotrexate-induced nephrotoxicity

Methotrexate (MTX) is one of the most widely used anticancer agents, and administration of high-dose MTX (>1 g/m^2), followed by leucovorin (LV) rescue, is an important component in the treatment of a variety of childhood and adult cancers (osteosarcoma, Burkitt lymphoma, and central nervous system lymphoma). MTX is also used in non-cancer diseases (psoriasis, rheumatoid arthritis). Administration of high doses of MTX (1–12 g/m^2) can result in the precipitation of MTX and its metabolite 7-hydroxy- MTX in the renal tubules, which results in tubular obstruction and nephrotoxicity, a phenomenon known as crystal nephropathy (Perazella and Moeckel, 2010; Lameire et al., 2011). MTX solubility is pH dependent, and individuals with true or effective volume depletion with low urine volume and acidic urine are at increased risk of renal toxicity. Direct tubular toxicity also may contribute to kidney injury. The overall incidence rate of AKI is approximately 1.8% (range 0–12%), and, in general, renal injury is reversible. Initially, an asymptomatic SCr increase develops with non-oliguria followed by more severe AKI. Early on, urine microscopy often shows renal tubular epithelial cells and/or casts. In general, this type of AKI may, in itself, be mild and dialysis is rarely needed, however, a reduced GFR means that 80–100% of MTX is not eliminated by the kidneys. Because MTX is mainly renally excreted, renal insufficiency following MTX administration prolongs exposure to MTX, which in turn increases the risk of other MTX-associated toxicities, particularly myelosuppression, mucositis, hepatitis, and dermatitis. In addition, competitive inhibition of the renal tubular secretion of MTX by coadministered medications such as probenecid, salicylates, sulfisoxazole (sulfafurazole), penicillins, non-steroidal anti-inflammatory drugs (Balis, 1986), and gemfibrozil and piperacillin (de Miguel et al., 2008) can increase the risk of renal toxicity. The incidence of AKI with high dose MTX is 1.8%, and the mortality among patients that develop AKI is 4.4% (Widemann et al., 2004).

Aggressive hydration and alkalinization of urine to prevent MTX and metabolite precipitation in renal tubules, and to promote MTX excretion, significantly decreases the rate of nephrotoxicity. Patients should be euvolaemic prior to receiving treatment with MTX. In addition, adjunctive hydration and urinary alkalinization should be included in therapy for patients receiving dosages equal to or exceeding 50 mg/m^2 (Isnard-Bagnis and Deray, 2003). The recommended volume infusion with 40–50 mEq sodium bicarbonate per litre of solution should be started at least 12 hours before MTX administration and should continue for up to 72 hours. A dose reduction of 50% is necessary in individuals with an eGFR between 10 mL/min and 50 mL/min; alternative chemotherapy is suggested for individuals with an eGFR < 10 mL/min (Sahni et al., 2009).

The toxicity of high-dose MTX is mitigated by administration of leucovorin (folinic acid), which is readily converted into tetrahydrofolate and thus represents a true MTX antidote.

Leucovorin, a MTX rescue agent routinely given with high-dose MTX, restores the reduced folate pool after conversion to its active metabolite, 5-methyltetrahydrofolate, and helps reduce MTX-associated toxicities, including nephrotoxicity (Widemann and Adamson, 2006). When leucovorin is given several hours after MTX, it allows very high MTX levels to exert cytotoxic effects on rapidly cycling cancer cells, but prevents systemic toxicity from prolonged exposure, hence the term 'leucovorin rescue'. Importantly, leucovorin rescue does not reduce levels of MTX itself. The efficacy of these protective measures is increased by routine monitoring of MTX levels.

Carboxypeptidase- G2 (CPDG2, glucarpidase (Voraxaze®)), a recombinant bacterial enzyme that rapidly hydrolyses MTX to inactive metabolites has become available for the treatment of high-dose MTX-induced renal dysfunction. CPDG2 administration has been well tolerated and resulted in consistent and rapid reductions in plasma MTX concentrations. The early administration of CPDG2 in addition to leucovorin may be beneficial for patients with MTX-induced renal dysfunction and significantly elevated plasma MTX concentrations (Widemann and Adamson, 2006). CPDG2 has been given to > 100 patients with toxic MTX concentrations and renal injury through compassionate release trials (Janeway and Grier, 2010). CPDG2 results in a rapid (15-minute) and almost complete (> 95%) reduction in MTX concentrations, but these trials were not designed to determine whether CPDG2 decreases the duration of, or the complications resulting from MTX-induced nephrotoxicity. The use of glucarpidase for high-dose MTX toxicity is very expensive—it costs $9800 per 1000 U vial and at a dose of 50 U/kg, the total cost to treat a 70-kg patient is $34,300. Meyers and Flombaum made the point that intracellular MTX is what causes toxicity and that glucarpidase does not affect intracellular MTX concentration, and that high-dose leucovorin alone may be sufficient in many cases (Meyers and Flombaum, 2011).

The standard treatment for MTX-induced nephrotoxicity is haemodialysis, which can both decrease MTX concentrations and, when renal failure is present, treat the complications of renal failure. However, conventional dialysis- based methods remove MTX with limited effectiveness and MTX levels can rebound following the cessation of haemodialysis.

It is noteworthy that a significant clearance of MTX can be achieved with high-flux dialysers and serum MTX levels can be successfully lowered in patients with MTX-induced AKI by charcoal haemoperfusion and sequential haemodialysis (Molina et al., 1987; Relling et al., 1988).

Prevention of tumour lysis syndrome

Malignancies with high tumour burden, rapid cell turnover, and increased sensitivity to chemotherapy (e.g. acute leukaemias and

high-grade lymphomas) are at highest risk for developing tumour lysis syndrome (TLS); however, TLS has recently been associated with tumours that were previously thought to be low risk, such as hepatocellular carcinoma, endometrial cancer, non-small cell lung cancer, colon carcinoma, chronic myelogenous leukaemia, and chronic lymphocytic leukaemia (Howard et al., 2011). Crystal-induced tissue injury occurs in the TLS when calcium phosphate, uric acid, and xanthine precipitate in renal tubules and cause inflammation and obstruction (for review, see Howard et al., 2011; Wilson and Berns, 2012). A high level of solutes, low solubility, slow urine flow, and high levels of co-crystallizing substances favour crystal formation and increase the severity of the TLS. High levels of both uric acid and phosphate render patients with the TLS at particularly high risk for crystal-associated AKI, because uric acid precipitates readily in the presence of calcium phosphate, and calcium phosphate precipitates readily in the presence of uric acid. Also, higher urine pH increases the solubility of uric acid but decreases that of calcium phosphate. An algorithmic approach to the prevention and treatment of TLS is given in Fig. 227.1 (Wilson and Berns, 2012). All patients who are at risk for the TLS should receive intravenous hydration to rapidly improve renal perfusion and glomerular filtration and to minimize acidosis (which lowers urine pH and promotes the precipitation of uric acid crystals) and oliguria (an ominous sign). This is usually accomplished with hyperhydration by means of intravenous fluids (2500–3000 mL/m^2 per day in the patients at highest risk) (Howard et al., 2011). Hydration is the preferred method of increasing urine output. Because diuretics do not have a proven role in reducing the incidence or severity of TLS, their routine use is not recommended unless there are clinical signs or symptoms of volume overload (Wilson and Berns, 2012).

Allopurinol and rasburicase, a recombinant urate oxidase preparation, decrease the synthesis of uric acid in patients with rapidly growing tumours and who are prone to uric acid nephropathy and TLS (Howard et al., 2011). Although allopurinol prevents the formation of uric acid, existing uric acid must still be excreted. The level of uric acid may take 2 days or more to decrease, a delay that allows urate nephropathy to develop. Moreover, despite treatment with allopurinol, xanthine may accumulate, resulting in xanthine nephropathy (Pais et al., 2006). Although alkalizing the urine is theoretically logical, no controlled human studies exist to inform the decision of whether to attempt alkalinization (Wilson and Berns, 2012). Although alkalinization improves urate solubility, a high pH decreases the solubility of xanthine, hypoxanthine, and calcium phosphate, potentially increasing the likelihood of intratubular crystallization. If alkalinization is used in this setting, serum phosphorus should be carefully followed and should be stopped when hyperphosphataemia develops, to minimize the risk of acute phosphate nephropathy (Humphreys and Sanders, 2013).

Rasburicase is a recombinant form of *Aspergillus*-derived urate oxidase and is very effective in the prevention of TLS. Urate oxidase catalyses the oxidation of uric acid to allantoin, which is 5–10 times more soluble than uric acid and is readily excreted. The US Food and Drug Administration-recommended dosing guidelines for rasburicase in paediatric patients are 0.15 mg/kg or 0.2 mg/kg

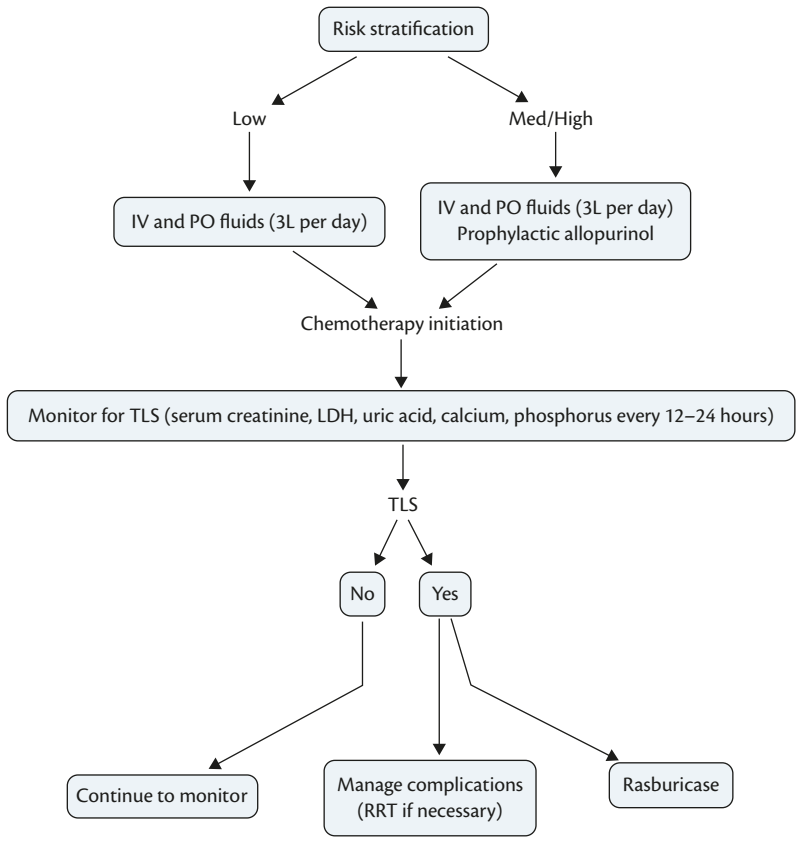

Fig. 227.1 Algorithmic approach to prophylaxis and treatment of tumour lysis syndrome (TLS). RRT = renal replacement therapy.
From Wilson and Berns (2012).

administered once daily for a maximum of 5 days. Treatment beyond 5 days or for more than one course of therapy is not recommended. The first dose of rasburicase should be administered 4–24 hours before starting chemotherapy. Rasburicase is given as an intravenous infusion over 30 minutes and should not be given as a bolus infusion. Currently, in the adult population, the dose often utilized in practice is 0.2 mg/kg. Compared with allopurinol, rasburicase lowers the serum uric acid levels more rapidly (Goldman et al., 2001). However, a Cochrane review (Cheuk et al., 2010) concluded that this area is hampered by the lack of randomized studies and that it is still unclear whether this translates into a reduction in mortality or renal failure. Clinicians should weigh the potential benefits of reducing uric acid and uncertain benefits of preventing renal failure or mortality from TLS against the potential risk of adverse effects.

The liberation of hydrogen peroxide which is induced by rasburicase can be devastating in patients with glucose 6-phosphate dehydrogenase (G6PD) deficiency, in whom the unchecked oxidative potential of hydrogen peroxide can lead to methaemoglobinaemia and haemolytic anaemia (Browning and Kruse, 2005; Elinoff et al., 2011). G6PD deficiency affects 400 million people worldwide, especially in regions with endemic malaria (Clark et al., 2009). Since most G6PD-deficient people have no history of haemolysis, testing before the administration of potent oxidizing agents (e.g. rasburicase) is warranted for patients at risk for G6PD deficiency, including those of African, Mediterranean, or Southeast Asian ancestry.

Acute phosphate AKI can also be part of the TLS and it has been suggested that wide use of rasburicase and urine alkalinization has resulted in a paradigm shift towards acute phosphate nephropathy in TLS-induced AKI (El-Husseini et al., 2012). TLS patients may develop recurrent ALS, a first episode secondary to spontaneous TLS-induced acute urate nephropathy, treated with rasburicase and allopurinol, and a second episode due to chemotherapy-induced TLS with acute phosphate nephropathy. A discussion of the association of AKI and electrolyte disturbances with many other anticancer drugs is beyond the scope of this chapter. Some of them are briefly discussed in Chapter 251. Comprehensive recent reviews are available in the literature and the reader is referred to these overviews (Lameire, 2010, 2011; Perazella and Moeckel, 2010; Humphreys and Sanders, 2013).

Prevention of acute kidney injury in tropical and emerging countries

Most causes of AKI in tropical and emerging countries are community-acquired. Many of the diseases causing tropical AKI are largely preventable, but doing so requires an integrated approach to reduce the disease burden. Such an approach requires a radical change in public policy and a change in focus away from hospital-based care and towards improvement of basic health needs, such as the provision of safe drinking water and improved sanitation, as well as improvements in the conditions of farm workers and the provision of obstetric care (Jha and Parameswaran, 2013; Lameire et al., 2013). Although preventive strategies for AKI in low-income countries are essentially the same as in high-income countries, they pose additional and unique ethical problems. Because healthcare is affected by social and economic factors, any intervention needs to address all health determinants, including educational, economic, and environmental factors (De Maeseneer and Flinkenflogel, 2010). Expensive interventions to prevent or treat AKI could affect the ability of a healthcare system to meet other needs. Conversely, the high mortality associated with primary diseases such as malaria and HIV/AIDS is frequently caused by serious AKI that cannot be treated because of a lack of dialysis facilities (Carter and Callegari, 2007). Because of the scarcity of resources and the presence of overwhelming health-related and other problems in these countries, prevention of AKI ought to target eradication of the most common causes (i.e. tropical and non-tropical infections), improve education and socioeconomic statuses, and support healthcare structures and access. In rural centres, primary-care physicians need to be able to treat common causes of AKI and to transfer individuals requiring critical care at the right time to hospitals with secondary and tertiary capacity to deal with AKI, including renal replacement therapy (De Maeseneer and Flinkenflogel, 2010). Innovative strategies, such as outreach programmes, improved transportation, involvement of community health workers, and strengthening of first-level health units, are needed to decrease the physical barriers to access of health services by marginalized populations. Special attention needs to be given to promotion of planned pregnancies with appropriate antenatal care by skilled midwives. Overall, most preventive efforts should focus at the primary healthcare level.

Because mass disasters cannot be predicted, they often overwhelm local healthcare systems, even in high-income countries. Such events necessitate careful advance planning and education and can need complex logistic measures once the disaster occurs. The Renal Disaster Relief Task Force of the International Society of Nephrology formulated comprehensive recommendations on how to react practically in difficult conditions (Sever and Vanholder, 2012).

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CHAPTER 228

Non-dialytic management of the patient with acute kidney injury

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Nutrition in acute kidney injury

Introduction

Patients suffering from severe and/or long-lasting diseases are at a high risk of malnutrition. This may be due to decreased physical activity, decreased food intake, and often the effects of the underlying disease. The impact of malnutrition on complication rate, length of hospital stay, and mortality has been demonstrated in various settings, including patients with AKI. Therefore, nutritional support has become an important cornerstone in the supportive therapy of hospitalized patients. Nutritional support aims to maintain or improve the nutritional status and preserve lean body mass. The therapeutic potential of nutritional support has been outlined in the last decade. With regard to this extended view, nutritional therapy should modulate immune functions, reduce oxidative stress, avoid metabolic derangements, improve endothelial function, and, last but not least, reduce mortality.

As the kidney plays a key role in the regulation of the metabolic environment profound changes in metabolism could be expected in acute kidney injury (AKI). Nutritional manipulations can both ameliorate or aggravate the patient's condition. Thus adequate nutritional therapy seems especially important in patients with AKI. In patients with chronic renal failure, protein-free diets were regarded as an alternative to dialysis until the 1960s. Nowadays, different and sophisticated treatment strategies are available. Although the goals are ambitious, the existing evidence regarding nutritional therapy in AKI is rare: 'we are unable to provide recommendations for the use of nutritional support for treating AKI' was the summary of a Cochrane Review published in 2012. (Li et al., 2012) Nevertheless, guidelines of both European (Cano et al., 2006) and American (Brown and Compher, 2010) Societies for Nutrition dealing with nutrition in AKI have been published and might serve as a recommendation in clinical practice. To illustrate the relatively weak evidence of the guidelines on nutrition in AKI, Box 228.1 summarizes the most recent Kidney Disease: Improving Global Outcomes (KDIGO) clinical practice guidelines on this topic (KDIGO Acute Kidney Injury Work Group, 2012).

Metabolism

Patients with AKI represent a very heterogeneous group ranging from patients with single-organ dysfunction to the critically ill with multiple organ failure. The latter often require respirator therapy and haemodynamic support in addition to renal replacement therapy (RRT). Such kinds of critical illness induce a characteristic metabolic stress response with increased protein breakdown (predominantly affecting muscle proteins) and consecutively negative nitrogen balance. This uniform response to severe stress or injury may be seen as an adaption to secure an optimal supply of amino acids as a source of acute phase proteins and a substrate for gluconeogenesis. This catabolic response is induced by the neuro-endocrinological system with increased concentrations of catabolic hormones (cortisol, adrenalin) and resistance to anabolic hormones (insulin, growth hormone). Furthermore, pro-inflammatory mediators such as cytokines or prostaglandins aggravate the catabolic condition.

In the case of AKI this catabolic response interacts with the ensuing acute uraemic state. Uraemic toxins alter protein, carbohydrate, and lipid metabolism pathways. Hypercatabolism may further be enhanced by imbalances in electrolyte and acid–base regulation. Additionally, extracorporeal circulation can lead to significant nutrient losses in patients treated with RRT.

In this complex setting termed 'protein-energy wasting', nutritional support should provide sufficient calories and nutrients without exacerbating metabolic derangements. The diagnosis of renal failure should never lead to restrictions in nutritional support with the aim of delaying initiation of RRT. Nevertheless nutrition has to be adapted to the presence and degree of renal failure. Typical complications of inadequate nutrition in AKI are:

- azotaemia (enhanced production of urea nitrogen)
- fluid overload
- electrolyte disturbances.

Taken together, patients with AKI often suffer from significant catabolism with protein-energy wasting. Nutritional requirements in AKI are determined more by the severity of the underlying disease than by AKI itself. Yet the decreased or missing regulation of the kidney leading to uraemia aggravates catabolic pathways and must be considered when providing nutritional support (Fiaccadori et al., 2008).

Nutritional assessment

Nutritional assessment should be the first step when planning nutritional therapy. Physical examination and determination of the body mass index may reveal undernutrition or obesity. The mid upper arm muscle area has been shown to estimate lean body mass. Furthermore, standard formulae such as the Subjective Global Assessment (SGA)

Box 228.1 KDIGO recommendations on nutrition in AKI patients

1. We suggest achieving a total energy intake of 20–30 kcal/kg/day in patients with any stage of AKI. (2C)*
2. We suggest avoiding restriction of protein intake with the aim of preventing or delaying initiation of RRT. (2D)**
3. We suggest administering 0.8–1.0 g/kg/day of protein in non-catabolic AKI patients without need for dialysis (2D), 1.0–1.5 g/kg/day in patients with AKI on RRT (2D), and up to a maximum of 1.7 g/kg/day in patients on continuous renal replacement therapy and in hypercatabolic patients. (2D)
4. We suggest providing nutrition preferentially via the enteral route in patients with AKI. (2C)

The strength of the recommendation (grade 1 or 2) and quality of the supporting evidence (A, B, C, D) according to the GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) system
2C*: weak strength of the recommendation and low quality of the supporting evidence.
2D**: weak strength of the recommendation and very low quality of the supporting evidence.

may be used to identify patients who are already malnourished at admission. Nevertheless, some of these standard methods of assessment may not be appropriate in the intensive care setting

Biochemical testing for malnutrition is covered by determination of albumin, cholesterol, and insulin-like growth factor 1. Yet it must be noted that serum concentrations of these markers are influenced by several non-nutritional factors such as hydration status or acute phase response. Therefore the usefulness of biochemical testing to reveal undernutrition has serious limitations in critically ill patients (Fiaccadori and Cremaschi, 2009).

Nitrogen balance as the difference between nitrogen input and output is an important marker of protein breakdown. Determination of urine urea is the standard procedure in hospitalized patients. In case of AKI, urea elimination by increased gastrointestinal secretion and RRT has to be considered. For that reason determination of nitrogen balance in patients with AKI is difficult in clinical practice.

It should be emphasized that even in patients without signs of malnutrition adequate nutrition therapy should be started before signs of malnutrition develop.

Energy requirements

Overfeeding in patients with AKI may result in serious metabolic complications such as hyperglycaemia, hypertriglyceridaemia, and pronounced azotaemia. Therefore caloric intake has to be adapted to the patient's needs.

Ideally energy requirements should be determined individually by indirect calorimetry. Unfortunately this procedure is not available for every patient with AKI in most hospitals. Furthermore, indirect calorimetry may not provide reliable results in patients on RRT due to the removal of carbon dioxide through the dialysis membrane. Thus energy requirement has to be estimated in the majority of patients (Strejc, 2005).

The caloric needs in patients with AKI are still controversial. Current studies could not confirm altered energy requirements in patients with AKI as a single organ failure. In contrast, oxygen consumption is markedly increased in patients with AKI and sepsis. These differences underline that caloric needs may be influenced more by the underlying disease than AKI itself (Fiaccadori et al., 2008).

As in other patient groups, basal energy expenditure G can be estimated using the Harris–Benedict equation:

$$\male\ G = 66.473 + (13.752 \times \text{weight in kg}) + (5.003 \times \text{height in cm}) - (6.755 \times \text{age in years})$$

$$\female\ G = 655.096 + (9.563 \times \text{weight in kg}) + (1.850 \times \text{height in cm}) - (4.676 \times \text{age in years}).$$

In patients with critical illness, multiplying the result with a factor of 1.2–1.3 seems appropriate.

In most patients with AKI it appears reasonable to adapt 20–30 kcal/kg/day to individual needs in case of underweight or obesity. The impact of RRT on energy requirements is not well defined. Heat loss may be a problem but is avoidable by temperature management in the extracorporeal circuit (Druml, 1999).

Macronutrients

Proteins

Massive protein breakdown is the predominant metabolic feature in the critically ill and may be aggravated in the presence of AKI. Moreover, protein synthesis of other than acute phase proteins is impaired. Negative nitrogen balance is clearly associated with worse outcome in critically ill patients with AKI. Achievement of a positive nitrogen balance seems to be a well-intentioned treatment goal but is often not feasible in the acute phase of illness. Typically the catabolic state cannot be overcome by simply providing exogenous substrates. Although there is still a lack of data concerning the optimal amount of protein supplementation in AKI it seems plausible to adapt this to the individual patient's situation. Both the degree of catabolism and the extent of amino acid loss by RRT have to be taken into account. This may be especially important in patients on continuous therapies. Using high-flux filters and high filtration rates, up to 5–10 g protein may be lost every day (Fiaccadori et al., 2011).

In patients with mild hypercatabolism and conservative therapy of AKI, provision of 0.8 g/kg protein seems appropriate. Protein nutrition should be increased to 1.0–1.5 g/kg in patients with moderate catabolism or undergoing RRT. In patients with severe hypercatabolism or on high-dose continuous RRT, 1.5–2.0 g/kg protein may be required. Although with even higher protein nutrition (> 2.0 g/kg) nitrogen balance may be improved in some patient groups, no reliable data are available concerning such regimens in patients with AKI. At present, such high-protein regimens can therefore not be recommended (Fiaccadori et al., 2008).

AKI induces changes in the amino acid profile. Some non-essential amino acids such as tyrosine become 'conditionally' essential in AKI. Therefore 'Nephro-Solutions' for parenteral nutrition with special proportions of essential and non-essential amino acids have been designed. To date, there are no convincing data that such solutions have any positive impact in patients with AKI (Druml 2010). The main advantage of 'Nephro-Solutions' may be the reduced fluid content allowing nutritional therapy in oliguric patients. There is also no evidence to enrich nutrition with glutamine, histidine, or arginine.

Carbohydrates

Insulin resistance and increased hepatic gluconeogenesis are characteristic for both stress response and AKI. Therefore hyperglycaemia is a frequent complication in such patients even in the absence of previously known diabetes. It is still unknown whether hyperglycaemia directly induces harm or rather represents a marker of disease severity and stress response. Nevertheless, the deleterious sequelae of hyperglycaemia with regard to impaired infection control and increased mortality have been well documented in various patient groups (Brealey and Singer, 2009). It seems thus plausible to treat hyperglycaemia in the critically ill, and to this end most patients with AKI will require continuous insulin therapy. Unfortunately there is still a lack of data defining the appropriate target range of blood glucose levels. Recently published trials like the NICE-SUGAR study failed to demonstrate a benefit for intensive insulin therapy with a target glucose range between 80 and 110 mg/dL (4.45–6.1 mmol/L) (Finfer et al., 2009). On the other hand, the potential hazards of intensive insulin therapy, namely episodes of hypoglycaemia, were clearly documented. This complication seems to be of importance; a consistent finding is that hypoglycaemia associates with increased mortality (Finfer et al., 2012). Therefore stringent glycaemic clinical protocol control are necessary during nutritional therapy and insulin administration in the critically ill.

Balancing potential benefits and risks, a blood glucose target range of 110–150 mg/dL (6.1–8.33 mmol/L) might be appropriate and has been recommended in the KDIGO practice guideline for AKI (KDIGO Acute Kidney Injury Work Group, 2012).

Recent research has demonstrated that hyperglycaemia, hypoglycaemia, and increased glycaemic variability have each been independently associated with increased risk of mortality in critically ill patients (Krinsley 2011). In a recent retrospective multicentre analysis, the impact of diabetic status on these three glycaemia domains was explored. (Krinsley et al., 2013). Among patients with diabetes, mean blood glycaemia from 80 to 110 mg/dL (4.41–6.1 mmol/L) was associated with increased risk of mortality and while a mean blood glycaemia from 110 to 180 mg/dL (6.1–10 mmol/L) was associated with decreased risk of mortality. Hypoglycaemia, defined as minimum blood glucose < 70 mg/dL (< 3.89 mmol/L), was independently associated with increased risk of mortality among patients with and without diabetes and increased glycaemic variability, defined as coefficient of variation > 20%, was independently associated with increased risk of mortality only among patients without diabetes. These findings suggest thus that patients with diabetes may benefit from higher glucose target ranges than will those without diabetes and that not a single blood glucose domain in critically ill patients should be targeted. Depending on the glucose concentration in dialysis and replacement fluids, either loss or absorption of glucose may occur during RRT. These effects must be taken into account and blood glucose measurements should be intensified when RRT procedures are changed in order to prevent severe blood glucose derangements (Wooley et al., 2005).

Lipids

Patients with AKI typically show an impaired lipolysis with increased serum concentrations of triglycerides and very low-density lipoprotein. The activity of both peripheral lipoprotein lipase and hepatic triglyceride lipase is reduced (Druml et al., 1983). This finding may also affect the ability to metabolize exogenous lipid emulsions. Nevertheless, lipids serve as an important energy substrate in patients with AKI. About 30–35% of energy supply should result from lipids (Fiaccadori et al., 2011). Triglyceride levels should be monitored under nutritional therapy. The administration of lipids has to be stopped when triglyceride concentrations exceed 400 mg/dL (4.52 mmol/L). Although the application of medium chain triglycerides theoretically may have some advantages, there are no clinical data available supporting this concept.

Micronutrients

The term micronutrients covers a heterogeneous group of substances such as electrolytes, vitamins, and trace elements. During AKI two problems may arise: firstly, the demand of such substances may vary depending on the severity of illness; secondly, RRT may lead to significant losses of micronutrients with the filtrate or dialysate.

Electrolytes such as potassium, phosphorus, and magnesium tend to accumulate in patients with AKI due to impaired renal excretion. Conversely, significant losses of these electrolytes may occur when RRT is initiated. Therefore electrolyte concentrations should be closely monitored during RRT and adequate substitution should be started when required in order to maintain the levels within the desired range (Lopez et al., 2011).

Only limited data regarding the requirements for vitamins and trace elements in patients with AKI are summarized (e.g. Gervasio et al., 2011). *In vitro* studies have shown that selenium, copper, chromium, and zinc are removed by RRT. This may explain the low serum levels of these micronutrients found in patients on continuous extracorporeal therapies. Nevertheless, the clinical relevance of these findings remains unclear. The same is true for vitamins. Water-soluble vitamins such as vitamin C, folic acid, and thiamine are lost in the extracorporeal circulation. Taking into account the low toxicity of most water-soluble vitamins and trace elements it may be advisable to administer a double dose of commercial preparations in patients on RRT. Vitamin C may be an exception—due to the risk of secondary oxalosis, the intake should be restricted to < 250 mg/day (Chiolero and Berger, 2007).

Although the results of some smaller studies are promising there is not enough evidence to recommend the routine administration of vitamin E, vitamin D, selenium, or thiamine in supraphysiological doses.

Practical aspects

Although studies could not demonstrate a difference in mortality comparing enteral with parenteral nutrition, enteral feeding should be the preferred route of nutritional therapy in patients with AKI (Casaer et al., 2008). Enteral application of nutrients may help to maintain the integrity of the gastrointestinal system and might reduce bacterial translocation. Furthermore, enteral feeding is associated with fewer complications and lower costs than parenteral nutrition. According to the patient's fluid status both standard formulae for critically ill patients or formulae designed for patients with chronic renal failure (high protein content, reduced volume and electrolytes) may be used.

Reduced gastrointestinal motility is a frequent complication in the critically ill. Under these circumstances sufficient enteral nutrition is often not feasible. In such cases nutrition should be supplemented by parenteral fluids in order to meet the patient's needs. Even total parenteral nutrition is frequently necessary in the first

phase of critical illness. The optimal time point of start of parenteral nutrition is still under debate. Actually recommendations differ between countries. European societies promote early start of parenteral nutrition (within 2 days) while American/Canadian guidelines suggest that parenteral nutrition should start later in the intensive care unit (ICU) course (generally after the first week). Recently, the EPANIC study reported an association between late initiation of parenteral nutrition (starting on day 8) with faster recovery and fewer complications such as infections or cholestasis compared to early initiation within 48 hours after admission. However, some points in this trial have to be considered. Firstly, mean ICU stay was only 3–4 days in this trial. Therefore the study population may not reflect the typical patient with critical illness. Furthermore, the patients in the 'early initiation group' received a rather hypercaloric nutrition with a high glucose content, Nevertheless, the results of this study would favour a 'late' start of parenteral nutrition (Casaer et al., 2011). A recent follow-up analysis of the EPANIC study (Gunst et al., 2013) showed that early parenteral nutrition did not affect the time course of creatinine and creatinine clearance but did increase plasma urea, urea/creatinine ratio, and nitrogen excretion beginning on the first day of amino acid infusion. In the group that received late parenteral nutrition, infusing amino acids after the first week also increased ureagenesis. During the first 2 weeks, ureagenesis resulted in a net waste of 63% of the extra nitrogen intake from early parenteral nutrition, indicating substantial catabolism of the extra amino acids, which leads to higher levels of plasma urea, probably explaining the previous finding of a prolonged duration of RRT observed with early parenteral nutrition.

A comprehensive checklist for nutritional therapy in AKI is provided in Fig. 228.1.

Infection control

Severe sepsis and septic shock are the leading cause of death in non-coronary ICUs (Russell, 2006) and severe infections and sepsis may lead to multiple organ dysfunction and AKI (see also Chapter 244). On the other hand, AKI predisposes patients to infectious complications. Both conditions are feared syndromes in an ICU and dramatically increase morbidity and mortality. Although increasingly investigated (Levy et al., 1996; Mehta et al., 2011), the pathogenetic mechanisms behind both conditions (septic AKI and AKI leading to sepsis) are not fully understood. The following sections will therefore deal with the epidemiology and management of AKI in patients with severe infections and sepsis. Mechanisms of infectious complications in patients with AKI and their prevention and management will also be discussed.

Epidemiology of severe sepsis/septic shock

As described in detail in Chapter 244, severe sepsis and septic shock are the leading cause of death in non-coronary ICUs and accounts for about 60,000 annual deaths in Germany (Engel et al., 2007). The mortality from severe sepsis is still unacceptably high and ranges around 50% (Russell, 2006; Engel et al., 2007). Septic AKI is usually part of the multiple organ dysfunction syndrome and is the most common cause of AKI in an ICU. The prevalence of renal dysfunction in sepsis is continuously increasing and has been consistently shown to be around 40–60% of patients (Schrier and Wang, 2004; Uchino et al., 2005; Wan et al., 2008). Amongst the failing organ systems, AKI is one of the most feared and life-threatening manifestations. Despite optimal supportive therapy and modern RRT the mortality remains unacceptably high. A number of studies have demonstrated that AKI is an independent risk factor for mortality, increasing the likelihood of a fatal outcome to 60–80% and more (Schrier and Wang, 2004; Gordon et al., 2010).

On the other hand, however, severe infections are not only the cause of AKI, but also feared sequelae of acute deterioration of renal function. There is sound evidence that AKI itself may have direct and indirect immunological consequences with an increased infection rate (Rabb, 2002; Kelly, 2003). Furthermore, application of RRT has effects on host immunity. Infections related to the vascular access or fluids are not to be underestimated.

Mechanisms of infectious complications after AKI

There is increasing evidence that AKI has severe consequences regarding host immunity. Mehta et al. (2011) found that 40% of the patients with AKI developed sepsis during their course of ICU stay. There seems to be a close interaction between the failing kidneys on one hand and remote organs such as heart, lungs, and the immune system on the other hand. As described in detail in Chapter 244, it was shown that experimental bilateral renal ischaemia affects immunological and inflammatory processes in the heart, lung, and liver (Kelly, 2003). Impaired monocyte cytokine production and elevated plasma cytokine levels have been associated with AKI (Himmelfarb et al., 2004). In patients with septic AKI, neutrophil function was impaired when compared to patients with sepsis, but without AKI (Rossaint et al., 2011).

Volume overload associated with AKI has long been recognized as a risk factor for infectious complications (Bouchard et al., 2009). Potential mechanisms may be soft tissue and gut oedema leading to subsequent translocation of bowel flora into the circulation and therefore, facilitating sepsis and multiorgan failure. Also, metabolic acidosis carries an increased risk of infections.

RRT itself and vascular access may contribute to the high prevalence of infections in patients with AKI. Contaminated dialysis and substitution fluids are nowadays only very rare causes of septic complications.

Diagnosis of infections in patients with AKI

The mortality of patients with AKI who remained without infection was 21% compared to 44% in patients who developed sepsis after the diagnosis of AKI in one study (Mehta et al., 2011). It seems therefore prudent to look for and treat infections in patients with AKI.

In mixed or medical ICUs, the most common focus of sepsis is the lung. In ambulatory patients, community-acquired pneumonia is the most frequent focus (Engel et al., 2007; Pletz et al., 2011). In surgical patients, the abdominal infections or when the patient is ventilated, ventilator-associated pneumonia, are the most frequent origins of sepsis, but also urinary tract infections (UTIs) including pyelonephritis show a high prevalence in AKI patients. Therefore, careful physical examination of lungs, abdomen, and kidneys is needed. Regular microbiological examination of tracheal aspirations and abdominal secretions are of high importance, first to diagnose infections and second to guide treatment. Urine microscopy and culture are essential for the diagnosis and therapy of UTIs. Patients with endocarditis may experience AKI. In these cases, a newly diagnosed heart murmur warrants prompt echocardiography and repeated blood cultures.

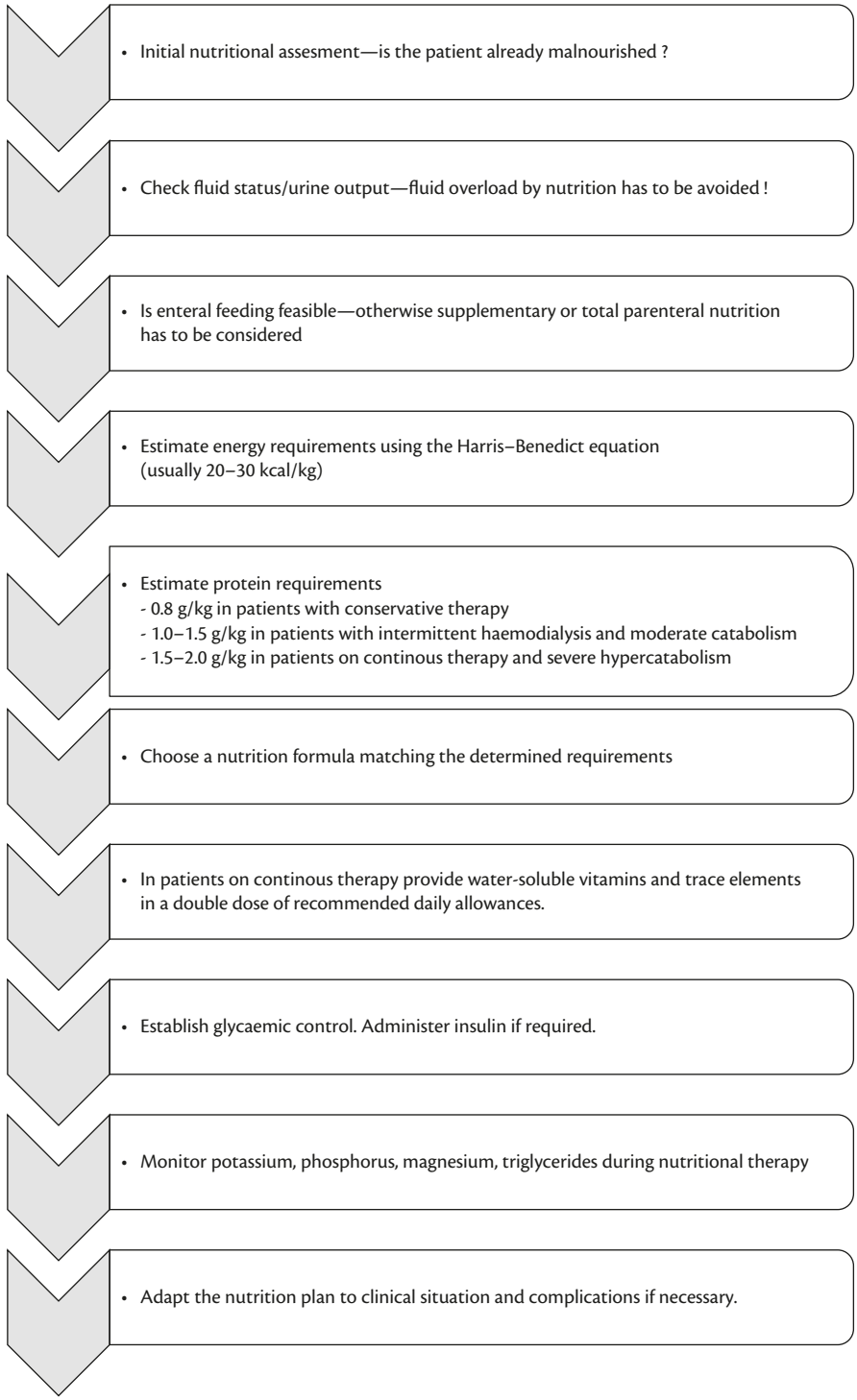

Fig. 228.1 Checklist for nutritional therapy in AKI.

Management of infections in patients with AKI

The cornerstone of non-dialytic management of AKI is antimicrobial chemotherapy, restoration of circulation, prevention of further infections, and avoidance of nephrotoxicity.

Antibiotic therapy

Several lines of evidence show that prompt and effective antibiotic therapy in patients with severe sepsis improves the outcome (Kollef, 2003; Kumar et al., 2006, 2010). A recent paper showed that the mortality rate due to sepsis-related as well as non-sepsis-related organ failure was improved under prompt and effective combination antibiotic therapy compared to monotherapy (Kumar et al., 2010). Antibiotic treatment should be initiated rapidly within the first hour of diagnosis with a broad-spectrum agent, preferably after obtaining cultures. High antibiotic levels at the site of infection are required. Patients should thus receive the full loading dose

of antibiotics regardless of their renal function for the first 24 hours. Also, the chosen antibiotic needs to penetrate into the infected tissue. In experimental settings, bactericidal antibiotic treatment resulted in more inflammation compared to no antibiotics. The resolution of renal dysfunction, however, was faster and correlated with survival (Peng et al., 2012). To administer a bactericidal broad-spectrum antibiotic early, therefore, seems to be a prudent approach. One should be cautious in avoiding nephrotoxic drugs.

The need for haemodynamic stabilization

Rapid infusion of crystalloid fluids is recommended, avoiding, however, fluid overload. Administration of hydroxyethyl starch should be avoided in sepsis as large prospective randomized studies have indicated that their use in critically ill patients is associated with worse outcomes including a significant increased risk of mortality and AKI (Brunkhorst et al,. 2008; Myburgh et al., 2012; Perner et al., 2012; Zarychanski et al., 2013). As the main phenomenon of circulatory collapse in sepsis is peripheral vasodilation, vasopressor support using norepinephrine (noradrenaline) is almost always needed. Vasoconstriction and hence increasing blood pressure does not expose the kidneys to increased stress (Bellomo et al., 2008). In fact, there is evidence that low-dose vasopressor support is beneficial in (septic) AKI. It may be hypothesized that this is due to vasoconstriction in the efferent arteriole (see Chapter 244).

Prevention of infectious complications of AKI

The prevention of infections is of utmost importance in critically ill patients with AKI. Therefore certain hygiene measures must be considered. It has been shown that repeated punctures for the insertion of central venous catheters increases the risk of catheter-related infections (Rebmann and Murphy, 2010; Vanholder et al., 2010). If possible, ultrasound-guided insertion should, therefore, be preferred. Sterile handling of the catheter is also needed. If cuffed catheters are less prone to be contaminated in an ICU is not yet known.

Drug dosing in acute kidney injury

Drug dosing in patients with AKI is complex and difficult: residual kidney function can be highly variable and may change from day to day; volume status of patients may fluctuate because of changes in diuresis, extracorporeal water removal, or extracellular fluid shifts; protein binding of drugs may be altered due hypoproteinaemia, by the presence of competing uraemic toxins, or both; and finally, drugs may be removed to a variable degree by extracorporeal procedures. As a consequence, the decision on dosing must take into account the patient's individual clinical characteristics, the mode of RRT, and the specific pharmacokinetic as well as pharmacodynamic characteristics of the drug to be administered.

The most important medications to be considered in the setting of critically ill patients with AKI are antibiotics, antifungal drugs, and antiviral drugs; sedatives and analgesics; and anticoagulants. However, all drugs that are eliminated by ≥ 25% via the kidney and/or have active metabolites which are renally eliminated might require dose adjustment. As infectious complications are a common and important threat in patients with AKI the following discussion will focus on antimicrobial chemotherapeutics. Information on pharmacokinetics in normal and abnormal renal function and in patients on RRT of individual drugs can be found in several handbooks.

Anticoagulants are discussed in detail in Chapters 233 and 234 and in the recent KDIGO clinical practice guidelines for acute kidney injury (KDIGO Acute Kidney Injury Work Group, 2012)

Pharmacokinetic considerations

Patients with AKI constitute a heterogeneous population who may exhibit pharmacokinetic profiles that are quite different from those in chronic renal failure or in healthy people (Boucher et al., 2006) (Box 228.2). Absorption of orally administered drugs may be reduced as a consequence of decreased intestinal perfusion and gastrointestinal dysmotility, common findings in critically ill patients that may be related to the underlying disease (e.g. circulatory shock) and/or the administration of vasopressors. Conversely, mucosal integrity might be compromised in the uraemic milieu, leading to increased absorption of certain drugs. Moreover, bioavailability of orally administered drugs may vary based on the type of enteral feeding chosen and/or oral co-medications such as H_2-receptor blockers and proton pump inhibitors.

Another area of uncertainty in critically ill patients is the volume of distribution especially for hydrophilic drugs (Roberts and Lipman, 2009). Often these patients experience considerable volume shifts from the intravascular space to the interstitium, for example, as a consequence of endothelial damage and capillary leakage in sepsis. This problem may be compounded by gains in total body water due to oliguria/anuria and/or large volumes of fluid resuscitation administered. Of note, fluid accumulation is not only a frequent finding in critically ill patients with AKI but is also related to increased mortality (Bouchard et al., 2009). Moreover, the volume of distribution of drugs may vary substantially based on decreased binding to serum proteins. Critically ill patients often display reduced levels of serum albumin which may be due to reduced albumin synthesis and/or increased extracellular shifts affecting protein binding of a given drug. In addition, protein binding may be altered by the accumulation of uraemic toxins that compete with drugs for binding sites (Ulldemolins et al., 2011).

Another facet of pharmacokinetic alterations in AKI is changes in non-renal elimination. Critically ill patients may have reduced

Box 228.2 Pharmacokinetic considerations in AKI

- Altered absorption of orally administered drugs:
  - Gastrointestinal dysmotility
  - Decreased intestinal perfusion
  - Compromised mucosal integrity
- Altered volume of distribution:
  - Gains in total body water
  - Volume shifts from intravascular space to the interstitium
  - Decreased binding to serum proteins
- Changes in renal elimination
- Changes in non-renal elimination:
  - Reduced hepatic blood flow
  - Extracorporeal drug elimination by RRT.

hepatic blood flow contributing to reduced hepatic drug metabolism. Finally, many drugs that are primarily eliminated by the kidneys are also removed by RRT. In general, extracorporeal drug clearances will be particularly relevant for low-molecular-weight compounds with a low degree of protein binding and a small volume of distribution. However, the chosen mode of RRT plays a major role in determining the amount of drug that is extracted. Diffusive therapies such as haemodialysis eliminate small-molecular-weight compounds more efficiently while convective therapies such as haemofiltration and haemodiafiltration also effectively remove middle-sized molecules (up to 15 kDa or even above). Moreover, the flux characteristics of dialysers and haemofilters (i.e. high flux versus low flux) as well as their adsorptive capacity will impact on drug clearances. Finally, the amount of drugs removed will largely be determined by the intensity of RRT, that is, dialysate and filtrate flow rates as well as treatment duration.

Pharmacodynamic considerations

In addition to the aforementioned pharmacokinetic considerations some pharmacodynamics aspects are of considerable importance. Most chemotherapeutics exert their antimicrobial activity either in a concentration-dependent or time-dependent fashion. Administration of the former group should therefore aim to achieve a high ratio of peak serum concentration to minimum inhibitory concentration (MIC), whilst for the latter group the percentage of the dosing interval above the MIC is most important to achieve therapeutic success (Roberts and Lipman, 2009). Examples for antibiotics with concentration-dependent antimicrobial activity are fluoroquinolones, aminoglycosides, and lipopeptides; antibiotics with time-dependent antimicrobial activity include penicillins, cephalosporins, carbapenems, glycopeptides, and oxazolidinones.

Practical drug dosing strategies

A decision tree for practical drug dosing in AKI is depicted in Fig. 228.2. As a first step, a careful evaluation of the patient's body weight, fluid status, and present kidney function is mandatory. The latter, however, is difficult as currently available formulae for estimation of glomerular filtration rate (GFR) are not validated for patients with AKI. Moreover, kidney function may change rapidly in a given patient. A reasonable strategy may thus be to estimate GFR based on the mean serum creatinine value measured at the beginning and end of an assessment interval that might well be < 24 hours in a rapidly changing situation (Matzke et al., 2011). Secondly, drug-specific pharmacokinetic and pharmacodynamic properties must be considered. In nearly all cases a loading dose of at least the magnitude recommended for patients with normal kidney function should be administered. As the volume of distribution especially for hydrophilic drugs will be increased in most critically ill patients with AKI, current KDIGO guidelines recommend an aggressive approach, that is, the initial loading dose at least for hydrophilic antibiotics such as penicillins, cephalosporins, and carbapenems should even be 25–50% greater than normal (Matzke et al., 2011). In a third step, adaptation of consecutive dosing must be considered on the basis of individual patient characteristics as well as the specific mode of RRT. In many situations where a patient suffers from life-threatening infection, maintenance regimens should be initiated at normal or near-normal dosing range, at least for compounds with limited potential for toxicity. In patients undergoing continuous RRT, the total creatinine clearance (renal + extracorporeal) can be calculated and dosing of dialysable drugs performed accordingly (Eyler and Mueller, 2011). In patients receiving intermittent haemodialysis, a post-dialysis supplementary dose should be administered on top of the estimated maintenance dose to account for the amount of drug removed during the dialysis procedure. For many dialysable antibiotics this post-dialysis dose will be similar to the loading dose. Of course, whenever possible, therapeutic drug monitoring should be performed to best guide the therapy. If in doubt, the chosen dose should rather be at the upper end of the considered range than at the lower end in order to achieve therapeutic targets, to prevent antibiotic resistance, and to optimize patient outcomes.

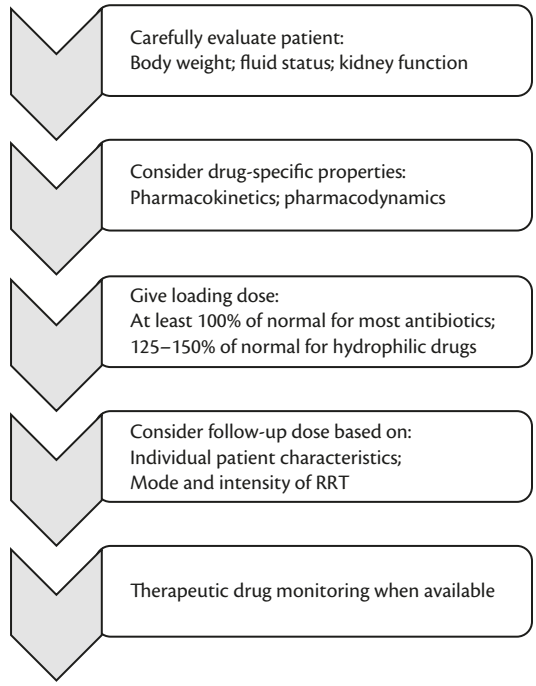

Fig. 228.2 Decision tree for drug dosing in AKI (see also Chapter 364).

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CHAPTER 229

Fluid overload in acute kidney injury

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Introduction

A central objective in the management of patients with acute kidney injury (AKI) is the restoration and maintenance of adequate systemic and renal perfusion. This is particularly important because in AKI the autoregulatory mechanisms to maintain a relatively constant renal blood flow despite changes in systemic blood pressure may be impaired, leaving these patients at increased risk of hypotension-induced kidney damage. In critically ill patients, the management of blood pressure and cardiac output can usually only be achieved by parallel administration of fluids and vasoactive drugs. Their adequate titration to the individual patient's needs, however, requires careful monitoring of fluid and haemodynamic status as vasopressors may further reduce renal perfusion if the circulating blood volume is reduced. Conversely, however, patients with AKI are often oliguric and thus at increased risk for fluid overload.

Fluid overload and clinical outcomes

In the past, the view has often prevailed that the negative effects of insufficient circulating blood volume outweigh the risks associated with continued fluid resuscitation despite increased intravascular volume. In recent years, it has become apparent that in critically ill patients with AKI there appears to be a direct link between fluid overload and mortality. This correlation was not only found in retrospective studies; a recent multicentre, prospective, observational study showed that critically ill AKI patients with fluid overload (> 10% increase in body weight) had significantly increased mortality within 60 days of enrolment (Bouchard et al., 2009). Also among dialysed patients, survivors had significantly lower fluid accumulation at initiation of acute dialysis compared to non-survivors. Importantly, fluid overload at AKI diagnosis was not associated with improved recovery of kidney function, but patients with fluid overload at peak serum creatinine were even less likely to recover kidney function (Bouchard et al., 2009). Similar results could be derived from the SOAP (Sepsis Occurrence in Acutely Ill Patients) study, a multicentre, observational cohort study in 3147 intensive care unit (ICU) patients. Overall, 1120 patients (36%) had AKI at some point during ICU treatment. In these patients, mortality at 60 days was significantly increased (36% compared to 16% in patients without AKI). In these patients, mean daily fluid balance was significantly more positive among non-survivors than among survivors, and in addition to age, a positive fluid balance was among the strongest prognostic factors for death (Payen et al., 2008).

A particular risk associated with excessive fluid resuscitation is the development of lung oedema with consecutive deterioration of pulmonary gas exchange. In a randomized study of 1000 patients with acute lung injury, the Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network compared a conservative and a liberal strategy of fluid management. The mean cumulative fluid balance during the first 7 days was −136 ± 491 mL in the conservative strategy group and 6992 ± 502 mL in the liberal strategy group. Although there was no significant difference in 60-day mortality, the conservative strategy improved the oxygenation index, the lung injury score, and shortened the duration of mechanical ventilation and intensive care without increasing non-pulmonary organ failures (Wiedemann et al., 2006). All the above discussed findings suggest that fluid overload may not just be a marker of disease severity, but rather a contributing factor to the high mortality of critically ill patients with AKI. However, this hypothesis will have to be confirmed by prospective, randomized clinical trials. Until such studies are available, the avoidance of fluid overload in patients with AKI seems prudent and should be the standard of care for these patients (Schrier, 2009, 2010).

Causes for fluid overload in patients with acute kidney injury

Fluid resuscitation is usually necessary to stabilize the patient with critical illness, particularly those with severe sepsis or septic shock who constitute approximately half of the patients with AKI in ICUs. Whilst early fluid resuscitation has long been a standard treatment in the management of hypotensive patients, protocolized haemodynamic management strategies have become widely used since the landmark study of Rivers and colleagues who demonstrated that early goal-directed therapy (EGDT) with predefined physiologic endpoints may prevent organ failure and improve the outcome of patients with septic shock (Rivers et al., 2001). Of note, in this study, EGDT resulted in more rapid use of fluids during the first 6 hours of treatment (4981 ± 2984 mL compared to 3499 ± 2438 mL in the standard therapy group), while the total volume administered during the first 72 hours was not different (13358 ± 7729 mL versus 13443 ± 6390 mL). However, rapid and aggressive fluid administration can be associated with oedema formation in tissues and organs, with the consequence of deleterious effects on organ function (Box 229.1). As blood volume is unable to expand much, haemodilution can be achieved with relatively small amounts of fluid infusion. Any further increase in blood volume then leads to oedema formation which will increase proportionally with the amount of further fluid administration. This is especially the case in the presence of altered capillary permeability, a frequent problem in patients

Box 229.1 Clinical sequelae of tissue oedema

- Impairment of pulmonary gas exchange
- Weaning failure
- Impairment of mental status
- Bowel dysfunction/impaired intestinal resorption
- Abdominal compartment syndrome
- Myocardial dysfunction
- Impaired wound healing
- Risk for decubital ulcers
- Muscle weakness/impaired mobilization.

with severe infections. Moreover, the problem of over-hydration will be compounded if oliguria develops and fluid infusion is not reduced accordingly. Overall, the relationship between volume status and the development of complications resembles a U-shaped curve indicating that there is only a fine margin between hypovolaemia and over-hydration, both of which will lead to complications (Fig. 229.1). As a consequence, hydration status must be carefully monitored and infusion strategies closely adapted to patients' needs (Glassford and Bellomo, 2011; Prowle et al., 2012).

Assessment and monitoring of hydration status

(See also Chapter 222.)

Clinical and laboratory findings

Intravascular fluid loss (either absolute or relative) typically triggers compensatory mechanisms to maintain adequate tissue perfusion and oxygenation. Fluid losses of > 15% of the blood volume will lead to reduced jugular vein filling and cardiac preload as well as stroke volume. In order to maintain cardiac output, a sympathetic response will be mounted leading to tachycardia and peripheral vasoconstriction. The mucous membranes become increasingly dry and skin turgor decreases. As signs of reduced renal perfusion, a decreased urinary output, an increased urinary osmolality, a decreased urinary sodium excretion and a metabolic alkalosis can be observed. Laboratory signs of haemoconcentration such as hypernatraemia, hyperproteinaemia, and high haematocrit may be present. Unfortunately, however, some of these typical signs are not reliable indicators in the critically ill as both underlying disease as well as therapeutic measures may interfere. Hypervolaemia may manifest itself in visible engorgement of jugular veins and tissue oedema including formation of pleural effusions and ascites. Pulmonary gas exchange can be impaired, and typical auscultation findings may be present. Serum biochemistry can show signs of haemodilution (hyponatraemia, hypoproteinaemia, and low haematocrit), but again these may not be reliable indicators.

Finally, two simple but important tools to monitor the time course of hydration status are the careful and precise evaluation of daily fluid intake/fluid output and body weight of the patient. The latter parameter is not always measurable in the often immobilized, critically ill ICU patient.

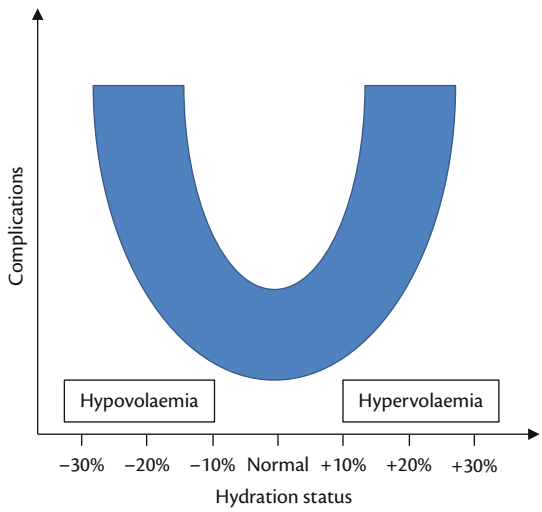

Fig. 229.1 Hydration status and rate of complications.

Haemodynamic parameters

In the critically ill patient with AKI, haemodynamic monitoring will usually at least comprise of central venous cannulation and invasive blood pressure measurement. In some cases, advanced haemodynamic monitoring using pulmonary artery catheterization or less invasive advanced haemodynamic monitoring techniques will be used, for example, in patients with shock and/or pre-existent heart disease. Less invasive techniques such as the PiCCO system (Pulsion Medical Systems, Munich, Germany) are based on pulse wave/contour analysis and allow the assessment of cardiac output and derived variables such as intrathoracic blood volume and extravascular lung water indexes.

Central venous pressure (CVP) and pulmonary capillary wedge pressure (PCWP) are clinically used in the assessment of fluid status as they are thought to reflect right ventricular (CVP) and left ventricular (PCWP) filling pressures. However, it has to be kept in mind that there is only a weak correlation between cardiac filling pressures and volumes (Kumar et al., 2004). Moreover, these measurements are only reliable in the absence of cardiac obstructions or valve disorders.

Invasive blood pressure measurement enables continuous monitoring of blood pressure and is generally more reliable than intermittent non-invasive measurement, in particular when the patient is hypotensive and/or requiring vasopressors. Additionally, in patients on mechanical ventilation, the evaluation of arterial blood pressure waveforms may help in the assessment of fluid balance as during inspiration, increased intrathoracic pressure reduces cardiac preload and stroke volume, an effect that is enhanced by hypovolaemia. Consequently, variations in pulse pressure and stroke volume may be helpful in guiding fluid administration. Likewise, continuous monitoring of cardiac output may also help to guide therapy with fluids and catecholamines. Of note, evaluating the time course of these parameters is generally more helpful than a single measurement as the response to therapeutic interventions can be closely observed. A simple bedside test to assess the need for further fluid resuscitation is passive leg raising to increase cardiac preload and observing its effects on haemodynamic parameters. Studies have

shown that changes in aortic blood flow induced by passive leg raising predict fluid responsiveness in ventilated patients (Monnet et al., 2006).

Radiological examination and ultrasound

A chest radiograph in a patient with fluid overload may show evidence of interstitial oedema with loss of definition of large pulmonary vessels, the appearance of septal lines, and interlobular septal thickening. In alveolar pulmonary oedema, increased vascular shadowing may impose as a classical bat wing peri-hilum pattern. Upper lobe blood diversion may be observed, indicating increased blood flow to the superior parts of the lung. Moreover, opacification of both lungs may occur, sometimes with increasing density towards the lung bases due to the presence of pleural effusions.

The diameter of the inferior vena cava (IVC) may vary in response to changes in intravascular volume. The sonographic measurement of IVC diameter and collapsibility is therefore often used as simple, rapid method to assess volume status. Whilst suffering from a considerable interpatient variability and being vulnerable to artefacts induced by chronic heart conditions or positive-pressure ventilation, a recent meta-analysis of clinical studies indicated that IVC diameter is consistently low in hypovolaemic status when compared with euvolaemic patients (Dipti et al., 2012). Inadequate dilatation of the IVC by fluid resuscitation might indicate insufficient circulating blood volume.

Quantification of preload can also be attempted by echocardiography assessing either left ventricular end-diastolic area or volume, however, this technique is rather investigator dependent. Moreover, echocardiography can be useful to visualize ventricular function and cardiac filling and even guide acute fluid resuscitation in haemodynamically critical situations.

Treatment of fluid overload

Fluid restriction

When a patient is diagnosed as being fluid overloaded, the first measure should be to restrict further fluid administration. To this end, oral fluid intake should be limited, and enteral nutrition solutions with high caloric content per volume chosen. Likewise, if total parenteral nutrition is required, preference should be given to highly concentrated solutions. Intravenous drugs (e.g. antibiotics) should be prepared and administered in the minimum fluid volume possible.

Diuretic therapy

Diuretics are frequently used in patients with AKI to facilitate fluid management and to 'create space' for medications and nutrition (Mehta et al., 2002; Uchino et al., 2004). As oliguric AKI has been shown to carry a worse prognosis than non-oliguric AKI, diuretics are also often prescribed to convert oliguric to non-oliguric AKI; however, even if this proves successful overall outcomes may not improve. Moreover, loop diuretics may decrease oxygen consumption in the loop of Henle by inhibiting sodium transport and thus may protect against AKI. However, randomized controlled trials showed that treatment with furosemide for AKI prevention or treatment is ineffective or even harmful (Cantarovich et al., 2004; Ho and Sheridan, 2006). The Kidney Disease: Improving Global Outcomes (KDIGO) guidelines therefore recommend not using diuretics to prevent AKI or to treat AKI, except in the management of volume overload (KDIGO Acute Kidney Injury Work Group, 2012 see Chapter 226). In such patients, a prudent approach would be a trial of, for example, furosemide with the aim of increasing diuresis. To this end, a single intravenous dose of 40 mg followed by a continuous infusion of up to 40 mg/hour may be tried. However, if a significant increase in urinary output cannot be achieved within 12–24 hours this treatment should be discontinued. A prolonged high-dose administration is not recommended as this might lead to side effects such as hearing loss.

Natriuretic peptides

Natriuretic peptides are presently evaluated for clinical use in the treatment of chronic heart failure or renal dysfunction and could potentially be useful to prevent or treat AKI. Atrial natriuretic peptide (ANP) was tested in a randomized placebo-controlled trial of 504 critically ill patients with AKI that failed to show a beneficial effect of ANP administration on 21-day dialysis-free survival, mortality, or kidney function (Allgren et al., 1997). Of note, subgroup analysis suggested that dialysis-free survival was significantly higher in the ANP group for patients with oliguria. However, subsequent trial of ANP in 222 patients with oliguric renal failure again failed to demonstrate any benefit (Lewis et al., 2000).

Two other natriuretic peptides that have been undergoing limited clinical testing are urodilatin and nesiritide (brain natriuretic peptide). The evidence today does not support their routine use to prevent or treat AKI, as is also recommended by the KDIGO guidelines (see chapter 226).

Extracorporeal fluid removal

If the conservative measures are not sufficient to treat fluid overload, extracorporeal fluid removal using sequential ultrafiltration, continuous renal replacement therapy, sustained low-efficiency dialysis (SLED), or intermittent haemodialysis will have to be performed. The detailed procedures are outlined elsewhere in this book (see Chapters 233 and 234).

Summary and conclusion

Abnormalities in fluid status require careful management in patients with AKI. Body weight and daily fluid intake/output should be recorded, and therapy with fluids must be re-evaluated at least daily. Patients must be continuously assessed for clinical signs of hypovolaemia or fluid overload, and adequate monitoring of laboratory and haemodynamic parameters performed. In case of fluid overload, fluid restriction is mandatory. If this is not sufficient, a course of loop diuretics may be attempted; however, if this proves unsuccessful within 12–24 hours, initiation of extracorporeal procedures must be considered.

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CHAPTER 230

Electrolyte and acid–base disorders in AKI

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Introduction

Acid–base and electrolyte disorders are common in the intensive care unit (ICU) and require prompt diagnostic steps and therapeutic interventions. In health, the kidneys play a fundamental role in maintaining physiological body fluid, electrolyte, and acid–base homeostasis. It is, therefore, not surprising that disorders of kidney function on one hand and electrolyte, acid–base, and volume homeostasis on the other hand are closely linked. It is essential that the clinician is able to recognize common disease patterns and their interdependencies (e.g. metabolic acidosis and hyperkalaemia or metabolic alkalosis and hypokalaemia with either volume depletion or volume expansion). This chapter reviews the basic principles of the most common disorders in acute kidney injury (AKI) and seeks to provide the reader with helpful information regarding diagnostic steps and management.

Electrolyte disorders

Sodium

Hyponatraemia and hypernatraemia are common electrolyte disorders especially in critical illness and primarily reflect a disturbance of water balance. Both disorders are associated with increased morbidity and mortality. See also Chapters 21, 22 and 28, 29.

Physiology

It is important to understand that sodium regulates the size of the extracellular volume (ECV) compartment whereas water regulates the osmolality. Because of the presence of Na/K-ATPase on the cell membrane, sodium (and subsequently water) accumulates in the extracellular compartment. Therefore, the sodium amount controls the size of the ECV space, and ECV depletion and expansion are consequences of primary sodium disturbances. The kidneys are pivotal in regulating the body's sodium content.

In contrast, hypo- and hyperosmolality are primary water disturbances. As the dominant extracellular osmolyte, and because of the law of electroneutrality, the sodium *concentration* allows us an easy estimate of osmolality using the equation 2 × Na + glucose + urea (all in mmol/L). Serum osmolality, and thus serum sodium concentration is tightly regulated at 140 mmol/L (Howanitz and Howanitz, 2007). This narrow range is regulated by several mechanisms including sensing serum osmolality in specialized brain cells, pituitary secretion of vasopressin (also known as antidiuretic hormone (ADH)), a vasopressin 2 receptor- and aquaporin 2-mediated response in the kidneys, and an undisturbed thirst thrive with free access to water. Any of these steps may be compromised in critically ill patients (see relevant chapters in Section 2).

A diagnostic challenge for the intensivist is to order all appropriate tests in patients with sodium disturbances in a relatively short time span with interventions such as infusion therapy taking place at the same time. The crucial diagnostic work-up can, therefore, only take place in a limited number of patients. A recent paper, in fact, highlights this and points at the (previously not recognized) association of prerenal acute kidney injury and hyponatraemia (Adams et al., 2011). The exact mechanisms behind this phenomenon are still to be established, but one may speculate that volume depletion may trigger an ADH response.

Hyponatraemia

Hyponatraemia, defined as a serum sodium of < 135 mmol/L, is the most common electrolyte disorder amongst critically ill patients (Verbalis et al., 2007; Howanitz and Howanitz, 2007; Funk et al., 2010; Pokaharel and Block, 2011; Adrogue and Madias, 2012) and carries a substantial morbidity and mortality.

Patients with sodium levels > 120–125 mmol/L are usually asymptomatic, unless carefully assessed for mental and gait abnormalities. Values < 120 mmol/L lead to symptoms mainly related to the central nervous system such as nausea and vomiting, headache, confusion, seizures, and coma. The precise clinical features are given in Chapter 28.

Diagnostic steps

Hyponatraemic patients can be hypovolaemic, hypervolaemic, or euvolaemic. To better understand the aetiology of the hyponatraemia, the volume status of the patient needs to be assessed. One should keep in mind that hypovolaemia is not easily detected clinically, making the distinction of eu- and hypovolaemia sometimes challenging. Extracellular fluid (ECF) accounts for one-third and intracellular fluid (ICF) for two-thirds of total body water (TBW). A given water excess follows this distribution pattern because water diffuses through membranes. Since only a third of the water excess expands the ECF compartment, no oedema is found in euvolaemic patients despite water excess as long as volume regulation is not compromised. Low plasma urea and uric acid concentrations are frequently present in euvolaemic hyponatraemic patients. It is helpful to measure osmolality both in plasma (to exclude pseudohyponatraemia) and urine and also assess urine sodium and potassium concentration (Fig. 230.1). Low urinary osmolality indicates

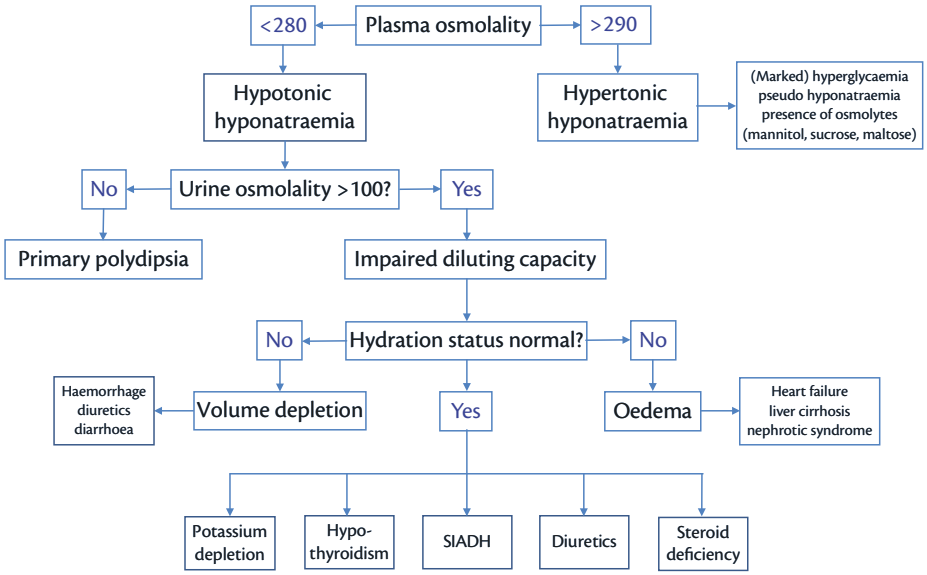

Fig. 230.1 Diagnostic algorithm for hyponatraemia.
Adapted from Faridi and Weinberg (2008).

low ADH and should be achieved by all patients with hyponatraemia, because of the need to excrete excess water. Particularly helpful is the determination of urinary sodium and potassium in the urine. Hyponatraemic patients should have a positive electrolyte-free water clearance to increase sodium concentration. Positive (free) water clearance is indicated by a sum of urinary sodium and potassium that is lower than serum sodium. A diagnostic algorithm for hyponatraemia is shown in Fig. 230.1.

Management

The management of hyponatraemia depends mainly on the actual serum sodium concentration, the presence of clinical symptoms, and the time period over which the condition developed. Hyponatraemia occurring within 48 hours carries a substantially higher risk of causing cerebral oedema (Reynolds et al., 2006; Adrogue and Madias, 2012), especially in patients with serum sodium levels < 120 mmol/L. Although the primary problem is the water excess, the therapeutic aim is to raise ECF tonicity to shift water from within the cells into the intravascular space to prevent or ameliorate oedema formation, especially in the brain. Although there is little consensus on the general management of hyponatraemia, therapeutic options include saline infusion (e.g. 3% NaCl), fluid restriction, and loop diuretics. Only recently, arginine vasopressin (AVP) receptor antagonists that increase the water clearance offer a new treatment option. Further, the treatment of the underlying illness needs to be addressed.

Severe hyponatraemia (serum sodium level < 120 mmol/L occurring within 48 hours) constitutes a medical emergency. Untreated, this extent of hyponatraemia can lead to serious neurological deficits such as coma, downward herniation, raised intracranial pressure, and death. This condition requires prompt intervention under careful monitoring. Here, hypertonic (3%) saline (sodium concentration of 513 mmol/L) is infused at a rate of 1–2 mL/kg per hour. A loop diuretic may be added to enhance free water clearance. Hyponatraemia should be corrected quickly by 1–2 mmol/hour until the symptoms improve, the sodium concentration is >120 mmol/L, or an increase in sodium concentration of 20 mmol is reached within 24 hours (Kumar and Berl, 1998). In a retrospective analysis, rapid correction of hyponatraemia to a serum sodium >120 mmol/L was an independent predictor of improved outcome (Nzerue et al., 2003). Of predominant importance is the correction of possible volume depletion. If saline infusion is administered it is mandatory to predict the effect of such an infusion on the sodium concentration. A formula may help the clinician to estimate the amount of saline infusion needed to correct the sodium deficit. The following formula is used for the infusion of 3% (513 mmol/L) saline (total body water [TBW] approximates the bodyweight multiplied by 0.6 in men and 0.5 in women) (Adrogue and Madias, 2000):

$$\text{Change in serum } Na^+ \left(\text{mmol / L}\right) = \frac{\text{infusate } Na^+ - \text{ serum } Na^+}{\text{TBW} + 1\text{ L}}$$

Although easy to use, this formula has certain limitations, as it does not take into account possible shifts of body water between volume compartments. In addition, the patient's water clearance may change over time. For these reasons, frequent monitoring of serum sodium and urinary sodium and potassium are mandatory. It is also important to take potassium substitutions into account because potassium is an effective osmolyte. The above mentioned equation has to be modified considering infusate Na + K.

Vasopressin receptor antagonists offer a potential treatment option for hyponatraemia (Gheorghiade et al., 2003; Verbalis, 2003; Wong et al., 2003). Conivaptan and tolvaptan are approved AVP antagonist in the United States and Europe. They block the V_{1a} and V_2 receptor, induce aquaresis, and are used in euvolaemic and hypervolaemic hyponatraemia including syndrome of inappropriate antidiuretic hormone secretion (SIADH), hypothyroidism and adrenal insufficiency, heart failure, and hepatic cirrhosis (Verbalis et al., 2007). Excessive free water clearance may lead to overcorrection of the hyponatraemia with the danger of central pontine myelinolysis.

In *chronic hyponatraemia*, patients tend to present with mild symptoms and only subtle neurological findings. When patients are

asymptomatic, treatment with fluid restriction is usually sufficient. Thiazide diuretics or other culprit medications need to be stopped. Loop diuretics may be initiated. Hypertonic saline infusion may be required, but only when patients are symptomatic.

Central pontine myelinolysis is the most feared complication of hyponatraemia and its correction. Hyponatraemia may cause entry of water into the brain resulting in cerebral oedema. Fortunately, intracellular solutes leave the brain tissues within hours, inducing a water shift and thus ameliorating cerebral hypertension. This process develops over a few days and explains why patients with chronic hyponatraemia are largely asymptomatic. Pontine demyelination is most often the consequence of overly rapid correction of chronic hyponatraemia. A correction rate < 12 mmol/day will allow most patients to recover from hyponatraemia without neurological complications (Reynolds et al., 2006; Verbalis et al., 2007).

Unfortunately, the duration of the hyponatraemia is often difficult to determine. The presence of symptoms rather than laboratory values should therefore guide treatment regimens.

Pitfalls in the management of hyponatraemia include fluid restriction in hypovolaemic patients. These patients have both a sodium deficit resulting in volume depletion and an absolute or relative water excess resulting in low sodium concentration. In this situation the sodium deficit should be targeted first, before the water excess is addressed. On the other hand normal saline infusion in SIADH patients may aggravate the symptoms as the infused salt is excreted via the kidneys resulting in a net water retention worsening the hyponatraemia. Endocrine disorders such as hypothyroidism and adrenal insufficiency should be searched for, especially in patients with concomitant hyperkalaemia.

Hypernatraemia

Hypernatraemia (serum sodium > 150 mmol/L) usually only leads to symptoms when it increases rapidly to levels > 160 mmol/L (Kumar and Berl, 1998; Reynolds et al., 2006). In health, thirst provides an important mechanism to prevent or limit the rise in sodium concentrations. However, in ICU patients with altered mental status or under sedation this defence mechanism may not function properly. Most cases of hypernatraemia in the ICU are iatrogenic. Fluid resuscitation using saline infusions may eventually lead to hypernatraemia. Another important mechanism is the widespread application of steroids (even in low doses) in patients with septic shock. Here, fluid resuscitation with saline and steroids may have additive effects. Although sodium retention is not widely accepted as being a regular problem of low-dose steroid therapy, all studies investigating low-dose steroids in septic shock found increases in serum sodium concentrations (Oppert et al., 2005; Sprung et al., 2008). Causes of hypernatraemia are summarized in Table 230.1.

Clinical manifestations of hypernatraemia correspond to the magnitude and velocity of the rise of serum sodium. They include weakness and neurologic symptoms ranging from confusion to coma and seizures.

Management

The treatment principle in hypernatraemia is twofold: first, reduction or cessation of ongoing water loss and second, replacement of water deficit. When hypernatraemia occurred quickly, rapid correction of serum sodium is warranted and improves prognosis without the risk of cerebral oedema. A reduction in serum sodium by 1 mmol/hour is usually without risk (Weiss-Guillet et al., 2003). In hypovolaemic states, alternating infusions of normal saline and glucose should be given, while enteral intake of hypotonic fluids is preferred in euvolaemic or hypervolaemic patients. In patients with central diabetes insipidus, hormonal interventions (such as desmopressin) should be considered. Here the sodium concentration must be monitored closely.

If hypernatraemia occurred over a longer period of time, water replacement should be slower. Half of the estimated deficit should be corrected within the first 24 hours, while the rest may be given over 24–48 hours and ideally via enteral fluid administration.

Table 230.1 Causes of hypernatraemia

Hydration status	Disorder
Hypervolaemia (TBW↑↑, $TBNA^+$↑)	
U-Na > 20 mmol/L	*Iatrogenic* ◆ Saline infusion ◆ Bicarbonate infusion ◆ Steroids ◆ Antibiotics containing sodium etc.
Euvolaemia (TBW ↔; $TBNA^+$↔)	
U-Na variable	*Renal losses* ◆ Diabetes insipidus ◆ Hypodipsia *Extrarenal losses* ◆ Fever ◆ Hyperventilation ◆ Mechanical ventilation
Hypovolaemia (TBW ↓; $TBNA^+$↓↓)	
U-Na < 20 mmol/L	*Extrarenal losses* ◆ Sweating ◆ Diarrhoea ◆ Vomiting ◆ Burns
U-Na > 20 mmol/L	*Renal losses* ◆ Diuretics ◆ Osmotic diuresis ◆ Post-obstruction ◆ Acute and chronic renal disease

Potassium

Physiology

Potassium is the predominant intracellular cation and has a normal serum concentration of 3.5–5.5 mmol/L (see also Chapters 23, 34). The intracellular/extracellular ratio is created by an energy consuming active transport aimed at stabilizing membrane potential. Acute changes in serum potassium levels are influenced, for example, by insulin, beta adrenergic drugs, and changes in acid–base balance. Potassium level is influenced by intake disorders, excretion disorders, or transcellular shifts. Potassium excretion occurs mainly in the kidney and is, among others, controlled by aldosterone effects in the collecting duct. Renal potassium loss is best measured by assessing potassium and osmolality in serum and urine. (For further detailed

Table 230.2 Causes of hypokalaemia and hyperkalaemia

Hypokalaemia	◆ Renal losses: • Diuretics • Drugs ◆ Enteral losses: • Diarrhoea • Vomiting • Laxatives • Nasogastric drainage • Tumours ◆ Transcellular shifts: • Alkalosis • Drugs (catecholamines, theophylline, etc.) • Insulin • Hypothermia • Thyrotoxicosis ◆ Others: • Renal tubular acidosis (type I and II) • Diabetic ketoacidosis • Increased sweating
Hyperkalaemia	◆ Increased potassium load: • Potassium infusions • Red blood cell transfusions • Potassium supplements ◆ Reduced renal excretion: • Renal failure • Drugs (angiotensin-converting enzyme inhibitors, AT_1-blockers, spironolactone, non-steroidal anti-inflammatory drugs, etc.) • Addison's disease • Uretrojejunostomy ◆ Increased cell release: • Haemolysis • Trauma including rhabdomyolysis • Tumour lysis syndrome • Acidosis • Drugs (beta blockers, succinylcholine, etc.)

mechanisms on potassium physiology, see Chapters 23 and 34.) The most important conditions leading to potassium abnormalities are listed in Table 230.2.

Hypokalaemia

Approximately 3500 mmol potassium reside intracellularly whereas only 70 mmol are distributed in the extracellular compartment. Hypokalaemia occurring within hours is virtually always due to intracellular/extracellular shifts. In patients with diabetic ketoacidosis (DKA), total body potassium may be severely reduced as a consequence of osmotic diuresis, vomiting, and poor nutrition. It is estimated that 1 mmol/L reduction of serum potassium reflects a deficit of approximately 300 mmol/L. Mild hypokalaemia (3.0–3.5 mmol/L) is usually not associated with major symptoms (Schaefer and Wolford, 2005). In patients with underlying cardiac disease, however, already minor changes in serum potassium may lead to arrhythmias, especially when digoxin is prescribed. Serum levels < 3.0 mmol/L may lead to serious symptoms, including weakness, arrhythmias (atrial tachycardias, AV conduction blocks, QT prolongation), paralytic ileus, and in severe cases (< 2.5 mmol/L) may lead to ascending paralysis causing respiratory failure, thus constituting a medical emergency.

Management

In the management one needs to consider the possible pathogenesis of hypokalaemia (Table 230.2). The history (including medications) is equally important as is to check the acid–base status and urinary potassium. In chronic and/or mild hypokalaemia, substitution with oral potassium appears to be a safe approach, as potassium is absorbed slowly and the risk of hyperkalaemia is reduced. However, it is important to realize that potassium can be administered as potassium chloride or potassium citrate. The former would be preferred in hypokalaemia associated with metabolic alkalosis, whereas the latter should be given when metabolic acidosis is present. In patients with symptomatic and/or severe hypokalaemia, aggressive treatment is indicated using intravenous substitution. As the amount of potassium depletion may be enormous, an infusion containing high potassium chloride concentrations may be required. This drip should be given via a central line. The amount of potassium needed may, however, vary greatly. For example, in patients with DKA the previous lack of insulin increases the intracellular shift when patients are infused with fluids and insulin. In fact, at the time of diagnosis, the serum potassium level may be normal. Due to possible cardiovascular events, close monitoring of cardiac function and laboratory parameters is warranted. Concomitant magnesium repletion should be considered. Special care must be taken in patients with hypokalaemia due to transcellular shifts as potassium repletion may lead to rebound hyperkalaemia (Tassone et al., 2004). In patients with hypokalaemic periodic paralysis, the administration of potassium will terminate an attack, but is not able to prevent further episodes.

Hyperkalaemia

It is difficult to differentiate between mild, moderate, and severe hyperkalaemia, as not only the absolute serum potassium level is important, but also the baseline level and the kinetics of the increase. Further the acid–base status and the serum calcium concentration need to be taken into account. Most often hyperkalaemia is due to reduced renal potassium excretion or increased endogenous release from cells (Gennari, 2002). In health, hyperkalaemia is rare, as the kidney is able to quickly excrete potassium following a relevant potassium load. Therefore, hyperkalaemia usually is the consequence of impaired potassium excretion or transcellular shifts. Potential mechanisms of hyperkalaemia are given in Table 230.2.

Symptoms of hyperkalaemia include general weakness, paralysis, and arrhythmias. An electrocardiogram (ECG) should be obtained to detect electrocardiographic changes including highly elevated T waves, widening of the QRS complexes, changes in the p wave and conduction blocks. A serum sample checking for creatinine, urea, glucose, and electrolytes should be taken. The transtubular potassium gradient is most informative of the aldosterone-dependent renal potassium excretion. A urine dipstick test should exclude haemolysis or rhabdomyolysis.

Management

The first step in managing a patient with hyperkalaemia is to decide whether the disorder is potentially life-threatening, thus requiring

urgent correction. Potassium levels < 6.5 mmol/L usually lead to few symptoms (unless the potassium level has risen very quickly), although one has to be cautious as considerable interindividual susceptibility to hyperkalaemia exists. Further, severe problems may occur without warning and ECG changes do not necessarily correlate with the degree of hyperkalaemia. Therefore, any patient with ECG changes consistent with hyperkalaemia or with proven potassium levels > 6.0 mmol/L constitutes a medical emergency and must be treated immediately.

The main options in the management of hyperkalaemia are to antagonize its adverse effects, to induce a shift of potassium from the extra- to the intracellular space, and to enhance its excretion.

Calcium gluconate (10 mL of 10% solution intravenously(IV)) is the preferred immediate treatment in life-threatening hyperkalaemia as it directly counteracts the membrane effects of potassium. A treatment effect thus may be expected rapidly, that is, within minutes but will usually be short-lived. Therefore, calcium infusion is a temporary emergency measure that must always be accompanied by further treatment to lower potassium levels (Schaefer and Wolford, 2005). Of note, IV calcium should be given with particular caution in patients under co-medication with digoxin as it may increase digoxin toxicity.

The next step in the management of hyperkalaemia is to induce a shift of potassium from the extracellular to the intracellular space. A potassium shift can be expected within 10–20 minutes after the application of IV insulin. To prevent hypoglycaemia, insulin should always be given together with a glucose infusion. Insulin is a reliable tool to lower potassium levels and may be given to all patients with hyperkalaemia irrespective of their acid–base status. Moreover, in patients with severe metabolic acidosis, the serum potassium may also be lowered with an infusion of 50–100 mmol of sodium bicarbonate. This approach has some disadvantages over insulin treatment as it is less effective in non-organic metabolic acidosis (lactic acidosis, ketoacidosis). Also, if repeated doses are needed, patients might receive large amounts of sodium which can be undesirable, especially in patients with heart failure and/or renal failure.

As with the infusion of calcium, insulin and bicarbonate are only temporary measures as they do not enhance potassium excretion. Thus, hyperkalaemic states due to potassium overload must be treated by measures leading to enhanced potassium elimination. In patients with preserved diuresis, renal excretion may be enhanced using loop and thiazide diuretics. Moreover, enteral potassium elimination can be achieved by oral application of an ion exchange resin (with a laxative to prevent constipation) and/or an enema containing ion exchange resins. The issue of exchange resins has provoked a recent controversy with respect to efficacy and side effects (Sterns et al., 2010; Watson, Abbott, and Yuan, 2010). In severe cases of hyperkalaemia, acute renal replacement therapy (RRT) provides an additional treatment option after the above mentioned acute measures are initiated. Haemodialysis against a low-potassium (e.g. 1 mmol/L) dialysate would then be the preferred treatment option. Serum potassium levels may safely be lowered by as much as 1–2 mmol/L per hour. However, haemodialysis primarily affects the extracellular component that contains < 2% of exchangeable potassium and may thus only remove a limited amount of total body potassium. Consequently, redistribution of potassium (which may have been shifted to the intracellular space with insulin prior to dialysis therapy) may occur after dialysis. Therefore, potassium levels need to be checked repeatedly even after initially successful management of hyperkalaemia.

Calcium

Physiology

Calcium (see also Chapters 26, 37, 38) is important for the normal function of many intracellular systems, muscle contraction (including the heart), nerve conduction, and coagulation pathways. It is kept within a narrow range of 2.1–2.6 mmol/L. Calcium homeostasis is regulated by complex interaction and feedback loops including parathyroid hormone (PTH) and vitamin D acting on the intestine, kidney, bone, and the parathyroid gland. One per cent of total body calcium is in the ECF, where the physiological active ionized fraction equals about 50%. The remainder is protein bound (mainly to albumin).

Hypocalcaemia

Hypocalcaemia is defined as a total serum calcium concentration of < 2.1 mmol/L (or ionized serum calcium of < 1.0 mmol/L). Its causes are given in Table 230.3. Symptomatic hypocalcaemia rarely occurs when the ionized calcium is > 0.7 mmol/L. In severe (and acute) hypocalcaemia (<0.7 mmol/L) neuropsychiatric and neuromuscular symptoms predominate. The most important sign of increased neuromuscular irritability is tetany. Weakness, cramps, laryngeal spasms, or bronchospasms may also occur. Patients may complain of perioral numbness (often seen in respiratory alkalosis due to hyperventilation) and distal paraesthesias. Cardiac symptoms include reduced myocardial contractility, arrhythmias, and a QT interval prolongation. The neuropsychiatric problems may consist of confusion, anxiety, and seizures.

Management

In the management of severe hypocalcaemia, IV supplements should be given until symptoms cease or the ionized calcium is > 0.9 mmol/L (Tohme and Bilezikian, 1993). A continuous infusion

Table 230.3 Causes of hypocalcaemia and hypercalcaemia

Hypocalcaemia	◆ Hypoparathyrodism (post radiation, post surgery) ◆ Vitamin D deficiency (low sun exposure, malnutrition, liver disease, renal disease) ◆ Drugs (bisphosphonates, calcitonin, citrate, chemotherapeutic drugs) ◆ Others (sepsis, pancreatitis, burns)
Hypercalcaemia	◆ Endocrine: • Hyperparathyrodism • Hypothyrodism • Vitamin D calcidiol intoxication ◆ Paraneoplastic: • Multiple endocrine neoplasia (MEN type I and II) • PTH-related protein • Non-small cell lung cancer • Multiple myeloma • Metastatic disease ◆ Excessive intake/increased bone resorption: • Milk-alkali syndrome • Thiazide diuretics • Lithium • Granulomatous disease

is preferred as a fast bolus injection carries the risk of severe arrhythmias including asystole, especially in patients with cardiac conditions or under digoxin (Tohme and Bilezikian, 1993). If hyperphosphataemia is present, fast correction of calcium carries the risk of soft tissue calcifications. In such a situation phosphate binders should be considered and calcium supplementation should be postponed for as long as possible. Haemodialysis may also constitute a rational therapeutic option.

Hypercalcaemia

In hypercalcaemia, elevations of serum calcium up to 3.0 mmol/L are usually associated with no or few symptoms (Weiss-Guillet et al., 2003). With serum calcium increasing further, non-specific symptoms such as malaise, nausea, vomiting, weakness, and abdominal pain may occur. Hypercalcaemia causes polyuria because calcium engages the calcium-sensing receptor in the loop of Henle thereby inhibiting the Na-K-2Cl co-transporter via 20-HETE. This effect leads to volume depletion and metabolic alkalosis. Severe hypercalcaemia (> 4.0 mmol/L) may lead to acute pancreatitis (Carnaille et al., 1998) and relevant cognitive disorders such as hallucinations, stupor, and coma (Petersen, 1968).

The most important causes of hypercalcaemia are PTH excess, malignant tumours, and treatment with long-acting vitamin D medications. Other reasons for hypercalcaemia are given in Table 230.3.

Management

The management of hypercalcaemia is based on adequate (re) hydration with saline infusions, increased calcium excretion via the kidneys, inhibition of bone turnover, and treatment of the underlying disease. The rapid infusion of normal saline is recommended in severe hypercalcaemia. After correction of volume depletion, loop diuretics (but not thiazides, as they increase calcium reabsorption in the kidney) should be given to maintain hydration status and also enhance renal calcium excretion. Moreover, bisphosphonates are an effective mode of therapy to decrease calcium mobilization from bones. In patients with vitamin D intoxication, lymphoma, sarcoidosis, or multiple myeloma, steroids are mandatory as they decrease calcitriol production (Gardner, 2001). Treatment effects with both steroids and bisphosphonates may, however, be delayed by 2–4 days. Calcitonin acts very rapidly (usually within 4–6 hours) and may safely be given in the meantime. In patients with severe symptomatic hypercalcaemia, haemodialysis against a low calcium dialysate may be indicated, especially in patients with renal and/or heart failure.

Phosphate

Less than 1% of total body phosphate is found in the serum. It is essential for the mineralization of the bone and cellular functions including energy metabolism and genetic encoding. The normal phosphate plasma concentration is 0.8–1.45 mmol/L. Ninety per cent of the phosphate is secreted via the kidneys. (For further details of phosphate physiology, see Chapters 25 and 39.).

Hyperphosphataemia

In critical illness, acute hyperphosphataemia may occur as a consequence of severe cell or tissue damage, for example, in tumour lysis syndrome or rhabdomyolysis. A summary of causes of hyperphosphataemia is given in Table 230.4. The management of hyperphosphataemia is described in detail in Chapter 39.

Table 230.4 Causes of hypophosphataemia and hyperphosphataemia

Hypophosphataemia	◆ Sepsis ◆ Decreased absorption: • Chronic diarrhoea • Vitamin D deficiency ◆ Renal losses: • Osmotic diuresis • Renal transplantation • Hyperparathyroidism • Steroid therapy ◆ Other losses: • Burns • Pancreatitis • Renal replacement therapy ◆ Transcellular shifts: • Alkalosis • Hormonal (calcitonin, insulin) • Hungry bone syndrome leukaemic crisis • Hypothermia
Hyperphosphataemia	◆ Renal failure ◆ Tumour calcinosis syndrome ◆ Bisphosphonates ◆ Rhabdomyolysis ◆ Tumour lysis syndrome ◆ Malignant hyperthermia ◆ Lactic acidosis

Hypophosphataemia

Hypophosphataemia is rare, but some patients are at greater risk. Table 230.4 gives a summary of the most relevant causes of hypophosphataemia. After successful renal transplantation a persistent hyperparathyroidism may lead to profound hypophosphataemia sometimes needing IV supplementation (see Chapters 25 and 39). In the ICU, patients undergoing continuous RRT may develop a severe decrease in phosphate. In this setting, phosphate should be monitored on a regular basis and supplemented if needed.

Management

In general, mild hypophosphataemia can be managed with oral supplements. Severe symptomatic hypophosphataemia (< 0.5 mmol/L) requires IV application of phosphate. The extent of the possible phosphate deficit is unpredictable and repletion therapy must be empiric. In the ICU, a single dose of 15–30 mmol over 2 hours or a dose of up to 0.08 mmol/kg body weight are considered safe and have been well tolerated (Charron et al., 2003). One should be cautious, however, when the serum calcium is grossly elevated due to the risk of soft tissue calcification. Calcium and phosphate repletion must be strictly separated, as precipitation may trigger anaphylactic reactions. Careful monitoring of phosphate and prevention of hypophosphataemia is therefore much safer than intravenous infusions.

Acid–base disorders

The kidneys and the lung play the fundamental role in maintaining acid–base balance. In patients with multiorgan dysfunction

syndrome, acid–base disorders are common. The exact mechanisms of acid–base handling of the kidney and its cellular consequences are described in Chapters 24 and 35.

Physiology and basic considerations

The normal pH in the blood is maintained in a very narrow range around 7.40 ± 0.02, despite the fact that laboratory reference values leave a much broader range of 'normal'. This balance of pH is due to very subtle interaction between buffers (bicarbonate, HCO_3^-) and volatile acid (pCO_2). To better understand acid–base imbalances, the clinician should look at the real changes in H^+ concentrations rather than merely looking at the calculated bicarbonate level. To this end the Henderson–Hasselbalch formula ($pH = pK + \log \times HCO_3^-/H_2CO_3$) can be simplified for practical use. This leads to the following formula: $[H^+] = 24 \times pCO_2/HCO_3^-$, where a normal HCO_3^- of 24 mmol/L (the metabolic component) and a normal pCO_2 (the respiratory component) of 40 mmHg lead to a normal concentration of H^+ of 40 mmol/L (Adrogue et al., 2009).

Attention should be paid to the anion gap. It is defined as the difference of the plasma sodium concentration and the sum of bicarbonate plus chloride concentrations. The anion gap is usually between 12 ± 2 mmol/L. One should bear in mind, however, that a reduction of serum albumin by 1 g/L will result in a decrease in the anion gap by as much as 2.5 mmol/L. From a clinical point of view the anion gap is very useful in differentiating metabolic acidosis and detecting the presence of organic or mixed metabolic acidosis. Metabolic acidosis always results in a low bicarbonate concentration. This may be due to gain of acids or loss of bicarbonate. The anion gap distinguishes both forms of metabolic acidosis from each other. Causes of high anion gap acidosis are ketoacidosis (diabetes, alcohol, starvation), intoxications (methanol, ethylene glycol, salicylates), and lactic and uraemic acidosis.

Acute metabolic acidosis

Acute metabolic acidosis is characterized by low pH and low plasma bicarbonate concentration lasting from minutes to days. Three degrees of severity are based on the level of the arterial pH: mild (pH 7.30–7.36), moderate (pH 7.20–7.29), and severe (pH < 7.20). Given a normal respiration this will correspond to the following decreases in bicarbonate concentrations: >20 mmo/L, 10–19 mmol/L, and <10 mmol/L, respectively. Acute metabolic acidosis is a feared and common complication in critical illness. It is essential to elaborate the underlying problem in order to target useful treatment. In normal (non-) anion gap acidosis the bicarbonate concentration falls and the chloride concentration rises. This is the case, for example, when bicarbonate is lost via the gastrointestinal tract or the kidneys. The latter is called renal tubular acidosis. Further causes are given in Table 230.5. In high anion-gap acidosis, however, bicarbonate is lowered by a gain of acid with its unmeasured anion being responsible for the increase in the anion gap. Acids such as lactic or uraemic acids or ketones are probably the most common causes of high anion-gap acidosis (Table 230.5).

Approach to a patient with acute metabolic acidosis

The treatment of metabolic acidosis is based on two principles: treatment of the underlying condition (e.g. diarrhoea or shock) and correction of the bicarbonate deficit. Sodium bicarbonate is usually the preferred agent to alkalinize the blood. If one considers a pH < 7.1(and consequently a bicarbonate level of <10 mmol/L) dangerous to cellular function, the administration of base seems a logical consequence. There is, however, a considerable controversy. In organic (i.e. anion gap) acidosis the administration is even more debated than in non-anion gap acidosis. In non-anion gap acidosis the loss of bicarbonate is a rationale to administer base. The threshold value should be a pH of about 7.1 for patients with organic acidosis and may even be higher in patients with non-gap acidosis. In patients with values above this limit, the treatment of the underlying illness (e.g. DKA or lactic acidosis) is usually sufficient. Alveolar ventilation should be sufficient when administering sodium bicarbonate, as it generates CO_2. This effect may itself cause respiratory acidosis. Tris-hydroxymethylaminomethane is an amino alcohol buffering without generation of CO_2. It has been shown to be effective but should be used with caution in patients with renal impairment as it is eliminated via the kidneys.

In an attempt to compensate the decrease in bicarbonate the patient is usually hyperventilating and, therefore, reducing their pCO_2.

Table 230.5 Causes of normal anion gap (hyperchloraemic) acidosis and anion gap acidosis

Normal anion gap (hyperchloraemic) acidosis	◆ Extrarenal loss of base: • Diarrhoea • Pancreatic fistula ◆ Renal loss: • Type II renal tubular acidosis • DKA • Toluene inhalation (glue sniffing) • Steroid therapy ◆ Extrarenal acid gain: • Ammonium • Sodium chloride ◆ Renal acid excretory defects: • Type I and IV renal tubular acidosis • Chronic kidney disease • Hypoaldosteronism • Sjögren syndrome • Renal transplant
Anion gap acidosis	◆ Ketoacidosis ◆ Lactic acidosis ◆ Uraemia ◆ Intoxication (salicylates, ethylene glycol, methanol)

Lactic acidosis

Lactic acidosis is a special form of metabolic acidosis that is frequently encountered in ICUs (Luft, 2001; Kraut and Madias, 2014). Inadequate oxygen supply to the cells leads to increased glycolysis without oxidative phosphorylation resulting in an accumulation of lactate that binds protons causing acidosis. Patients with various forms of shock (i.e. septic and cardiogenic), renal failure, and liver failure are most prone to develop lactic acidosis. As these disorders are usually not reversed within a few hours, treatment may take longer. Base administration would

therefore lead to volume and sodium overload as well as hyperosmolality. RRT may (under certain circumstances) be a treatment option (Heaney et al., 1997; Hilton et al., 1998). This approach is, however, only practical when the underlying condition can be treated. In order 'to buy' time one can start with a haemodialysis session lasting 4–6 hours and then switching to a continuous form of treatment. Haemofiltration has been advocated for the treatment of lactic acidosis, on the basis of anecdotal experiences. However, kinetic studies of lactate removal do not suggest that removal can counteract lactate production in any meaningful way. The ideal treatment is to stop acid production by treating the underlying disorder (Luft, 2001; Kraut and Madias, 2014).

Metabolic alkalosis

Metabolic alkalosis is associated with increased mortality (Anderson and Henrich, 1987). It may be due to either acid loss or gain of bicarbonate. In health, however, the kidney is able to excrete enough bicarbonate so that even an infusion of bicarbonate will not result in alkalosis. The most common mechanism contributing to alkalosis is volume depletion, either absolute or relative (e.g. in heart failure). This leads to reduced glomerular filtration rate and secondary hyperaldosteronism with enhanced bicarbonate absorption and generation in the tubulus. In patients with volume expansion, however, primary mineralocorticoid excess is usually the underlying condition, especially when hypertension is present.

Treatment is directed at the underlying condition (i.e. volume expansion in patients with volume depletion or cardiac recompensation if the patient is in heart failure). In patients with mineralocorticoid excess, the administration of a mineralocorticoid receptor antagonist should be considered.

The compensation mechanism of metabolic alkalosis is hypoventilation with an increase in $paCO_2$.

Respiratory acidosis

Respiratory acidosis is the result of alveolar hypoventilation leading to an increased pCO_2. The onset may be acute or chronic. In acute respiratory acidosis, the main causes are either acute airway obstruction, pulmonary infections or neuromuscular (e.g. narcotics, stroke, Guillain–Barré syndrome, myasthenia, or intoxications). An increase in pCO_2 results in cerebral vascular contraction leading to lethargy and eventually coma. The treatment should be directed at the underlying condition. It may be necessary to antagonize intoxications or to reverse airway obstruction. In a number of cases ventilator support is needed. In chronic respiratory acidosis, symptoms are most often less dramatic, despite higher $paCO_2$ levels. In such a case, treatment must be more careful to avoid post-hypercapnic alkalosis. Patients with respiratory acidosis usually increase their bicarbonate levels over several days in an attempt to compensate.

Respiratory alkalosis

Respiratory alkalosis results from alveolar hyperventilation and leads to decreased $paCO_2$. Possible causes are hypoxaemia, pulmonary embolism, agitation, and pain. Occasionally, it may occur in pregnancy, sepsis, and heat stroke. Treatment is aimed at the underlying condition. Patients with chronic respiratory alkalosis reduce their bicarbonate over a number of days.

Conclusions

Electrolyte and acid–base disorders are extremely frequent in the ICU and in the emergency department. The most important imbalances of electrolyte homeostasis include disorders of sodium, potassium, calcium, and phosphate. Hyponatraemia and hyperkalaemia are the most common disorders and require prompt and safe correction, once the diagnosis is made and the underlying illness is identified. Thus, the main emphasis is on the causes and management of electrolyte abnormalities. Patients with hyponatraemia are at high risk of cerebral oedema, while hyperkalaemia may lead to life-threatening cardiac arrhythmia. The differentiation of normal or high anion-gap acidosis is clinically important, as the underlying diagnoses are very different. Alkalosis is also associated with increased mortality. Prompt recognition and effective management of these disorders will limit the risk of life-threatening consequences.

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CHAPTER 231

Coagulation disturbances in acute kidney injury

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Introduction

The coagulation systems serve to maintain the integrity of the vasculature. Under normal circumstances their activation is limited to the site of injury. Physiologically, coagulation can be divided into cellular and humoral haemostasis although *in vivo* both systems are closely linked to each other. The first steps of coagulation include the adhesion of platelets to exposed subendothelial matrix with subsequent aggregation of further thrombocytes. This platelet thrombus has to be stabilized by the formation of thrombin which has been generated by humoral haemostasis. The simultaneous activation of intrinsic anticoagulant/fibrinolytic systems balances the extent of coagulation to the level required for haemostasis.

Bleeding is a typical complication of critical care patients that may lead to substantial morbidity and mortality and is often caused by coagulation disturbances. Impaired coagulation and bleeding complications in patients with acute kidney injury (AKI) may derive from three different conditions: firstly, AKI itself with ensuing uraemia has an impact on coagulation. Secondly, the underlying disease may cause both AKI and coagulation disorders. Thirdly, renal replacement therapy (RRT) affects coagulation as a consequence of blood–membrane interactions and, usually, the administration of anticoagulants.

Not unexpectedly, the rate of spontaneous bleeding episodes seems to be increased in patients with AKI. As an example, gastrointestinal haemorrhage was the second leading cause of death in patients with AKI before the introduction of RRT (Kleinknecht et al., 1972). Furthermore, patients with AKI often require percutaneous procedures (e.g. vascular access for RRT) which predispose to sometimes serious bleeding complications.

Coagulation in patients with uraemia

Uraemic toxins may impair coagulation, mainly affecting thrombocyte adhesion and aggregation. The result is a prolonged bleeding time with bleeding diathesis. Although most studies of platelet dysfunction in uraemia dealt with patients in chronic renal failure, these changes may also appear in patients with AKI.

Normal haemostasis requires the adhesion of platelets to the vascular endothelium as the first step. This adhesion is mediated by the glycoprotein GPIb and von Willebrand factor (vWF). In the uraemic milieu, platelet expression of GPIb is markedly decreased. This may be due to an increased proteolysis of GPIb to glycocalicin, which is found to be elevated in patients with renal failure. The degradation product glycocalicin contains binding sites for thrombin and vWF and may further contribute to diminished platelet adhesion by competitive binding. In uraemia, normal or elevated levels of vWF can be detected. Nevertheless, the activity of vWF seems to be impaired, suggesting structural or functional defects in the uraemic milieu.

The second step in the formation of the platelet thrombus is the aggregation of thrombocytes. This is mediated by the glycoprotein GPIIb/IIIa, the receptor for fibrinogen. Levels of GPIIb/IIIa in patients with renal failure are usually normal. However, in uraemia the post-adhesion conformational change in GPIIb/IIIa that is necessary for binding to the receptor is impaired.

Nitric oxide (NO) may be another factor inhibiting platelet–endothelium interaction. Uraemic toxins induce NO synthase in platelets and endothelial cells resulting in high levels of NO in patients with renal failure. In the experimental setting, bleeding time can be normalized by administration of the NO synthase inhibitor L-NMMA.

Routine tests for humoral haemostasis (international normalized ratio (INR), partial thromboplastin time (PTT)) are not changed in patients with uraemia.

The causative therapy of uraemia-associated platelet dysfunction is to deliver adequate RRT. Although dialysis itself may cause defects in platelet receptors, the reduction of uraemic toxins may at least partly correct platelet dysfunction.

In case of acute bleeding in patients with renal failure, the administration of cryoprecipitate (containing vWF and fibrinogen) or desmopressin (releasing vWF from platelet and endothelial stores) improves bleeding time. For the latter, application of 0.3–0.4 micrograms/kg intravenously may be an appropriate dose recommendation. Repeated doses result in depletion of vWF stores with declining effectiveness (tachyphylaxis) (Boccardo et al., 2004; Hörl, 2006).

Diseases affecting both kidney and coagulation systems

In many cases, AKI represents only one facet of a complex clinical situation, with multiple organ dysfunction being caused by the underlying disease. Thus there may be a high coincidence of AKI and conditions with impaired coagulation. Sepsis and thrombotic microangiopathies are examples of diseases associated both with AKI and profound changes in coagulation systems.

Sepsis

Nowadays sepsis is the predominant cause of AKI in the intensive care unit setting (see Chapter 244). AKI and coagulation disturbances are common complications in patients with septic multiple organ failure. Thrombocytopenia is a frequent finding in patients with sepsis and is closely related to mortality. Several causes induce thrombocytopenia in this setting: bone marrow suppression by various mediators results in reduced platelet production. Furthermore, released thrombocytes may be destructed by non-specific platelet-associated antibodies which can be detected in many patients with sepsis. Last but not least, as platelets link coagulation and inflammation, they may be consumed by the immunological host response.

Thrombocytopenia is also a marker for disseminated intravascular coagulation (DIC). This severe complication in sepsis is characterized by simultaneous activation of coagulation, inhibition of fibrinolysis, and consumption of coagulation inhibitors, ultimately leading to a procoagulant state. The result is inadequate fibrin removal and fibrin deposition in the microvasculature. In contrast to 'simple' thrombocytopenia this consumptive disorder presents with abnormal testing for humoral haemostasis markers (INR, PTT, D-dimers, and fibrinogen).

Thrombotic microangiopathies

In patients presenting with severe thrombocytopenia and AKI the presence of thrombotic microangiopathies must be considered. Several entities such as haemolytic uraemic syndrome (HUS), thrombotic thrombocytopenic purpura (TTP), and HELLP syndrome belong to the family of microangiopathic haemolytic anaemia (see Chapter 174). They usually share an unfavourable prognosis if unrecognized and not treated adequately. Key features are the formation of occluding thrombi in the microcirculation of terminal arterioles and capillaries with subsequent mechanical fragmentation of erythrocytes in the narrowed capillaries. Clinical consequences are both ischaemic damage of affected organs and an increased risk of severe bleeding due to significant thrombocytopenia. Laboratory abnormalities include thrombocytopenia, anaemia, and signs of haemolysis with markedly elevated levels of serum lactate dehydrogenase. The detection of fragmentocytes on peripheral blood smear and the negative Coombs test confirm the diagnosis of thrombotic microangiopathy.

Renal involvement is typical in HUS. This most frequent form of thrombotic microangiopathy is caused by Shiga toxin produced by some strains of *Escherichia coli* or *Shigella dysenteria*. Clinical findings include bloody diarrhoea with subsequent evolution of both thrombocytopenia and renal failure. Although formerly regarded as a paediatric disease, a recent outbreak in Europe affected mostly middle-aged women. Supportive treatment covers management of renal failure, anaemia, and fluid balance. Antibiotic therapy should be avoided unless bacteraemia is present or other infectious complications require treatment. The role of plasma exchange in the therapy of HUS is still under debate.

Severe neurological involvement is common in patients with TTP. Nevertheless, virtually any organ including the kidney may be affected. Most cases of TTP are caused by genetic or immune-mediated abnormalities of the metalloproteinase ADAMTS13. This enzyme cleaves ultralarge vWf multimers derived from endothelial cells. In case of deficient cleavage these multimers accumulate and cross-link thrombocytes via platelet glycoprotein Ib/IX/V and IIb/IIIa even in the absence of fibrinogen. Plasma exchange both eliminates inhibiting antibodies and provides the enzyme and therefore is the treatment of choice. Substitution of thrombocytes should be avoided except in patients with life-threatening bleeding because it may fuel further thrombus formation.

Coagulation during renal replacement therapy

Coagulation systems may be changed during RRT by two different mechanisms. Firstly, in most patients application of anticoagulants is necessary in order to ensure extracorporeal circuit patency. Secondly, RRT itself may impact on coagulation as a consequence of blood–membrane interaction.

Extracorporeal circuits for RRT consist of large artificial surface areas. The contact of blood with these surfaces activates leucocytes, platelets, and the plasmatic coagulation system. In order to prevent clotting, the application of anticoagulant strategies is usually necessary. Systemic anticoagulation may be performed using heparin, low-molecular-weight heparins, heparinoids, prostaglandins, or direct thrombin inhibitors. Obviously, the administration of these substances increases the risk of bleeding, especially during continuous RRT. In order to treat such complications, substances with a short half-life and/or for which specific antagonists are available would seem preferable. Unfortunately, however, protamine for antagonizing unfractionated heparin is the only such drug available. Systemic heparinization is widely used but may be associated with the risk of heparin-induced thrombocytopenia type II (HIT II) as a serious complication. Prostaglandins are effective anticoagulants with a short half-life but are too expensive for routine use.

Taking this background into account the development of regional anticoagulation in the extracorporeal circuit using citrate should be considered an important advance. Although regional citrate anticoagulation may be associated with metabolic complications this procedure has substantially improved RRT in patients at risk for bleeding complications.

Beside the necessary anticoagulation, RRT itself may alter coagulation. During the passage of the extracorporeal circuit platelets are activated and release platelet-derived factors resulting in platelet exhaustion. Furthermore, as a consequence of limited biocompatibility of the dialysis membrane, pro-inflammatory mediators like tumour necrosis factor-alpha may activate platelets via nitric oxide pathways. Although dialysis therapy improves platelet function in general there may be a transient aggravation of platelet dysfunction induced by RRT. Nevertheless the clinical relevance of this finding is still unclear.

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CHAPTER 232

Renal replacement therapy in the patient with acute kidney injury: overview

Jang Won Seo and Ravindra L. Mehta

Modalities of dialysis

Dialysis techniques have evolved over the last two decades with the advent of newer membranes, improved machines that can deliver multiple modes, newer techniques for anticoagulation, and controls for monitoring. However, the general principles of dialysis have not altered significantly. All techniques utilize diffusion, convection, and adsorption as the main mechanisms for manipulating solute and fluid balance; however, they vary in the operational characteristics. Intermittent haemodialysis (IHD) is the mainstay for all renal replacement therapy (RRT) techniques and continues to be the most commonly used therapy worldwide. IHD depends on diffusion-based solute transfer facilitated by high-flow dialysate and short durations. The net result of high small-solute clearance over a few hours is usually adequate for rapidly correcting acid–base and electrolyte imbalances and reducing solute levels; however, the intermittency of the procedure ranging from every alternate day to daily contributes to a see-saw effect on solute levels. Fluid balance is achieved by rapid removal of fluids during the procedure and often results in intolerance to the procedure and large shifts in fluid in the intradialytic period coupled with fluid gains in the interdialytic period. These limiting aspects of IHD have been addressed with the development of hybrid therapies; slow low-efficiency dialysis (SLED) and extended daily dialysis (EDD) that utilize standard IHD machine technology while providing slower solute and fluid removal. These therapies maintain the reliance on diffusion as the principal operational force but slow the process by reducing blood and dialysate flow rates and extending the duration of therapy to 6–16 hours. Continuous renal replacement therapies (CRRTs) harness diffusion and convection applied over a long duration to optimize solute and fluid management. Since time on therapy is prolonged, the operational characteristics capitalize on slower blood and dialysate flow rates; however, circuit longevity is a key factor determining the efficiency of these techniques. Peritoneal dialysis (PD) was the earliest form of continuous dialysis and is still widely used across the world but its application for AKI patients has been somewhat limited. PD utilizes both diffusion and convection and is dependent on the inherent characteristics of the peritoneal membrane and its response to high dextrose solutions for achieving solute and fluid removal. Automated PD utilizing cyclers has made the process simpler; however, the relatively low efficiency of PD may be somewhat rate limiting particularly when AKI is associated with multiorgan failure and shock. The proliferation of new technologies has led to the availability of a broad range of options for the management of RRT in patients with AKI. Table 232.1 provides a comparison of the key features of these techniques.

A careful understanding of the particular benefits, limitations, and potential complications of each modality coupled with a thorough assessment of the individual patient's needs formulate the basis for a dialysis modality selection. In certain circumstances, the more conventional intermittent therapies are sufficient, whereas in other settings, CRRT techniques are advantageous. The impact of modality selection on outcome remains an area of significant controversy (Abdeen and Mehta, 2002). The available evidence does not support any robust recommendations regarding the choice of RRT in the intensive care unit (ICU). Each therapy has its own advantages and limitations depending on how and when it is applied. Continuous therapies may not offer a convincing survival advantage but have been shown to be equivalent therapy to IHD. With the wide availability of CRRT machines and the increasing complexity of critically ill patients, it is likely to remain one of the preferred modalities of renal replacement in the ICU. The use of new hybrid modalities, such as SLED, is increasing as more centres develop familiarity with this technique. SLED may also serve as a bridging modality, as patients are transitioned from CRRT to conventional IHD. Prolonged intermittent RRT (PIRRT) is increasingly reported as a treatment for critically ill patients with AKI. Using retrospective data from three general ICUs in different countries, a change in predominant therapeutic approach from CRRT to PIRRT was not associated with any change in patient mortality risk. Further study of PIRRT is needed in patient populations in the form of randomized clinical trials and also in clinical situations where there is less equipoise about modality choice, such as those with cardiogenic shock, fulminant hepatic failure, and brain injury (Marshall et al., 2011). In addition, RRT modality preferences to treat critically ill children have shifted from PD to CRRT as a result of improvements in CRRT technologies. Optimal care for the paediatric patient requiring RRT demands an understanding of the causes, patterns, and timing of paediatric AKI and multiorgan dysfunction syndrome (MODS) and recognition of the local expertise with respect to the personnel and equipment resources (Goldstein, 2011).

Table 232.1 Principles, technical advances, theoretical advantages, and disadvantages of CRRT, IHD, SLED, and PD

Modality	Potential setting in AKI	Principles	Technical advances	Advantages	Disadvantages
IHD	Haemodynamically stable patients with single-organ failure	Diffusion ± ultrafiltration	Use of high efficiency, high-flux dialysis membrane Use of ultrapure Dialysate Use of nafamostat mesilate	Rapid removal of toxins and low-molecular-weight substances	Hypotension with rapid fluid removal
CRRT	Patients with catabolic multiorgan failure in ICU setting	Convection (haemofiltration) and diffusion (haemodialysis)	Third-generation machines High-volume haemofiltration (HVHF) Application of neonatal CRRT Use of nafamostat mesilate	Continuous removal of toxins Haemodynamic stability Easy control of fluid balance	Slower clearance of toxins Need for prolonged anticoagulation Patient immobilization
SLED	Haemodynamically unstable patients with limited needs for solute and volume control	Diffusion ± ultrafiltration		Slow volume and solute removal Haemodynamic stability	Slower clearance of toxins Technically more complex and demanding
PD	Patients with coagulopathy Difficult vascular access	Diffusion by peritoneal membrane	Use of more physiological dialysate	Technically simple Haemodynamic stability No anticoagulation	Poor clearance in hypercatabolic patients Risk of peritonitis

CRRT = continuous renal replacement therapy, IHD = Intermittent haemodialysis, PD = peritoneal dialysis, SLED = sustained low-efficiency dialysis.

Modified from Matzke et al. (2011) and Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group (2012).

As no single modality has emerged as the standard of care, choosing a renal replacement strategy for the critically ill patient relies primarily on the resources available and personal expertise in any given institution (Abi Antoun and Palevsky, 2009). We believe that the available modalities are effective tools for managing patients with AKI. We recommend clinicians be familiar with each modality and optimize management of patients by selecting the modality best suited to the patients need at any given moment. For instance, critically ill patients with multiorgan failure can be initially supported with CRRT as it offers the advantage of continuous support for fluid and solute management. As the patient improves, SLED and IHD could bridge the patient to recovery of native kidney function. Renal replacement has developed to the point that a multifaceted intervention directed at supporting the function of several organs appears feasible and safe (Ricci and Ronco, 2011).

When should renal replacement therapy be initiated and stopped for acute kidney injury?

Patients with AKI frequently require initiation of RRT. Currently there is considerable variation worldwide on the indications for and timing of initiation and discontinuation of RRT for AKI. Numerous parameters for metabolic, solute, and fluid control are generally utilized to guide the initiation and discontinuation of RRT. However, there are currently no standards in this field (Bagshaw and Gibney, 2007). The lack of consensus on what parameters should guide the decision to start dialysis has led to a wide variation in dialysis utilization. One of the major limitations in establishing parameters for optimal timing of dialysis for AKI is that there are no large studies that have demonstrated that timing of dialysis initiation is a factor that determines patient outcomes in AKI (Macedo and Mehta, 2011). Some observational studies and few randomized trials in the modern era of dialysis have evaluated the timing of dialysis initiation and outcomes. However, the main difficulty in developing a strategy of early initiation is a lack of definitions of what constitutes early versus late. Most of the studies examining the effect of dialysis initiation on outcomes used arbitrary thresholds of traditional serum biomarkers, or urine output volume to define early versus late initiation (Table 232.2) (Macedo and Mehta, 2011). In ICU patients requiring RRT, there was marked variation in factors that influence the start of RRT. RRT initiation with fewer clinical triggers was associated with lower mortality. Timing of RRT may modify survival but requires appraisal in a randomized trial (Bagshaw et al., 2012). Most clinicians base their initiation of dialysis on the presence of pre-specified indications for dialysis. In general, these have been based on severe consequences of the failing kidney including acid–base and electrolyte imbalance, fluid overload, and high levels of BUN (blood urea nitrogen) and creatinine. The indication-based approach is also strengthened by potential safety concerns regarding earlier dialysis initiation, including increased risk for infection from an indwelling dialysis catheter, hypotension, potential for delayed renal recovery, and leucocyte activation from contact with dialysis membranes, among others (Table 232.2) (Teehan et al., 2003; Venkataraman et al., 2005; Macedo and Mehta, 2011).

Given the uncertainty regarding the optimal time to initiate RRT in patients with AKI, we suggest a comprehensive approach considering initiation of dialysis when the 'demand' exceeds the 'capacity' of the kidney to regulate solute and fluid balance. This demand capacity mismatch could result from several conditions such as catabolic state, fluid accumulation, nutritional loading, poisoning, and decreased glomerular filtration rate from AKI. In most

Table 232.2 Factors influencing the decision to start RRT

Parameters used in different studies to compare early vs late RRT initiation	Patient safety	Factors affecting implementation
Clinical symptoms	Unnecessary procedure: Possibility of patient recovering renal function	Logistics
Solute level:	Risk associated with RRT procedure: Complications associated with catheter placement	Vascular access availability
BUN	Hypotension and cardiac events during procedure	Availability of equipment and personnel
SCr	Fear of prolonging renal injury after initiation of RRT	Time of decision to initiation (Sundays, late night)
Interval between ICU/hospital admission and RRT initiation		Treating physician decision
Days between biochemical diagnosis of AKI and RRT		
Severity of AKI:		
AKIN/RIFLE classification		
Prognostic scores		
Number of organ failure		

BUN = blood urea nitrogen; sCr = serum creatinine; AKI = acute kidney injury; RRT = renal replacement therapy.

Modified from Macedo and Mehta (2011).

instances, the criteria for initiating RRT would thus be individualized and based on the existing dynamic conditions rather than any set of absolute conditions that would need to be met (Macedo and Mehta, 2011). For instance, emerging evidence suggests that fluid overload is independently associated with increased mortality in patients with AKI and contributes to worsen outcomes in critically ill patients (Bouchard and Mehta, 2009a). However none of the trials to date have focused on fluid accumulation as a factor for initiating RRT (Bouchard and Mehta, 2010). Based on current knowledge, we would recommend assessing patients for changes in renal function and utilizing dialysis to support organ function and prevent complications rather than waiting for complete renal shut down prior to renal replacement. Future research in this timing of dialysis initiation is desperately needed and should include a combination of clinical and emerging biomarkers to inform these decisions (Macedo and Mehta, 2011).

When and how a course of acute extracorporeal renal support including CRRT should be stopped is also subject to significant variation. It is likely that appropriate cessation of RRT (which includes both when and how) is critical to clinical and economic outcomes. No studies have specifically addressed these issues. The decision to stop a course of treatment or to change modality of treatment is influenced by a variety of factors, including patient characteristics (haemodynamic status, urine output, volume status) and logistic characteristics (staff availability, cost, circuit clotting) (Gibney et al., 2008). We suggest using an approach of 'weaning' from RRT similar to that utilized for mechanical ventilation. As the 'demand' is reduced and the kidney recovers its 'capacity' the therapeutic need for dialytic intervention can be adjusted by transitioning from modalities, for example, from CRRT to SLED and IHD. As a general recommendation, before weaning from RRT, the physician should wait for adequate urine output (without diuretic therapy) and optimized creatinine values (the additional effect of patient glomerular filtration rate and treatment clearance should lead to normal or subnormal creatinine values while on RRT). Once renal function appears close to the baseline or 'pre-AKI' level, it seems reasonable to interrupt the treatment without any specific weaning protocol. It is possible, on the other hand, that patients with signs of only partial renal recovery may benefit from more specific and prolonged weaning algorithms. Examples would be a decrease of ultrafiltration rate, or prescription of intermittent treatments where the therapy was previously continuous (Cruz et al., 2010). A precise level of kidney function needed to allow discontinuation of renal support has not been established; however, a creatinine clearance < 12 mL/min is probably inadequate to allow discontinuation of therapy. In the ATN study, renal support was discontinued when the measured creatinine clearance exceeded 20 mL/min and was left to the discretion of providers when in the range of 12–20 mL/min (Palevsky et al., 2008). Furthermore, evaluation of new renal biomarkers as prognostic factors is intriguing in order to explore if they can predict when patients have recovered sufficient renal function to allow them to remain RRT free once RRT is stopped (Cruz et al., 2010).

Treatment dose of renal replacement therapy

Prescribing dialysis to manage AKI is common and recently has become a controversial area for physicians. The concept of dialysis 'dose' initially was developed for end-stage renal disease and has been extended to AKI in the last decade. Extrapolation of these techniques to critically ill patients with AKI is difficult because of a non-steady state leading to a variable increase in urea generation rate, alterations in total body water and its compartmental distribution, and changing renal excretory capacity (Bouchard et al., 2010). Furthermore, it should not be forgotten that patient care needs to

be individualized—more intensive therapy may be required for the treatment of hyperkalaemia, metabolic acidosis, or extreme hypercatabolism—and that the true adequacy of RRT is defined by more than just the clearance of small solutes (Palevsky, 2009). A positive fluid balance and overt clinical fluid overload, in particular when refractory to medical therapy (that is, diuretics), is also an important circumstance when RRT initiation may prove beneficial. The prevention or management of fluid overload is evolving as a primary trigger/indicator for extracorporeal fluid removal, and this may be independent of dose delivery or solute clearance (Bagshaw et al., 2008). RRT techniques are often required for volume management and require an accurate assessment of fluid status, an adequate comprehension of the principles of fluid management with ultrafiltration, and clear treatment goals (Bouchard and Mehta, 2009b).

While there is increasing evidence that more intensive renal support is associated with better outcomes in AKI, an optimal Kt/V_{urea} and treatment frequency for IHD remain to be established. Similarly, although data had suggested that continuous veno-venous haemofiltration (CVVH) should be dosed at no less than 35 mL/kg/hour (post dilution) (Ronco et al., 2000), intensive renal support in critically ill patients with AKI did not decrease mortality, improve recovery of kidney function, or reduce the rate of non-renal organ failure as compared with less-intensive therapy involving a defined dose of IHD three times per week and CRRT at 20 mL/kg/hour (Palevsky et al., 2008). In critically ill patients with AKI, treatment with higher-intensity CRRT in the form of post- dilution CVVH with an effluent flow of 40 mL/kg/hour did not reduce mortality at 90 days (Bellomo et al., 2009).

Assessing and delivering a specific dialysis dose has become an important issue in the management of patients with AKI. There is ongoing debate as to which is the best marker for this purpose. The assessment and expression of dose for small solutes (e.g. urea) should use dialysate-side measurements and include residual renal function expressed as clearance (mL/min) to provide a uniform dose expression comparable across modalities. Fluid accumulation and fluid balance should be incorporated as measures of dose for all RRT techniques. The dose concept should be extended, including not only urea clearance but the clearance of middle molecules, the achievement of acid–base homeostasis, and fluid balance (Table 232.3) (Claure-Del Granado and Mehta, 2011). Modality transitions add another complexity in quantifying dose as the operational characteristics of each modality (IHD, SLED, and CRRT) have a different influence on dose measurements. There are several methods for quantifying different RRT in a manner that makes dose comparable, among those are the standard Kt/V (stdKt/V) and the solute removal index (SRI) (Gotch, 1998) (Leypoldt et al., 2004). A simulation model of Diaz-Buxo and Pérez showed that StdKt/V constitutes a valuable tool to compare dialytic efficiency between different dialysis modalities and frequencies (Diaz-Buxo and Loredo, 2006).

Table 232.3 Proposed parameters for delivered dose assessment and dose applications for each dialysis modality

Dialysis modality	Dose applications	Assessment of dose	Parameter	Measurement	Tools
IHD	Three-times per week with monitoring of the delivered dose of therapy to ensure a minimum delivered Kt/V of 1.2 per treatment	Frequency (3 per weeks vs daily)	Solute: very small waste products	K^+, Na^+, phosphate H^-	Blood levels of K, Na, PO_4 Phosphate clearance pH, HCO3 AG, SIDeff, SIDapp, SIG, Delta gap Delta ratio.
SLED	At blood and dialysate flow rates of 150 mL/min for 6–8 hours during the day or for 12 hours overnight				
CRRT	Prescribed dose of 25–35 mL/kg/hour				
EDD	Monitoring of the delivered dose of dialysis to ensure delivery of a Kt/V of at least 1.2 per treatment or daily treatment of 6–12 hours	BUN levels	Solute: small waste products	Urea	Clearance (mL/min) EKR (mL/min) StdKt/V
IHD with high flux membrane and CRRT	3 or 4 hours of IHD with standard settings or CRRT at 25–35 mL/kg/hour of effluent flow rate	Serum β_2 microglobulin level	Solute: Middle-sized molecules	Serum β_2 microglobulin	β_2 microglobulin clearance
IHD, SLED, CRRT(CVVH, CVVHD, CVVHDF, HVHF) and couple plasma filtration and adsorption	Combination of above dose applications	Frequency of session per week and Kt/V for IHD and SLED; Ultrafiltration volume (mL/kg per hour) for CRRT	Fluid	Weight (kg) Inputs – outputs BIA BNP	Weight changes Fluid accumulation Fluid overload BIVA BNP profile

AG, anion gap; AKI, acute kidney injury; BIA, bioelectrical impedance; BIVA, bioimpedance vector analysis; BNP, brain natriuretic peptide; BUN, blood urea nitrogen; CRRT, continuous renal replacement therapy; CVVH, continuous veno-venous haemofiltration; CVVHD, continuous veno-venous haemodialysis; CVVHDF, continuous veno-venous haemodiafiltration; EDD, extended daily dialysis; EKR, equivalent urea clearance; H, hydrogen ions; HCO_3, bicarbonate; HVHF, high-volume haemofiltration; IHD, intermittent haemodialysis; K, potassium ions; Na, sodium ions; PO_4, phosphate; SIDapp, apparent strong ion difference; SIDeff, effective strong ion difference; stdKt/V, standard Kt/V; SLED, sustained low-efficiency dialysis.

Modified from Claure-Del Granado and Mehta (2011).

Table 232.4 Complications of RRT and potential solutions

Complications	Potential solutions
Hypotension with intermittent haemodialysis	Decrease the ultrafiltration rate Increase the frequency of dialysis sessions Increase the duration of each session Increase the dialysate sodium concentration Decrease the dialysate temperature Increase the vasopressor dose Switch to continuous or hybrid renal replacement therapies
High bleeding risk Heparin-induced thrombocytopenia	Use regional citrate anticoagulation or no anticoagulation
Citrate toxicity	Decrease or stop the citrate infusion rate Decrease the blood flow rate Increase the calcium infusion rate
Severe hypothermia	Use a blood line or fluid warmer Use an external warming device
Nutritional deficiencies	Ensure timely initiation of feeding Consult a clinical nutritionist Measure and replace dialyable elements such as phosphorus, enterally or parenterally
Inappropriate dosing of drugs	Adjustment of drugs based on sieving properties Therapeutic drug monitoring

Modified from Shingarev et al. (2011).

Recognition and management of complications in renal replacement therapy

RRTs are frequently employed for treatment of patients suffering from AKI in the ICU. Multiple modalities of RRT are currently available. These include IHD, CRRTs, and hybrid therapies, such as SLED. Because of the high complexity of ICU patients, physicians must be aware of the limitations and complications of both intermittent and continuous dialysis modalities that can contribute to patient morbidity and mortality. In the ICU, the major RRT-related complications are hypotension with IHD, high bleeding risk or heparin-induced thrombocytopenia, citrate toxicity in case of citrate anticoagulation, severe hypothermia, and nutritional deficiencies (Table 232.4) (Shingarev et al., 2011). Special attention should be paid to the impact of different forms of RRT on the possible loss of both macro- and micronutrients and vitamins, as well as to the risk of metabolic complications. Finally, close integration between nutritional support and RRT is required, aiming at carefully tailoring both therapies on patients' changing needs. Recent guidelines have suggested that the enteral route should be the preferred one, even though parenteral nutrition is often required to target nutritional needs (25–30 kcal/kg body weight/day, and 1.5 + 0.2 g/kg/day to compensate for amino acid losses during RRT) (Fiaccadori et al., 2011). Renal estimating equations most often overestimate renal clearance in AKI. Additionally, it is well recognized that some drugs are significantly cleared by extracorporeal therapy. Patients with AKI are therefore at risk for adverse outcomes of drug therapy. It has been reported that approximately half of patients with reduced renal clearance receive drug doses that are 2.5 times higher than the recommended maximum dose. To ensure efficacy and prevent toxicity, therapeutic drug monitoring is highly recommended. However, in the absence of drug monitoring, adequate concentrations can only be inferred from clinical response. A clinician must weigh the risks and benefits of possible overdosing or underdosing based on the therapeutic index of the drug and the clinical situation (Awdishu and Bouchard, 2011). In order to achieve the desired goal in a timely fashion, a stepwise approach to adjust drug dosage regimens for patients with CKD and AKI that includes multiple considerations for each individual drug has been proposed (Matzke et al., 2011).

Looking to the future

Our current approaches to RRT for AKI are likely to undergo further enhancements based on advances in technology and availability of biomarkers (Cruz et al., 2011; Ricci and Ronco, 2011; Ronco et al., 2011). Technological advances include development of monitoring capabilities that capture the machine parameters and integrate these with clinical parameters to give an overview of patient status in relation to the delivered therapy (Davenport, 2011c). These parameters can be monitored remotely and coupled with telemedicine capabilities will usher in a new era of managing patients with RRT (Chand and Bednarz, 2008). Online techniques for measuring delivered dose have been available for IHD for some time and are being developed for CRRT (Ricci and Ronco, 2011). These will enable assessment of dialysis dose adequacy in real time. Newer membranes with higher cut-offs and coupled adsorptive capabilities are bringing in alternative techniques to manipulate higher-molecular-weight solutes and modify the activity of blood cells (Davenport, 2011b; Ding et al., 2011a, 2011b). Various biomarkers of kidney injury are now emerging and will help refine strategies for initiating and stopping RRT and identifying patients most likely to benefit from a particular modality (Cruz et al., 2011). These advances will likely result in widening applications for these therapies, for instance, in management of liver failure and heart failure (Ricci et al., 2006; Davenport, 2011a). Several concerns and RRT complications, such as bleeding and anticoagulation strategies, still need further exploration and development (Basso et al., 2010). In summary, the clinician has several options currently with RRT for AKI. It remains for us to utilize these methods appropriately and in a timely manner to improve outcomes from AKI.

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CHAPTER 233

Intermittent acute renal replacement therapy

Mark R. Marshall

Introduction

General considerations

Intermittent haemodialysis (iHD) for acute kidney injury (AKI) is the earliest application of extracorporeal blood purification for uraemia (Haas, 1923, 1952). Over the years, a clearer understanding of patient response to therapy has led to variations of iHD that provide slower solute and fluid removal over longer periods of time, resulting in greater haemodynamic stability and increased solute clearance (Table 233.1) (Marshall and Golper, 2013). These variants are best referred to using the umbrella term prolonged intermittent renal replacement therapy (PIRRT), a term more aligned to nomenclature endorsed by the Acute Dialysis Quality Initiative (Fig. 233.1) (<http://www.adqi.net>).

Overall, iHD is the most common acute renal replacement therapy for critically ill patients (Ricci et al., 2006; Overberger et al., 2007; Basso et al., 2010). This is particularly so in the United States, where therapy prescription and delivery is largely managed by nephrologists. In Australia, the opposite situation exists and continuous renal replacement therapy (CRRT) is most common and managed by intensivists. European practice patterns vary by region. Overall, PIRRT is less common than CRRT in the United States and Europe, being prescribed by 20–30% of clinicians and to about 10% of patients. PIRRT is more common in the Asia-Pacific region, however, with up to 25% patients treated with PIRRT in Australasia, Malaysia, and the Philippines.

This chapter will describe current best practice with respect to iHD and PIRRT and provide strategies for avoiding common complications with both therapies. The chapter uses appropriate clinical practice guidelines as starting points for discussion, making summarial note of their recommendations (Box 233.1) (European Best Practice Guidelines Expert Group on Hemodialysis and European Renal Association, 2002; Kidney Disease Outcomes Quality Initiative (KDOQI) Vascular Access Work Group, 2006; Pratt et al., 2007; Hirsh et al., 2008; Moran et al., 2008; O'Grady et al., 2011; Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group, 2012).

Therapeutic objectives for iHD and PIRRT

Most critically ill AKI patients die from their original disease or pre-existing conditions rather than from complications of AKI. The apportionment of attributable risk underpins the concept of 'corrected mortality', defined as the excess mortality in this population that is due to AKI itself (Kennedy et al., 1973). Corrected mortality is low in non-critically ill AKI patients. However, it rises sharply with illness severity and may exceed 50% for those at the severe end of the spectrum. The main contributors to corrected mortality are intractable infection, non-resolving shock, and haemorrhage (Liano et al., 1998). These conditions can be considered as an 'acute uraemic syndrome' mediated by retained substances in AKI, in contrast to the more familiar 'chronic uraemic syndrome' observed in end-stage kidney disease (ESKD).

Well-conceived and executed studies have established clinical targets for care in some key areas such as dialysis dose. Future progress looks most likely through research into putative mediators of the 'acute uraemic syndrome'. These mediators include a variety of medium-sized (300–12,000 Da) and large (> 12,000 Da) molecules that are produced through uncontrolled activation of humoral pro- and anti-inflammatory cytokine systems (Scheel et al., 2008). Such molecules are essential for the local host responses to disease but in excess have cardio-depressant, vasodilatory, and immunosuppressive properties (Rimmele and Kellum, 2011). They are promising therapeutic targets that are potentially amenable to blood purification via a number of means (Honore and Matson, 2002; Bellomo et al., 2003; Valbonesi et al., 2004; Tumlin et al., 2008; Cruz et al., 2009). To date, however, there are only preliminary clinical studies to support this approach (Honore et al., 2011; Peng et al., 2012). The minimum recommendation, therefore, is that acute renal replacement therapy should correct or prevent threatening acidosis or hyperkalaemia, refractory hypervolemia, and traditional features of the uraemia such as pericarditis or coma. Serum electrolyte and bicarbonate concentrations should be maintained in the normal range. Although specific laboratory thresholds for starting and stopping therapy are unknown, dialysis dose should be measured to and adjusted to meet minimum targets (see 'Dialysis dose')

Vascular access

General considerations

iHD and PIRRT should be performed using arteriovenous angioaccess in those patients who have it, although most cases requires a double-lumen short-term catheter in the internal jugular (IJ), subclavian (SC), or femoral (FE) veins (Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group, 2012). Reliable and well-functioning angioaccess is crucial for iHD

Table 233.1 Variants of intermittent haemodialysis providing slower solute and fluid removal over longer periods of time

PubMed search term	Identified articles as of 1 January 2013	Cumulative total as of 1 January 2013
Sustained low efficiency (daily) dialysis	65	65
Sustained low efficiency (daily) diafiltration	6	68
Slow low efficiency (daily) dialysis	7	74
Slow low efficiency (daily) diafiltration	1	74
Go slow dialysis	2	76
Extended (daily) dialysis	82	153
Extended (daily) diafiltration	4	157
Prolonged (daily) intermittent renal replacement therapy	6	163
Accelerated venovenous filtration	1	165

and PIRRT to ensure that dialysis dose targets are met. Ideally, there should be as low resistance to flow as possible allowing a blood flow rate (Qb) of 200–400 mL/min, and minimal access recirculation (AR).

Catheters should have design features that facilitate simple and safe insertion, low rates of infection and thrombosis, and minimal long-term damage to central vessels. Long-term, tunnelled, cuffed catheters have better hydraulic performance than short-term catheters, but are difficult to insert and exchange and should be reserved for patients who require prolonged renal replacement therapy (> 3 weeks), or with non-recovery of renal function who are transitioning to maintenance dialysis (Kidney Disease Outcomes Quality Initiative (KDOQI) Vascular Access Work Group, 2006; Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group, 2012, O'Grady et al., 2011). Complications such as infection and thrombosis are discussed in more detail in 'Vascular access', as are the various preventative strategies to avoid them.

Hydraulic performance

Different brands of catheters will perform differently due to variations in design. Resistance to flow is inversely proportional to the fourth power of the lumen diameter, and larger-bore catheters allow higher Qb. Catheter rigidity prevents lumen collapse at high negative pressures, and those constructed from polyurethane and its polymers are preferred to silicone since the material is inherently stronger allowing for thinner catheter walls and a slimmer profile. Polyurethane is also thermoplastic allowing for safe placement of catheters tips in the right atrium for best performance. Carbothane (a polyurethane/polycarbonate co-polymer) has the added benefit is that it resistant to chemicals (i.e. iodine, peroxide, or alcohols).

Left-sided IJ and SC catheters provide less reliable blood flow at a rate that is up to 100 mL/min lower than elsewhere (Oliver et al., 2002; Parienti et al., 2010). Resistance to flow is related to the catheter length, and left-sided catheters are longer. Moreover, they traverse anatomical features that create kinks and strictures, and their tips often abut the walls of the superior vena cava.

Overall, AR in all short-term catheters averages 10% at Qb of 250–350 mL/min, but may rise to as much as 35% at Qb of 400–500 mL/min. Furthermore, up to half of acute treatments will require catheters to be utilized with inflow and outflow lines in reversed configuration which markedly increases recirculation. AR is least in IJ catheters, and highest in FE catheters especially in those with length < 20 cm. Several studies show lower dialysis dose with FE catheters than elsewhere despite identical operating parameters (Leblanc et al., 1996; Liangos et al., 2004; Brzosko et al., 2008; Parienti et al., 2010). Fig. 233.2 models the impact of AR on urea clearance as a function of catheter location.

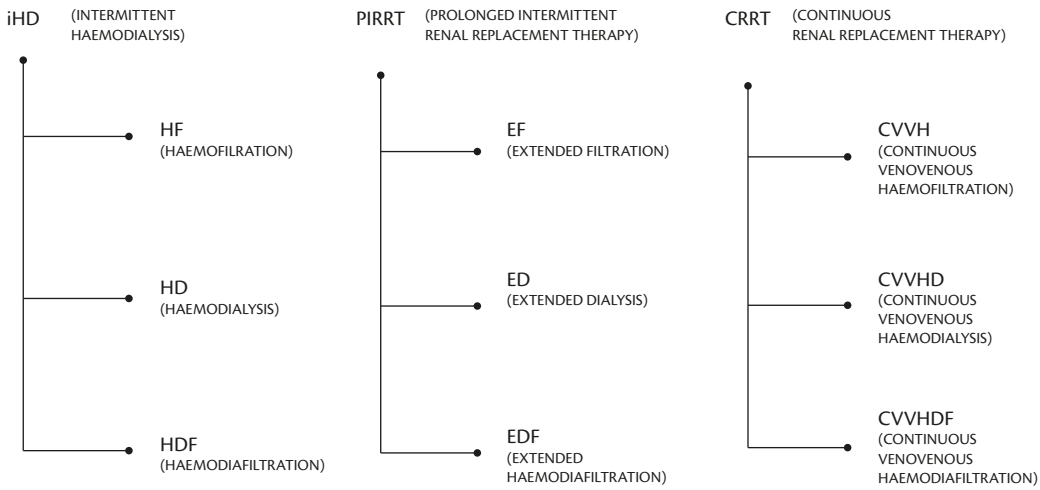

Fig. 233.1 Variants of intermittent haemodialysis, referred to by favoured terminology, contextualized with other extracorporeal acute renal replacement therapy modalities.

Box 233.1 Key clinical practice guidelines quoted in this chapter

- Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guideline for Acute Kidney Injury (Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group, 2012)
- Kidney Disease Outcomes Quality Initiative (KDOQI) Vascular Access Work Group. Clinical practice guidelines for vascular access (Kidney Disease Outcomes Quality Initiative (KDOQI) Vascular Access Work Group, 2006)
- Healthcare Infection Control Practices Advisory Committee (HICPAC) of the Centers for Disease Control and Prevention (CDC) Guidelines for the Prevention of Intravascular Catheter-related Infections (O'Grady et al., 2011)
- National evidence-based guidelines for preventing healthcare-associated infections in NHS hospitals in England (Pratt et al., 2007)
- Institute for Healthcare Improvement How-to Guide: Prevent Central Line-Associated Bloodstream Infections
- International Organization for Standardization documents ISO 11663 (Quality of dialysis fluid for haemodialysis and related therapies), ISO 13958 (Concentrates for haemodialysis and related therapies), ISO 13959 (Water for haemodialysis and related therapies), and ISO 26722 (Water treatment equipment for haemodialysis applications and related therapies) (<http://www.iso.org>)
- Parenteral anticoagulants: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (Hirsh et al., 2008)
- European Best Practice Guidelines for Haemodialysis (Part 1). Section V. Chronic intermittent haemodialysis and prevention of clotting in the extracorporeal system (European Best Practice Guidelines Expert Group on Hemodialysis and European Renal Association, 2002)
- Locking solutions for haemodialysis catheters; heparin and citrate – a position paper by American Society of Diagnostic and Interventional Nephrology (Moran et al., 2008).

Recent advances in catheter design minimize blood mingling and AR. Conventional catheters have ports separated by 2–3 cm (step-tip or split-tip design). However, some catheters now use symmetrical (non-stepped) yet bias-cut spiralled ports on their tips, so that kinetic energy returns blood in a jet from the outflow lumen in a blood-path that remains separate from the inflow one (Tal Palindrome Catheter, Covidien, Dublin, Ireland). In both animal and preliminary human studies, this design results in minimal or acceptable AR in both normal and reversed configurations, making them the preferred option for iHD and PIRRT (Tal, 2005; Spector et al., 2008; Hwang et al., 2012).

Overall, the data support a reasonable recommendation for the use of right-sided IJ catheters with bias-cut spiralled ports as the first choice for iHD and PIRRT, and FE and left-sided IJ catheters as the second and third choices respectively (Parienti et al., 2008; Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group, 2012).

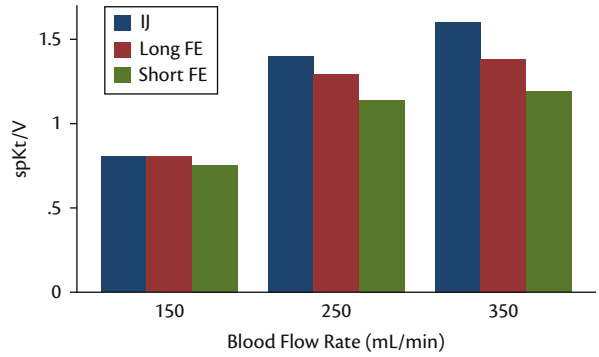

Fig. 233.2 The relationship between single-pool Kt/V (spKt/V) and blood flow rate as a function of catheter site. Intermittent haemodialysis treatments are modelled under the following conditions; duration 240 min, dialysate flow 500 mL/min, haemodialyser mass transfer coefficient 911 mL/min, V 40 L, nPCR 0.8 g/kg/day, internal jugular (IJ) catheter with no recirculation, 20 cm femoral (long FE) catheter assumed to have access recirculation (AR) of 0% at 150 mL/min, 8.5% at 250 mL/min, and 17% at 350 mL/min, 15 cm femoral catheter (short FE) assumed to have AR of 5% at 150 mL/min, 20% at 250 mL/min and 30% at 350 mL/min.
Adapted with permission from Marshall and Golper (2006).

Techniques

General considerations and modality choice

In general, choice of modality depends on the most clinically appropriate rate of solute and fluid removal for the clinical situation. Certain patients are best treated with a lower-efficiency modality, such as those who are haemodynamically unstable including those with cardiogenic shock (Marshall and Golper, 2011). Tolerance to ultrafiltration can be improved in some patients such that a higher-efficiency modality such as iHD is possible (see 'Intradialytic hypotension'). However, often patients still require a change to lower-efficiency modality as evidenced by contamination between the arms in the Hemodiafe study (Vinsonneau et al., 2006). Given the risks of hypotension and subsequent fresh ischaemic injury, PIRRT and CRRT are often more desirable than iHD for such patients.

The same applies to those who are at risk from dialysis disequilibrium syndrome. Solute disequilibrium should be minimized to avoid water influx into the brain in those with cerebral oedema or high intracranial pressure, and influx into the abdomen in those with compartment syndrome (Davenport, 2001; Bagshaw et al., 2004; Betro and Kaplan, 2009). Ultimately, modality choice will be motivated by the clinical needs of the individual situation, as well as by the experience and skills of the staff and organizational culture within the institution.

Prescription of iHD and PIRRT

iHD prescription follows the general principles covered in sections on the treatment of ESKD, although consideration should be given to complications that are specific to the AKI setting and strategies to avoid them (see 'Complications').

PIRRT uses standard iHD equipment and consumables, but with lower solute clearances and ultrafiltration rate (UFR) maintained for prolonged periods of time (Marshall and Golper, 2013). Typically, treatment duration is between 6 and 18 hours. The systems are fully monitored with computerized ultrafiltration control. Dialysate flow rate (Qd) and urea clearances are lower and

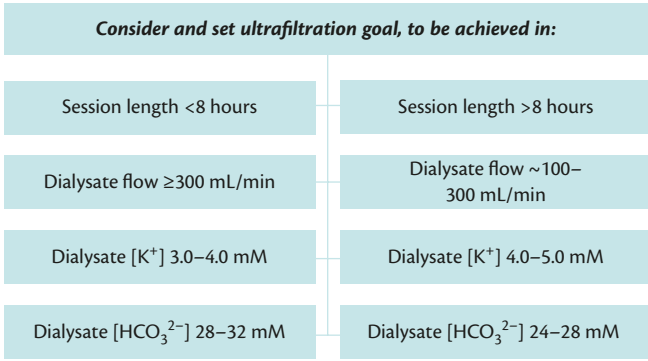

Fig. 233.3 Overview of the decision processes for prolonged intermittent renal replacement therapy prescription.

higher than in iHD and CRRT respectively, which allows for scheduled down time without compromise in dialysis dose. With longer treatments, phosphate replacement may be required at 0.1–0.2 mM/kg or by adding 30–45 mL of Fleet Phospha-soda® to dialysate. In addition, protein prescriptions should be supplemented by 0.2 g/kg per day of PIRRT. A prescription algorithm is shown in Fig. 233.3.

PIRRT provides a high dose of dialysis with minimal urea disequilibrium, excellent control of electrolytes, and good tolerance to ultrafiltration (Marshall et al., 2002; Kielstein et al., 2004). PIRRT is usually delivered as a diffusive therapy, although there is increasing experience combined diffusive and convective clearance (Marshall et al., 2004; Berbece and Richardson, 2006; Holt et al., 2008; Lee et al., 2012).

Machinery

iHD and PIRRT are usually undertaken using machines used in maintenance dialysis programmes. Varying levels of technical complexity are available for increased accuracy of treatment monitoring, a broader range of operating functions, and a larger degree of automation. Experienced operators, however, can perform safe and effective treatments with basic equipment. Most manufacturers are providing machines with integrated functions for PIRRT that can be selected from start-up without any manual adjustments. There are, however, workarounds that allow almost any iHD machine to be utilized for PIRRT (Marshall and Golper, 2013).

Certain technical features are helpful for critically ill AKI patients to minimize intradialytic hypotension (IH). Haemodynamic stability is facilitated by precise and predictable fluid removal, especially when the UFR is greater than that required for the restoration of euvolaemia, such as for haemodiafiltration (HDF). Machines with computerized flow or volumetric ultrafiltration control are therefore preferred. Haemodynamic stability is also facilitated by sodium and ultrafiltration profiling which should be available. There is less or no benefit of online blood temperature and blood volume monitoring and these features are not mandatory. More detail and discussion of IH and its management is provided in 'intradialytic hypotension'.

Most iHD machines reconstitute dialysate from electrolyte concentrate and purified water in a single-pass arrangement. Alternatively, machines can utilize a batch delivery system where the dialysate in already reconstituted. The Genius® machine (Fresenius AG, Hamburg, Germany) is the most popular batch system, and technical elements of the machine and reported patient outcomes appear to be satisfactory (Fliser and Kielstein, 2004). A disadvantage to this machine may be the fixed volume and composition of dialysate, and hence limited clearance and lack of capacity for sodium profiling.

HDF is usually performed for critically ill AKI patients as CRRT. However, intermittent HDF has also been reported in this setting (Pettila and Tiula, 2001). However, there is as of yet no definitive evidence that filtration (convection) improves clinical outcomes over dialysis (diffusion), whether applied during intermittent or CRRT (Rimmele and Kellum, 2011). HDF remains an experimental therapeutic strategy in this setting, especially during iHD and PIRRT, and is not a mandatory technical feature.

Dialysate

Dialysate $[K^+]$ and (ionized) $[Ca^{2+}]$ range from zero up to 4 and 1.75 mM, respectively. For both iHD and PIRRT, a dialysate $[K^+]$ of 3 or 4 mM is required for potassium homeostasis in the AKI setting, unless there is intake of potassium or efflux from the intracellular pool. If lower dialysate $[K^+]$ is used, it is important to monitor serum [K+] periprocedurally to detect hypokalaemia. A dialysate $[Ca^{2+}]$ of 1.25 mM is usually adequate, although dialysis against a low or $[Ca^{2+}]$-free dialysate is often useful for treatment of threatening hypercalcaemia in the AKI patient.

Nowadays, bicarbonate is the standard buffer rather than acetate and the default for critically ill AKI patients. Dialysate generally needs to be alkalotic to maintain normal acid–base status, and bicarbonate concentration can be varied between approximately 24–40 mM using the proportioning system. The default prescription for iHD is 35 mM. The prescription for PIRRT is as per Fig. 233.3, titrated to the clinical situation.

Dialysate sodium concentration can be varied between approximately 130 and 150 mM. The default for iHD and PIRRT is approximately 145 mM to avoid changes in sodium mass balance which can lead to marked fluid shifts and therefore IH.

Water can be delivered either by a central purification plant, a portable purification system, or by a batch system. Water purification itself is achieved by reverse osmosis (RO). If water is soft (< 0.10 dH, 1.8 ppm $CaCO_3$) then only a particle filter and charcoal cartridge are needed with the RO treatment to purify water, otherwise a water softener is needed (Dhondt et al., 2001). Most intensive care units (ICUs) do not have a central water purification plant, although this an increasingly common practice amongst units who perform online HDF for either iHD or PIIRT. The ICU may be able to share a water loop from a maintenance dialysis facility although an auxiliary pump is often needed. Microbiological water quality is important since bacteria in dialysis fluid produce products such as endotoxin which cross into the blood path especially with the use of very permeable membranes. The clinical impact of water quality in the setting of critical illness has not been well studied, although there is clear potential to exacerbate the existing inflammatory milieu. At this time, the reference standards for the AKI setting are the same as those for the ESKD setting: International Organization for Standardization documents ISO 11663, ISO 13958, ISO 13959, and ISO 26722, which encompass standards set by the Association of Medical Instrumentation (AAMI) and European Pharmacopoeia (<http://www.iso.org>).

For iHD, the prescription of Qd follows the general principles covered in sections on the treatment of ESKD. For PIRRT, Qd depends on treatment duration (see Fig. 233.3).

Haemodialysers

The extracorporeal blood circuit activates complement during contact with blood, releasing products of leucocyte activation (e.g. reactive oxygen species, pro-inflammatory cytokines) and activating other cellular pathways. Haemodialysers made of unsubstituted cellulose (e.g. cuprophan (CU)) have exposed hydroxyl groups that activate complement efficiently via the alternative pathway. These hydroxyl groups can be substituted with tertiary amino groups or acetate. Alternatively, haemodialysers can be made entirely from synthetic plastics such as polysulphone and polyamide. In general, these haemodialysers activate less complement and are regarded as biocompatible. Biocompatibility is a membrane characteristic that includes the membrane's activating capacity on complement and leucocytes; a membrane with a high capacity is bioincompatible, and a low capacity is biocompatible. This property is usually attributed by consensus of opinion leaders, due to the lack of formal definitions.

These immune processes are potential contributors to mortality and renal recovery in critically ill AKI patients. Clinical studies of biocompatibility, however, are often contradictory and frequently confounded. Various meta-analyses have divergent results (Jaber et al., 2002; Subramanian et al., 2002), and larger and better conducted studies are probably required to fully resolve the issue. However, they are unlikely to be forthcoming and a general recommendation can be made against the use of unsubstituted CU in view of reasonable doubt regarding a deleterious effect. This usually adds little to the total cost of care, but may amount to a substantial cumulative cost given many patients over time.

The structure of the haemodialyser membrane determines the mechanism of solute removal. Solutes can either move down their concentration gradient via Brownian motion during dialysis (diffusion), or be dragged across the membrane during filtration or ultrafiltration (convection). Low-flux haemodialyser membranes have pores in the skin (as opposed to support) layer with a diameter of approximately 1.0–2.0 nm, and high-flux membranes approximately 3.0–5.0 nm. These sizes generally equate to a molecular weight cut-off (MWCO, the minimum molecular weight at which rejection of solutes is 90%) of approximately 10 KDa and 50 KDa respectively. Diffusion through these pores is the main mechanism for mass transfer of small solutes, while convection is more important for middle-sized and larger solutes (Leypoldt, 2000). A third and often underappreciated modality of solute removal is adsorption, which is important for some solutes such as cytokines. These have sieving coefficients (proportionality constant between the rate of solute movement and fluid movement across the membrane) frequently well below 1, and adsorptive removal of these solutes may be up to 10-fold higher than convective removal (De Vriese et al., 1999). Adsorption is critically dependent on an open pore structure and hydrophobic membrane for binding. The impact of modality of extracorporeal solute removal on clinical outcomes is discussed immediately below (Schetz, 1994).

HDF and high-flux iHD

The extracorporeal removal of inflammatory mediators has been the rationale for experimental therapeutic approaches that maximize convective mass transfer. This can be achieved to a minor degree through the use of high-flux or even 'super high-flux' membranes (MWCO approximately 100–150 KDa) (Haase et al., 2007; Naka et al., 2010). HDF provides more effective removal large solutes with subsequent blood purification by the infusion of crystalloid substitution fluid that dilutes solutes remaining in the body. Most often, substitution fluid is generated online from dialysate, purified by a series of dialysate filters and then diverted by a separate pump to be infused directly into the extracorporeal blood circuit.

Convective therapy as a universal approach must be considered theoretical at present, and its benefits remain unclear. In humans, studies suggesting benefit are uncontrolled, and definitive controlled reports are awaited. Furthermore, it has been shown that convective therapies are unselective and remove both pro and anti-inflammatory cytokines, raising the potential for exacerbation of the patient inflammatory milieu. The limited clinical data concerning intermittent HDF or high-flux iHD for critically ill AKI patients have demonstrated no clinical or laboratory advantage over conventional iHD (Gastaldello et al., 2000; Pettila and Tiula, 2001; Ponikvar et al., 2001). At the present time, more studies are needed before this approach can be recommended.

Anticoagulation

Clot formation occurs at increased rates in patients with AKI due to endothelial damage, activation of platelets and deficiencies in protein C, protein S, and antithrombin (Davenport, 1997). Renal replacement therapy exacerbates this situation through contact between blood and the extracorporeal circuit which further activates the coagulation cascade. Bubble traps are especially thrombogenic because of slower blood flow, stasis, and the air–blood interface. A higher UFR during haemofiltration and HDF may also promote circuit clotting through haemoconcentration (Klingel et al., 2004).

Circuit clotting reduces dialysis dose and increases operational cost and inconvenience. Anticoagulation is therefore necessary other than for a subset of auto-anticoagulated patients. However, it exposes patients to a risk of significant bleeding. 'High-risk' patients can almost always successfully avoid anticoagulation during iHD utilizing saline flushes (Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group, 2012), although this is less successful during PIRRT and regional anticoagulation strategies are often required (Marshall and Golper, 2013).

Unfractionated heparin is the most commonly used anticoagulant for all intermittent modalities, and is infused in the proximal part of the extracorporeal circuit to keep the activated partial thromboplastin time (aPTT) in the venous blood line 1.5–2 times the control value. This typically requires an initial bolus dose of approximately 2000 U and maintenance infusion of approximately 500 U/hour. Advantages of unfractionated heparin include low cost, extensive cumulative clinical experience, and relative ease of monitoring. Additionally, the anticoagulant action of heparin has a short half-life and an antagonist, protamine sulphate, is readily available. The risks of unfractionated heparin (other than bleeding) include hyperkalaemia, transaminitis, and heparin-induced thrombocytopenia (HIT) in 3–5% of patients.

Low-molecular-weight heparins (LMWHs) exert their anticoagulant effect primarily through inhibition of coagulation factor X activity. The advantages of LMWHs include a lower incidence of HIT, but are generally outweighed by its disadvantages that include a prolonged half-life (approximately doubled in AKIN 3 stage, with no significant clearance during iHD or PIRRT),

incomplete reversal with protamine (both protamine and recombinant factor VIIa are required to treat bleeding (Ng et al., 2003)), and limited availability of appropriate monitoring by serial anti–factor Xa determinations (recommended level 0.25–0.35 U/mL) (Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group, 2012). Meta-analyses and the American College of Chest Physicians (ACCP) guidelines conclude that the use of LMWH is associated with major bleeding in patients with a creatinine clearance of < 30 mL/min, and recommend either unfractionated heparin or a reduction in LMWH dose by 50% for such patients (Lim et al., 2006; Hirsh et al., 2008). LMWH dosing is not interchangeable between different drugs. Most experience is with dalteparin, administered as single bolus of approximately 20–30 U/kg for iHD, followed by an infusion of approximately 10 U/kg/hour for PIRRT. Overall, evidence does not support a recommendation of LMWH over unfractionated heparin in terms of safety and efficacy in the critically ill AKI setting.

Alternatives to systemic anticoagulation include regional citrate anticoagulation (RCA), regional heparin anticoagulation, and prostacyclin (epoprostenol). Heparin coated membranes are expensive and probably not as effective as regional approaches (Evenepoel et al., 2007). The lowest rates of bleeding and greatest prolongation of extracorporeal blood circuit life are with RCA. RCA involves calcium chelation in the extracorporeal blood circuit with calcium reversal. For iHD and PIRRT, this most commonly involves an infusion of 4% trisodium citrate (TSC) into the proximal circuit, with zero calcium dialysate and an infusion of calcium chloride into the venous blood line. Alternatively, the TSC infusion can be combined with low or normal calcium dialysate and no calcium infusion. The positive calcium flux through the haemodialyser maintains calcium balance without the need for a separate infusion and provides partial chelation of the undialysed citrate. Several useful regimens for RCA during PIRRT have been published, although adherence to a strict protocol with close monitoring and titration of citrate and calcium dose are needed to keep the ionized calcium within a therapeutic range (Morgera et al., 2004; Finkel and Foringer, 2005; Clark et al., 2008; Szamosfalvi et al., 2010). The major complications of RCA are systemic hypocalcaemia and metabolic alkalosis from citrate toxicity, particularly if hepatic metabolism of citrate is seriously impaired. Regional heparin anticoagulation involves an infusion of heparin into the proximal circuit with protamine reversal. This approach seems to be effective although it may be complicated by rebound bleeding (neutralization with protamine wears out faster than the anticoagulation from heparin) and sudden anaphylactoid reactions from activation of inflammatory mediators and deposition of protamine-heparin complexes (Carr and Silverman, 1999).

Prostacyclin is a potent inhibitor of platelet aggregation and is an effective alternative anticoagulant during PIRRT (Fiaccadori et al., 2007). However, it is a vasodilator, with a dose-dependent risk of occasionally marked hypotension. Moreover, there is a risk of worsening ventilation–perfusion mismatch, and lactic acidosis in patients with multiorgan dysfunction, and a risk of increasing intracranial pressure in patients with combined liver and kidney failure (Davenport et al., 1990, 1991a, 1991b; Langenecker et al., 1994).

Other approaches are available such as direct thrombin inhibitors (e.g. argatroban), antithrombin-dependent factor Xa inhibitors (e.g. fondaparinux), and serine protease inhibitors (nafamostat mesilate). There are relatively few safety and efficacy data for these drugs, and their role is usually limited to anticoagulation of patients with HIT. Argatroban does not cross react with heparin antibodies and is the preferred approach due to its hepatic clearance (half-life approximately 35 min, no significant clearance during iHD or PIRRT (Murray et al., 2004)), and ease of monitoring with aPTT. It is administered as a 0.1 mg/kg bolus prior to iHD or an infusion of 0.1–0.2 mg/kg/hour during PIRRT, titrated according to aPTT). Further management of HIT is provided in guidelines from the ACCP and the European Best Practice Guidelines (European Best Practice Guidelines Expert Group on Hemodialysis and European Renal Association, 2002; Hirsh et al., 2008).

Dialysis dose

The relationship between small solute clearance and the outcomes of critically ill AKI patients is now established. A key study from 20 years ago showed that delivered single-pool Kt/V (spKt/V) > 1.0 per iHD treatment was associated with improved survival in patients with intermediate illness severity, although the study did not relate outcomes to frequency of treatments (Paganini et al., 1996). Subsequently, a prospective, controlled trial demonstrated that delivered spKt/V of 0.9–1.0 per iHD treatment six or seven times per week improved survival compared to this dose three to four times per week. However, the time-averaged blood urea nitrogen (BUN) in the lower dose group (104 mg/dL) clearly indicated underdialysis by current standards (Schiffl et al., 2002). Most recently, a well-conceived and executed prospective, randomized controlled trial showed that delivered spKt/V of 1.2–1.4 per iHD or PIRRT treatment five or six times per week did not improve survival compared to this dose thrice weekly (Palevsky et al., 2008). There are consistent data restricted to PIRRT from the Hannover Dialysis Outcome Study, a smaller but well executed randomized clinical trial (see below) (Faulhaber-Walter et al., 2009).

Optimal iHD dose therefore appears to be related to small solute clearance, although there appears to be a dose above which survival becomes dose independent. The minimum recommended iHD and PIRRT dose is a delivered spKt/V ≥ 1.3 per treatment at least thrice weekly (Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group, 2012). This mandates routine measurement of dose to guide appropriate adjustment of operating parameters. Delivered dose tends to be low in this population, and is optimized by measures summarized in Box 233.2. If this dosing target cannot be achieved, dose should be maintained as high as possible and treatment frequency increased. The required number of treatments per week and dosing interval can be established from the nomogram in Fig. 233.4 expressing combinations of iHD dose and treatment frequency as a continuous small-solute clearance (expressed as the corrected equivalent renal urea clearance (EKRc)), aiming for a value ≥ 12.6 mL/min (Casino and Lopez, 1996; Casino and Marshall, 2004; Claure-Del Granado et al., 2012). This expression of dose is useful to frame interpretation of the Hannover Dialysis Outcome Study: patients treated with daily PIRRT to keep plasma urea 11.3 ± 4 mM (EKRc equal to 20 mL/min, assuming urea generation of 20 mg/min) had indistinguishable outcomes to those treated to keep plasma urea 19 ± 6 mM (EKRc equal to 13 mL/min) (Faulhaber-Walter et al., 2009).

Box 233.2 Measures to increase intermittent haemodialysis dose

- Maximize haemodialyser surface area (up to 2.0–2.2 m^2)
- Maximize blood flow rate by:
  - large-bore catheter (internal diameter up to 2.0–2.2 mm)
  - titration of blood flow rate to maximum arterial and venous pressures (up to minus and plus 300–350 mmHg respectively)
  - correct positioning of catheter tip as appropriate
  - right-sided internal jugular > femoral > left sided internal jugular catheters
- Minimize access recirculation by:
  - correct positioning of catheter tip as appropriate
  - internal jugular > femoral catheters
- Maximize dialysate flow (up to 800–1000 mL/min)
- Optimize anticoagulation to reduce haemodialyser fibre bundle clotting
- Optimize circulatory status to reduce compartmental urea sequestration
- Increased treatment duration (up to 5–6 hours)
- Increased treatment frequency (up to daily)
- Consider prolonged intermittent or continuous renal replacement therapy.

Adapted with permission from Marshall and Golper (2006).

Complications

Vascular access

Complications relating to access include infection, dysfunction, and trauma to great vessels.

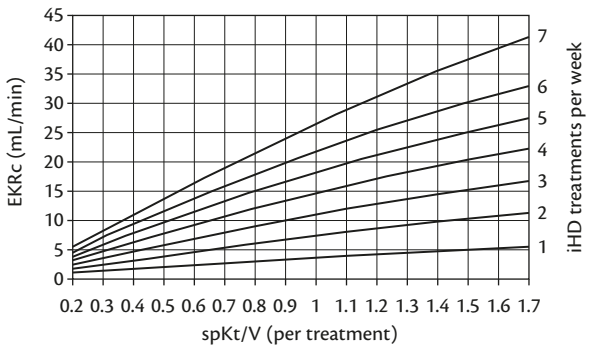

Fig. 233.4 The relationship between continuous urea clearance corrected to a V of 40L (EKRc) and variable volume single-pool Kt/V (spKt/V). The solid lines relate EKRc to spKt/V for a given intermittent haemodialysis (iHD) schedule.
Adapted with permission from F. G. Casino and T. Lopez, The equivalent renal urea clearance: a new parameter to assess dialysis dose, *Nephrology Dialysis Transplantation*, 1996, 11/8, by permission of Oxford University Press.

Infection

The epidemiology of dialysis catheter-associated bloodstream infections (CABSIs) is not described in the AKI setting, and assumed to be equivalent to that of non-dialysis CABSIs when adjusted for illness severity (Souweine et al., 1999, 2006). Older literature is also outdated as a result of changing practice patterns and generally improved rates of infection over the last few years (2011). Notwithstanding, CABSI in this setting appears common, costly, and associated with a mortality risk estimated at 10–50% (Soufir et al., 1999, Pittet et al., 1994, Shannon et al., 2006).

A CABSI is defined by the Centers for Disease Control and Prevention (CDC) as a primary bloodstream infection in a patient that had a central venous catheter within the prior 48-hour period, and unrelated to an infection at another site. Low CABSI rates require both adherence to specific clinical guidelines, and grounding of activities within a formal quality improvement framework (Shannon et al., 2006). There is a strong evidence base in this area from well designed and conducted multicentre trials (Pronovost et al., 2006; Scales et al., 2011). Central venous catheter insertion and care can and should be standardized, and results in a close to zero CABSI rate (Bonnal et al., 2010; McLaws and Burrell, 2012). The relevant guidelines in choosing interventional bundles are those contained in Institute for Healthcare Improvement's (IHI) and the CDC's Healthcare Infection Control Practices Advisory Committee (CDC/HIPAC) position statements (O'Grady et al., 2011). The core elements in these guidelines appropriate for dialysis catheters are in Box 233.3.

Of note, there is ongoing controversy about the first choice for catheter insertion site from the point of view of infection. The SC is recommended by both the IHI and CDC, but is not appropriate for critically ill AKI patients due to the increased risk of mechanical complications. Moreover, the lower associated infectious complications of the SC approach are most obvious when catheters are inserted by inexperienced critical care doctors or in uncontrolled environments (Richet et al., 1990; Merrer et al., 2001). In standard and routine clinical practice, this association is less obvious (Deshpande et al., 2005; Parienti et al., 2012). The avoidance of the FE site for catheter insertion is also questionable following a prospective randomized clinical trial in 750 patients, where rates of catheter colonization and CABSI were not significantly different between the jugular and femoral sites (Parienti et al., 2008). On balance, the IJ site is preferred although it is likely that the way the catheter is handled is more important at preventing CABSI than the site in which it is inserted.

Antibiotic (minocycline and rifampin) or antiseptic (chlorhexidine and silver sulfadiazine) impregnated lines are recommended by the CDC for those whose catheters are expected to remain in place for a prolonged period (> 5 days and in the setting of optimal maximal adherence to measures to reduce CABSI), and also patients at high risk for infection (patients with extensive burn injury, neutropenia, and arguably AKI). A potential downside of these lines is anaphylaxis especially to chlorhexidine, and this should be considered for patients with a suggestive history (Stephens et al., 2001; Pittaway and Ford, 2002). Topical antibiotic ointments are not recommended because of their potential to promote fungal infections and antimicrobial resistance. Catheter-restricted locking solutions are effective at reducing CABSI in outpatient maintenance HD settings (Jaffer et al., 2008; Labriola et al., 2008; Yahav et al., 2008), and are empirically recommended in patients with long-term

Box 233.3 Best practice to minimize catheter-associated bloodstream infection

Insertion

- Hand hygiene and aseptic technique (including early replacement of catheters inserted in uncontrolled settings if adherence to these measures cannot be ensured)
- Maximum barrier precautions (hat, mask, sterile gloves, sterile gown, and full patient drape)
- Appropriate skin preparation (2% chlorhexidine in 70% alcohol)
- Avoidance of the femoral site for catheter placement, especially in obese patients
- Avoidance of catheter placement near to open wounds.

Maintenance

- Daily review of the need for the line, with prompt removal of unnecessary lines
- Appropriate dressing with sterile gauze or a sterile, transparent, semipermeable dressing
- Appropriate schedule for dressing changes according to condition and type of dressing
- Daily review of the catheter exit site by inspection or palpation with minimal disturbance to the dressing unless clinically indicated
- Appropriate skin preparation before accessing ports
- Daily cleansing of patients using a 2% chlorhexidine wash
- Use of a suture-less securing device for catheter stabilization.

catheters who have a history of multiple CABSI despite optimal maximal adherence to measures to reduce infections (Pratt et al., 2007; O'Grady et al., 2011). Their efficacy and effectiveness for critically ill AKI patients is an unresolved issue, however, and merits further study.

Catheter dysfunction

It is important to minimize dialysis catheter dysfunction to provide adequate dialysis dose. Notwithstanding formal definitions (Kidney Disease Outcomes Quality Initiative (KDOQI) Vascular Access Work Group, 2006), a pragmatic definition is the inability to achieve Qb sufficient to deliver an adequate dialysis dose within a clinically or logistically appropriate dialysis schedule. In the AKI setting, the key factors are catheter position and thrombosis. The former issue is discussed previously, and the latter dealt with below.

Catheter thrombosis is prevented through the instillation of anticoagulant locking solutions. Systemic anticoagulation and antiplatelet agents are ineffective with no role in acute renal replacement therapy. Heparin-coated catheters have not been shown to reduce the catheter dysfunction (Clark et al., 2009; Jain et al., 2009). Locking solutions remain most effective for maintaining lumen patency: heparin at 1000 U/mL or 4% sodium citrate are recommended in a position statement from the American Society of Diagnostic and Interventional Nephrology, with injected volumes not exceeding the internal volume of the catheter (Moran et al., 2008).

There are risks from heparin-based locking solutions from systemic anticoagulation. Critically ill AKI patients are often vulnerable as a result of bleeding diatheses and postoperative status. All dialysis catheters have some degree of leakage of locking solution. This is highest in non-tunnelled catheters and those with proximately situated or side ports. Leakage begins immediately after instillation, and (despite *in vitro* studies to the contrary) continues for many hours possibly by a process of diffusion rather than convection. For instance, one study of such catheters reported an average of 1.21 mL of leakage over the interdialytic period, amounting to 41.9% of the total volume and an average systemic dose of heparin of approximately 6075 U. Leakage is higher if luminal clot reduces its effective volume, which is more likely with the pro-thrombotic state and generally less anticoagulant locking solutions used in the AKI setting. Overall, 4% trisodium citrate is the preferred locking solution for catheters in critically ill AKI patients. The majority of studies show similar efficacy and lower bleeding risk. Other benefits include possible reduction in biofilm formation, avoidance of heparin antibody formation, and lack of interference with coagulation assays (Moran et al., 2008).

Problematic or recurrent catheter thrombosis can still occur despite standard locking. So long as the risks of anticoagulation are acceptable, catheter lock overfill by 20% might be attempted, or the use of higher concentrations of heparin (5000 and 10,000 U/mL). However, even in the ESKD setting, increased concentration of heparin is associated with an almost 10-fold risk of composite bleeding events, with 7.7% of patients experiencing a severe episode (Yevzlin et al., 2007). Another strategy is a 6-day per week heparin locking regimen (Oran and Eser, 2008), although there is potential to increase the risk of infectious contamination through increased handling. Fibrinolytic agents (tissue plasminogen activator (rt-PA) 1 mg/mL or 1 mg in each lumen) improves patency and bleeding risk in the ESKD setting (Schenk et al., 2000; Hemmelgarn et al., 2011), but is a more expensive approach with a lack safety and efficacy data in acute renal replacement therapy.

Trauma to great vessels

Central venous catheterization can lead to central vein thrombosis/stenosis due to trauma and compromise subsequent attempts to establish permanent arteriovenous angioaccess. The risk is higher with SC compared to IJ catheters, and with left-sided compared to right-sided catheters due to greater vessel contact throughout the length of the catheter. The preferred site from the perspective of minimizing trauma is the right IJ, and least preferred the SCs.

Meta-analyses and clinical practice guidelines conclude that ultrasound guidance increases the probability of successful catheter placement during insertion, reducing the risk of complications, the need for multiple catheter placement attempts, and the time required for the procedure (Randolph et al., 1996; Karakitsos et al., 2006; Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group, 2012).

Intradialytic hypotension

IH is detrimental for end-organ function, and both general and renal recovery of critically ill patients. Renal vascular reactivity is abnormal in post-ischaemic AKI, and with reduced autoregulation and

paradoxical vasoconstriction in response to reduced renal perfusion pressure (Conger et al., 1991). Critically ill AKI patients develop fresh ischaemic lesions in kidney biopsy specimens in the course of their illness (Solez et al., 1979), and episodes of IH are known to reduce residual renal function (Sigler et al., 1994; Manns et al., 1996).

Frequent treatments and prolonged treatment time will minimize ultrafiltration goals and rates, and are the most effective measures for IH. The following strategies can also be applied.

Bicarbonate buffered dialysate

Hyperacetataemia has a peripheral vasodilating and myocardial depressant effect, and acetate buffered dialysate is associated with an increased frequency of IH relative to bicarbonate buffered dialysate (Man et al., 1982; Wizemann et al., 1993; Herrero et al., 1994). Bicarbonate buffered dialysate should be standard in critically ill AKI patients.

Sodium and ultrafiltration profiling

Solute removal during iHD rapidly reduces serum osmolality. The intercompartmental transfer of these solutes is not instantaneous, and osmotic forces therefore promote water movement into cells reducing in extracellular volume and effective circulating volume. Sodium profiling involves higher dialysate sodium concentration at the start of dialysis, with decrements thereafter until the base concentration in achieved at the end of treatment. The increased serum osmolarity facilitates fluid transfer into vascular compartment, thereby maintaining effective circulating volume during ultrafiltration (Stiller et al., 2001). Another widespread practice is ultrafiltration profiling, which involves variation in UFRs during the treatment. The commonest practice uses a higher rate at the start of the treatment with a lower rate later in the treatment. This technique has not been shown to have a clinical benefit when used in isolation, although it may be useful when combined with sodium profiling (Oliver et al., 2001).

These may be helpful to prevent IH in critically ill AKI patients. In one study, those randomized to sodium profiling (160 mM at the start of treatment, 140 mM base concentration) combined with ultrafiltration profiling (50% of ultrafiltration volume removed in the first one-third of the treatment, the rest removed over the remainder) had improved haemodynamic stability compared to those treated with conventional iHD (Paganini et al., 1996). Further study is needed to determine the exact contribution of individual interventions and the value of simpler approaches such as high sodium dialysate without profiling.

Blood volume and temperature monitoring

Blood volume and temperature monitoring (BTM, BVM) involve biofeedback systems that automatically adjust iHD operating parameters. BVM adjusts UFR and dialysate sodium content in response to a fall in circulating blood volume, and BTM maintains the patients' blood temperature at target value by controlling thermal transfer to and from dialysate to avoid vasodilation and decreased vascular resistance. These systems improve IH in ESKD patients who are prone to this complication (Dheenan and Henrich, 2001; Santoro et al., 2002). In the AKI setting, neither technique has been shown to prevent IH (Maggiore et al., 2002; Tonelli et al., 2002; du Cheyron et al., 2013). The likely reasons pertain to different causes and compensatory mechanisms for hypotension in two settings, which are not necessarily comparable between ESKD and critically ill AKI patients (Garg and Fissell, 2013).

Dialysate calcium

High dialysate calcium (1.75 mM) may preserves left ventricular function in patients with cardiomyopathy during dialysis in the ESKD setting, and improve blood pressure in patients prone to severe IDH (Alappan et al., 2001). This technique is limited by the development of hypercalcaemia, however, and awaits study in the critically ill AKI patient cohort.

Modality

A number of observational studies in the late 1970s and early 1980s demonstrated superior cardiovascular stability during intermittent HDF in the ESKD setting, although prospective controlled trials on balance have not supported this finding (Locatelli et al., 1996; Movilli et al., 1996; Grooteman et al., 2012; Ok et al., 2013). Although there are no definitive studies, it is unlikely that intermittent HDF reduces IH in critically ill AKI patients.

There is large cumulative clinical experience that lower-efficiency modalities of acute renal replacement therapy provide better haemodynamic stability because of slower fluid and solute removal. This is supported by meta-analyses showing better preservation of blood pressure and less vasopressor requirements in those treated with CRRT rather than iHD (Rabindranath et al., 2007; Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group, 2012). Several prospective clinical trials and many observational studies have shown comparable haemodynamic stability between CRRT and PIRRT (Kielstein et al., 2004; Kumar et al., 2000; Kielstein et al., 2010; Schwenger et al., 2012), and lower-efficiency prescriptions of PIRRT and CRRT are suitable for ameliorating IH, and the most appropriate first choice as acute renal replacement modality for haemodynamic unstable patients.

Outcomes

AKI in critically ill patients is associated with high in-hospital and post-discharge mortality although outcomes appear to be gradually improving over time despite a higher degree of illness severity (Bagshaw et al., 2007). On the basis of current evidence, the indiscriminate use of one modality of acute renal replacement modality over another is unlikely to translate to overall clinical benefit if applied to all patients, either in terms of mortality or renal recovery (Rabindranath et al., 2007; Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group, 2012). Therapy choice depends on the patient's condition and the clinical objectives of the prescribing clinician. Moreover, the skill and experience of staff providing therapy probably influences patient outcomes more than the type of therapy per se (Lameire et al., 1999). Overall, iHD and PIRRT are probably less expensive than CRRT, although as with every economic analysis this depends heavily on local conditions. Ultimately, the modality that is the easiest to organize and least expensive to perform will be the most successful, if all outcomes are equivalent.

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CHAPTER 234

Continuous renal replacement therapy

Miet Schetz and Andrew Davenport

Introduction

Continuous arterio-venous haemofiltration (CAVH) was introduced by Kramer et al. (1977) primarily to control volume overload in intensive care unit (ICU) patients, delivering small solute clearances of around 16 mL/min (Lauer et al., 1983). To improve solute clearances, diffusion (contraflow dialysate) was added, continuous arterio-venous haemodialysis (CAVHD) (Stevens et al., 1988; Davenport et al., 1990), and to increase ultrafiltration volumes, reduce the risk of clotting within the haemofilter, and increase circuit survival, the site of fluid replacement was switched from post dilution to pre dilution (Kaplan, 1985). Initially no specially developed replacement solutions or dialysates were available and hypertonic peritoneal dialysates were often used. The introduction of a blood pump led to the development of veno-venous continuous renal replacement therapy (CRRT) (haemofiltration, dialysis, and the combination haemodiafiltration). This was soon followed by the development of specially designed replacement solutions/dialysates for CRRT and dedicated CRRT machines. A comprehensive review on the use of CRRT in critically ill patients was published recently (Tolwani, 2012).

Continuous renal replacement therapy techniques

CRRT typically utilizes high-flux dialysers/haemofilters designed to allow passage of solutes up to 20 kD (Leypoldt et al., 1983). During treatment the membrane becomes protein coated thus reducing permeability to larger solutes (Colton, 1987). Some solute removal may occur due to adsorption within this protein layer. Solute clearance during haemodialysis is based on diffusion driven by a concentration gradient between blood and dialysate. Since diffusion is a molecular weight-dependent process, haemodialysis primarily clears small solutes. Haemofiltration uses convection whereby solutes are carried along with the plasma water that is driven through the membrane by a hydrostatic pressure gradient (Henderson, 1983). Convective solute clearance is independent of molecular weight up to the cut-off of the membrane. Haemodiafiltration combines both diffusion and convection (Fig. 234.1). Both haemodialysis and haemofiltration can only effectively clear solutes that are free and not bound in plasma water.

During intermittent RRT, dialysis provides better small solute clearances than haemofiltration whereas the reverse is true with regard to larger solute clearances (Floege et al., 1987). However, during CCRT, due to the lower flow rates, and assuming similar effluent flow rates, haemofiltration and haemodialysis have similar small solute clearances, whereas haemofiltration provides higher middle molecule clearances (Brunet et al., 1999; Ricci et al., 2006a). Predilution haemofiltration, where fluid is infused before the filter (Fig. 234.2), reduces haemoconcentration and solute concentration within the dialyser/haemofilter and reduces overall clearances due to the dilutional effect (Brunet et al., 1999). To achieve similar solute clearances to post dilution, predilution requires more replacement fluids, and is therefore more costly. However these increased costs may be compensated by increased circuit survival, due to reduced haemofilter clotting (Uchino et al., 2003) (Box 234.1)

Vascular access

Adequate RRT requires a good functioning vascular access, implying the delivery of an adequate blood flow (120–200 mL/min for CRRT), sustained patency, minimal trauma to the intima (with associated risk of thrombosis and stenosis), and low incidence of catheter-related infection (Schetz, 2007b).

Catheter design and material

Most centres use a dual-lumen catheter with an outer diameter between 11 and 14 French. The lumens can be arranged in a double-D, double-O, or coaxial manner. Although not formally evaluated in a clinical trial, the double-D is probably the best configuration because it has the highest volume to surface ratio and therefore the lowest shear rate (Ash, 2008).

Acute dialysis catheters are generally made from polyurethane or silicone as they are both less thrombogenic than older materials. Polyurethane has thermoplastic properties implying that it is semi-rigid during insertion and softens at body temperature, thus minimizing trauma to the vessel wall. Silicone catheters are softer and more difficult to insert and are used for tunnelled catheters. A small randomized controlled trial (RCT) comparing tunnelled and non-tunnelled dialysis catheters in patients with acute kidney injury (AKI) reported more insertion problems but less dysfunction (defined as the need for treatment interruption or line reversal) and fewer infectious and thrombotic complications with tunnelled catheters (Klouche et al., 2007). However, evidence in AKI is limited to this small study and in most centres initial access for acute RRT is established with a short-term, non-cuffed, non-tunnelled catheter. The optimal timing for switching to a tunnelled catheter in patients with prolonged need for RRT has not been established.

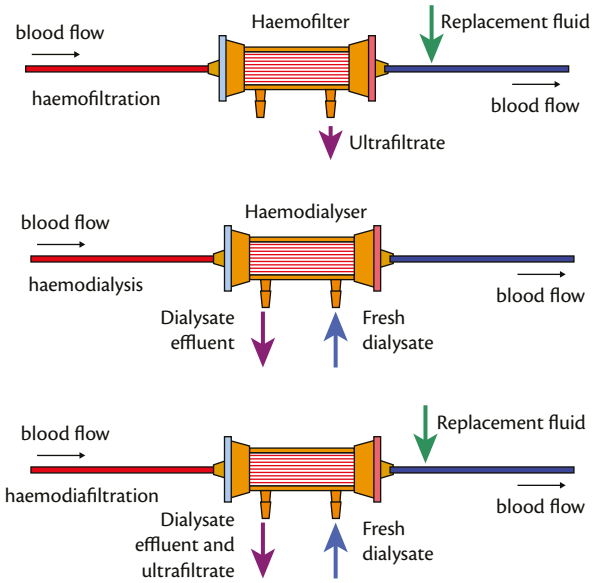

Fig. 234.1 Schematic circuit diagrams to demonstrate the differences between post-dilutional haemofiltration, dialysis, and post-dilution haemodiafiltration.

Although catheters treated with anti-infective agents may be useful in preventing central venous catheter (CVC) colonization and catheter-related bloodstream infections (CRBSIs) (Casey et al., 2008; Hockenhull et al., 2009) many of the included studies have important methodological shortcomings and very divergent incidence rates in the control groups. The emergence of resistant organisms also remains an important concern and requires continued surveillance, especially in the ICU setting. Only one RCT evaluated the efficacy of antibiotic-coated dialysis catheters for prevention of catheter-related infection in the setting of AKI in cancer patients. The study included 130 patients that were randomized to a standard or an antibiotic-coated femoral catheter. Although the authors report a reduced incidence of 'catheter infections' with coated catheters (0% vs 11%), the incidence of colonization (24.6 vs 31.3/1000 catheter days) and of a strictly defined CRBSI (0 vs 2/1000 catheter days) was not significantly affected (Chatzinikolaou et al., 2003). Because of reservations about the quality of evidence, current infection control guidelines recommend antiseptic- or antimicrobial-impregnated CVCs only in patients whose catheter

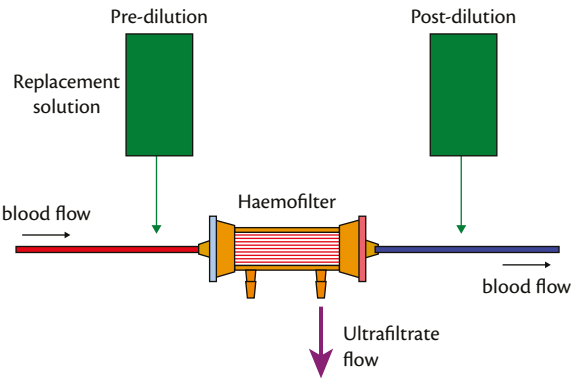

Fig. 234.2 Schematic circuit diagram showing the sites of pre-dilution and post-dilution fluid replacement for CRRT.

Box 234.1 Adavntages of pre-dilution and post-dilution

Advantages of pre-dilution during CRRT

- Improved filter survival due to reduced haemoconcentration and membrane fouling
- Reduced filter costs
- Increased thermal losses.

Advantages of postdilution

- Increased solute clearances (for similar replacement rate)
- Reduced requirement for replacement fluids (for similar clearance)
- Reduced fluid costs.

is expected to remain in place for > 5 days in settings where, despite compliance with basic strategies for prevention of CRBSI, the rates of CRBSI remain above the goal set by the individual institution (≥ 3.3 CRBSIs/1000 days) (Pratt et al., 2007; Marschall et al., 2008; O'Grady et al., 2011). Other indications for antiseptic- or antimicrobial-impregnated CVCs are patients with limited venous access and a history of CRBSI and patients at heightened risk for severe sequelae from CRBSI (Marschall et al., 2008). It seems reasonable to extend these guidelines to dialysis catheters in AKI. Antibiotic-impregnated dialysis catheters are expensive and not available everywhere.

Catheter insertion site

The choice of catheter insertion site requires weighing the risks and benefits for each potential site with regard to mechanical, thrombotic, and infectious complications. Despite its lower infection risk, both the Centers for Disease Control (CDC), the National Kidney Foundation (NKF), and Kidney Disease Improving Global Outcomes (KDIGO) guidelines consider the subclavian vein as a last choice for dialysis access (Vascular Access 2006 Work Group, 2006; O'Grady et al., 2011; Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group, 2012). The rationale is the higher incidence of thrombosis/stenosis shown in observational studies in chronic kidney disease (Barrett et al., 1988; Cimochowski et al., 1990; Schillinger et al., 1991). Central vein stenosis will jeopardize the function of a subsequent permanent vascular access in the ipsilateral upper limb in case the patient would progress to end-stage renal disease. The major risk factor for development of thrombosis/stenosis is contact of the catheter with the vessel wall (Yevzlin, 2008). The right jugular vein offers the most direct route to the superior vena cava whereas catheters in the subclavian or left jugular vein may have several points of contact with the vessel wall. Whether temporary left jugular catheters are also associated with a higher risk of stenosis has not been formally evaluated.

Observational studies suggest a higher infection risk with femoral than with jugular catheters (Goetz et al., 1998; Ishizuka et al., 2009) and most infection control guidelines indeed suggest avoiding femoral catheters (Pratt et al., 2007; Marschall et al., 2008; O'Grady et al., 2011). However, a recent French multicentre RCT, comparing

femoral and jugular dialysis catheters in 750 AKI patients, found no difference in the incidence of catheter colonization on removal (primary endpoint), nor in catheter-related bloodstream infections or thrombotic complications. Stratification of the patients according to their body mass index (BMI) revealed that a low BMI was associated with more colonization of jugular catheters whereas, not unexpectedly, a high BMI was associated with more colonization of femoral catheters (Parienti et al., 2008).

Besides the risk of infection and thrombosis, the optimal insertion site also depends on the risk of malfunction that can be related to kinking of the catheter, suctioning against the vessel wall, a thrombus in or a fibrin sheath around the catheter. Several mostly observational trials show more malfunction with femoral than with jugular catheters and also more malfunction with a left jugular catheter than with a right one, which is not really unexpected (Oliver et al., 2002; Hryszko et al., 2004; Naumovic et al., 2004). A post hoc analysis of the previously mentioned multicentre trial could not establish a difference in catheter dysfunction between jugular and femoral catheters. However, a separate analysis of the right and left jugular catheters showed a clear trend towards more dysfunction with femoral than with right jugular catheters. On the other hand, there was significantly more dysfunction with left jugular compared with femoral catheters (Parienti et al., 2010), which is not unexpected in view of the angulations in a left jugular catheter that may impair adequate blood flow. In summary, the right jugular vein is the first option for insertion of an acute dialysis catheter. Femoral catheters are preferred over left jugular catheters because of reduced malfunction and the subclavian vein should only be considered a rescue option. Individual patient characteristics or operator experiences may require a different order of preferences. (See Box 234.2.)

Insertion procedure

Use of ultrasound is recommended to facilitate the insertion (increase the success rate) and reduce the risk of insertion-related complications such as bleeding, arterial puncture, and haematoma formation. This was shown in two meta-analyses comparing ultrasound guidance with the landmark technique for placement of central venous catheters (Randolph et al., 1996; Hind et al., 2003). Subsequent large randomized trials have confirmed the superiority of ultrasound guidance for placement of a central venous access (Karakitsos et al., 2006, Leung et al., 2006), including trials on dialysis access (Bansal et al., 2005; Prabhu et al., 2010). The NKF guideline for vascular access also recommends using ultrasound-assisted insertion (Vascular Access 2006 Work Group, 2006). Continuous electrocardiographic monitoring is recommended during insertion of a subclavian or jugular catheter in order to detect arrhythmias. After the insertion of a jugular or subclavian acute dialysis catheter, the correct position (at the junction of the superior vena cava and the right atrium) should be confirmed with a chest X-ray before RRT is started.

In order to provide an adequate blood flow and reduce the risk of recirculation, the tip of the catheter should be in a large vein. Recirculation occurs when blood flows directly from the outflow port back to the inflow port. The same blood passes again through the extracorporeal system resulting in decreased efficiency of the treatment. The risk of recirculation depends on the relationship between the extracorporeal blood flow and the flow in the vein and thus on the location and the design of the tip and on the desired blood flow. Because CRRT uses lower blood flows than intermittent haemodialysis (IHD), recirculation is less an issue. It is evident that recirculation increases with line reversal, where the access line is connected to the return lumen of the catheter and vice versa. Impaired catheter flow is detected through an increased negative access pressure and/or an increased positive return pressure. In order to assure placement of the tip in a large vein, the length of an acute dialysis catheter should be 12–15 cm for the right internal jugular vein, 15–20 cm for the left internal jugular vein, and 19–24 cm for the femoral vein (Leblanc et al., 1996; Little et al., 2000; Oliver, 2001).

Box 234.2 Order of preference for insertion of an acute dialysis catheter

1. Right jugular vein
2. Femoral vein
3. Left jugular vein
4. Subclavian vein.

Catheter care

Insertion and post-insertion catheter care should comply with guidelines for infection prevention (Pratt et al., 2007; Marschall et al., 2008; O'Grady et al., 2011; Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group, 2012). Maintaining catheter patency during treatment interruptions requires an anticoagulant catheter lock. Traditionally unfractionated heparin has been used for this purpose. The usual concentration is 5000U/mL but lower concentrations of 2500 or 1000U/mL may also be used. Using a heparin lock is associated with a risk of haemorrhage and heparin-induced thrombocytopenia and may enhance the risk of biofilm formation (Moran et al., 2008). Recent evidence suggests the superiority of citrate lock solutions with regard to haemorrhagic complications and prevention of both catheter-related infection and thrombosis (Weijmer et al., 2005; Bosma et al., 2010; Maki et al., 2011). Citrate not only acts as an anticoagulant by chelating calcium but it also chelates essential components for biofilm formation such as iron, calcium and magnesium and has antimicrobial activity against bacteria and fungi (Raad et al., 2008).

Results and indications for continuous renal replacement therapy

Continuous or intermittent renal replacement therapy: the theory

Since the introduction of CRRT into clinical practice in the early 1980s, this treatment has found widespread acceptance in ICUs around the world (Guérin et al., 2002; Gatward et al., 2008; Langford et al., 2008; RENAL Study Investigators, 2008; Vesconi et al., 2009). Theoretically, CRRT indeed has many advantages over IHD. Fluid and solute removal occur slowly thus facilitating refilling of the vascular compartment and preventing intracellular fluid shifts. This results in more haemodynamic stability and better control of fluid balance. Especially in patients requiring substantial fluid removal, the continuous nature of the treatment

Box 234.3 Advantages and disadvantages of continuous renal replacement therapy (CRRT) in comparison with intermittent haemodialysis (IHD)

Advantages of CRRT

- More haemodynamic stability
- No worsening of cerebral oedema
- Easier fluid removal
- Optimal flexibility
- User-friendly machines may be operated by ICU nurses.

Disadvantages of CRRT

- Patient immobilization
- Continuous anticoagulation
- Treatment should be interrupted for patient transport
- Higher 'in-hospital' costs
- Slow removal of toxins.

represents a significant advantage. The improved haemodynamic stability may also promote renal recovery by preventing further treatment-induced kidney injury. Avoiding large fluctuations in solute concentration and the associated fluid shifts also reduces the risk of worsening cerebral oedema. CRRT allows greater flexibility with the possibility to adapt the treatment, particularly the fluid removal rate, to the patient's situation at any time of the day and the night. CRRT machines are relatively simple and user-friendly and can thus easily be managed and monitored by ICU nurses.

Disadvantages of CRRT include the need for relative immobilization, the need to interrupt the treatment for diagnostic and therapeutic procedures, the need for continuous anticoagulation, the risk of hypothermia, and the higher costs. The problem of continuous anticoagulation and associated bleeding risk can largely be circumvented by the use of citrate anticoagulation (Oudemans-van Straaten, 2010). The slow removal of solutes may also represent a problem when fast removal of toxins is required such as in severe hyperkalemia, certain intoxications, and tumour lysis syndrome (Box 234.3).

Continuous or intermittent renal replacement therapy: the evidence

The optimal RRT modality for critically ill patients with AKI still remains controversial (Himmelfarb, 2007; Davenport, 2008; Ronco et al., 2008; Vanholder et al., 2011). Several RCTs have addressed this issue (Mehta et al., 2001; Augustine et al., 2004; Uehlinger et al., 2005; Vinsonneau et al., 2006; Lins et al., 2009). None of these trials could demonstrate an improved outcome with CRRT compared with IHD (Table 234.1). The two available meta-analyses also do not confirm the superiority of continuous or intermittent therapy (Rabindranath et al., 2007; Bagshaw et al., 2008). The most inclusive meta-analysis by the Cochrane Collaboration found similar hospital mortality, ICU mortality, length of hospitalization, and renal recovery in survivors (free of dialysis on discharge). Meta-analysis of haemodynamic endpoints was hampered by the use of different parameters in different studies. Consequently, the analyses are based on a rather limited number of patients, resulting in wide confidence intervals and absence of significant effects, with the exception of the mean arterial pressure at the end of the treatment and the number of patients requiring escalation of vasopressor therapy. For the latter two parameters CRRT appeared to be superior (Rabindranath et al., 2007). Clinical experience clearly contradicts the results of these meta-analyses. Intermittent dialysis-induced hypotension is a generally recognized problem and many clinicians have experienced the superior haemodynamic tolerance of CRRT versus IHD in patients with AKI. The discrepancy between the RCTs and the clinical experience can be explained by the questionable generalisability of the results of the RCTs. Indeed, most of these trials had very (s)low inclusion rates and some explicitly excluded patients with hypotension or maximized efforts to improve the haemodynamic tolerance of IHD. The largest trial also showed improved survival rates over time in the intermittent group whereas this was not the case in the continuous group, suggesting changes in dialysis practice over time (Vinsonneau et al., 2006). Other issues with the trials comparing different treatment modes include baseline imbalances, improper randomization, and high rates of cross-over between the treatment arms.

Table 234.1 Results of randomized controlled clinical trials comparing continuous renal replacement therapy and intermittent haemodialysis. Mortality is defined as hospital mortality. Renal recovery is defined as being independent of dialysis or having a GFR > 15 mL/min at hospital discharge

	Mehta et al., 2001	Augustine et al., 2004	Uehlinger et al., 2005	Vinsonneau et al., 2006	Lins et al., 2009
N	166	80	125	359	316
Mortality CRRT (%)	65	67	47	67	58
Mortality IHD (%)	47	70	51	68	62
Renal recovery CRRT (%)	86	38	97	98	83
Renal recovery IHD (%)	93	33	96	100	73

The effect of treatment modality on renal recovery has also been investigated in two large observational trials. A Swedish trial looked at 90-day survivors of dialysis requiring AKI and found that a higher percentage of patients that were originally treated with IHD had persistent renal failure. The main problem of this trial is that they did not correct for baseline serum creatinine, which is an important determinant of long-term renal outcome (Bell et al., 2007). In the BEST KIDNEY database, 66% of the IHD patients were independent of dialysis at hospital discharge compared with 85.5% in the CRRT group and this difference remained significant after exclusion of patients with chronic kidney disease on admission (Uchino et al., 2007). However, observational trials are not sufficient evidence and adequately designed prospective trials will be required to address the impact of RRT modality on renal recovery.

A recent systematic review and meta-analysis compared the rate of dialysis dependence among survivors of severe AKI according to the choice of initial RRT modality applied (continuous or intermittent RRT (Schneider et al., 2013)). The authors concluded that initial treatment with intermittent RRT might be associated with higher rates of dialysis dependence than continuous RRT. However, they cautioned that this finding largely relies on data from observational trials, potentially subject to allocation bias, so that further high-quality studies are necessary.

Another frequently used argument in favour of intermittent dialysis is the reduced costs. A first comparative analysis was limited to the in-hospital costs and showed that CRRT is definitely more expensive than IHD. The excess costs for CRRT are mainly related to the consumables, whereas human costs are somewhat higher for IHD (Farese et al., 2009). A Canadian group performed a simulation that looked beyond hospitalization and showed that whether CRRT is cheaper or more expensive depends largely on its effect on renal recovery. If, as suggested in two large observational studies, CRRT indeed reduces chronic dialysis dependence, this may have a tremendous impact on the total healthcare costs (Klarenbach et al., 2009). Interestingly, a recent assessment of the cost utility (CU) from a societal perspective of acute renal replacement therapy (RRT), irrespective of using intermittent or continuous modalities revealed that CU was acceptable (< 50 000 €/QALY) in patients who survived for more than a year and did not need chronic RRT. Cost utility decreased with increasing age exceeding 1.0 million €/QALY in the older groups (Laukkanen et al., 2013).

Continuous renal replacement therapy: indications

Despite the results of the previously mentioned RCTs, the mostly widely accepted indication for CRRT is AKI in patients with haemodynamic instability, especially if combined with fluid overload. Achieving a negative fluid balance in fluid-overloaded patients is far better tolerated with CRRT than with the classical IHD that will frequently induce hypotension. It should also be noted that none of the RCTs has specifically looked at the effect of different modalities of RRT in patients with shock.

The presence of cerebral oedema represents another accepted indication for CRRT (Box 234.4). IHD may increase brain damage by compromising cerebral perfusion pressure, resulting from both a decrease of mean arterial pressure (dialysis-induced hypotension) and an increase of cerebral oedema and intracranial pressure (dialysis disequilibrium). Dialysis disequilibrium results from the rapid removal of solutes from the extracellular compartment resulting in intracellular fluid shifts. Both hypotension and dysequilibrium can be avoided by the slow progressive removal of fluids and solutes that occurs during CRRT (Davenport, 2009). Small observational trials and case reports in patients with intracranial pressure monitoring indeed reported increases in intracranial pressure with IHD (Bagshaw et al., 2004; Lin et al., 2008). Using computed tomography scans to measure brain density, Ronco et al. showed an increase of brain water content after IHD, whereas no such changes were observed after CRRT (Ronco et al., 1999).

Box 234.4 Indications for the use of CRRT

1. Haemodynamic instability
2. Severe fluid overload
3. Cerebral oedema.

Relative contraindications for CRRT include the need for patient mobilization and the need for high efficiency solute removal such as in severe hyperkalemia, tumour lysis syndrome, and some intoxications. Whether CRRT-induced hypothermia represents an advantage or a disadvantage depends on the specific condition of the patient.

Since each modality has advantages and disadvantages (Box 234.3), none of them is perfect for every patient. Instead, the treatment should be tailored to the individual patient's needs. In addition, local resources and the skills and familiarity of the healthcare workers with the locally available technique might be more important than the choice of the modality per se.

Dose of continuous renal replacement therapy

What is CRRT dose?

The quantity of blood cleansing, or in other words the dose or intensity of CRRT, is traditionally assessed by measures of small solute clearance. Assuming that the sieving coefficient (filtrate concentration Cf/plasma concentration Cp) or dialysate saturation (dialysate concentration Cd/Cp) of small unbound solutes equals 1, the dose of CRRT in continuous haemodialysis and in postdilution haemofiltration or haemodiafiltration equals effluent flow (the total outflow of the filter being a combination of ultrafiltrate and dialysate outflow) (Equation 234.1). In contrast to IHD, the operational characteristics of CRRT, with blood flow greatly exceeding dialysate flow rate, indeed permit assumption of complete saturation of the effluent dialysate with regard to small solutes. Reductions in membrane permeability over time, due to protein interactions with the membrane and clotting in dialyser/haemofilter fibres, may invalidate this assumption (Del Granado et al., 2011; Lyndon et al., 2012). In predilution haemofiltration or haemodiafiltration the prefilter dilution of solutes reduces the sieving coefficient/dialysate saturation and should be corrected for (Equation 234.2).
CVVHD or postdilution CVVH or CVVHDF:

$$\text{Small solute clearance} = \text{Qeffl} \tag{234.1}$$

Predilution CVVH or CVVHDF:

$$\text{Small solute clearance} = \text{Qeffl} \times \text{Qb} / \left(\text{Qb} + \text{Qspre}\right) \tag{234.2}$$

where Qeffl = effluent flow, Qb = blood flow, and Qspre = prefilter replacement rate

In clinical practice, the prescribed CRRT dose varies markedly (Ricci et al., 2006b; Uchino et al., 2007; RENAL Study Investigators, 2008; Vesconi et al., 2009). In addition, many centres still use a fixed filtration rate not adapted to patient weight (Ricci et al., 2006b; Overberger et al., 2007; Uchino et al., 2007; RENAL Study Investigators, 2008; Vesconi et al., 2009).

What is the optimal CRRT dose?

Over the past years the optimal dose or intensity of CRRT has been the subject of several RCTs that have yielded conflicting results

Table 234.2 Results of randomized controlled trials comparing different doses of CRRT

	Ronco et al., 2000	Bouman et al., 2002	Saudan et al., 2006	Tolwani et al., 2008	VA/NIH Acute Renal Failure Trial Network et al., 2008	RENAL Replacement Therapy Study Investigators et al., 2009
N	425	106	206	200	1124	1464
Prescribed dose low (mL/kg/hour)	20		25	20	21,5	25
Delivered dose low (mL/kg/hour)	18.9	20	22	17	22	22
Prescribed dose high (mL/kg/hour)	35 or 45		43	35	36.2	40
Delivered dose low (mL/kg/hour)	33.6–42.4	48	35	29	35.8	33.4
Mortality low dose (%)	59	31.2	61	40	51.5	44.7
Mortalty high dose (%)	43	25.7	41	36	53.6	44.7
Renal recovery low dose (%)	95	97	71	80	49.8	87.8
Renal recovery high dose (%)	92	100	78	69	44	85.6

(Table 234.2) (Ronco et al., 2000; Bouman et al., 2002; Saudan et al., 2006; Tolwani et al., 2008; VA/NIH Acute Renal Failure Trial Network et al., 2008; RENAL Replacement Therapy Study Investigators et al., 2009). Not all patients in the ATN trial (VA/NIH Acute Renal Failure Trial Network et al., 2008) were treated with CRRT, since the decision to use CRRT or IHD was determined by their haemodynamic status (cardiovascular SOFA score). Earlier trials showed benefit with more intensive treatment (Ronco et al., 2000; Saudan et al., 2006). However, two large multicentre trials executed in the United States and in Australia/New Zealand (VA/NIH Acute Renal Failure Trial Network et al., 2008; RENAL Replacement Therapy Study Investigators et al., 2009) and two subsequent meta-analyses (Jun et al., 2010; Van Wert et al., 2010) could not demonstrate an improved outcome with higher doses of RRT. Neither mortality nor renal recovery (defined as independence from RRT in survivors) differed significantly between patients prescribed high (effluent flow 35–48 mL/kg/hour) and low (effluent flow 20–25 mL/kg/hour) doses of CRRT. In addition, none of the prespecified subgroups (sepsis, oliguria, severe organ failure, vasopressor requirement, baseline estimated glomerular filtration rate) benefited from more intensive RRT. Higher doses also induced more hypophosphatemia, hypokalemia, and circuit clotting (VA/NIH Acute Renal Failure Trial Network et al., 2008; RENAL Replacement Therapy Study Investigators et al., 2009). Based on these results, and despite the fact that lower doses have not been formally evaluated in clinical trials, the currently recommended CRRT dose is the effluent flows that were used in the less intensive treatment arms of the available RCTs (20–25 mL/kg/hour) (Box 234.5). Since fluids represent a major cost in CRRT (Farese et al., 2009), using lower effluent flows with reduced consumption of replacement fluid and/or dialysate also significantly reduces the costs of CRRT.

Prescription of the CRRT dose should take into account a discrepancy between the prescribed and the delivered dose, as has been shown in most of the RCTs (Table 234.2). In addition, this discrepancy is expected to be larger outside the controlled setting of a randomized trial (Venkataraman et al., 2002; Vesconi et al., 2009). The major cause of the incomplete delivery of the prescribed dose is filter downtime secondary to filter clotting or patient transfer for procedures. Other impediments to delivery of the prescribed dose are technical problems such as poor blood flow (catheter problems) and recirculation, and reduced efficiency of the haemofilter due to membrane fouling. In order to account for this difference it is recommended to prescribe a dose of 25–30 mL/kg/hour.

An unresolved issue in determining the optimal dose is the normalization for body weight: should we use 'dry weight' or real measured weight (taking into account the expansion of extracellular volume) and how do we measure it in critically ill patients? It is also not clear whether actual or ideal body weight should be used in obese patients.

Besides small solute clearance, the dose of CRRT may also be driven by the severity of electrolyte (e.g. severe hyperkalemia) or acid–base disturbances. Small solute clearance also does not necessarily correlate with clearance of larger molecules. Theoretically, elevated convective doses (the so-called sepsis doses) may contribute to the removal of inflammatory mediators and thus improve the outcome of patients with sepsis, but this hypothesis (as well the clinically important removal of inflammatory mediators as the associated clinical benefit) remains yet to be proven.

Anticoagulation for continuous renal replacement therapy

As clearances achieved during CRRT are much lower than those during IHD, CRRT circuits need to operate for prolonged periods to achieve similar overall solute clearance. Although some patients, particularly those with thrombocytopenia, may not require any anticoagulation to maintain extracorporeal circuit patency, most ICU patients are prothrombotic, due to the close link between inflammation and the coagulation system. Many options are

Box 234.5 Current recommended doses for CCRT

The currently recommended dose for CCRT in critically ill patients with AKI is an actually delivered effluent flow of 20–25 mL/kg/hour. In order to account for the discrepancy between prescribed and delivered dose, it is recommended to prescribe an effluent flow of 25–30 mL/kg/hour.

Table 234.3 Comparison of the more commonly used anticoagulants for CRRT

	UFH	LMWH	Citrate	Hirudin	Argatroban	Danaparoid	PGI_2
CRRT circuit anticoagulant	++	+++	++++	+++	+++	+++	++
Systemic anticoagulant	+++	+++	–	+++	+++	+++	–
Risk of haemorrhage	+++	++	–	++++	++++	++	–
Ease of monitoring	++++	+	+++	+	+++	++	+
Cost	+	++	+++	+++	++++	+++++	++++

available for anticoagulation during CRRT (Amanzadeh and Relly, 2006; Oudemans et al., 2006) (Table 234.3).

Systemic anticoagulants

Unfractionated heparin

Unfractionated heparin (UFH) remains the most commonly used anticoagulant for CRRT worldwide (Amanzadeh and Reilly, 2006; Oudemans et al., 2006). The anticoagulation effect of UFH varies in the critically ill, potentiated by endogenous heparinoids and reduced by low levels of antithrombin. In addition, UFH non-specifically binds to plastic tubing if infused at high concentration, and to plasma proteins and cell surfaces. As such, UFH regimens tend to be pragmatic with a typical loading dose of 10–20 IU/kg (500–1000 IU), followed by an infusion of 5–20 IU/kg (250–1000 IU) (Brooks, 2000; Schetz, 2001), aiming for a post-heparin but predialyser activated partial thromboplastin time (aPTT) ratio of 1.5. Some centres do not administer a load dose or use post-haemofilter or systemic aPTT monitoring. Increased risk of circuit clotting has been reported with systemic aPTT times < 35 seconds, and conversely increased risk of *de novo* bleeding with an aPTT of 45–55 seconds (van de Wetering et al., 1996). However, other authors found no correlation between aPTT and filter life (Bellomo et al., 1993). It should be recognized that aPTT is an *in vitro* test and may not reflect the balance of prothrombotic and fibrinolytic pathways in the critically ill patient.

As many patients in the intensive care setting have reduced levels of antithrombin, recombinant antithrombin infusions have been shown to reduce circuit clotting for patients with levels reduced below 60% of normal (du Cheyron et al., 2006), although the cost has prevented widespread usage.

Low-molecular-weight heparin

Low-molecular-weight heparins (LMWHs) are a series of different compounds, with an average size of 5 kD. Although generally much more expensive than UFH, they have the advantage of a more predictable dose response and a lower incidence of heparin-induced thrombocytopenia. However, their half-life is increased in kidney failure and more expensive laboratory testing for anti-factorXa activity is required for monitoring to prevent accumulation and risk of bleeding, particularly with prolonged use. Reversal with protamine varies between LMWHs, depending upon the ratio of LMWH activity against clotting factors II and X. Randomized prospective trials have yielded conflicting results comparing circuit life with UFH (Journois et al., 1990; Reeves et al., 1999; Joannidis et al., 2007). Just as with UFH, LMWHs can be given as a bolus followed by an infusion, for example, 0.15 mg/kg enoxaparin bolus followed by a maintenance infusion of 0.05 mg/kg/hour (Joannidis et al., 2007), or nadroparin 2850 IU (3800 IU if > 100 kg) followed by 380 IU/hour (456 IU/hour if > 100 kg) (Oudemans-van Straaten et al., 2009b) aiming for an anti-Xa activity between 0.25 and 0.30 IU/L. Some of the initial bolus can be lost when given predialyser/haemofilter, before the membrane has become protein coated. Several groups have therefore omitted the bolus dose, and simply started with a continuous infusion of dalteparin 600 IU/hour, or tinzaparin 400–800 IU/hour, achieving a mean anti- Xa activity of 0.49 IU/mL, within 1 hour, and then reducing the infusion rate (de Pont et al., 2000; van der Voort et al., 2005).

Heparin reversal for the treatment of haemorrhage

Protamine can be used to readily reverse haemorrhage in cases of excessive dosage with UFH (1 mg per 1000 IU UFH). Protamine only antagonizes the anti-IIa effect. Since LMWHs differ in anti-Xa/IIa ratio (Makris et al., 2000), protamine is less likely to reverse haemorrhage following enoxaparin compared to tinzaparin. Protamine can cause acute anaphylactic reactions, with cross reactivity in patients with allergies to salmon.

Heparin-induced thrombocytopenia and thrombosis syndrome

There are many causes of thrombocytopenia in the ICU patient, but occasionally thrombocytopenia is due to platelet activation by an IgG autoantibody directed against heparin-platelet factor 4 complex (Warkentin and Greinacher, 2004). These antibodies are more common when bovine UFH has been used, compared to porcine UFH, and least with LMWHs. Similarly antibodies are more likely to develop when patients have been exposed to high doses of UFH, such as during cardiac surgery (Jenq et al., 2004). As platelets become activated, this syndrome can be associated with a range of clinical scenarios ranging from repeated CRRT circuit clotting through to catastrophic life-threatening arterial and venous thrombosis. If heparin-induced thrombocytopenia and thrombosis syndrome (HITTs) is suspected, all heparins, including line locks and flushes, should be avoided, and patients should be systemically anticoagulated with direct thrombin inhibitors, or danaparoid.

Heparinoids

Endogenous heparinoids are often increased in critically ill patients. Danaparoid, a mixture of glycosaminoglycans (84% heparan sulphate, 12% dermatan sulphate, and 4% chondroitin sulphate), has been used to anticoagulate CRRT circuits in cases of HITTs. Although there may be some cross reactivity in the laboratory, this has rarely been shown to have a clinical effect. Indeed danaparoid may actually help to reduce the risk of thrombosis in HITTs compared to the direct thrombin inhibitors (Kramel et al., 2008). After

an initial bolus dose of 500–1000 IU, or alternatively priming the CRRT circuit with 1500 IU, an infusion is required to maintain anti-Xa activity > 0.2 and < 0.4 anti-Xa U, typically around 140 IU/hour (Lindhoff-Last et al., 2001; De Pont et al., 2007). Danaparoid, similarly to LMWHs, has a prolonged half-life in AKI, and accumulates with time. In cases of haemorrhage fresh frozen plasma or activated factor VII concentrate may be required.

Argatroban

Argatroban is a synthetic reversible thrombin inhibitor, derived from L-arginine, with predominant hepatic clearance. Its half-life is about 35 min in chronic dialysis patients. Anticoagulation with argatroban requires a continuous infusion starting around 2 micrograms/kg/min, but reduced to 0.5 micrograms/kg/min for patients with liver disease, aiming for a target aPTTr of 1.5–2.0 (Link et al., 2009). As argatroban is not significantly removed by CRRT and the major metabolite (M1) has biological activity, infusion rates typically reduce with time. Lower infusion rates of 0.5 micrograms/kg/min are therefore often used for critically ill patients. Argatroban also causes prolongation of the prothrombin time, and, although it reversibly binds to thrombin, has no antidote. Major bleeding requires the administration of fresh frozen plasma and, eventually, activated factor VIIa concentrate.

Hirudin

Hirudin is an irreversible thrombin inhibitor, cleared by the kidney. Normal half-life of 60–100 min is therefore substantially increased in AKI. Although hirudin can be cleared during convective CRRT and adsorbed onto the membrane, its irreversible action with a prolonged half-life and no antidote may be problematic (Benz et al., 2007). Both continuous infusions (0.005–0.02 mg/kg/hour), and repetitive boluses (0.2 mg/kg) have been used, aiming for a target aPTT ratio (aPTTr) of 1.5–2.0. Even with aPTT monitoring there is a significant risk of haemorrhage as, with higher hirudin levels, the aPTTr does not increase in proportion to the plasma hirudin concentration. Viper venom based tests of thrombin activation have been introduced (ecarin clotting time), but these require standardization (Ulbricht et al., 2006; Guy et al., 2008). Many centres simply monitor plasma hirudin concentrations rather than relying on the aPTTr. In addition, patients may develop antibodies to hirudin, which prolongs the biological activity, so increasing the risk of bleeding (Eichler et al., 2000). As hirudin is an irreversible thrombin inhibitor, overdosage and consequent haemorrhage are serious risks, requiring activated factor VII concentrates. Occasionally hirudin may cause anaphylactoid reactions, and in these cases further hirudin administration is contraindicated.

Regional anticoagulants

Unfractionated heparin with protamine reversal

Regional heparinization has been used for CRRT, using a heparin infusion pre and a protamine infusion post dialyser/haemofilter (1 mg per 1000 IU UFH) (Kaplan and Petrillo, 1987). This increases the complexity of the CRRT circuit requiring monitoring of anticoagulation post heparin and post protamine, and then adjusting the two infusions. The heparin–protamine complex is taken up by the liver, and protamine released, which may lead to protamine accumulation over time with CRRT. As studies have failed to show an advantage for regional heparinization (Bellomo et al., 1993; Fealy et al., 2007) this has generally been abandoned by most centres.

Citrate

Citrate ($C_6H_7O_7$) has gained popularity as a regional anticoagulant for CRRT (Oudemans-van Straaten, 2010). It chelates calcium and prevents activation of both the coagulation cascades and platelets. Citrate is infused prior to the haemofilter/dialyser adjusted to blood flow to achieve a concentration of 3–6 mmol/L, with a post-dialyser/haemofilter ionized calcium (iCa^{2+}) concentration of < 0.35 mmol/L. Most centres monitor citrate anticoagulation by simply measuring the iCa^{2+} post haemofilter/dialyser. As citrate is a small molecule, the majority of the calcium–citrate complex is freely filtered during haemofiltration or moves across the membrane by diffusion during dialysis and is lost in the ultrafiltrate or dialysate effluent. A systemic calcium infusion is required to replace the calcium lost in the effluent. Any calcium–citrate complex remaining returns to the patient and is metabolized indirectly to bicarbonate by the liver, kidney, and skeletal muscle. Each citrate molecule potentially yields three bicarbonate molecules, and calcium released from the calcium–citrate complex helps restore normal serum iCa^{2+} levels. Alternatively, according to the Stewart approach it is the infusion of sodium with a subsequently metabolized anion that increases strong ion difference and thus corrects acidosis (Oudemans-van Straaten, 2010).

Until recently, standardized citrate solutions were not commercially available (Cointault et al., 2004), and customised, hospital pharmacy-formulated solutions were used with a variety of CRRT circuits (Fig. 234.3). Dialysate is typically calcium free. All circuits require a systemic calcium infusion. Various trisodium citrate concentrations have been used ranging from 0.32% up to 30%, with lower concentrations used in combined citrate and replacement solutions. The actual citrate delivery rate varies between 17 to 45 mmol/hour, depending on the blood flow and the target citrate level in the filter. Higher citrate delivery is associated with longer circuit patency, but greater risk of citrate toxicity or metabolic alkalosis, depending on the patient's capacity to metabolize citrate (Davenport and Tolwani, 2009; Oudemans-van Straaten, 2010).

If citrate is infused separately, then the pre- or post-replacement fluid is usually hyponatraemic to avoid hypernatremia from the high sodium content of the citrate solution and contains no or minimal anionic buffer (bicarbonate or lactate) to avoid metabolic alkalosis from citrate metabolism (Gabutti et al., 2002). Thus one of the potential problems with citrate CRRT systems is disturbance of acid–base and sodium balances. Although the use of a separate citrate infusion is more complex, the anticoagulation effect is not coupled to metabolic or solute control (Tolwani et al., 2001), whereas in the combined replacement fluid and citrate solutions there is no such flexibility. In addition, separate solutions increase the risk of potential nursing errors, with the possibility of pre-filter replacement solutions administered post filter, or as dialysates and vice versa.

If citrate cannot be adequately metabolized, in cases of acute liver failure or cardiogenic shock, citrate–calcium complexes will accumulate. This will result in a decrease of ionized calcium levels or an increased exogenous calcium requirement to maintain normal ionized calcium levels. Since total calcium measures both free and complexed calcium, the ratio of total calcium to iCa^{2+} will increase, with a ratio above 2.1–2.5 (if total calcium is measured in mmol/L, or >10 if measured in mg/dL) suggesting citrate accumulation (Nowak and Campbell, 1997; Meier-Kriesche et al., 2001; Bakker et al., 2006; Hetzel et al., 2006). In cases of citrate toxicity,

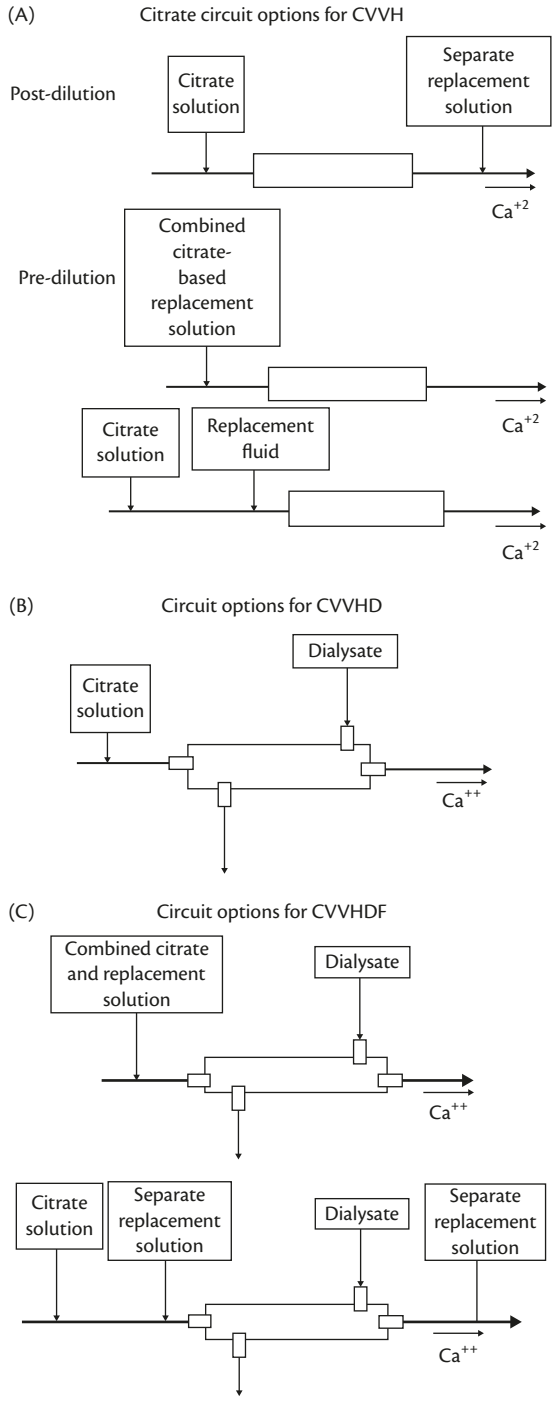

Fig. 234.3 Various options for citrate CRRT. During haemofiltration, although citrate must be given pre haemofilter, replacement solution can be given post or pre haemofilter and citrate can be given in a separate concentrated solution or combined with the replacement fluid.

the infusion rate should be decreased or stopped. Alternatively, metabolic alkalosis can develop if too much calcium–citrate complexes reach the patient and are metabolized.

Compared to UFH, more intensive monitoring is required to adjust the citrate infusion to blood flow, monitor citrate metabolism, and ensure calcium homeostasis. Despite these disadvantages citrate is gaining in popularity for CRRT as it is an effective extracorporeal anticoagulant with reduced risk of bleeding compared to UFH, and either similar or longer CRRT circuit life compared to UFH (Monchi et al., 2004; Kutsogiannis et al., 2005; Betjes et al., 2007; Hetzel et al., 2011). One trial even found an improved survival with citrate compared to LMWH (Oudemans-van Straaten et al., 2009a).

Nafomostat mesilate

Nafamostat mesilate is a serine protease inhibitor, which essentially acts as a regional anticoagulant due to its short half-life of 5–8 minutes (Akizawa, 1990). As some 40% is cleared during CRRT circuit, an infusion starting at 20–40 mg/hour adjusted to maintain a target aPTTr of 1.5–2.0, is required after an initial bolus of 10–20 mg (Akizawa et al., 1993). Nafamostat has been reported occasionally to cause myalgia, arthralgia, eosinophilia, and rarely anaphylactoid reactions and agranulocytosis.

Prostanoids

Prostacyclin (prostaglandin I2 (PGI_2)) and its analogue epoprostenol, are potent antiplatelet agents and have been used as regional anticoagulants for CRRT, with variable success (Journois et al., 1990; Langenecker et al., 1994; Kozek-Langenecker et al., 2003; Gainza et al., 2006). Although both agents are potent arterial vasodilators, most patients do not develop symptomatic hypotension at the doses used (PGI2 5 nanograms/kg/min, range 2.5–10 nanograms/kg/min), as some 40% of the dose is lost during passage through the dialyser. Hypotension can be minimized by increasing the dose slowly and ensuring that patients are not hypovolemic. Coupled with a short half-life of around 2 minutes PGI2 is a regional anticoagulant with a reduced risk of *de novo* haemorrhage in patients at risk of bleeding.

Other prostanoids, such as PGE_1 (alprostadil), PGE_2, and PGD also have antiplatelet effects and can be used as extracorporeal anticoagulants. As these prostanoids are less potent the recommended dose of alprostadil is 5–20 nanograms/kg.min.

PGI2 does not have any direct effect on the plasma coagulation pathways and therefore can not be readily monitored (Davenport et al., 1994). As PGI_2 does not prevent thrombin generation, some centres have advocated a combination of both heparin and PGI_2 (Langenecker et al., 1994), using 2–6.5 nanograms/kg/min of PGI_2 or 2.5–10 nanograms/kg/min alprostadil with 200–500 IU/hour of UFH.

Complications of continuous renal replacement therapy

As outlined above, circuit clotting and complications associated with both anticoagulants and vascular access may occur, Other complications include errors in fluid balance; thermal, nutrient, and drug losses; and electrolyte and acid–base disturbances.

Errors in fluid balance

Fluid balance is of major importance in the critically ill patient. Contemporary CRRT machines contain pumps designed to accurately control fluid volumes with errors of 2% or less. However, cumulative balancing errors can potentially occur due to repeatedly overriding machine alarms (Gibney et al., 2008). Volume errors are obviously more critical in the management of the newborn than adults. Although modern CRRT machines now incorporate safety

systems in their software designed to stop treatment if fluid balance errors exceed a critical threshold level, this does not prevent nursing and prescription errors. Occasionally fluid balance errors can occur due to blocked drains.

Electrolyte and acid–base disturbances

As CRRT developed, specialized dialysates/replacement solutions were introduced based on extracellular fluid composition (Table 234.4). Until recently all haemofiltration replacement fluids and dialysates did not contain phosphate, and as such hypophosphataemia is a well recognized complication of CRRT, particularly when higher volumes are exchanged for prolonged periods (Fall and Szerlip, 2010). (See also Chapter 230.)

There is a wide variation in electrolyte composition between different manufacturers. During high-volume CRRT, electrolyte imbalances may develop after several days of CRRT in haemofiltration mode, with patients becoming hypo- or hypernatremic depending upon the choice of fluid, or developing hypochloremic alkalosis if solutions containing the combination of a low-chloride and high-lactate concentration are chosen, and conversely hyperchloremic acidosis if the opposite combination of a high-chloride and low-lactate concentration is chosen (Davenport et al., 1988). Hyponatremia may occur if replacement fluids with lower sodium concentration are used in post-dilutional mode, particularly coupled with aggressive fluid removal.

Initially haemofiltration replacement solutions were lactate based, but more recently bicarbonate-based solutions have been introduced. Although there were initial reports of improved correction of metabolic acidosis and cardiovascular stability with bicarbonate (McLean et al., 2000), these have not been universally replicated (Nimmo et al., 1993; Agarwal et al., 2011). This may relate to the varying bicarbonate concentrations used in different studies. The use of bicarbonate based fluids has not been observed to improve patient survival.

Following the popularity of citrate anticoagulation for CRRT, commercial solutions specifically designed for citrate anticoagulation have recently been introduced. One of these solutions designed to be administered as a predialyser/haemofilter combined citrate and replacement solution is relatively hyponatremic and therefore may lead to hyponatremia, particularly if high volumes of haemofiltration are performed with no dialysis.

Table 234.4 Comparison of the electrolyte composition of extracellular fluid (ECF), intracellular fluid (ICF) in both red blood cells (RBC) and muscle, and range of haemofiltration replacement solutions (HF) (Schetz et al. 2002). All electrolyte concentrations are in mmol/L

Electrolyte	ECF	RBC ICF	Muscle ICF	HF solution
Sodium	145	25	12	130–145
Potassium	4	145	155	0–3
Calcium	2.4	1.1	1.8	1.65–2.0
Magnesium	1.2	1.1	1.4	0.5–1.5
Chloride	115	85	5	98–120.5
Bicarbonate	28	20	1	0–32
Other anions/lactate	20	20	174	30-44.5

Thermal losses

Heat is lost during passage of blood through the CRRT circuit despite warming of dialysates and replacement solutions (Santoro et al., 2003). On the positive side, cooling leads to increased sympathetic drive with improved cardiovascular stability (Van der Sande et al., 2001), and also reduces the risk of clotting in the CRRT circuit (Krouzecky et al., 2009). Thermal losses are greater with predilution (Beerenhout et al., 2003). However, it is unknown whether cooling has any disadvantages particularly in terms of the immune system. As such, there is no data on the optimum temperature for replacement solutions and dialysates.

Nutrient losses

Haemofiltration and dialysis will lead to the unselective losses of small water-soluble solutes, which are not protein bound and as such there will be some losses of nutrients including, amino acids (Davenport and Roberts, 1989), glucose, water-soluble vitamins, carnitine, and trace elements (Berger et al., 2004). Most centres pragmatically prophylactically administer water-soluble vitamins and trace elements. (See also Chapter 228.)

Drug losses

As most drugs are in the low-molecular-weight range, important extracorporeal drug losses may potentially occur during CRRT. In general, this extracorporeal removal is negligible for those drugs with predominant hepatic or non-renal elimination, or those with high protein binding, whereas drugs that require dosing adaptation for kidney failure mostly require dosing adjustment for extracorporeal removal. Dosing needs to account for drug pharmacokinetics properties (volume of distribution, protein binding and extra-renal clearance), that may differ in critical illness, and the CRRT modality, clearance, and to a lesser extent membrane characteristics (Schetz, 2007a). In the intensive care setting antibiotic losses during CCRT have been most investigated (Awdishu and Bouchard, 2011), as antimicrobial activity depends upon both pharmacokinetics and pharmacodynamics. Antibiotics with a narrow therapeutic index such as aminoglycosides and vancomycin require standard drug monitoring. However, also other antibiotics, for which there is no readily available monitoring, including cephalosporins, levofloxacin, carbapenems (Bilgrami et al., 2010), piperacillin-tazobactam, daptomycin, and linezolid, and the antifungals, fluconazole, and voriconazole, all have reported increased clearances during CRRT. In the absence of therapeutic drug monitoring several different approaches have been adopted, and the clinician should weigh the risks and benefits of over- and under-dosing on an individual patient basis (Schetz, 2007a; Choi et al., 2009). (See also Chapter 231.)

Recent more detailed discussions on pharmacokinetic and pharmacodynamic aspects of drug dosing in acute kidney disease patients, including adaptations of the doses in different modalities of renal replacement therapy are available (Matzke et al., 2011; Perazella, 2012).

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CHAPTER 235

Peritoneal dialysis in acute kidney injury

Wim Van Biesen

Introduction

Reports on dialysis requiring acute kidney injury (AKI) have over the last two decades increasingly dealt with continuous renal replacement therapy (CRRT), claiming this is the most optimal and practical renal replacement therapy (RRT) for AKI. However, over the last decade, intermittent haemodialysis (IHD) regained its credibility, as different studies found no proof of superiority for CRRT over IHD, the former being much more expensive and labour intensive (Van Biesen et al., 2008). This discussion in the literature has created the impression that peritoneal dialysis (PD) has no place in the debate on RRT for AKI, with as consequence, that the interest for PD in AKI, is rather low. However, in developing countries, and where resources of healthcare are low, PD is still widely used in the management of AKI (Arogundade et al., 2005). Also in developed countries, PD might have its place as a RRT modality in certain conditions, and it is quite likely that it is underused (Fraedrich et al., 1980; Ash, 2004; Burdmann and Chakravarthi, 2011). In the paediatric setting, with its special conditions and limitations due to size, PD remains the mainstay of RRT (Abbad and van Amstel, 1983; Flynn et al., 2001; Bonilla-Felix, 2009; Raaijmakers et al., 2011).

Outcome of peritoneal dialysis in the acute kidney injury setting

Whereas the place of PD is clear in settings where there is no alternative for PD to bridge renal dysfunction, it is evident that in situations where there is an alternative treatment, and where resources to support that treatment are available, the modality with the best outcome should be preferred. A landmark study (Phu et al., 2002) compared outcome in infection-mediated AKI using either daily haemofiltration or high-volume PD, concluding that haemofiltration was superior, with an odds ratio of 5 for both mortality and recovery of renal function. Whereas this seems to establish the inferiority of PD in these conditions, some caveats in the way PD was performed in this study should be mentioned (Bazari, 2003). The first point of concern is the use of rigid catheters, with their enhanced risk of bowel perforation and infection. Second, the dialysis fluid was prepared on-site with all its associated risks of contamination and impurities. As a consequence of the two previous remarks, > 40% of patients suffered from peritonitis, an extremely and unacceptably high rate in current PD practice. Third, the dialysate contained acetate as a buffer, leading to haemodynamic instability and poor tolerance. Fourth, dwells were performed per cycle of 30 minutes, potentially leading to sodium sieving and hypernatremia, a well-recognized complication of this type of treatment regimen. It is thus hard to draw meaningful conclusions from this study in the light of current PD practice with low peritonitis rates, lactate or bicarbonate buffer, and appropriate dwell times. Another, more recent randomized controlled trial (RCT) (Gabriel et al., 2008) compared daily haemodialysis with high-flow PD in 120 consecutive patients. In this study, a blind bedside Seldinger technique was used to introduce a flexible Tenckhoff catheter; also in this study, acetate was used as buffer, but the solution was industrially prepared. There was no difference in survival between the two modalities (58% vs 53%). Another matched control study (Arogundade et al., 2005) in 40 patients compared PD to IHD in the treatment of AKI, also demonstrated equal outcomes. However, the peritonitis rate was very high, probably because of local production of PD fluid, so it cannot be excluded that results would have been better if industrially prepared fluids had been available. In a retrospective study of 206 children with need for RRT, need for vasopressor therapy was the most important independent predictor of outcome, and was associated with HD versus PD use (Bunchman et al., 2001). In contrast, another retrospective paediatric study comparing PD (N = 81), haemodiafiltration (HDF) (N = 31) and IHD (N = 18) found that outcome was best with IHD, while HDF had the worst outcome (Krause et al., 2011).

Overall, a recent systematic review on the use of peritoneal dialysis in AKI concluded that there is currently no evidence to suggest significant differences in mortality between peritoneal dialysis and extracorporeal blood purification in AKI. There is however a need for good-quality evidence in this important area. (Chionh et al., 2013).

Principles and physiology of peritoneal dialysis: consequences for AKI

In PD, the peritoneal membrane is used as a semipermeable membrane to allow diffusive and convective transport of uraemic retention products between the blood and the dialysate. Osmotic agents are added to the dialysate, to generate ultrafiltration capacity for removal of water and salt.

Different physicochemical principles guide transport of solute and water across the peritoneal membrane:

Diffusion: in diffusion during PD, the rate of transport is determined by the size and form of the solute, the concentration gradient between the blood and the dialysate, the number of available pores, and the peritoneal blood flow. The relation between size of the solute

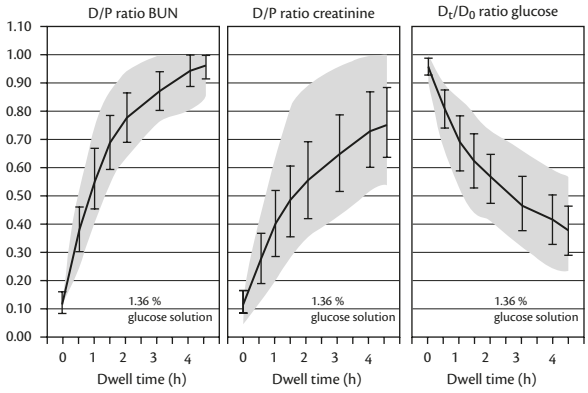

Fig. 235.1 Dialysate to plasma ratios during a normal PD dwell for urea (left panel), creatinine (middle panel), and glucose (right panel). Full line indicates the mean values; the grey zone indicates upper and lower limits. It can be observed that absolute inter-individual variation in transport rate between the different transport types is more pronounced for smaller molecules, such as urea, than for larger molecules, such as creatinine.

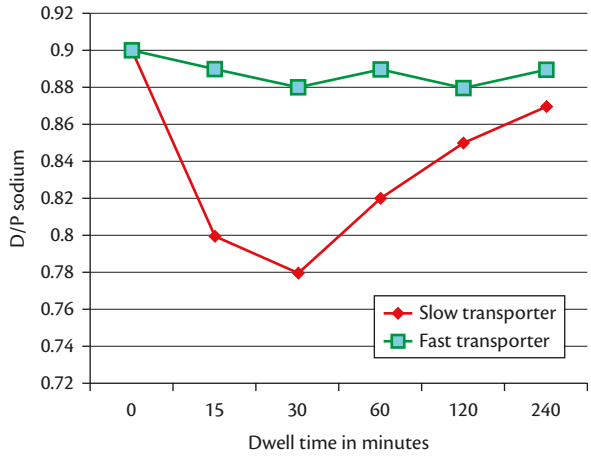

Fig. 235.2 Approximation of dialysate to plasma ratio for sodium during a normal dwell with 3.86% glucose for a slow transporter (red line) and for a fast transporter (green line). In the slow transporter, due to the substantial transport of free water over the aquaporins in the first part of the dwell, there is a gradual decrease in D/P sodium. However, over time, the increasing sodium concentration gradient between dialysate and plasma will induce a diffusive transport of sodium in the second half of the dwell. In the fast transporter, due to the faster diffusive transport, the sodium concentration gradient will be much less expressed.

and transport rate is not linear, but exponential. As a consequence, small solutes are easier to remove than larger solutes, with already substantial differences for the transport of urea and creatinine (Fig. 235.1), although the molecular weight of both substances is only marginally different. Another consequence is that large solutes, such as beta-2 microglobulin, phosphate, or protein-bound molecules, are more difficult to remove. The concentration gradient between blood and dialysate is greatest at the beginning of the dwell, but as solutes move from blood to dialysate, their concentration in the dialysate increases, and the concentration gradient diminishes, until, at a certain moment in time, an equilibration is obtained, and there is no further net transport. The non-linear behaviour of transport rate is far less expressed for larger solutes, and becomes nearly linear for solutes with a molecular size near to the cut-off of the membrane. As such, using more short dwells versus longer dwells increases removal of urea and creatinine much more rapidly than it increases the removal of larger solutes, for example, phosphate or cytokines.

For a description of the membrane characteristics, the best validated model is the three-pore model (Rippe, 1993). In this model, diffusion of small solutes, such as urea and creatinine, but also glucose, occurs through the small pores (around 5 nm). The physical correlate of the small pores is thought to be the tight junctions between the endothelial cells in the peritoneal capillary beds, so the more vascularization or vascular recruitment, the faster the transport. As inflammation, and thus vascular recruitment, is a common feature of patients with AKI, most of these patients behave as 'fast transporters', so short dwells should be advised to avoid rapid dissipation of glucose and negative ultrafiltration (van Biesen et al., 2010). The transport of larger solutes, for example, albumin, occurs through large pores (> 25 nm), correlating to intercellular clefts. Typically, inflammation will lead to higher leakiness of the membrane, and thus higher clearance (leakage) of large solutes (Van Biesen et al., 2006). Another factor contributing to a high prevalence of fast transporters in patients with AKI is the vascular recruitment, resulting in an increase of the vascular surface area available for transport. In addition, in patients with a hyperdynamic circulation, the higher blood flow might also result in a higher transfer of molecules across the membrane, whereas in patients with cardiogenic shock, a low perfusion might result in the opposite effect. However, the impact of these haemodynamic factors, if any at all, is probably rather small (Rosengren and Rippe, 2003). As inflammation and vasodilation lead to vascular recruitment and a hyperdynamic circulation, most patients with AKI, especially during sepsis, are fast transporters.

Ultrafiltration: the third type of pores, the aquaporins, allow only transport of water, and glucose acts as an ideal osmotic agent over these pores (Rippe, 2008). As a consequence, in the first part of a dwell, when the osmotic gradient is the highest, there will be influx of free water from the patient to the dialysate. It is important to note that this 'ultrafiltration' is only free water, and barely leads to sodium removal (van Biesen et al., 2010). As progressive dilution of the sodium dialysate concentration occurs due to the water influx, the concentration gradient between the plasma and dialysate sodium concentrations increases, driving diffusive transport of sodium in the later part of the dwell (Fig. 235.2). It is important to understand this two-tiered removal of water and salt, as otherwise, with too short dwells, only free water is removed and not sodium, leading to hypernatremia and/or volume overload. However, this mechanism is less present in fast transporters, which most patients with AKI are, because of the presence of inflammation, as explained above.

As a summary, in PD, the peritoneal membrane is used as a semipermeable membrane. However, as this is a living tissue, the properties of this membrane vary from patient to patient, and can change according to the situation. In AKI, which is most often associated with inflammation, most patients behave as fast transporters. Under these conditions, relatively short dwell times (1.5–2 hours) are safe and efficient to increase clearance of small solutes, whilst avoiding negative ultrafiltration as a consequence of glucose gradient dissipation. In patients with slower transport characteristics, care should be taken to avoid sodium sieving.

Prescription of peritoneal dialysis for acute kidney injury

Techniques

PD can be performed under two major forms: completely manually, or by a machine (a so-called cycler). The underlying principles are

not fundamentally different, so only logistical issues should affect the selection of the modality. However, when available, the use of a cycler has many advantages in the intensive care unit (ICU) setting:

- Fewer connections, so reduced risk of peritoneal infection
- Most patients with AKI have a fast transport status, and therefore will need short dwells.
- Reduces the workload of the nurses
- Allows tidal regimens to optimize flow characteristics.

In situations where a cycler is available, the patient is mostly connected once daily by the PD nurse, for example, in the morning, and enough dialysate fluid reserve is connected for the next 24 hours. In this way, the PD nurse is free during the day, and the ICU nurse should only manage basic alarms of the machine if they occur.

Alternative techniques, such as continuous flow peritoneal dialysis (CFPD) have been proposed (Gastaldi et al., 1981; Raaijmakers et al., 2011), however these are without proven clinical benefit. In CFPD, dialysate is continuously infused in the abdomen at one location, and drained from another location. As a consequence, there is a continuous refreshment of the intra-abdominal dialysate, so that the concentration gradient for diffusion is always optimal. As a drawback, two catheters or a double-lumen catheter are needed, increasing the potential for infections and/or mechanical complications. In addition, large amounts of dialysate are used, increasing cost and toxicity.

Number of cycles

The number of cycles is determined by the ideal dwell length, that is, the dwell length which gives the optimal relation between ultrafiltration, clearance, and loss of dialysis time due to in- and outflow (van Biesen et al., 2010). Even in fast transporters, transport rate remains relatively high during the first 1.5–2 hours of the dwell, and having shorter dwells does not increase the clearance. Demetriou et al. (2006) compared a regimen of 13 rapid exchanges to one with five exchanges over a 9-hour period, all with 2–3 L fill volume and did not find any substantial difference in clearance.

It is also important to realize that clearance depends on the total *drained* volume, so negative ultrafiltration will impact negatively on clearance. During the drain and fill, there is no dialysate in contact with the peritoneal membrane, and thus no exchange of solutes or water. Drainage speed is relatively constant in the first part of the drain, and much lower in the second part (Fig. 235.3). It is important to establish the 'break point', that is, that point of the curve where it bends to a lower drainage speed. The cycler should be programmed to restart filling at this point of the outflow. If the residual volume is substantial (i.e. with an early break point), this modality is often called 'tidal peritoneal dialysis', as only part of the intra-abdominal volume is replaced by each cycle. Of note, if the residual volume is too large, this leads to a decrease in concentration gradient, and thus a decrease in transport and ultrafiltration capacity.

Chitalia et al. (2002) compared tidal peritoneal dialysis (TPD), using 2000 mL baseline and 675 mL tidal cycles of 20 minutes to CAPD with 2000 mL fill volume and dwell times of 240 minutes, using the same total volume/day. TPD was much more efficient in solute removal than CAPD, but this was completely attributable to the low ultrafiltration in the CAPD group. Unfortunately, no evaluation of transport characteristics was available, but most likely, the majority of patients were fast transporters, leading to lower ultrafiltration volumes in the too long dwells of CAPD.

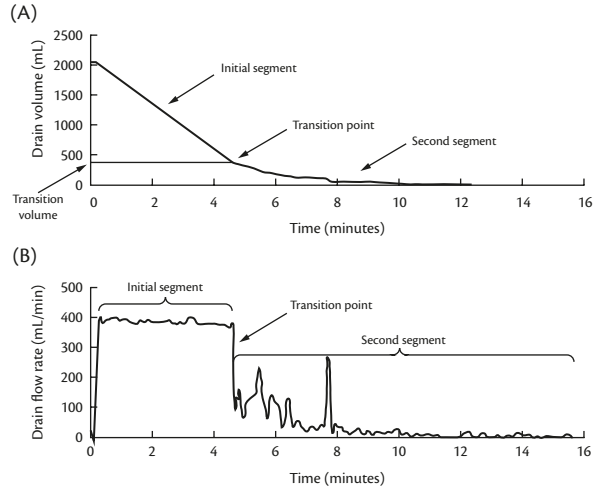

Fig. 235.3 Outflow over time curve: outflow speed is the inclination of the line (A); the point where the curve 'bends' is the break point. Continuing drainage after this point results in loss of dialysis efficiency, as not enough dialysate is left in the abdomen to allow meaningful transport of solutes (B).
Reprinted from *American Journal of Kidney Diseases*, 25/4, James C. Brandes, Warren J. Packard, Shelly K. Watters, Claire Fritsche, Optimization of dialysate flow and mass transfer during automated peritoneal dialysis, pp. 603–610, Copyright 1995, with permission from Elsevier.

All of the above described reasons explain why very short dwells (<1.5 hours) rarely lead to better clearances. In view of the fast transport status in most ICU patients, the ideal dwell time is 1.5–2 hours.

Fill volume

The fill volume per dwell is usually 2 L in adults. This volume can safely be increased up to 3 L, depending upon the body size of the patient. However, while increasing the fill volume, caution should be paid to the intraperitoneal pressure. This can easily be measured using a three-way valve and a water manometer (Fischbach et al., 2003). There is evidence that a too high intraperitoneal pressure can lead to peritonitis (Dejardin et al., 2007), probably because it limits the intestinal perfusion (Fig. 235.4), which is often already compromised in ICU patients (Olofsson et al., 2009). Also ventilation characteristics, especially the sigh volume in pressure ventilation mode, might change by changing the intraperitoneal volume (Bunchman et al., 1992), and attention should be paid to this when increasing fill volume. Also in children, the fill volume should be optimized under guidance of intraperitoneal pressure (Fischbach et al., 1996). On the other hand, increasing the fill volume leads to better use of the peritoneal surface, and maintains concentration gradients for a longer time, so that saturation of the dialysate will take longer.

Dose of dialysis

Ideally, any form of RRT should be able to replace kidney function completely. This is of course not realistic with any of the currently available techniques. As in AKI, the suppression of renal function is mostly temporary, the RRT system should only be so efficient to allow patient survival until recovery of renal function. The most important aspect of dialysis is thus to eliminate those substances

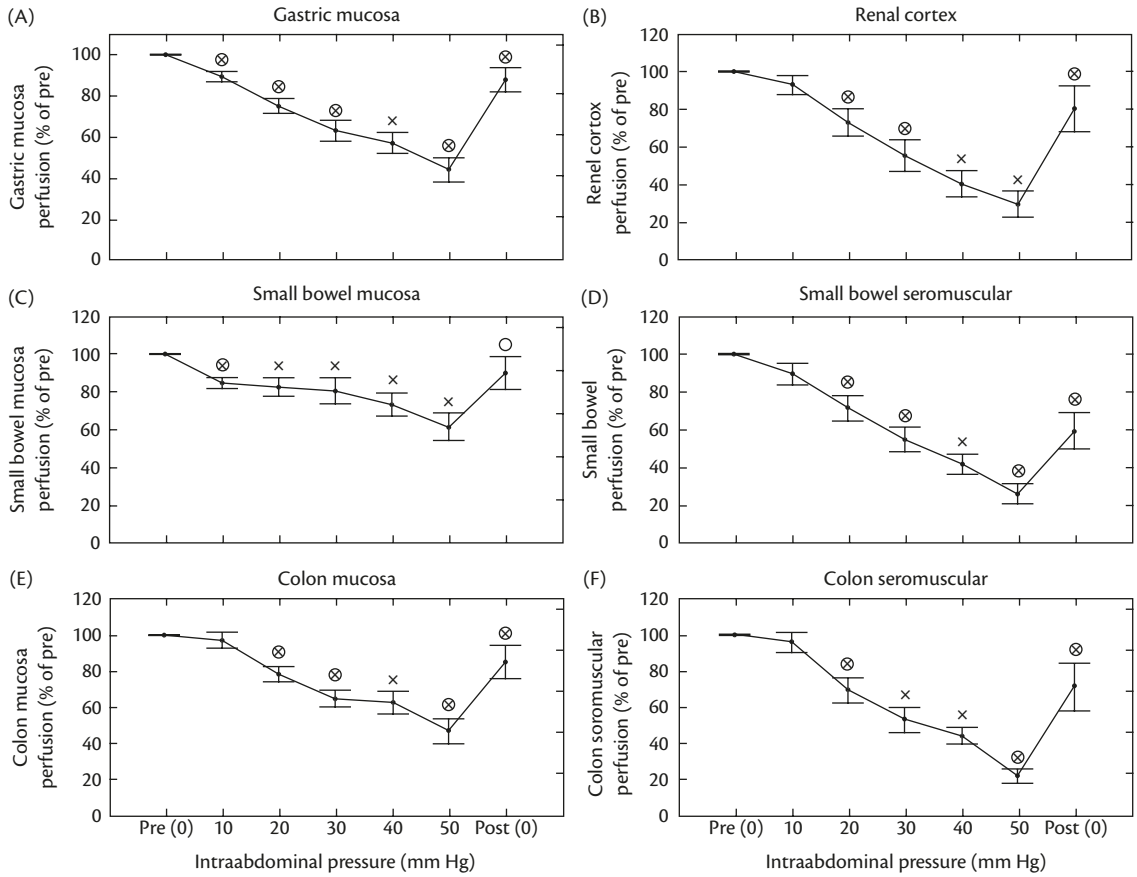

Fig. 235.4 Arterial blood flow curves in function of intra-abdominal pressure in different organs. With increasing intra-abdominal pressure, perfusion of intra-abdominal organs decreases.

Reproduced from Pia Olofsson, Sören Berg, Henrik Ahn, *et al.*, Gastrointestinal microcirculation and cardiopulmonary function during experimentally increased intra-abdominal pressure, *Critical Care Medicine*, 37, 1, Fig. 2, p. 233.

and factors normally cleared by the kidney, which cause immediate harm. In most patients, this comes down to removal of water and salt, avoidance of hyperkalaemia, correction of metabolic acidosis, and, to a lesser extent, hyperphosphataemia. As such, these parameters should thus be considered as important endpoints in the assessment of adequate dialysis.

First, there is no consensus on the ideal dose of dialysis, not only regarding the number that should be achieved, nor on the way this should be expressed or measured. Some authors advocate using Kt/V_{urea}. This concept is problematic in PD patients, as 'V' has to be estimated, which is cumbersome in critically ill AKI patients. Second, due to the particular physiology of transperitoneal transport, urea clearance is much easier to achieve than the clearance of larger solutes, for example, of creatinine and certainly of middle molecules or protein-bound solutes. Comparison of Kt/V achieved by PD as compared with other modalities, for example, CRRT or IHD, is not very meaningful. Using cycles of 1.5 hours, and fill volumes of 2–3 L, total volumes of 24–36 L can be achieved, resulting in urea and creatinine clearances of 17–32 L and 12–28 L/day, respectively. These values are substantially higher than what is recommended, in chronic PD patients, where there are data from RCTs to provide some indication on required dose of dialysis.

Solutions in peritoneal dialysis for acute kidney injury

Different brands and types of dialysis solutions can be used for PD. Their composition differs with regard to osmotic agent (glucose, polyglucose, amino acids), buffer (acetate in the past, currently lactate or bicarbonate or a mixture), final pH (around 5 or around 7), and electrolyte composition. Further, dialysis solutions can differ in their commercial presentation as single-, double-, or triple-chamber bag and in the way the bags have to be connected to the peritoneal catheter (Luer lock, spike, specific connectology).

Osmotic agent

Glucose is definitely the most widely used osmotic agent because of its relative biocompatibility and low toxicity when absorbed (Van Biesen et al., 1998). Typically, glucose is available in different concentrations (or 'strengths'): 1.36%, 2.27%, or 3.86% glucose solutions. The higher the glucose concentration (hypertonic bags), the more ultrafiltration can be achieved. Of note, as explained above, the additional ultrafiltration obtained with increasing glucose strength is always associated with more free water than sodium removal, explaining why an excess use of hypertonic bags can lead to hypernatremia. As glucose is absorbed during the dwell, the

Box 235.1 Warning

In patients using polyglucose solutions, metabolites like maltose and trimaltose are absorbed in the circulation. Most machines for point-of-care glycaemic control will register these as 'regular' glucose, falsely indicating high glucose levels, especially if they are based on a glucose dehydrogenase reaction, leading to a discrepancy between real and measured glycaemia (Wens et al., 1998). This can lead to dangerous situations with deep hypoglycaemia. As a rule, glycaemia in PD patients on polyglucose should *not* be measured using a point-of-care method, but only with regular laboratory methods using an hexokinase reaction (Flore and Delanghe, 2006, 2009). All institutions providing PD should develop protocols and strategies to reduce these dangerous events by the use of information leaflets and warning stickers.

additional calories provided in this way should be added to the daily nutritional intake in AKI patients.

During heat sterilization of the dialysate, part of the glucose will degrade into different glucose degradation products (GDPs) (Wieslander et al., 1996). To avoid this, heat sterilization should be performed under acidic pH of around 2 (Wieslander et al., 2001). This low pH is of course not acceptable for a solution that needs to be instilled in the patient's abdomen. As a compromise, conventional dialysis solutions have a pH around 5, and contain rather high concentrations of GDPs. Instillation of these acidic solutions, with high GDP concentrations results in vasodilation of the mesenteric circulation and haemodynamic changes (Mortier et al., 2002). To avoid this, several manufacturers provide dual-chamber bags, where the glucose is heat sterilized under very low pH, which is than corrected later by addition of the second compartment containing a lactate or bicarbonate buffer, resulting in a neutral pH and much lower GDP concentrations. As a consequence, the haemodynamic impact of these solutions on the peritoneal membrane is much reduced (Pletinck et al., 2008; Verbeke et al., 2008). However, despite extensive animal and *in vitro* data, clinical evidence of superiority of this type of 'biocompatible' solutions is at present still not convincing, although a recent large randomized trial demonstrated a better preservation of residual diuresis in chronic PD patients (Johnson et al., 2012).

Polyglucose is a mixture of large polymers of glucose with a wide range of molecular weights, at a concentration of 7.5% (Mistry and Gokal, 1994) (Box 235.1). This results in an iso-osmolar solution, with a slow and gradual ultrafiltration due to the fact that the polyglucose molecules do not disappear through the small pores. Polyglucose is therefore well suited for the long dwell, especially in high transporters. As in the acute PD setting most patients will have an even distribution of dwells over the day, the place of polyglucose is rather limited in acute PD, unless it is used to bridge the long night dwell when PD is applied in a manual modality. Polyglucose barely induces sodium sieving, and it can lead to substantial sodium removal during the long dwell. Some centres mix polyglucose with a glucose solution by connecting both to the same line of the cycler, to enhance sodium removal (Jenkins and Wilkie, 2003; Dallas et al., 2004).

Amino acid solutions (Faller, 1996) do not contain GDPs, but the presence of certain amino acids can lead to disturbance of endothelial function (Dallas et al., 2004). Theoretically, the absorption of the amino acids during the dwell should lead to an improved nutritional status, but this occurs only if at the same time a non-protein energy source, for example, glucose is added (Faller et al., 1995). Many centres therefore mix the amino acid solution with a glucose solution by connecting both to the same line on the cycler.

Buffer

The correction of AKI-associated acid–base disturbances occurs in PD by the absorption of the dialysate buffer during the dwell. Currently, lactate and bicarbonate are the most widely used buffers in PD solutions. From an industrial production-based perspective, lactate-based solutions are easier to produce than bicarbonate solutions. During the dwell, the lactate is absorbed, and converted in the liver and muscle to bicarbonate in an equimolar fashion. However, this metabolization can be impaired in patients with sepsis or shock, potentially leading to a slower correction of acidosis or even an accumulation of lactate (Thongboonkerd et al., 2001). Although there was no difference in survival, a recent Cochrane review comparing studies with lactate- versus bicarbonate-buffered solutions indicated that correction of acidosis was faster, and lactate levels lower in patients treated with bicarbonate (Bai et al., 2010).

Electrolyte composition

PD solutions normally do not contain potassium. However, because of the slow equilibration, PD is not the preferred option for treatment of serious hyperkalaemia, unless there is an underlying acidosis.

The normal sodium concentration of commercial PD solutions is 132 mmol/L. It is possible to produce dialysis solutions with lower sodium concentration but as the sodium also contributes to the overall osmolarity of the solution, care should be taken to replace them with equivalent osmotic power, for example, by increasing the glucose concentration (Davies et al., 2009).

A wide range of calcium concentrations is available: 1.0, 1.25, 1.50, or 1.75 mEq/L. The higher calcium concentrations can potentially add to haemodynamic stability, however, it should be taken into account that these solutions can induce a positive calcium balance.

In principle, PD solutions can also be produced locally, even if no provider of 'genuine' dialysate is available, by adding the desired glucose (15 g/L) and electrolytes to sterile pyrogen-free water. Utmost attention should be paid to sterility, as even a minor contamination can have dramatic consequences.

Indications for peritoneal dialysis in acute kidney injury

In view of its somewhat technical simplicity, the absence of extracorporeal circulation (and thus anticoagulation), and the continuous but low efficiency clearance (and thus haemodynamic and metabolic stability), the optimal indications for PD are the following:

Paediatric intensive care unit

In small children, haemodialysis is often very cumbersome, due to the lack of suitable vascular access, and the small circulating plasma volume, which necessitates small extracorporeal volumes, and ultra-precise volume control. PD does not have these disadvantages, and can even be performed in infants with a body weight

< 1 kg (Coulthard and Vernon, 1995). It is thus no surprise that the majority of PD in AKI is performed in paediatric cases (Coe and Lail, 2007; Hayat et al., 2007; Bonilla-Felix, 2009; Goldstein, 2009; Morimatsu et al., 2009; Baskin et al., 2010). Paediatric patients have a relatively large peritoneal volume for their total body mass, which enhances the potentially achievable clearances. Several studies reporting on relatively large series of children treated with PD, either post cardiac surgery or in sepsis, demonstrate that major complications related to PD were few, and strongly support that PD is a simple, safe, feasible, and robust dialysis modality for the management of AKI in children (Pedersen et al., 2008). Acute PD is the preferred dialysis technique for AKI in low-income countries where it is easier to start, and mostly economically more feasible (Lameire et al., 2013). The Sustainable Kidney Care Foundation, together with industry, universities, the International society of Nephrology, and funding organizations, tries to establish PD programmes for AKI in African countries with a special focus on treating children and women of childbearing age (Carter et al., 2012). (See also Chapter 239.)

Contraindications for systemic anticoagulation or high risk of (postoperative) bleeding

The use of anticoagulation can lead to bleeding, which in certain conditions can be devastating, for example, in burn (Pomeranz et al., 1985) or neurosurgical patients. Also in patients with heparin-induced thrombocytopenia, PD can be a valuable option. In patients with renal failure associated with cholesterol embolization, the use of systemic anticoagulation can lead to further systemic and renal deterioration, and PD can also then be a suitable alternative.

Congestive heart failure

Patients with acute cardiac decompensation or an underlying cardiomyopathy often have also accompanying renal insufficiency, due to poor renal perfusion, leading to the so-called cardiorenal syndrome. These patients mostly tolerate haemodialysis poorly, because of the myocardiac stunning and further deterioration of cardiac output (McIntyre, 2010; Selby and McIntyre, 2011). In such cases, fluid accumulation does not occur in the circulating volume, but rather in the third space, making gradual removal necessary. PD is an excellent technique for such conditions, allowing gradual, slow ultrafiltration. Also, the intraperitoneal pressure induced by the dialysate will stabilize cardiac preload.

Thermoregulation problems (cooling or heating)

Peritoneal lavage can be used to either warm up hypothermic patients, or cool down patients (e.g. with head trauma), or during interventions where slow tissue metabolism is desired. It results in a slow and steady change of body core temperature, in contrast to external heating/cooling systems that will impact on skin temperature and perfusion as a first step, before they alter core temperature, adding further to the haemodynamic instability.

Catheter insertion for peritoneal dialysis in acute kidney injury

Good access to the peritoneal cavity is a prerequisite for PD and catheter-related problems remain the most important hurdle in the provision of PD in the AKI setting (Murphy et al., 1987; Lewis and Nycyk, 1992).

Catheter design

In the past, access to the peritoneal cavity was obtained with a rigid catheter using a stylet for introduction. This catheter type was prone to cause mechanical trauma to the intra-abdominal structures and infection. Nowadays, mostly silicone or polyurethane-based catheters are used (Murala et al., 2010). Different forms are available, with differences in the design of the final portion (straight or pigtail), the middle portion (straight or Swan neck), and the number of cuffs (one or two). Different alternative configurations are also available, like the presence of silicone discs (Toronto Western), a self-locating tungsten device, or the use of a disc-ball type inner cuff, but they are less suited for the acute setting, as their placement and removal is more cumbersome. Besides evidence for superiority of Swan neck and double cuff, none of the other designs has a proven benefit (Bouts et al., 2004).

Catheter placement techniques

Peritoneal catheters can be implanted by different techniques, from simple bedside guidewire assisted, over open surgery placement to laparoscopy-guided techniques.

The guidewire-assisted technique is easy to perform, and requires only minimal technical equipment (Fig. 235.5), the most important being the peel-away sheet. The procedure can be performed under local anaesthesia, which is an advantage in unstable patients. In this technique, a small (2–3 cm) midline incision is made some centimetres below the umbilicus, with a blunt dissection of the fat layer until the upper fascia of the musculus rectus is reached. This muscle is then perforated with a needle to gain access to the peritoneal cavity. Through this needle, 1 L of pre-warmed dialysate or isotonic saline is introduced in the intraperitoneal space to create an artificial ascites. Once this has been accomplished, the guidewire is introduced through the needle, which is then removed, leaving the guidewire in place. A peel-away sheet can then be introduced over the guidewire, directing the point to the Douglas poach. The catheter can afterwards be introduced through the peel-away sheet in the peritoneal cavity. Once the catheter is in place, the subcutaneous tunnel can be created. A disadvantage of this technique is the rather high leakage rate, as the internal cuff is embedded above the fascia and not in the muscle, so no tight connection is available.

In the open mini-laparotomy technique, a pararectal incision is made some centimetres below the umbilicus. The fascia and the muscle are bluntly dissected, to visualize the peritoneal blade. A purse string is created once on the peritoneal blade and once on the lower fascia. Then the catheter is inserted in the peritoneal cavity, aiming at the Douglas poach, using either a stylet, or a long Kocher. The purse string is then closed, ensuring that the inner cuff is locked between the suture of the lower fascia, and not inside the peritoneal cavity.

Although the laparoscopic technique is gaining popularity over the other two techniques, it is probably too complex to justify its use in peritoneal access creation in the acute setting.

None of the techniques described has a proven benefit, so the locally available expertise should drive the decision on which technique to use.

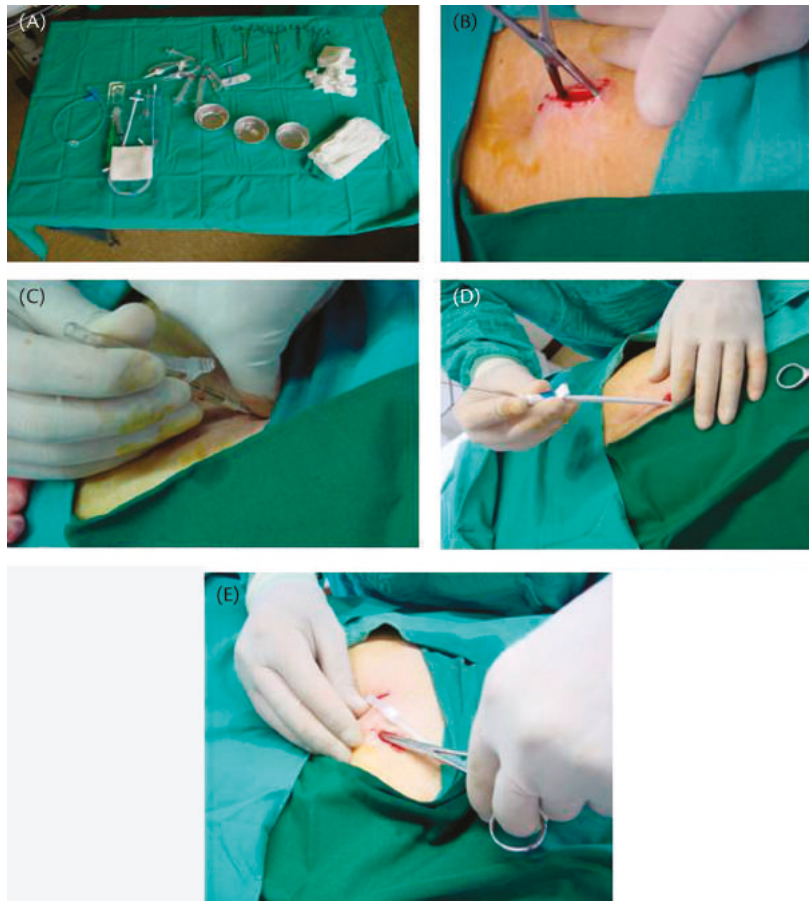

Fig. 235.5 Bedside placement of peritoneal dialysis catheter using the Seldinger technique. (A) Materials of a placement kit. (B) Incision of the skin at the midline, two fingers below the umbilicus, with blunt dissection to the upper fascia of the musculus rectus. (C) Puncturing the musculus rectus with an introducer needle, through which the guidewire can be passed. (D) Over the guidewire, first a dilator, and then afterwards a peel-away sheet are introduced. The peel-away sheet is oriented to the Douglas pouch, and the catheter is introduced through it. (E) Tunnelling of the catheter.

Complications and troubleshooting in acute peritoneal dialysis

Peritonitis

Peritonitis is usually defined as the presence of two out of three of the following symptoms and signs:

- 1° cloudy effluent, with > 100 white blood cells/μL, with at least 50% polymorphonuclear cells
- 2° clinical signs of peritonitis, such as pain, abdominal defence, fever, vomiting;
- 3° growth of bacteria or presence of bacteria on Gram staining of dialysate fluid.

As the second point is often not interpretable in AKI patients at ICU, this definition should not be applied too strictly, and the presence of cloudy effluent should urge the start of culturing dialysate and administration of antibiotics. Intraperitoneal infection can be due to contamination during a PD exchange, but can also be induced by an intra-abdominal source of infection, for example, diverticulitis, cholecystitis, or even increased transluminal migration of toxins or bacteria as a consequence of intestinal ischaemia. In these conditions, Gram-negative organisms and even yeasts or fungi are prevalent causal organisms.

The route of administration of antibiotics is mostly intraperitoneal or intravenous. If the patient needs systemic antibiotics for other reasons however, the intravenous route should be preferred.

Hydrothorax

If a leak is present between the abdominal and the pleural cavity, dialysate can accumulate in the pleural space and cause dyspnoea, or deterioration of ventilatory parameters. Diagnosis can be made with chest X-ray. When there is doubt concerning the nature of the pleural fluid, a diagnostic puncture showing high glucose content might be helpful. A low glucose concentration does not, however, exclude peritoneal-pleural leakage.

Glycaemic control

Due to the rapid absorption of glucose, especially when hypertonic exchanges are used, glycaemic control can be impaired during PD (Fig. 235.6). As insulin adsorbs in an unpredictable fashion to the polyvinylchloride material of the bags and tubings of the dialysate delivery system, it is not recommended to add insulin to the bags.

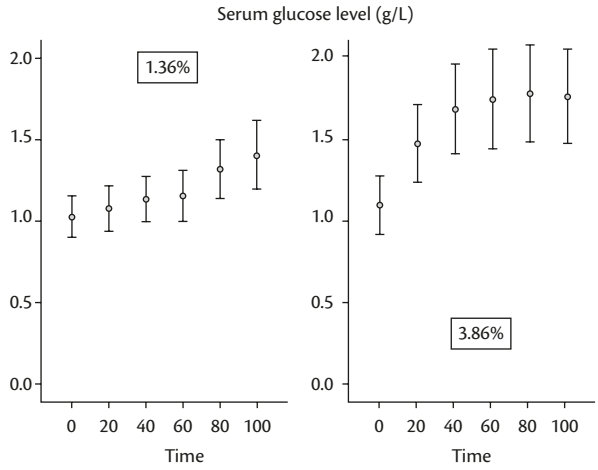

Fig. 235.6 Serum glucose levels in non-diabetic peritoneal dialysis patients after infusion of a 1.36% (left panel) or 3.86% (right panel) glucose solution.
Reproduced from Anneleen Pletinck, Francis Verbeke, Luc Van Bortel, Clement Dequidt, Denise Vijt, Wim Van Biesen, Raymond Vanholder, Acute central haemodynamic effects induced by intraperitoneal glucose instillation, *Nephrology Dialysis Transplantation*, 2008, 23, 12, p. 4032, by permission of Oxford University Press.

Rather, an intravenous insulin pump with regular control of glycaemia should be applied.

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CHAPTER 236

Scoring systems in acute kidney injury patients

Angel Candela-Toha, Teresa Tenorio, Aurora Lietor, and Fernando Liaño

Introduction

The nephrologist attending an intensive care unit (ICU) patient with acute kidney injury (AKI) or chronic kidney disease (CKD) should be familiar with severity of illness scoring systems. In this chapter, we provide an overview of these tools including some basic methodological aspects of prognostic models, their classification, evolution, and state of the art, and their application and performance in AKI patients. Specific AKI scoring systems are also briefly reviewed. The chapter ends with comments on the future role of these tools in the management of patients with AKI. The prognostic capacity of the new functional classification systems (RIFLE, AKIN, KDIGO) is outside the scope of this chapter.

The first scoring systems for ICU patients were published 30 years ago. Their main goal was to predict in-hospital mortality from information collected at ICU admission. In an era of scarce resources, the need for tools that would help to decide which patients would benefit most from ICU admission was urgent. The Acute Physiology and Chronic Health Evaluation (APACHE) model (Knaus et al., 1981) is considered the first severity of illness scoring system. Since then and up to now, consecutive generations of scoring systems have improved, updated, and amplified their predictive ability.

When these scoring systems were used in specific cohorts of patients, their performance was fair. This finding was expectable as they were developed from more heterogeneous groups of patients. So, in a further step, specific systems for organs and diseases were developed. Among these, an important number were focused on AKI patients. A second generation of scoring systems for AKI patients is now available. These new models are based on prospective multicentre studies, some of them using data collected from patients recruited for randomized controlled trials.

Prognostic models: basic methodological aspects

The ultimate goal of a prognostic model is to estimate the probability of the occurrence of a future event in a particular subject from a quantity of information. So the first steps to take when building a model are to define a population of interest, to define an event, and to select the variables to be incorporated in the model.

In severity of illness scoring systems the population of interest are patients admitted to the ICU. However, almost every model excludes some particular type of patients (i.e. burns, patients under 16, cardiac surgery). So the model is not expected to work well when subjects of these subpopulations are included in the sample to test.

The event is usually vital status at discharge or death by any cause during a predefined period of time (i.e. 60 days). When the event of interest is binary (alive or dead at discharge) the most common statistical technique used for model development is logistic regression. When we are interested in time to the event, the usual technique is Cox's proportional hazards regression.

The way variables are chosen is of paramount importance and establishes differences among systems. In generic models, usually three kinds of variables plus age are considered: physiological (clinical and laboratory), comorbidities, and diagnostic or admission related. Some systems include interactions between two variables. The timing of data collection is also important and differs depending on the model: during the first hour after admission, or during the first 24 hours, and the same applies to the way data are captured, either manually or electronically. The use of clinical information systems can affect the performance of a model that was developed using hand data recording. The former usually capture more extreme values, summing up higher scores and over-predicting mortality (Bosman et al., 1998; Breslow and Badawi, 2012a). Electronic data abstraction should be checked for accuracy.

The development of a model needs a large sample of subjects. The first versions of most known scoring systems were based on samples which included < 1000 patients. Last generations of APACHE and Mortality Probability Model (MPM), and the Intensive Care National Audit & Research Centre (ICNARC) model were developed from data > 100,000 subjects. Usually the sample is randomly split into two cohorts (split sample design), one for development (usually the bigger one) and one for validation of the model. In the development sample, variables are chosen by their association with the event of interest, although considering their contribution in terms of clinical information. By logistic regression the independent association of each variable with the event can be tested and estimated with an odds ratio (OR). The weight of each variable in the model is provided by its coefficient. A more conservative

estimation of coefficients and ORs can be obtained by an iterating technique called bootstrapping. The number of variables in the final model is limited by the number of events in the sample to prevent overfit, and the model shall be tested for co-linearity (two or more variables contributing with similar information). Prediction of the model is tested in the validation cohort.

The accuracy of a model is measured by exploring its discrimination and calibration. Discrimination measures the ability of the model to distinguish between subjects with and without the event. The most common measure of discrimination is the area under the receiver operating characteristic curve (AUROC). Graphically, sensitivity is plotted against 1 – specificity. The value of the AUROC ranges between 0 and 1, and reflects the probability of a subject with the event to be assigned a greater probability than a subject without the event. A model with an AUROC value of 1 can distinguish 100% of the time between pairs of subjects, while a model with an AUROC value of 0.5 is not better than chance. Developers seek discrimination values > 0.8 for their models.

Calibration measures the ability of a model to predict the event across different risk groups by comparing observed versus predicted events in each risk group. If the model discriminates poorly there is no sense in measuring calibration. The usual statistic test to evaluate calibration is Hosmer–Lemeshow's goodness-of-fit. Basically it is a chi-square test with n – 2 degrees of freedom (n being the number of risk groups). The model is considered well calibrated when no significant ($P > 0.05$) differences are found between observed and predicted events.

Another measure of the prediction ability of a model is the standardized rate of the event. For scoring systems predicting mortality, the measure used is the standardized mortality rate (SMR) calculated as the ratio between the number of deaths observed and the number of deaths predicted by the model. SMR is often used as a measure of ICU performance. SMR values < 1, point to an ICU performance better than the average. However caution should be applied in interpreting these results, as the SMR is greatly influenced by the high risk groups of patients (Breslow and Badawi, 2012b).

Both discrimination and calibration face methodological caveats that must be known. When a model's discrimination is very good or excellent (AUROC > 0.8–0.9), the introduction of new variables rarely improves it. This is due to the fact that a significant improvement in the AUROC requires a marked association between the variable and the outcome. However, small (statistically non-significant) increases in the AUROC can improve the reclassification of patients. Two new statistical tests, net reclassification index and integrated discrimination index, have been proposed to measure the improvement of new models (Pencina et al., 2008). These tools are already being used in the evaluation of new biomarkers, but not yet in model comparison. On the other hand, in assessing calibration, it is well known that the Hosmer–Lemeshow goodness-of-fit test is greatly influenced by the sample size (Kramer and Zimmerman, 2007). The bigger the size, the higher the probabilities of finding a statistically significant, although probably clinically irrelevant, difference between observed and predicted events and a 'poor calibration'. This will happen even if the deviance of the model is small and irrelevant. For these cases, the plotting of a calibration graph can help. Alternatively other statistical tests and measures of model performance like Brier's score or Saphiro's *R* statistic can be used (Shapiro, 1977).

External validation should be tested to check model performance in a different population. Discrimination in the new sample is usually lower due to differences in case mix. Even with a good discrimination, the model can be poorly calibrated. Some reasons for 'poor calibration' are variations in case mix, differences in structure and processes of care between units, or improvements in standards of care due to the time elapsed since the inclusion of the patients in the original cohort (usually between 5 and 10 years). In this case, an overestimation of mortality is usually seen. A poorly calibrated model can be recalibrated or customised.

Prognostic models can be turned into scores. This can be done by transformation of coefficients into integers that can be added up. This simplifies their use in terms of applicability and diffusion, but there is always some loss of information. Currently interactive calculators and other web applications are easily available for most prognostic models.

Classification of scoring systems

Scoring systems in ICU patients are classified by the population studied (Vincent and Moreno, 2010; Keegan et al., 2011). Generic systems are those studying the global population of patients admitted to an ICU, while specific systems are those focusing on an organ or disease (e.g. Ranson, Glasgow). Among generic systems, three basic subtypes can be distinguished depending on their goal: (1) those measuring severity of illness at admission as a way to estimate in-hospital mortality risk (Lemeshow and Le Gall, 1994): APACHE, simplified acute physiology score (SAPS), MPM, and ICNARC; (2) those focused on the severity of organic dysfunction: organ system failure score (OSF), multiple organ dysfunction score (MODS), logistic organ dysfunction score (LODS), and sequential organ failure assessment (SOFA); and (3) those assessing severity of illness indirectly by their effect on nurse workload: the therapeutic intervention scoring system (TISS), and nine equivalents of nursing manpower use score (NEMS) (Fig. 236.1).

Generic scoring systems in ICU patients: evolution and state of the art

The most used generic scoring systems in ICU patients are APACHE, SAPS, MPM, and in Great Britain the ICNARC model. Although their original goal was to predict mortality, they are increasingly being used for risk stratification (both in observational and experimental studies), quality control to measure improvements along time, and benchmarking. Additional general information of these systems is available in Table 236.1.

The APACHE system

The APACHE acronym encodes the three aspects considered by a panel of experts in the design of the first version of this system: acute physiology, age, and chronic health (Knaus et al., 1981; Zimmerman and Kramer, 2008). It was developed in an American ICU and included 34 physiological variables with their correspondent score. The final 'acute physiological score' (APS), was the sum of all of them and was thought to reflect the severity of illness. Also, both an age score, and a categorical chronic health status, identified using a four-letter designation (A, B, C, and D) were contemplated. Its use was hampered by the great number of variables considered.

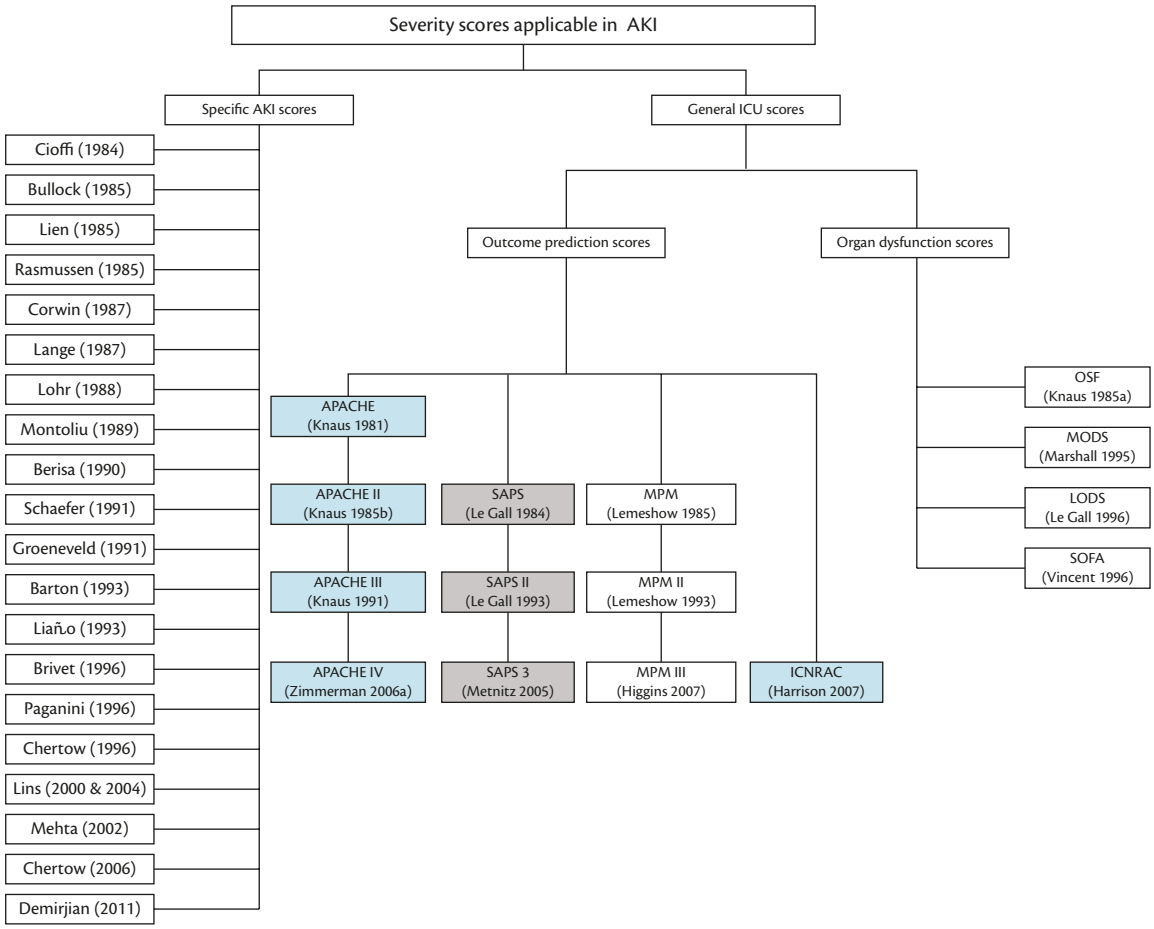

Fig. 236.1 Severity scoring systems applicable to AKI patients.

To overcome this problem APACHE II quickly appeared maintaining its original three components (Knaus et al., 1985b). The APS was reduced to 12 variables measured during the first 24 hours of ICU admission. The age score was modified, and the chronic health status was transformed into a quantitative score. The sum of these three subscores results in the final APACHE II score (range 0–71 points).

APACHE III, published in 1991, was built with data from 17,440 patients admitted to 42 medical and surgical ICUs in the United States (Knaus et al., 1991). This prognostic system allows two options: (1) an APACHE III score, and (2) a prognostic equation. The APACHE III score (range 0–299 points) is calculated by using the worst value during the first 24 ICU hours of 17 acute physiological variables (APS), together with a new age score and a new chronic health evaluation score. Combining APACHE III score with a major disease category (78 considered in the original version), and prior patient location, several prognostic equations enable estimation of mortality risk and ICU length of stay (LOS). Unfortunately APACHE III is a proprietary tool and commercial burdens have hampered the use of these equations.

APACHE IV represents a readjustment of the previous version using information from 110,558 US patients admitted to 104 ICUs between 2002 and 2003 (Zimmerman et al., 2006). Authors maintained the same APS, age, and chronic health items and weights used in the APACHE III score. However each of these components, rather than the composite APACHE III score, was used in the mortality model. This predictor also includes ICU admission diagnosis (116 categories), admission source, LOS before ICU admission, need for emergency surgery, mechanical ventilation and thrombolytic therapy, and two items related with Glasgow coma scale and PaO_2/FiO_2. At the end, 142 *items* are considered in the mortality equation, a factor of complexity for manual capture. APACHE IV is also able to estimate the ICU LOS in groups of patients, a useful tool for benchmarking and for analysis of structural, managerial, and patient factors affecting ICU stay.

SAPS family

SAPS was developed to overcome the inherent difficulties associated with the use of the first APACHE version (Le Gall et al., 1984). Published in Europe, this model only included 13 variables, chosen by a panel of experts, obtained during the first 24 hours of ICU admission.

A new version of this model, SAPS II, appeared 9 years later. It was developed and validated in 13,152 patients aged > 18 years old (excluding burns, coronary, and cardiac surgery patients), from 137 surgical and mixed ICUs in 12 American and European countries (Le Gall et al., 1993). SAPS II includes 17 variables selected using logistic regression. These are 12 physiological variables (including serum urea concentration and urinary output), age, type of

Table 236.1 Main characteristics and evolution of generic scoring systems for ICU patients

Score	APACHE	APACHE II	APACHE III	APACHE IV	SAPS	SAPS II	SAPS 3	MPM	MPM II	MPM III	ICNARC
Publication year	1981	1985	1991	2006	1984	1993	2005	1985	1993	2007	2007
Selection of variables	Experts' panel	Multiple logistic regression	Multiple logistic regression	Multiple logistic regression	Experts' panel	Multiple logistic regression	Multiple logistic regression	Multiple logistic regression	Multiple logistic regression	Multiple logistic regression	Multiple logistic regression
Population[a]	805	5815	17,440	110,558	679	13,152	16,784	755	19,124	124,855	216,626
Source of data: ◆ Country/ies ◆ Setting	USA 2 ICUs	USA 19 ICUs	USA 42 ICUs	USA 104,ICUs	France 8 ICUs	European & USA 137 ICUs	All continents 303 ICUs	USA 1 ICU	12 European & USA 137 ICUs	USA 135 ICUs	England, Wales, & N. Ireland 163 ICUs
Data collection period	1979	1979–1982	1988–1990	2002–2003	NP	1991	2002	1983	1989–1991	2001–2004	1995–2003
Variables considered:											
◆ Number	34	17	16	16	14	17	20	11	15	16	12
◆ Type	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Age	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Acute physiology	Yes*	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
Chronic health co-morbidity	No	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
Others											
Moment of data collection:	First 32 h in the ICU	First 24 h in the ICU	First 24 h in the ICU	First 24 h in the ICU	First 24 h in the ICU	First 24 h in the ICU	ICU admission ± 1 h		MPM_0-II: ICU admission ± 1 h MPM_{24}-II: First 24 h in the ICU	MPM_0-III: ICU admission ± 1 h	First 24 h in the ICU
Score (range)	Yes	Yes (0–71)	Yes (0–299)	Yes	Yes	Yes	Yes (0–217)	No	No	No	Yes (0–100)
AUROC	–	0.86	0.90	0.88		0.86	0.85				0.87
H-L GOF C-test (*P*) at publication	–	–	–	16.8 (0.08)		--	14.3 (0.16)				74.3
External validation	–	++++	+++	+	--	+++	++				+
Simplicity of scoring	–	++++	++	+	+++	++++	+++				+
Extension of use	–	++++	++	+	+	+++	+				+
Mortality prediction	No	Yes	Yes (not available on public domain)	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes

APACHE = acute physiology and chronic health evaluation; AUROC = area under the ROC curve; H-L GOF = Hosmer & Lemeshow's goodness-of-fit C test; ICNARC = Intensive Care National Audit & Research Center; ICU = intensive care unit; MPM = mortality prediction model; N = number of variables; NP = not provided; SAPS = simplified acute physiology score. a = including developing and validation populations; * = categorical variables identified by letters; °° = except Africa.

admission (scheduled surgical, unscheduled surgical, or medical), and three underlying disease variables (AIDS and metastatic or haematological cancer). The main advantage of this score system is its simplicity.

SAPS 3 is the first worldwide approach to prognosis in the ICU setting. It was built with data from 16,784 patients admitted, over a 2-month period in 2002, to 303 ICUs from all continents except Africa (Metnitz et al., 2005). SAPS 3 allows calculation of both an admission score and the probability of death at hospital discharge. The first includes 20 variables distributed in three subscores concerning respectively to: (I) patient characteristics before ICU admission, (II) circumstances of ICU admission, and (III) acute physiology (10 variables) evaluated in a time frame of 1 hour within ICU admission. Interestingly the highest explanatory power came from subscore I (50%), while those of subscores II and III were 22.5% and 27.5%, respectively. Probability of death is calculated using SAPS 3 score and a logistic equation provided by the authors. In addition, specific equations customised for seven geographical areas worldwide were developed, allowing regional implementation of the model. Another model for ICU septic patients, the SAPS 3 PIRO (predisposition, injury, response, and organ response to infection), has been developed using a subset of 2628 patients of the total cohort (Moreno et al., 2008).

MPM system

MPM was designed with the same purpose as its coetaneous version of SAPS (Lemeshow et al., 1985; Higgins et al., 2008). A multiple logistic regression analysis of data from 755 patients admitted to a single ICU, allowed identification of seven physiological variables including age. Two models to predict prognosis at admission (MPM_0-I), and at 24 hours (MPM_{24}-I) were obtained.

A second version of this system, MPM II, was developed and validated with data from 19,124 patients of medical and surgical ICUs in 12 developed countries (Lemeshow et al., 1993). MPM II also considers two models, MPM_0-II and MPM_{24}-II. Both estimate the probability of death at hospital discharge. MPM_0-II is calculated, at the time of the patient's ICU admission, by using 15 categorical variables including AKI. MPM_0-II score provides an estimation of the probability of death before ICU treatments could have an influence on the outcome.

MPM_{24}-II was designed for those patients remaining in the ICU 24 hours or longer. It contains five variables from MPM_0-II and eight additional variables collected at 24 hours. Two of them were associated with renal function impairment: serum creatinine concentration > 2 mg/dL and a urine output < 150 mL/8 hours.

The last version of this system, MPM_0-III, was constructed and validated with data from 124,885 patients admitted between 2001 and 2004 to 135 ICUs in the United States (Higgins et al., 2007). The model allows simple data collection within the first hour after ICU admission. All the variables (the same used for MPM_0-II with recalculated coefficients plus two new ones) with the exception of age have a binary character. A prediction of death could be obtained with them and some interaction terms provided by the authors.

The ICNARC model

This interesting British model was developed from an ongoing, high-quality database which covers nearly 75% of adult general critical care units of that country (Harrison and Rowan 2008). The model, published in 2007, was mainly designed for comparative audit, and it avoids methodological problems of previous models (Harrison et al., 2007). It is centred on patient factors, as far as possible, factors related to treatment were excluded. It has no exclusion criteria, a common problem in preceding models, so it can be applied to every adult patient. Different definitions of some specific factors (i.e. neurologic status) were studied in order to choose the best performance, and interactions between physiological variables and diagnostic categories were taken into account. It includes a physiology score (12 variables), age, five categories of past medical history, six different sources of admission, and diagnostic categories (124 including interactions with the physiology score). Data from > 30,000 patients admitted to 20 new ICUs after the development of the model provided prospective external validation.

Practical scope

Despite the great progress in this area, the number of units using any of these systems is estimated to be < 20% (Breslow and Badawi, 2012b). So currently their main role lays in risk stratification.

Organ dysfunction scores

Organ dysfunction scores (ODS) were not designed to predict mortality, but to evaluate the number of organs in failure, the severity of dysfunction of each affected organ, and its evolution over time for a given subject. However, as would be expected, organ failure is related with mortality. To note, sequential evaluation of patients with these systems is a suitable tool for estimating their clinical outcome. Six organ systems are usually considered: cardiovascular, respiratory/pulmonary, renal, haematology/coagulation, neurologic, and hepatic. A summary of these systems is provided in Table 236.2.

OSF was the first ODS published (Knaus et al., 1985a). It considered the presence or absence of failure in five organ systems (liver excluded). Consequently it ranged between 0 and 5. Mortality rate increased in relation with the number of organs in failure, and with the persistence of failure of any organ during more than one day. Due to its dichotomous character, the major drawback of this score was its inability to grade the intensity of each organ dysfunction, a defect that was overcome in the next generation of ODS.

MODS was developed from 612 patients, 10% of them with AKI, treated in a Canadian ICU (Marshall et al., 1995). The usual six organs were included in the model, with a range of 0–4 points depending on functional derangement.

LODS was developed with the same database used for developing SAPS II (Le Gall et al., 1996). Twelve physiologic variables were included, two for each of the same six organic systems. The variables, recorded as the worst value in the first 24-hour period in the ICU, take values that depend on the organ and the grade of dysfunction. Final LODS score ranges from 0 to 22 points. Using this score probability of death could be estimated.

SOFA score was initially developed in Europe from 1643 septic patients although it was later validated and applied to other ICU patients (Vincent et al., 1996). The same six organs previously cited were considered. The score of each organ ranges from 0 (normality) to 4 (highest derangement). So, the score ranges from 0 to 24. Its two main advantages are its simplicity, and the ability to measure patients' morbidity daily along their clinical course. SOFA is the most frequently used ODS, and has also been used in the AKI setting.

Table 236.2 Main characteristics of organ dysfunction scores (ODS)

Score	MODS	LODS	SOFA
Publication year	1995	1996	1996
Methodological design	Literature review & multiple logistic regression	Multiple logistic regression	Panel of experts
Source of data: ◆ Country ◆ Setting	Canada 1 ICU	12 European/North American 137 medical-surgical ICUs	Belgium 1 surgical-medical ICU
Organ systems included: (score range for each system)	Cardiovascular (0–4) Respiratory (0–4) Renal (0–4) Neurologic (0–4) Haematologic (0–4) Hepatic (0–4)	Cardiovascular (0–5) Respiratory (0–3) Renal (0–5) Neurologic (0–5) Haematologic (0–3) Hepatic (0–1)	Cardiovascular (0–4) Respiratory (0–4) Renal (0–4) Neurologic (0–4) Haematologic (0–4) Hepatic (0–4)
Score range	0–24	0–22	0–24
Value to be recorded	The first parameter each day	The worst value in the first 24 h of admission	The worst value in the first 24 h of admission
Possibility of daily determination	Yes	Yes for a week (not considered in the initial publication)	Yes
Simplicity of use	+++	++++	++++
External validation	Yes	Yes	Yes
Utilization frequency	+	+	++++
Probability of death	No	Yes	No

LODS: Logistic Organ Dysfunction Score; MODS: Multiple Organ Dysfunction Score; SOFA: Sequential Organ Failure Assessment.

Application and performance of generic systems in acute kidney injury patients

After publication, generic scoring systems for ICU patients have undergone external validation. Some of them have also been tested in specific subpopulations (i.e. septic patients, AKI patients). The accuracy of these systems in patients with AKI has been hampered by design and methodological problems. To cite just a few: the definition of ARF/AKI used, the collection of data (retrospective vs prospective), the origin of the sample (single centre vs multicentre), the type and severity of AKI (acute tubular necrosis, those needing renal replacement therapy (RRT)), collection time (at ICU admission, at diagnosis, at start of RRT), or the exclusion of some patients depending on aetiology or location.

In general, the accuracy of generic systems is lower when applied to patients with AKI. This finding is expectable considering the limited number of patients with AKI included in the original development cohorts. Very few scores reach an AUC > 0.8 and calibration is variable depending on the model and the sample studied. Table 236.3 shows a summary of those studies which gave data on discrimination and calibration.

Some details deserve additional consideration. The time of data recollection, and hence, application of the score, has an impact on its performance. As shown in Table 236.3, discrimination improves for later data collection times. This effect was first observed by Chang (1989), and is recognized as dynamic severity scoring or serial evaluation. It is based on the fact that an increase in the score during the first days of admission points to an absence of response to therapies applied during that period, and hence to a greater risk of death.

Data on calibration are scarce, and with the exception of SAPS 3, generic systems underestimate mortality (SMR > 1). This is especially true when AKI diagnosis is made late in the clinical course, some days after ICU admission.

The existence of at least three different widely used scoring systems, limits possible comparisons of severity of illness across studies whenever the models used differ. To solve this problem, equations correlating two systems have been developed from a database with > 37,000 patients with AKI (Schneider et al., 2012). Correlation was especially fine between APACHE III and SAPS II ($r^2 = 0.78$). The use of these equations could allow the comparison of patients' severity across studies even with different severity scores.

Specific prognostic models and scores for acute kidney injury patients

The high mortality rate observed in AKI patients during the last decades of the past century prompted researchers to study risk factors for mortality in this population. The main goal was to detect those patients with no possibility of survival aiming to prevent unnecessary suffering to them and their relatives, and at the same time, to improve resource use. These studies soon began to include

Table 236.3 Performance of generic scoring systems in AKI patients

Authors (year of publication)	Type of study	AKI patients included	Timing of score calculation	Generic scoring systems studied	Discrimination	Calibration GOF H-L C (*p value*) [SMR]
Douma et al. (1997)	Single-centre retrospective G & S	238 patients needing RRT	24 h before starting RRT	APACHE II APACHE III SAPS MPM	0.62 0.74 0.66 0.71	NP
Fiaccadori et al. (2000)	Single-centre prospective	425 patients 69% ATN MV excluded	At admission (first 24 h)	APACHE II SAPS II MPM_{24} II	0.75 0.77 0.85	15.67 (*0.047*) 32.53 (*0.0001*) 21.86 (*0.005*)
Clermont et al. (2002)	Single-centre prospective	254 admissions	At admission (first 24 h)	APACHE III	NP	[1.21]
Mehta et al. (2002)	Multicentric prospective G & S	605 patients (59.1% RRT)	Day of nephrology consultation	APACHE II APACHE III SAPS II SOFA	0.634 0.756 0.766 0.756	(*0.78*) (*0.19*) (*0.03*) (*0.35*)
Uchino et al. (2005)	Multicentric prospective G & S	1742 patients (62.7% RRT)	At admission (first 24 h)	SAPS II	0.645	1006.2 (<*0.01*)
Chertow (2006)	Multicentric prospective G & S	618 patients (64.4% RRT)	ARF diagnosis Nephrology consultation Start of RRT	APACHE II APACHE III SAPS II SOFA	0.63–0.66–0.67 0.66–0.70–0.67 0.69–0.70–0.71 0.64–0.70–0.73	NP
Torres Costa e Silva et al. (2009)	Single-centre prospective G & S	366 patients	Diagnosis day, Nephrology consultation (N = 196)	APACHE II SAPS II	0.66–0.77 0.73–0.83	NP
Maccariello et al. (2010)	Multicentric prospective	244 patients needing RRT	Start of RRT (± 1 h)	MPM_0 III SAPS 3 (GEq) SAPS 3 (CSA)	0.73 0.82 0.82	14.9 (*0.061*) [2.42] 10.2 (*0.254*) [1.26] 9.3 (*0.315*) [1.04]
Torres Costa e Silva et al. (2011)	Single-centre prospective	366 patients (DD) 196 (NCD)	Diagnosis day, Nephrology consultation (N = 196)	APACHE IV SAPS 3 (GEq) SAPS 3 (CSA) MPM III	0.74–0.79 0.73–0.80 0.73–0.80 0.73–0.81	[1.92]–[1.46] [1.35]–[1.15] [1.09]–[1.00] [1.89]–[2.09]
Demirjian et al. (2011)	Multicentric prospective G & S	1122 patients needing RRT	Start of RRT	APACHE II	0.68	NP

ATN = acute tubular necrosis; DD = diagnosis day; G & S = study included both generic and specific scoring systems for AKI patients; GOF H-L C = Value of Hosmer & Lemeshow goodness-of-fit C test; MV = mechanical ventilation; NCD = nephrology consultation day; NP = not provided; RRT = renal replacement therapy; SAPS 3(CSA); SMR = standardized mortality rate.

prognostic models. By 1985 when the APACHE II version was published, four different specific models for patients with AKI were available (Cioffi et al., 1984; Bullock et al., 1985; Lien and Chan, 1985; Rasmussen et al., 1985). Although commendable by their aim, these models were limited by their methods. Many of them were retrospective, data collection was based on chart review, sample sizes were small, and none explained the approach to missing values. Although all studied patients had AKI, each study had its own definition and exclusion criteria, preventing comparisons. Despite clear definitions of variables, time of collection was not always clear, and in fact some definitions were referred to late phases in the evolution of the syndrome avoiding early prognosis. Discrimination and calibration values were not provided mainly due to the absence of proper statistics tools at the moment of publication. These values have been provided later during the process of external validation.

Variable data capture time is a key factor to consider. It seems reasonable that values should be collected at diagnosis. However due to differences in AKI definitions, the moment will vary from one study to another. Alternatively some researchers have used the time of consultation with the nephrologist. There is an inherent bias in this election as it can vary widely depending on local practices. Finally, some works use values just before the start of RRT. Again this moment is problematic because indication for this therapy can

Table 236.4 Main characteristics of specific AKI scoring systems and prognostic models

Prognostic model (author, year) [centres/countries] (*data collection period*)	Outcome of interest (%) Number of patients	Population studied	Variable selection	Moment/s of data collection	Variables in the model (number)	Discrimination AUROC #	Calibration
(Cioffi et al., 1984) [1/1] (*1973–1982*)	In-hospital mortality (81%) 65	Postop. Pts with ARF requiring RRT	Discriminant function analysis	NP retrospective	Age, number of transfusions, cardiac surgery, cardiac failure, sex, vascular surgery ≠AAA, interval from ARF to RRT, preoperative hypotension (8)	NP	NP
(Bullock et al., 1985) [1/1] (*1971–1978*)	In-hospital mortality (66.4%) 462	ATN (Cr > 2.5 or a BUN > 100 or increase > 2.5)	Multiple logistic regression	ARF diagnosis	Diuresis, pulmonary complications, age, Jaundice, CV complications, hypercatabolism (6)	NP	NP
(Rasmussen et al., 1985) [1/1] (*1977–1981*)	In-hospital mortality (53%) 148	ATN (Cr > 2 or a 50% increase)	Discriminant function analysis	NP retrospective	Acute cardiac illness, neoplasia, oliguria, acute pancreatitis, trauma, pre-existing renal disease, other surgery, CNS damage, respiratory failure, pre-existing heart disease (10)	0.63 Douma	NP
(Lien and Chan, 1985) [1/1] (*1980–1984*)	In-hospital mortality (63.8%) 58	ARF patients requiring RRT	Multiple logistic regression	NP retrospective	Age, CNS depression, & inotropic support after 1st week (3)	NP	NP
(Lohr et al., 1988) [1/1] (*1979–1985*)	In-hospital mortality (75%) 126	ARF patients requiring RRT	Multiple logistic regression	NP retrospective	SBP < 110 mmHg, MV, CHF, sepsis, gastrointestinal dysfunction (5)	NP	NP
(Liaño et al., 1989) [1/1] (*1977–1985*)	In-hospital mortality (56%) 228	ATN	Multiple linear regression	Nephrologist consultation	Oliguria, MV, hypotension, coma (4)	NP	NP
(Schaefer et al., 1991) [1/1] (*1985–1988*)	In-hospital mortality (56.7%) 134	ARF ICU patients requiring RRT	Linear discriminant	Just before RRT 24–48 h later	MV, MBP, liver cirrhosis, blood glucose, heart failure, septic shock/heart rate/prothrombin time (6; 7–8)	0.65 Douma 0.65 Mehta	NP
(Liaño et al., 1993) [1/1] (*1977–1988*)	In-hospital mortality (53%) 328	ATN	Multiple linear/ logistic regression	Nephrologist consultation	Age, sex, oliguria, nephrotoxic, hypotension, jaundice, MV, neurologic state (8)	0.78 Douma 0.63 Mehta 0.698 Uchino 0.67–0.77 Torres 0.53–0.56 Chertow	71.2
(Brivet et al., 1996) [20/1] (*1991*)	In-hospital mortality (58%) 360	ARF ICU patients (Cr > 3.5 or increase > 1.7 mg) Cr > 3.4 excluded	Multiple logistic regression	ARF diagnosis	Age, previous health status, hospitalization before ICU, SAPS, septic cause, ARF during ICU stay, oliguria (7)	NP	NP

(*Continued*)

Table 236.4 Continued

Prognostic model (author, year) [centres/countries] (*data collection period*)	Outcome of interest (%) Number of patients	Population studied	Variable selection	Moment/s of data collection	Variables in the model (number)	Discrimination AUROC #	Calibration
CCF (Paganini et al., 1996) [1/1] (*1988–1992*)	In-hospital mortality (66.4%) 506	ARF ICU patients requiring RRT	Multiple logistic regression	Admission and treatment day 1	Sex, MV, haematologic failure, Bil, no surgery, Cr on Trt day 1, increase in BUN from admission, organ failure (8)	0.643 Uchino 0.718 Mehta 0.58–0.65 Chertow	NP
ANP study (Chertow et al., 1998) [59/2] (*1993–1995*)	30–60-day mortality or dialysis (36%) 256	ATN (other causes of ARF and Cr > 3 excluded)	Multiple logistic regression, & Cox regression	At randomization	Male sex, MV, oliguria, AMI, acute stroke or seizure, hypertension, bicarbonate/bilirubin, albumin, chronic immunosuppression (7–9; 5)	0.81 (30-day mortality) 0.61 Uchino 0.726 Mehta	1056.8
SHARF (Lins et al., 2000) [1/1] (*1996–1997*)	In-hospital mortality (53%) 197	ARF ICU patients (Cr > 2 or a 50% increase)	Multiple linear regression	(1) ARF diagnosis/ ICU admission: T0 (2) 48 h later: T48	Age, albumin, prothrombin time, MV, heart failure (5; 5)	T0: 0.87; T48:0.898 0.71–0,81 Torres 0.63 Kohle 0.645 Mehta 0.56–0.60 Chertow	SMR 0.759
(Mehta;2002) [4/1] (*1989–1995*)	In-hospital mortality (51.9%) 605	ARF (Cr > 2 or BUN > 40 or increase > 1 mg) CHD, prerenal and obstructive excluded	Multiple logistic regression & Cox regression	Day of nephrology consultation	Age, male gender, respiratory failure, liver failure, haematologic failure, Cr, BUN, HR, log urine output (9–10)	0.832 0.67 Uchino 0.51–0.63 Torres 0.693 Kohle	1352.2 SMR 1.22
SHARF II (Lins et al., 2004) [8/1] (*1997–1998*)	In-hospital mortality (50.5%) 293	ARF (Cr > 2 or a 50% increase) Cr > 3 excluded	Multiple linear regression	(1) ARF diagnosis/ ICU admission: T0 (2) 48h later: T48	Age, albumin, prothrombin time, MV, heart failure, bilirubin, sepsis, hypotension (8; 8)	T0: 0.82; T48:0.83 0.668 Kohle 0.733 Mehta	SMR 0.95
PICARD (Chertow et al., 2006) [5/1] (*1999–2001*)	Death within 60 days of ARF diagnosis (37%) 618	ARF (Cr increase 0.5 or 1 mg depending on basal Cr) Cr > 5 excluded	Multiple logistic regression & Cox regression	(1) ARF diagnosis (2) Nephrologist consultation (3) RRT start	Age, CKD IV, BUN, liver failure, sepsis or S. shock/age, BUN, liver failure (5–3) Age, log UO, Cr < 2, BUN, liver failure, ARDS, platelets, sepsis or S. shock/age, log UO, Cr < 2, BUN, liver failure, ARDS, Platelets (8–7) Age, Cr, BUN, liver failure, respiratory failure, platelets, sepsis or S. shock/age, liver failure, platelets, sepsis or S. shock (7–4)	0.62 0.68 0.72	0.20* 0.67* 0.16*
ATN (Demirjian et al., 2011) [27/1] (*2003–2007*)	60-day all-cause mortality (53%) 1122	ATN requiring RRT	Multiple logistic regression	At RRT start	Age, chronic hypoxaemia, CV disease, malignancy, immunosuppressive therapy, ischaemic AKI, postsurgery, HR, MBP and UO at RRT start, VM and FiO2, pH, paO2, Cr, HCO3, phosphate, alb, Bil, INR, platelet (21)	0.85	0,76*

AAA = abdominal aortic aneurysm; AMI = acute myocardial infarction; ARDS = acute respiratory distress syndrome; ARF = acute renal failure; ATN = acute tubular necrosis; AUROC = area under the ROC curve; Bil = bilirubin; BUN = blood urea nitrogen; CHF = chronic heart failure; CKD = chronic kidney disease; CNS = central nervous system; Cr = serum creatinine; CV = cardiovascular; HR = heart rate; INR = international normalized ratio; log UO = logarithm of urine output; MBP = mean blood pressure; MV = mechanical ventilation; NP = not provided; Postop = postoperative; pts = patients; RRT = renal replacement therapy; SAPS = simplified acute physiology score; SBP = systolic blood pressure; SMR = standardized mortality rate. # First author of the study for that AUCROC value; * p value of the Hosmer-Lemeshow goodness-of-fit C test.

vary across centres, and because these measures are usually applied late in the evolution of the syndrome and only to the most severely ill patients, limiting its application.

Some AKI scores have undergone serial evaluation. This is the case for Schaefer (before RRT and 24 and 48 hours later), the SHARF score (at diagnosis or ICU admission, and 48 hours later) (Lins et al., 2000, 2004), and Chertow's model (at diagnosis, at nephrologist consultation, and at RRT start) (Chertow et al., 2006). In these systems, as in generic models, discrimination improves with the evolution of the syndrome.

Recent studies can be considered second-generation-specific AKI models (Chertow et al., 1998, 2006; Demirjian et al., 2011). All these systems were developed from prospective and multicentre studies. With one exception all of them have very good discrimination. The number of variables ranges between 5 and 21, and some are still awaiting external validation. Despite the long period of years studied, mortality of AKI is quite uniform. Most studies show figures around 55%, ranging between 36% and 81%. For additional data on specific AKI models see Table 236.4.

Future role of scoring systems in acute kidney injury patients

Generic systems have already been used for risk stratification in important AKI trials. In the next years we will see how specific AKI models are used with this same goal. There is an urgent need to improve AKI mortality and at the same time, we need to improve our mortality prediction models for AKI patients. With improvements in risk stratification we will be able to detect the therapies that will work best for each patient. The inclusion of new variables (i.e. biomarkers) and the use of new statistical techniques will help to make this goal achievable.

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CHAPTER 237

Overall outcomes of acute kidney injury

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Introduction

A systematic review (Ympa et al., 2005) covering studies on prognosis of severe acute kidney injury (AKI) between 1956 until 2004, concluded that despite technical progress in its management, mortality rates remained unchanged at around 50%. This lack of improvement in survival probably reflected a change in epidemiology, at least in the developed world (Lameire et al., 2006) and it is conceivable that a decrease in the proportion of patients with isolated AKI was neutralized by a corresponding increase in the number of older patients and patients with AKI complicating multiorgan dysfunction syndrome.

As explained in Chapter 220, the Risk, Injury, Failure, Loss, and End-stage renal disease (RIFLE) and Acute Kidney Injury Network (AKIN) classification systems are based on the observation of an association between small increases in serum creatinine (SCr) of at least 0.3 mg/dL (26.4 μmol/L) and patient mortality (Chertow et al., 2005; Lassnigg et al., 2004, 2008). However, the absolute mortality rates of AKI vary according to the different patient groups studied (intensive care unit (ICU), hospital, and population based), differences in parameters used for the criteria of AKI, differences in acquisition of baseline SCr, differences between need of renal replacement therapy (RRT) or not, and timing of endpoints (in-hospital mortality, 30 days, 60 days, or longer). In many instances, particularly in critically ill patients, AKI occurs in the setting of other diseases, such as sepsis, which are associated with a significant mortality risk. In such cases, AKI appears to amplify the risk of death associated with the underlying disease (Murugan et al., 2010).

Short-term prognosis

Community- and hospital-acquired AKI

The association between the development of AKI and higher in-hospital mortality has been well known for decades. Two single-centre studies illustrate the change over the years in epidemiology and outcome of AKI. Hou et al. (1983) found in 1983 that 4.9% of hospitalized patients developed AKI, defined as a relative increase in SCr of 0.5 (44.2), 1.0 (88.4) or 1.5 (132.6) mg/dL (or μmol/L) respectively, depending on the baseline SCr. The crude in-hospital mortality rate was 25% and was higher in those with more significant degrees of AKI. Almost two decades later, the same group (Nash et al., 2002) using similar definitions of AKI reported a higher incidence of hospital-acquired (HA)-AKI of 7.2%—but the in-hospital mortality rate (19.4%) was slightly lower.

Liano et al. (1996) prospectively assessed all AKI episodes in tertiary-care hospitals in Madrid, Spain. AKI was defined as a sudden rise in SCr to > 177 μmol/L (> 2 mg/dL) in patients with previous normal renal function, or as a sudden rise (≥ 50%) in patients with previous mild-to-moderate chronic kidney disease (SCr < 264 μmol/L (< 3mg/dL)). The crude mortality (45%) and the mortality corrected for underlying disease (26.7%) were much higher than the mortality of patients without AKI (5.4%).

A comparative study in incidence, associated risk factors, and outcome between community-acquired (CA) and HA-AKI in African Americans (Obialo et al., 2000) showed that overall mortality was higher in HA-AKI (59% vs 33%). The mortality was high in younger patients with CA-AKI and in older patients with HA-AKI, and the dialysis-related mortality rate was threefold higher among patients with HA-AKI, compared to CA-AKI. All these seem to suggest that AKI is rather a marker of severity of disease, and that it is the underlying condition that mainly determines the prognosis.

One of the first population studies identified all patients with increased SCr (150 and 130 μmol/L (1.7 and 1.5 mg/dL) for men and women, respectively) in a 6-month period (Ali et al., 2007). Unlike other studies, this report included all patients from a defined geographic area, independent of the need for dialysis and of location of treatment. The median age of this population was 76 years for AKI and 80.5 years for acute-on-chronic renal failure. *De novo* AKI and acute-on-chronic renal failure were differentiated and showed a hospital mortality of 30.7% and 38.8%, respectively. Using the RIFLE criteria, in-hospital mortality progressively increased from 27% (Risk), to 36% (Injury) and 41% (Failure).

In a prospective population study including all cases of AKI treated by RRT (Prescott et al., 2007), mortality was high with 48% dying within 90 days of starting RRT. Age, comorbidity, sepsis, and recent surgery were independent risk factors for death in those without pre-existing CKD.

Two studies have utilized large administrative or claims databases, covering the years 1988 to 2004, to study trends in the epidemiology and mortality of AKI in the United States between 1988 to 2002 (Waikar et al., 2006), and 1992 to 2001 (Xue et al., 2006). Using the same International Classification of Diseases, Ninth Revision (ICD-9-CM) codes to identify AKI and a similar

and partially overlapping study population, the two studies found a marked rise in the incidence and a fall in the mortality associated with AKI and AKI requiring dialysis. Hospital mortality was 32.9% in AKI patients who required RRT and 27.5% in those who did not, as compared to 4.6% in patients without AKI (Xue et al., 2006). In the study of Waikar et al. (2006) a steady decline of in-hospital mortality both in patients with AKI (40.4% to 20.3%) and in those dialysed because of AKI (41.3% to 28.1%), was observed, despite presence of greater co-morbidity.

Liangos et al. (2006) also using a nationally representative hospital discharge database generated in the United States but different from the one used by Waikar et al. (2006) observed a similar decrease in hospital mortality from 40.4% in 1988 to 20.3% in 2002 for all patients with AKI and from 41.3% to 28.1% among AKI patients who required RRT. Despite a decreased overall mortality, an AKI code at discharge of the hospital was associated with an adjusted prolongation of hospital length of stay (LOS) by 2 days, an adjusted odds ratio (OR) of 4.1 for hospital mortality, and of 2.0 for discharge to short- or long-term care facilities (Liangos et al., 2006).

AKI developed in 631 patients admitted with community-acquired severe (N = 329) and non-severe pneumonia (N = 302) and sepsis (Murugan et al., 2010). Nearly two thirds of patients developing AKI already had AKI at hospital admission (truly community acquired). Patients with AKI had a higher risk of death at hospital discharge (11% vs 1.3%) at 90 days (24% vs 9.8%), and at 1 year (36.3% vs 20.1%). Also, the patients with non-severe pneumonia not admitted to ICU who developed AKI versus those who did not develop AKI, had a significantly higher risk of death. In patients hospitalized in an urban academic medical centre in the United States, the mortality rate for AKI was 10.8%, compared to 1.5% for cases without AKI (Wang et al., 2012). Larger increases in SCr were associated with higher mortality rates: AKIN stage 1, 6.3%; stage 2, 16.5%; and stage 3, 23.7%. AKI remained independently associated with in-hospital mortality after adjusting for demographic factors, such as baseline estimated glomerular filtration rate (eGFR) of < 60 mL/min/1.73 m^2, and medical centre expected mortality score. When considering time to peak SCr (early: ≤ 7 days vs late: > 7 days), AKI remained independently associated with mortality, but the OR for death was higher among those with more prolonged hospitalizations and SCr peak values occurring after the seventh hospital day.

That the development of AKI portends a higher risk of in-hospital death has also been demonstrated in special target groups such as elderly patients or specific settings such as myocardial infarction or cardiovascular surgery.

The above mentioned study of Waikar et al. (2006) also showed that in elderly patients with AKI, in-hospital mortality decreased over the years. At least two studies compared survival in older versus younger patients with AKI and found that the risk for death associated with AKI for elderly patients aged > 65 years was not significantly greater than for those < 65 years (Pascual and Liano, 1998; Lameire et al., 1999). Thus, although the incidence of AKI is increasing in elderly patients (Hsu et al., 2007), it appears that the immediate consequences associated with AKI are following trends similar to outcomes witnessed with AKI in younger patients (Coca, 2010).

A retrospective analysis recently studied 3210 patients with acute coronary syndrome (ACS) (Marenzi et al., 2013). Based on the AKIN criteria, overall 409 patients (13%) developed AKI. In-hospital mortality was greater in patients with AKI than in those without AKI (21% vs 1%; P < 0.001). Compared to no AKI, the adjusted OR for death was 3.5 with stage 1 AKI and 31.2 with stages 2 and 3. In patients with ACS, AKI is a frequent complication and it is not surprising that those patients with AKI stage 2 or 3 showed a higher incidence of major cardiac events compared to patients without AKI.

Another analysis of a much larger database including 33,249 consecutive hospitalizations in 31,532 unselected patients with acute myocardial infarction across 56 US centres, examined the temporal trends in AKI incidence from 2000 to 2008 (Amin et al., 2012). Despite the ageing population and rising prevalence of AKI risk factors, AKI incidence declined from 26.6% in 2000 to 19.7% in 2008, which is somewhat in contradiction with previously mentioned administrative databases, but in-hospital mortality also declined over time from 19.9% in 2000 to 13.8% in 2008.

Also in post-cardiac surgery (Weir et al., 2011), mortality rates range from 18% to 80% and from 0.9% to 6.4% in those who do versus those who do not develop AKI. The mortality in this setting has also declined over the years. For example, Thakar et al. (2007) studied postoperative hospital mortality between 1993 and 2002. Whereas between the first and second halves of the study period the incidence of AKI increased from 5.1% to 6.6%, the associated mortality rate decreased from 32% to 23% (P < 0.0001). Similarly, the incidence of RRT-requiring AKI also increased from 1.5% to 2.0%, with a decrease in associated mortality from 61% to 49% (P < 0.01). However, in a risk-adjusted model, AKI patients with need of dialysis and with other organ system failures did not show improvement in survival, suggesting that either the diagnosis of AKI as well as the indication to start RRT have become more 'liberal' over time.

Using data from the Nationwide Inpatient Sample, the annual rates of AKI, AKI requiring dialysis (AKI-D), and inpatient mortality after cardiac surgery in the United States in the years 1999 through 2008 were calculated (Lenihan et al., 2013). Compared with 1999, the odds of AKI and AKI-D in 2008, adjusted for demographic and clinical factors, were 3.30 (95% confidence interval (CI) 2.89–3.77) and 2.23 (95% CI 1.78–2.80), respectively. Inpatient mortality with AKI and AKI-D decreased from 27.9% and 45.9%, respectively, in 1999 to 12.8% and 35.3%, respectively, in 2008. This most recent large database thus confirms that despite improvements in individual patient outcomes over the decade 1999 to 2008, the number of subjects developing AKI and AKI-D after surgery increased over the same period resulting in a relatively unmodified overall mortality rate. It can be questioned whether this is a real 'improvement' or if it just represents a shift in the criteria to diagnose AKI and start RRT in milder cases.

Khatri et al. (2014) found that AKI complicated 14% of ischaemic stroke and 21% of intracerebral haemorrhage (ICH) hospitalizations. AKI was associated with increased hospital mortality from ischaemic stroke (OR 3.08) but not ICH (OR 0.82), except for those surviving at least 2 days (OR 2.11). AKI thus occurs frequently after stroke and as in many other dramatic diseases, is associated with increased hospital mortality.

Overall, in many of these association studies additional work is needed to establish if the association between the underlying disease and AKI is causal and if measures to prevent AKI would result in decreased mortality.

Although exact data on outcome of AKI in emerging countries are scarce, mortality reported to be associated with AKI seems in general to be lower, at between 10% and 40% (for reviews, see Cerda et al., 2008; Jha and Parameswaran, 2013; Lameire et al., 2013). Under-reporting could influence these estimates, but the lower mortality in developing countries might also be a function of the younger age of affected individuals, and because AKI is less frequently associated with multiple organ failure. Moreover, in emerging countries, CA-AKI is commonly due to volume-responsive AKI, which is rapidly reversible upon correction. Conversely, the mortality of AKI associated with specific diseases such as severe malaria remains very high. For example, the overall mortality rate among malaria patients with AKI ranges from 15% to 50% in different series (reviewed in Mishra and Das, 2008). Similarly, the mortality rate of patients with cerebral malaria increased from 14% to 40% in the presence of AKI. Recent studies on CA-AKI in India reported mortalities between 16% and 26.2% (Kaul et al., 2012).

Costs attributable to HA-AKI were addressed by Fischer et al. (2005), involving administrative data from 23 hospitals in Massachusetts, United States. Patients with uncomplicated AKI (i.e. excluding patients in the ICU) incurred median direct hospital costs of $2600, median hospital LOS of 5 days, and, in this study, a mortality of 8%. The cost represented the third highest median direct hospital costs after acute myocardial infarction and stroke.

Transient (prerenal) AKI

Little is known about the short-term prognosis of patients who either present or who develop an increased SCr level during hospitalization, but in whom the level rapidly returns to normal.

As discussed in Chapters 220 and 222, Uchino et al. (2010) found that 'transient AKI', defined as a rapidly recovering AKI (return to no-AKI risk, injury, failure, loss, end-stage (RIFLE) class within 72 hours of onset) represents close to a third of all cases of HA-AKI, and is independently associated with a significantly higher risk of death. Tian et al. (2009) defined AKI as an increase in SCr level of ≥ 0.3 mg/dL (≥ 26.4 μmol/L) within 48 hours and analysed cases where the SCr returned either to normal or declined with ≥ 0.3 mg/dL (≥ 26.4 μmol/L) within 48 hours. A control group consisted of patients who were hospitalized with a SCr level ≤ 1.2 mg/dL (≤ 106 μmol/L) but without an increase of ≥ 0.3 mg/dL (≥ 26.4 μmol/L) within 48 hours during their hospital stay. Using the authors' definitions, from a total of 6033 patients, 12% developed AKI. Of these AKI patients, in 60% the SCr subsequently decreased by ≥ 0.3 mg/dL (≥ 26.4 μmol/L) within 48 hours; 27% even normalized the levels within 48 hours. Nevertheless, the latter category of patients had significantly greater mortality rates (14.8%) than patients without AKI. Even a small increase in SCr level of ≥ 0.3 mg/dL (≥ 26.4 μmol/L-stage 1 of AKIN) during 48 hours of hospitalization is thus associated with worse outcomes even if the SCr returns to normal. On the other hand, patients who present to the hospital with an increased SCr level (≥ 1.2 mg/dL or ≥ 106 μmol/L) that returns rapidly to normal have outcomes approaching those with SCr levels consistently in the normal range. If this retrospective study is confirmed by prospectively collected data it would mean that, by applying the AKIN definition, 10–15% of a hospitalized population will suffer from any form of AKI but that roughly two-thirds of these patients will show a decline of the SCr by ≥ 0.3 mg/dL (≥ 26.4 μmol/L) within 48 hours. Even a quarter of them will return to normal SCr levels. However, these patients, presumably mainly suffering from 'prerenal AKI', have a significantly greater mortality than patients without AKI.

Critically ill patients

The increasing severity of illness in critically ill patients with AKI is one of the contributors to its persistently high mortality rates. The cause of AKI in the ICU is commonly 'multifactorial' and frequently develops from a combination of hypovolaemia, sepsis, medications, and haemodynamic disturbances. Sepsis is the most common cause of AKI in a general ICU, accounting for up to 50% of cases (for review, see Dennen et al., 2010). Two severity of illness scoring systems are widely used and are often applied in AKI patients: the Acute Physiology and Chronic Health Evaluation (APACHE) score and the Sequential Organ Failure Assessment (SOFA) score (de Mendonca et al., 2000; Chawla et al., 2007). In one study (Chawla et al., 2007) the predictors of AKI were log plasma levels of interleukin 6 and the APACHE II score in a multivariable Cox regression analysis including also other risk factors. In the study by Mendonça et al. (2000), AKI patients had significantly higher organ failure scores and most of the risk factors for AKI or mortality were already present on admission in the ICU; a strong relation between the onset of multiorgan failure and AKI was noted (de Mendonca et al., 2000). Despite apparent improvement in overall prognosis, the mortality in a general ICU population with AKI is still between 30% and 60% (Metnitz et al., 2002; Uchino et al., 2005). The international observational Beginning and Ending Supportive Therapy for the Kidney (BEST Kidney) study in critically ill patients with AKI (Uchino et al., 2005) found an ICU mortality of 52%, with an additional 8% mortality in the hospital after ICU discharge, giving an overall hospital morality of 60.3%. The hospital mortality varied widely among centres and countries (ranging between 50.5% and 76.8% among countries contributing more than 100 patients). Study centre, older age, time between hospital admission and study inclusion, SAPS II score, use of mechanical ventilation, and vasopressor use were significant independent risk factors for mortality. Most survivors (86%) were dialysis independent at discharge. In the same database, septic AKI had a higher in-hospital mortality rate than non-septic AKI (70.2 vs 51.8%; $P < 0.001$), even after adjusting for relevant covariates (Bagshaw et al., 2007). The multicentre Stuivenberg Hospital Acute Renal Failure (SHARF) study comparing two different dialysis modalities (intermittent vs continuous RRT) also found an overall hospital mortality of 50.5% in ICU patients without different impact of the modality (Lins et al., 2004).

Increasing RIFLE severity grades are associated with increasing ICU mortality (Ricci et al., 2008). In the study by Hoste et al. (2006) in 5383 critically ill patients in seven ICUs, AKI occurred in 67% of patients with 12% achieving a maximum RIFLE class of R, 27% I, and 28% F. Patients with a maximum score of R had a mortality rate of 8.8%, compared to 11.4% for I and 26.3% for F, respectively and compared with a mortality rate of only 5.5% in patients without AKI. Furthermore, RIFLE-I (hazard ratio (HR) 1.4) and RIFLE-F (HR 2.7) were independently associated with hospital mortality after adjusting for other variables known to predict outcome in critically ill patients.

Of 2164 ICU patients recorded in the NEiPHROS-AKI multicentre prospective study (Cruz et al., 2007), only 234 (10.8%) developed AKI, 19% with RIFLE-R, 35% RIFLE-I, and 46% RIFLE-F, respectively. Overall mortality (49.5%) was highest among those with RIFLE-F(ailure). Ostermann and Chang (2007), observed

hospital mortality rates in RIFLE-R of 20.9%, 45.6% in RIFLR I, and 56.8% in RIFLE F, respectively, compared to 8.4% in patients without AKI. Interestingly, need for RRT was not an independent risk factor for hospital mortality. Applying the AKIN staging to the same ICU population (Ostermann and Chang, 2008) multivariate analysis showed that AKI stage 3, but not stages 1 and 2, was independently associated with ICU mortality. In a large heterogenous cohort of critically ill patients (Bagshaw et al., 2008b), each RIFLE category was independently associated with hospital mortality (OR R(isk) 1.58, I(njury) 2.54, and F(ailure) 3.22). In 71,486 US army veterans with AKI (22% of a large ICU cohort), after adjusting for severity of illness, the odds of death were 2.2 (95% CI 2.17–2.3) for AKIN stage 1, 6.1 (95% CI 5.74–6.44) for stage 2, and 8.6 (95% CI 8.07–9.15) for stage 3 (Thakar et al., 2009). Joannidis et al. (2009) studied 16,784 patients admitted to 330 ICUs across Austria. The ORs for hospital mortality based on RIFLE criteria were: R(isk) 1.38, I(njury) 1.90, and F(ailure) 2.99.

Two recent trials have studied the effect of different intensities of RRT in ICU patients with AKI. In one trial (Bellomo et al., 2009), the 90-day mortality was 44.7% while in the other (Palevsky et al., 2008) an overall mortality of 52.5% was observed. Moreover, 24.6% of survivors with severe AKI were still receiving RRT on day 60 (Palevsky et al., 2008). These data are, however, limited by the fact that RRT is often reserved for the most severely ill patients and that the initiation RRT, which automatically constitutes AKIN stage 3, is highly variable across physicians.

Finally, a prospective observational multicentre study in 10 ICUs in Italy revealed that AKI versus non-AKI patients had a higher crude ICU mortality (28.8% vs. 8.1%) and a longer ICU length of stay (median 7 vs 3 days). Crude ICU mortality and ICU length of stay increased with greater severity of AKI (Piccinni et al., 2011). Septic patients had more severe AKI, and were more likely to receive RRT with lower frequency of renal function recovery.

All these studies clearly indicate that mortality associated with severe AKI is one of the highest observed in the overall population of critically ill patients, particularly when RRT is required. For example, in non-AKI trials, 60-day mortality was 28% for patients with adult respiratory distress syndrome (ARDS) (Wiedemann et al., 2006) and 28-day mortality was approximately 32% for individuals with septic shock (Sprung et al., 2008). Half of AKI cases in critically ill patients are sepsis-related (Uchino et al., 2005; Bagshaw et al., 2007; Hoste et al., 2010) and AKI develops in 31–65% of septic shock patients (Lopes et al., 2007; Oppert et al., 2008; Bagshaw et al., 2009). AKI in septic patients is consistently linked to higher mortality rates and increased consumption of healthcare resources (Lopes et al., 2007; Bagshaw et al., 2008a, 2009; Oppert et al., 2008). Why short-term outcomes for severe AKI in critically ill patients are so poor remains incompletely understood (Elapavaluru and Kellum, 2007). One issue is that many studies define AKI severity by the need for RRT which can be misleading. For example, if RRT is reserved for the most severely ill patients, mortality will be very high. If, on the other hand, RRT is applied to patients with a low risk of death, mortality will be low. Of course, neither strategy is desirable; rather one should identify which patients with AKI will benefit from RRT. Unfortunately, as discussed in Chapter 232, this issue remains an open question exemplified by highly variable practice patterns (Uchino et al., 2007). Even if one defines severe AKI as RIFLE class F (with or without RRT), hospital mortality rates for individuals with this disease are typically 20–40%, as high as or higher than patients with multiple organ failure (Vincent et al., 1996).

Table 237.1 Hazard ratios: results of multivariate Cox regression analysis for 60-day mortality in critically ill patients with AKI

Characteristic	Hazard ratio	95% CI	P value
Age	1.02	1.01–1.03	< 0.001
SAPS II (per point)	1.03	1.02–1.04	< 0.001
Heart failure	1.38	1.05–1.81	0.02
Medical admission	1.68	1.35–2.08	< 0.001
Mean fluid balance, L/24 hours	1.21	1.13–1.28	< 0.001
Mechanical ventilation	1.55	1.14–2.11	< 0.001
Liver cirrhosis	2.73	1.88–3.95	< 0.001

CI = confidence interval; SAPS II = Simplified Acute Physiology Score II.

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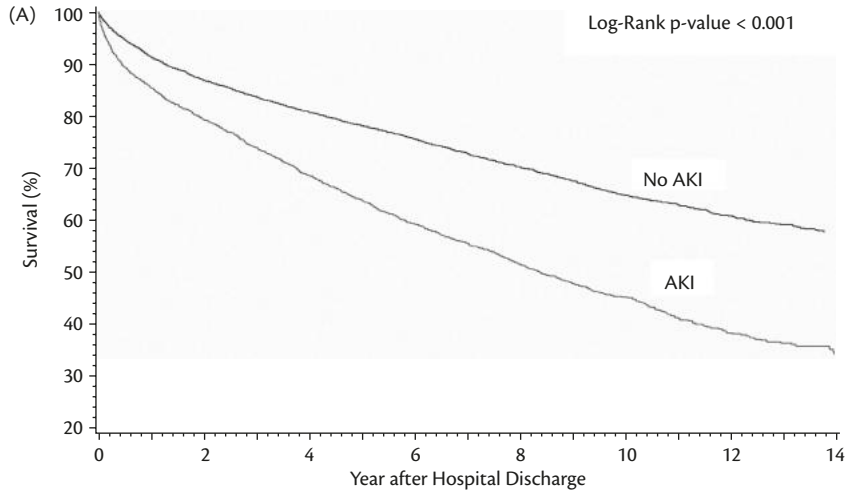
Sustained AKI can profoundly alter fluid, electrolyte, acid–base, and hormonal regulation and can lead to abnormalities in the central nervous, immune, and coagulation systems (Grams and Rabb, 2012). Many patients with AKI already have multisystem organ failure but the incremental influence of AKI on remote organ function and how it affects outcome is unclear.

Table 237.1, taken from the Sepsis Occurrence in Acutely Ill Patients (SOAP) study (Payen et al., 2008), summarizes the most important factors associated with mortality in critically ill septic patients with AKI. Among the many independent risk factors for 60-day mortality in the patients with AKI like age, Simplified Acute Physiology Score II (SAPS II), heart failure, liver cirrhosis, or medical admission, two important negative factors on outcome are related to fluid overloading of the patient and need for mechanical ventilation.

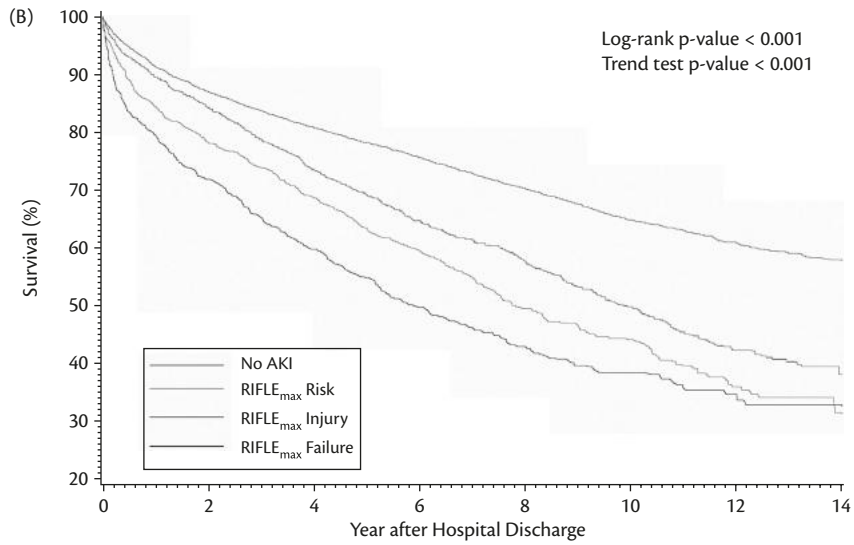
Long-term overall outcomes

The association of AKI with long-term mortality has received less attention, probably due to the apparent reversibility of the clinical episode as observed by subsequent improvements in SCr (Coca et al., 2009).

Hobson et al. (2009) retrospectively analysed the relationship between long-term mortality of AKI up to 10 years after hospitalization after various cardiothoracic surgery procedures. Compared to patients without AKI, long-term survival was not only worse but it was proportional to its severity, with an adjusted HR of 1.23 for the least severe RIFLE-R class and 2.14 for the RIFLE-F class. Remarkably, even patients with complete renal recovery after AKI had an increased adjusted HR for death of 1.28 compared to patients without AKI. A similar analysis by the same group of authors (Bihorac et al., 2009), focused on patients without CKD and in whom *de novo* AKI occurred after major general/gastrointestinal, vascular, cardiothoracic, or neurosurgery. Fig. 237.1 taken from this paper (Bihorac et al., 2009), illustrates that survival up to 5 years of follow-up was worse among patients with AKI and was again proportional to its severity. Even patients with complete renal recovery after AKI had an increased adjusted HR for death of 1.20 compared



Follow Up (years)		T=0	T=2	T=4	T=6	T=8	T=10	T=12	T=14
At risk (n)	No AKI	7192	6246	5800	4468	3188	2007	955	106
	AKI	3326	2627	2242	1604	1051	605	273	30



Follow Up (years)		T=0	T=2	T=4	T=6	T=8	T=10	T=12	T=14
At risk (n)	No AKI	7192	6246	5800	4468	3188	2007	955	106
	Risk	1535	1290	1123	823	574	355	173	19
	Injury	927	724	627	442	275	148	61	9
	Failure	864	621	499	344	205	104	39	2

Fig. 237.1 (A) Long-term survival of patients with and without an episode of AKI during hospitalization. (B) Long-term survival of patients stratified by AKI severity: RIFLEmax Risk (50% increase in SCr), RIFLEmax Injury (100% increase in SCr), and RIFLEmax Failure (threefold increase in SCr)
Reproduced with permission from Bihorac, A., Yavas, S., Subbiah, S., *et al*. (2009). Long-term risk of mortality and acute kidney injury during hospitalization after major surgery. *Ann Surg*, 249(5), 851–8.

to those without AKI. Long-term mortality was also assessed in several observational studies in contrast-induced AKI (CI-AKI). Although mortality rates varied from study to study, one consistent finding was that both short- and long-term mortality rates (up to 1 year or more after contrast administration) were significantly greater in patients with CI-AKI compared to those without (for review, see Rudnick and Feldman, 2008). As mentioned before, the data demonstrating an association between CI-AKI and death do not prove a causal relationship. Most of the patients in these studies had underlying risk factors that, in addition to increasing the patient's risk of CI-AKI, could have directly increased mortality. A critical question remains whether a reduction in CI-AKI incidence will result in a reduction in morbidity and mortality.

Lo et al. (2009) used a large database of adult patients who were hospitalized over an 8-year period and had a pre-admission eGFR ≥ 45 mL/min/1.73 m^2. All patients survived the hospitalization; 703 of these patients developed dialysis-requiring AKI. From this total, 295 died (42%) and 65 survived but failed to regain sufficient renal function to become dialysis independent (9%), resulting in only 343 AKI patients surviving without ESRD within 30 days of

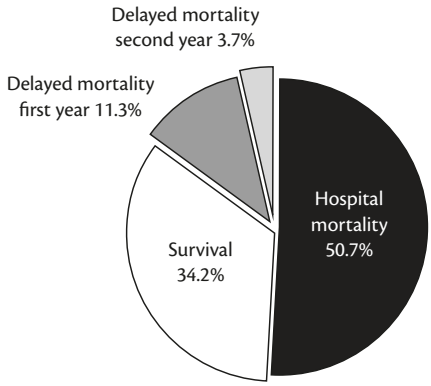


Fig. 237.2 Mortality in AKI patients admitted to the ICU. Mortality could be traced for all patients at 1 and 2 years after discharge. Delayed mortality = mortality during the first/second year after discharge.
Reproduced with permission from Van Berendoncks, A. M., Elseviers, M. M., and Lins, R. L. (2010). Outcome of acute kidney injury with different treatment options: long-term follow-up. *Clin J Am Soc Nephrol*, 5(10), 1755–62.

hospitalization (49%). After controlling for potential confounders such as baseline kidney function and diabetes, an independent long-term risk of mortality with an adjusted HR of 2.3 (95% CI 1.8–3.0) was found in this surviving dialysis-free cohort. The primary outcomes in this study were the development of CKD and ESRD with mortality being a secondary outcome (see below).

Coca et al. (2009) summarized 48 studies on the long-term risk (at least a 6-month follow-up) of adverse outcomes after AKI of any aetiology. The incidence mortality rate was 8.9 deaths per 100 person-years in survivors of AKI and 4.3 deaths per 100 patient-years in survivors without AKI (rate ratio of 2.59). Only two studies examined cardiovascular endpoints after AKI following percutaneous coronary intervention. At 1 year after AKI, 15.4% of survivors of AKI and 7.0% of survivors without AKI suffered a myocardial infarction (relative risk 2.05; 95% CI 1.61–2.61; $I^2 = 0\%$) (Rihal et al., 2002; Lindsay et al., 2003). One of the two studies (Rihal et al., 2002) examined the risk of myocardial infarction at three points of follow-up (0.5 years, 1 year, 5 years) and this increased risk persisted over time (relative risk 1.6, 1.85, 1.75, respectively, at each time point).

Lafrance and Miller (2010) retrospectively analysed data from US veteran patients who survived at least 90 days after discharge from a hospitalization in which they developed non-dialysis requiring AKI. They found that, independently of residual kidney function, the adjusted mortality risk associated with AKI was 1.41 and increased with increasing AKI stage.

A recent study used a propensity score-matched cohort method to retrospectively evaluate the risks of death and *de novo* CKD after reversible, hospital-associated AKI among patients with normal pre-hospitalization kidney function (Bucaloiu et al., 2012), traditionally not considered as an at-risk population. A number of 1610 patients with reversible AKI that resolved within the 90 days were successfully matched across multiple parameters with 3652 control patients who had not experienced AKI. Median follow-up was 3.3 and 3.4 years (AKI and control groups, respectively). In Cox proportional hazard models, the risk of death associated with reversible AKI was significant (HR 1.50); however, adjustment for the development of CKD (see below) during follow-up attenuated this mortality risk (HR 1.18).

A quite illustrative mortality pattern of critically ill patients with AKI and admitted in ICUs based on the multicentre SHARF study (Van Berendoncks et al., 2010) is represented in Fig. 237.2. The in-hospital mortality was 50.7%. The long-term mortality could be traced for all 595 surviving patients at 1 and 2 years after hospital discharge. Of the 595 hospital survivors 23% died within 1 year and 7.6% died during the second year after discharge, respectively. Total mortality, including hospital mortality, increased from 50.7 to 65.7%, 2 years after AKI.

All these studies thus seem to suggest that also the long-term prognosis of patients who develop AKI during their hospitalization is negatively affected, even after so-called full recovery of their renal function.

Quality of life in surviving acute kidney injury patients

Despite the availability of some reports of health-related quality of life (HRQOL) among survivors of AKI in the ICU, many of these studies are limited by small sample size and low response rate. As pointed out by Johansen et al. (2010), follow-up times are variable, ranging from 3 months to several years and several measures of HRQOL have been used, leading to a great variability in the results. HRQOL has been measured in survivors of AKI with tools like the SF-36 and the Nottingham Health Profile, which measure psychometric health status, and the EQ-5D and Health Utilities Index Mark 3 (HUI3).

On balance, despite that some limitations in patient mobility were fairly common, patients generally reported a favourable health status, with 62–77% of patients reporting 'good' or 'excellent' health status (Hamel et al., 1997; Morgera et al., 2002).

An analysis based on data from the large ATN trial (Palevsky et al., 2008) revealed a low overall HUI score 60 days after the onset of AKI, indicating severely compromised health utility (Johansen et al., 2010). A recent follow-up study of the same cohort found that those patients with poorer HRQOL, had a higher risk of death at 1 year (Joyce et al., 2012). A follow up study of the SHARF trial followed 204 critically ill patients who had survived a serious episode of dialysis-requiring AKI (Van Berendoncks et al., 2010). These patients were studied with home visits at a mean of 20.3 ± 7.3 months after hospital discharge and quality of life was assessed by the Medical Outcome Survey SF-36. The main finding was that in relation to age the physical component scores declined while the mental component scores remained stable in comparison with the 'healthy' population. Apart from age, other parameters such as severity of disease and clinical parameters during hospitalization did not show significant relationship with the SF-36 summary scores. This observation thus confirmed the statement of Maynard et al. (2003) that HRQOL is difficult to predict from data available at the time of acute illness in AKI patients.

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CHAPTER 238

Renal outcomes of acute kidney injury

Norbert Lameire

Renal recovery in survivors of acute kidney injury

Definition of renal recovery

The rate of development of end-stage renal disease (ESRD) after acute kidney injury (AKI) remains ill defined, particularly among elderly individuals, who represent the fastest growing segment of the ESRD population (Ishani et al., 2009). There are a number of methodological issues that are still not resolved and that makes the interpretation of the literature on long-term renal prognosis after AKI problematic (Liu et al., 2009; Lo et al., 2009). Current consensus definitions of AKI include heterogeneous disease entities such as prerenal AKI and acute tubular necrosis (ATN) that likely are associated with different risks of long-term outcome. Baseline renal function is often not well defined, which is problematic when the primary research question is to compare renal trajectory before and after an episode of AKI. Finally, there is concern that any observed association between AKI and future decline in renal function is due to confounding by severity of baseline renal dysfunction or other risk factors for AKI that are also risk factors for progressive loss of renal function (e.g. presence of diabetes mellitus).

Very often, 'complete' renal recovery is defined on the basis of serum creatinine (SCr) measurements, which may in fact reflect only partial renal recovery in many patients because of changes in muscle mass after a critical illness. Alternatively, the increased risk of mortality may be a result of changes in renal function that are poorly described by SCr measurements or other measures of glomerular filtration rate (GFR) and there might be an effect of residual confounding despite adjustment for multiple covariates. The latter is a limitation of virtually all observational studies. All these concerns should be kept in mind for a correct actual interpretation of the literature on this topic.

Recovery from AKI can indeed only be correctly evaluated in the context of a specific definition of AKI (Macedo et al., 2008). For example, the Risk, Injury, Failure, Loss, and End-stage renal disease (RIFLE) classification proposes that complete renal recovery exists if the SCr returns to the baseline classification within the RIFLE criteria, whereas partial renal recovery exists if there is a persistent change in RIFLE classification (R, I, or F) without persistent need for renal replacement therapy (RRT) (Bellomo et al. 2004). The majority of studies addressing renal recovery before the RIFLE/Acute Kidney Injury Network (AKIN) classification was described included predominantly critically ill patients requiring dialysis and considered renal recovery as dialysis independency at hospital discharge. However, a significant proportion of AKI patients are not in the intensive care unit (ICU), are not dialysed, and may require alternate definitions for assessing renal recovery. It is highly likely that patients with incomplete renal recovery and patients who did not receive dialysis after AKI are underrepresented in most early epidemiologic studies, creating the false belief that most patients who survive an AKI episode, in particular those suffering from ATN, recover either completely or at least partially their renal function (Firth, 2005).

Renal recovery in earlier studies

Kjellstrand et al. (1981) observed a survival of only 31% in ATN patients who needed dialysis and one-quarter of them were left with moderate renal insufficiency (SCr of 1.5–3 mg/dL or132–264 μmol/L). Ten per cent of the patients with long-term (>1-month follow-up) had severe renal failure (SCr > 3 mg/dL or > 265 μmol/L) and four other patients never recovered renal function and needed chronic haemodialysis. The authors concluded that 'acute renal failure is numerically important but not very time demanding on the capacity of chronic dialysis units'. Based on earlier studies (Kjellstrand et al., 1981; Bonomini et al., 1984; Druml et al. 1994), a major review on AKI (Esson and Schrier, 2002) quoted that survivors of ATN generally have a good prognosis for renal recovery and that only between 5% and 11% of these patients ultimately needed long-term dialysis.

Most early studies estimating long-term risk after an episode of AKI consisted of small prospective observational series of incident patients with AKI (Golestaneh et al., 2009). Although these studies consistently found a decrease in GFR some months after the initial insult this was seldom < 50 mL/min and was therefore ignored.

However, over the years, a single-centre study observed a growing fraction of surviving patients with need for permanent dialysis (Bhandari and Turney, 1996). Whereas in 1984–1986, only 6% of the survivors required long-term dialysis, by contrast, in 1993–1995, this percentage had increased to 21%. In addition, it had already been pointed out in 1995 that among surviving ICU patients with dialysis-requiring ATN, up to 33% may need long-term dialysis, and 28% may require institutional care (Chertow et al. 1995).

Renal recovery in recent studies

Recent epidemiological studies suggest that incomplete recovery of renal function after AKI may be an important contributor to a

growing number of incident ESRD cases, largely in excess of the global growth in chronic kidney disease (CKD) prevalence (Hsu et al., 2004, 2007; Coresh et al., 2005, 2007; Levey et al., 2007). Also the 2009 United States Renal Data System report revealed that adults with an AKI episode during hospitalization have an approximately 10-fold greater risk of progressing to ESRD by 12 months compared to patients who did not experience AKI (Collins et al. 2009).

In the population-based study of Ali et al. (2007), a threshold SCr value of 150 μmol/L (1.7 mg/dL) in men or 130 μmol/L (1.47 mg/dL) in women was defined and full renal recovery was accepted when the SCr concentrations fell below threshold (or fell to the baseline in cases of acute-on-chronic kidney injury). Partial recovery was defined as SCr remaining above the threshold (or remaining above the baseline in cases of acute-on-chronic kidney injury) while non-recovery occurred if the patient remained dialysis dependent at 90 days. Full renal recovery was achieved in 68%, 5% partially recovered, and in 27%, recovery could not be determined because the patient died in the acute phase. After exclusion of the latter patients, 92.5% of all cases showed full renal recovery, 7% had partial recovery, and only 0.6% had no recovery. However, almost half of patients in the RIFLE-F(ailure) category showed incomplete renal recovery. Piccinni et al. (2011) recently evaluated all incident admissions in 10 ICUs in Italy. Complete renal recovery was considered if discharge SCr was within 120% of baseline; partial recovery when discharge SCr was 121–150% of baseline; and non-recovery when SCr was > 150% of baseline, or when RRT was still applied. Of 576 AKI patients, 59.4% had complete renal recovery, 13.5% had partial renal recovery, and 27.2% had not recovered renal function. Septic patients had more severe AKI, and were more likely to receive RRT with lower frequency of renal function recovery. Lo et al. (2009) explored the long-term risk of progressive CKD after dialysis-requiring AKI in patients with normal or near normal initial kidney function. After controlling for potential confounders, dialysis-requiring AKI was independently associated with a 28-fold increase in the risk of developing stage 4 or 5 CKD over a 6-year follow-up and more than a twofold increased risk of death.

In a systematic review covering 47 studies between 1985 through October 2007, Coca et al. (2009) pointed out that reliable calculation of the relative risk for CKD and ESRD after AKI was unattainable, because of a lack of follow-up of appropriate controls without AKI. However, they confirmed that patients who develop AKI may have long-term adverse kidney outcomes even if they did not have kidney disease at the time of development of AKI. Bucaloiu et al. (2012) used a propensity score-matched cohort method to retrospectively evaluate the risks of death and *de novo* CKD after reversible, hospital-associated AKI among patients with normal pre-hospitalization kidney function. Of 30,207 discharged patients alive at 90 days, 1610 with reversible AKI that resolved within the 90 days were successfully matched across multiple parameters with 3652 control patients who had not experienced AKI The duration of AKI was 24 hours or less in 75% of patients, and between 2 and 4 days in 16.3%; only in 8.6% of patients did AKI fail to resolve within 4 days; only four subjects required RRT. The mean recovery of estimated GFR (eGFR) for patients in the AKI group was 98.5 ± 22 mL/min/1.73m^2. Despite the mild and completely reversible nature of the AKI, a significant risk of *de novo* CKD (hazard ratio 1.91) was calculated. When CKD developed, it occurred relatively early after hospital discharge. A first report by Wald et al. (2009) provides valuable insights into the complex complications faced by survivors of an episode of severe AKI requiring acute RRT. Using linked administrative health databases, these authors conducted a population-based cohort study of adult patients in Ontario, Canada, with AKI who required in-hospital dialysis and survived free of dialysis for at least 30 days after discharge. These individuals were matched with patients without AKI or dialysis during their index hospitalization. Matching was by age plus or minus 5 years, sex, history of CKD, receipt of mechanical ventilation during the index hospitalization, and a propensity score for developing AKI requiring dialysis. Although there was no difference in all-cause mortality between both groups the incidence rate of chronic dialysis was 2.63 per 100 person-years among individuals with AKI requiring dialysis, versus 0.91 per 100 person-years among control participants (adjusted hazard ratio (HR) 3.23). From the perspective of a clinician caring for an individual with severe AKI, these findings allow a quantitative estimate that even in the best of circumstances—meaning survival during hospitalization and recovery of kidney function sufficient to stop dialysis for a month—there is almost a 10% chance of requiring chronic dialysis in the next few years. As commented upon by Waikar and Winkelmayer (2009), the chronic dialysis incidence rate reported by Wald et al. (2009) is 72 times higher than that reported for the general population in the United States in 2006 (366 per 1 million person-years) (United States Renal Data System, 2008). This finding has important implications for the post-discharge care of patients who have been successfully treated with acute temporary dialysis: follow-up care with a nephrologist for secondary prevention is absolutely necessary. These numbers also highlight the magnitude of the problem of AKI as a cause of ESRD: extrapolating from the data of Wald et al. (2009), a rough estimate of the yearly incidence of ESRD due to AKI should be 0.3 per 100,000 population, which is approximately one-third of the incidence of ESRD secondary to, for example, cystic kidney disease. The true magnitude is even higher because this estimate does not consider the individuals who were excluded from the final cohort due to the need for dialysis during the 30 days following hospitalization. If only 30% of those individuals developed ESRD, then the yearly incidence would be 1.0 per 100,000, accounting for approximately 3% of the overall yearly incidence of ESRD in the United States.

A second and similar follow-up analysis, but this time focusing on AKI patients who did not require in-hospital dialysis, and who survived free of dialysis > 30 days after discharge, was recently published by the same group (Wald et al. 2012). The median follow up was 2 years. The incidence of chronic dialysis was 1.78 per 100 person-years among those with AKI and 0.74 per 100 person-years among unaffected controls (adjusted HR 2.70; 95% confidence interval (CI) 2.42–3.00). Rates also were higher for all-cause mortality (15.34 vs 14.51 per 100 person-years) and rehospitalization (44.93 vs 37.18 per 100 person-years). The absolute risk of death was more than eight times the rate of chronic dialysis. It appears thus that even when acute dialysis is not required, survivors of AKI remain at higher risk of receipt of chronic dialysis thereafter.

Amdur et al. (2009) used a Veterans Affairs database to ascertain long-term renal function in 113,272 patients. Of these, 44,377 had established CKD and were analysed separately. A cohort of 63,491 patients was hospitalized for acute myocardial infarction or pneumonia and were designated as controls. The remaining 5404 patients had diagnostic codes indicating AKI or ATN. Renal

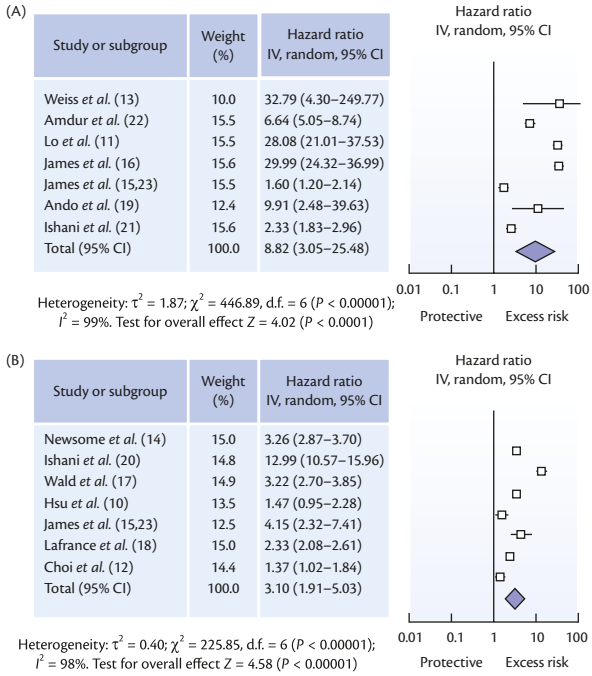

Fig. 238.1 Meta-analysis of chronic kidney disease (CKD) and end-stage renal disease (ESRD) associated with acute kidney injury (AKI). (A) Pooled adjusted hazard ratios (HRs) for CKD after AKI. (B) Pooled adjusted HRs for ESRD after AKI. Reproduced with permission from Coca, S. G., Singanamala, S., and Parikh, C. R. (2012). Chronic kidney disease after acute kidney injury: a systematic review and meta-analysis. *Kidney Int*, 81(5), 442–8.

function deteriorated over time in all groups, but with significantly greater severity in those who had AKI and ATN compared to controls. Patients with AKI, particularly with codes of ATN, were more likely than controls to enter stage 4 CKD, but this entry time was similar to that of patients who initially had CKD. These patients had a reduced survival time when compared to control patients. Some results, taken from a recent meta-analysis and systematic review on various cohorts of patients who survived AKI (Coca et al., 2012), are presented in Fig. 238.1. This meta-analysis strongly suggests that patients who survive AKI have a greater risk for CKD, and ESRD, compared with patients without AKI after adjustment for several important confounding variables. The relationship between AKI and CKD or ESRD was graded, with a greater risk associated with increasing severity of AKI.

The presence of decreased baseline GFR modified the relationship between AKI and both progressive CKD and ESRD. In the two studies in this meta-analysis (James et al. 2011; Lo et al., 2009) that reported the risk for CKD after AKI in both those with and without decreased baseline GFR, the relative risk for CKD was higher in patients without decreased baseline GFR (adjusted HR 38.8; 95% CI 21.9–68.7) than in those with decreased baseline GFR (adjusted HR 24.4, 95% CI 15.3–38.9). Similarly, in the three studies (Choi et al. 2010; Ishani et al., 2009; Wald et al., 2009) that reported the risk for ESRD in both those with and without decreased baseline GFR, the relative risk for ESRD was higher in those with AKI and without decreased baseline GFR (adjusted HR 9.1, 95% CI 4.1–20.3) compared with those with decreased baseline GFR (adjusted HR 1.9, 95% CI 1.6–20.3).

Two studies compared the association of AKI with either CKD (Choi et al., 2010) or ESRD (James et al., 2010b) in patients with varying degrees of underlying baseline proteinuria. Patients with AKI who had pre-existing proteinuria (and normal baseline GFR) had lower relative risk for CKD (defined as doubling of creatinine or ESRD) (HR 9.7) compared with patients without any proteinuria (HR 30.0; 95% CI 24.3–37) (James et al., 2010b). The modifying effect of pre-existing proteinuria was less robust for the outcome of ESRD alone (adjusted HR 3.7; 95% CI 2.4–5.7) with no proteinuria versus with proteinuria (adjusted HR 1.4, 95% CI 0.9–2.2) (Choi et al., 2010).

Patient outcomes and renal recovery in acute kidney injury superimposed on chronic kidney disease

In the analysis of studies on progression of AKI to CKD or ESRD, a distinction should be made between patients without CKD (eGFR ≥ 60 mL/min 1.73 m^2) when they develop AKI and patients who develop AKI on a background of pre-existing CKD.

As discussed in Chapter 220, it is widely accepted that pre-existing CKD increases the risk of developing AKI (Hou et al., 1983; Leblanc et al. 2005) and that this risk is proportional to the respective CKD stage (Hsu et al. 2008; Khosla et al. 2009; Lo et al., 2009; Ishani et al. 2011). On the other hand, any episode of AKI in a patient with underlying CKD inflicts additional damage on already compromised kidneys and thereby substantially increases the rate of transition to ESRD (Hsu et al., 2009; Ishani et al., 2009; Khosla et al., 2009). Progressive kidney disease is more likely after an episode of acute-on-chronic kidney injury than after simple AKI alone (Khosla et al., 2009). Ishani et al. (2009) assessed the difference in developing ESRD between elderly AKI individuals with and without pre-existing CKD. Out of a cohort of 233,803 patients with a mean age of ≥ 67 years on discharge, 3.1% survived to discharge with a diagnosis of AKI, and 5.3 per 1000 developed ESRD. Among patients who received treatment for ESRD, 25.2% had a previous history of AKI. The likelihood of initiating ESRD treatment among patients with AKI increased steadily after discharge (Fig. 238.2). Considering patients with AKI only (Fig. 238.2A), the likelihood of initiating ESRD treatment after AKI was 0.96% within 30 days, 2.69% within 180 days, 4.08% within 365 days, and 6.96% at the end of 2 years of follow-up. The corresponding likelihoods for patients without AKI were 0.04%, 0.14%, 0.25%, and 0.49%, respectively. Considering patients with both AKI and CKD (Fig. 238.2B), the likelihood of initiating ESRD treatment after AKI was 1.61% within 30 days, 4.76% within 180 days, 7.91% within 365 days, and 14.29% at the end of 2 years of follow-up. Triverio et al. (2009) described that out of 89 ICU patients followed up for 3 years after surviving an episode of dialysis-dependent AKI, CKD was present in 32 patients from the onset, and developed *de novo* in 25 patients. ESRD developed in nine patients (of whom eight had pre-existing CKD), and 29 patients died. At 3 years, survival was 67% overall; mortality was 50% for those with pre-existing kidney disease, 71% for those with new-onset CKD, and 82% in patients without CKD.

Lafrance et al. (2010) followed a cohort of CKD patients for a median time of 19.4 months after they achieved an eGFR value ≤ 30 mL/min/1.73 m^2. AKI was defined as a decrease in eGFR of ≥ 25% compared to a moving baseline eGFR within 25 days. Of the CKD patients, 44.9% had at least one AKI episode and 15.3% died before

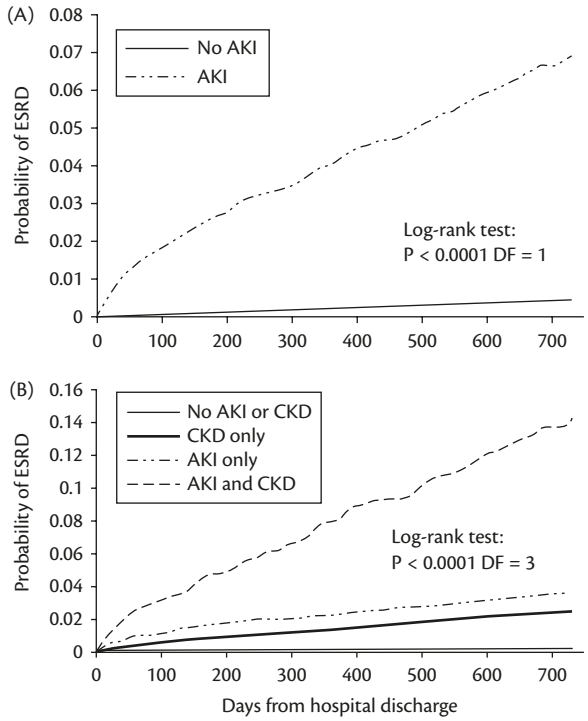

Fig. 238.2 Estimated probability of initiating treatment of ESRD, using the Kaplan–Meier method. (A) Curves by AKI status. (B) Curves by AKI and CKD status. DF = degrees of freedom.

Reproduced with permission from Ishani, A., Xue, J. L., Himmelfarb, J., *et al.* (2009). Acute kidney injury increases risk of ESRD among elderly. *J Am Soc Nephrol*, 20(1), 223–8.

dialysis and 18.1% initiated dialysis. AKI was associated with both a higher risk of death and an increased risk of dialysis. It is important to note that even transient increases in SCr levels of > 25 μmol/L (> 0. 28 mg/dL) were associated with increasing risk for both progression to dialysis and death. Hsu et al. (2009) tracked members of an integrated healthcare delivery system in northern California who had a pre-hospitalization eGFR < 45 mL/min/1.73 m^2. Superimposed AKI was defined as having both a peak inpatient SCr greater than the last outpatient SCr by ≥ 50% and receipt of acute dialysis. Overall, 26% of CKD patients who suffered superimposed AKI died during the index hospitalization. There was a high risk for developing ESRD within 30 days of hospital discharge that varied with pre-admission renal function, being 42% among hospital survivors with baseline eGFR 30–44 mL/min/1.73 m^2 and 63% among hospital survivors with baseline eGFR 15–29 mL/min/1.73 m^2. These patients had a 30% higher long-term risk for death or ESRD than patients who had CKD and did not experience superimposed AKI. An episode of superimposed dialysis-requiring AKI was thus associated with very high risk for non-recovery of renal function also in a community-based cohort of CKD patients. Wu et al. (2011) quantified the risk of postoperative AKI in patients who survived to hospital discharge after major surgery. CKD was defined as a baseline eGFR < 45 mL/min/1.73 m^2. Patients with AKI-on-CKD during hospitalization had significantly worse long-term survival over a median follow-up of 4.8 years compared to patients with AKI, but without CKD. Finally, Pannu et al. (2011) explored how the relationships between AKI and clinical outcomes vary with baseline kidney function. The latter was defined as mean eGFR based on outpatient SCr measurements within 6 months before the index hospitalization, and the diagnosis of AKI was based on consensus criteria. AKI occurred in 18.3% of the hospitalized cohort and the risk of AKI increased with decreasing eGFR, like it was found in earlier studies. In multivariable Cox models, AKI of any severity was associated with death during the index hospitalization across all levels of eGFR. The preponderance of evidence from epidemiologic studies thus supports the notion that even after adjustment for several important covariates, AKI is independently associated with an increased risk for both CKD and ESRD

Impact of acute kidney injury on progression rate of renal function: epidemiology of developing chronic kidney disease stages 1–4

The previously mentioned long-term follow-up study of Amdur et al. (2009) showed that patients who were hospitalized for acute myocardial infarction or pneumonia and suffered AKI, especially ATN, deteriorated renal function with significantly greater severity compared to control patients with the same diseases. The incidence rate of CKD (stage 4 or worse) is approximately 120 per 1000 person-years after non-dialysis-requiring AKI (Amdur et al., 2009) and 479 per 1000 person-years in those who required dialysis for AKI (Lo et al., 2009). Based on both studies (Amdur et al., 2009; Lo et al., 2009), these absolute incidence rates of developing CKD are commensurate with adjusted HRs of at least 4 for non-dialysis-requiring AKI and 28 for dialysis-requiring AKI (compared to no AKI, respectively).

Risk factors for developing chronic kidney disease or end-stage renal disease after acute kidney injury

Several risk factors for the subsequent development of CKD among survivors of AKI have been identified. Besides well-known risk factors for CKD, such as hypertension, older age, congestive heart failure, diabetes, and proteinuria, AKIN staging also predicts longitudinal CKD development. These characteristics allow the identification of at-risk AKI patients at the time of hospital discharge and may allow for the timely implementation of appropriate screening and surveillance (Chawla et al.,2011; Bucaloiu et al., 2012; Chawla et al., 2014).

Age at the occurrence of AKI

CKD patients who are older and have a higher burden of co-morbid illness when they develop AKI, have increased risk for non-recovery of renal function, chronic dialysis, and long-term mortality (Ali et al., 2007). These findings were confirmed in a study on the impact of CKD on AKI outcomes in critically ill patients (Khosla et al., 2009).

Other studies on the differences in renal recovery between the young and the old report, however, conflicting data. A meta-analysis including studies assessing renal recovery stratified patients based on age ≥ 65 or < 65 years. Overall, older age was associated with a greater chance of non-recovery of renal function back to baseline after AKI by the time of hospital discharge (Schmitt et al., 2008). These results are limited by significant heterogeneity. Schiffl and

Fischer came to different conclusions (Schiffl and Fischer, 2008). From a cohort of 425 ICU patients with AKI, 226 survivors who required RRT were followed for 5 years after hospital discharge. Of these, 57% had a complete recovery of renal function, 43% had a partial recovery, and none of the patients were dependent on RRT. Patients with complete or partial recovery did not differ significantly in mean age. However, the particularly good renal outcome in the elderly noted in this report may be partially explained by the fact that none of the included patients had pre-existing renal disease (Schiffl and Fischer, 2008). In the above mentioned analysis of Wald et al. (2009), the older group (> 65 years) had a higher risk of chronic dialysis. More importantly, it is evident from the Kaplan–Meier curves in this study that the risk of chronic dialysis and death persists for many years post-discharge.

Severity of AKI

An important risk factor for developing CKD/ESRD is the severity of the AKI episode; in elderly patients, the risk for ESRD after a single episode of AKI is elevated twofold in those with mild AKI (Newsome et al., 2008), and elevated by 3- to 13-fold in those with more severe AKI (Newsome et al., 2008; Ishani et al., 2009; Wald et al., 2009; James et al., 2010b). In patients undergoing cardiac catheterization, (James et al., 2010a), the rate of decline in eGFR was 1.0 mL/min/1.73 m^2 per year after mild AKI and 2.8 mL/min/1.73 m^2 per year after moderate or severe AKI (compared with 0.1 mL/min/1.73 m^2 per year in those without AKI). AKI was categorized by the magnitude of increase in SCr (mild (50–99% or ≥ 0.3 mg/dL (≥ 26.4 μmol/L)) and moderate or severe (≥ 100%)) within 7 days of coronary angiography. Compared to patients without AKI, the adjusted odds of a sustained decline in kidney function at 3 months following angiography increased more than fourfold for patients with mild to more than 17-fold for those with moderate or severe AKI. These rates were adjusted for age (along with proteinuria and co-morbidities).

Proteinuria

Besides the level of baseline renal function (see above), the degree of proteinuria (James et al., 2010b) also modifies the effects of the relationship between AKI and progressive CKD.

It is not surprising that a low serum albumin concentration is also a strong predictor of poor long-term renal outcome, since low albumin levels have been associated with poor outcomes in a variety of diseases, including ESRD (Friedman and Fadem, 2010). Hypoalbuminaemia can be due to either nutrition-related factors and/or high levels of inflammation, volume overload, or heart failure (Friedman and Fadem, 2010). Given that multiple studies have linked inflammation to AKI, it is likely that the predictive value of low concentrations of serum albumin to CKD progression is in fact a measure of increased inflammation (Murugan et al., 2010).

Diabetes mellitus

Thakar et al. (2011) examined the effects of AKI episodes during multiple hospitalizations on the risk of CKD in a cohort of patients with diabetes mellitus. The primary outcome was reaching stage 4 CKD (GFR of <30 mL/min per 1.73 m^2). AKI during hospitalization was defined as ≥ 0.3 mg/dL (≥ 26.4 μmol/L) or a 1.5-fold increase in SCr relative to admission. The effect of the first AKI episode and up to three episodes as time-dependent covariates, on the risk of stage 4 CKD was examined. In multivariable Cox proportional hazards models, any AKI versus no AKI was a risk factor for stage 4 CKD and each AKI episode doubled that risk. This study suggests thus that AKI episodes are associated with a cumulative risk for developing advanced CKD in diabetic patients, independent of other major risk factors of progression

That the progression of CKD like diabetic nephropathy does not always follow a linear course is nicely illustrated in a biopsy study by Kelly and Dominguez (2010). In 15 of the 22 biopsied patients, CKD was characterized by a succession of seemingly random episodes of usually self-limited AKI manifested by SCr surges and subsequent renal inflammation, which appear to accelerate progression and eventual kidney loss. Fig. 238.3, taken from this study (Kelly and Dominguez, 2010), illustrates that these seemingly random fluctuations in renal function could be visualized with straightforward connecting lines. These fluctuations could be easily masked by drawing best fit linearized plots with acceptable correlations. Only seven out of the 22 diabetic patients in whom a kidney biopsy was performed did not have detectable acute episodes of AKI, while the number of AKI episodes averaged 1.7 ± 0.4 for the entire group. Those seven without detectable AKI had slightly longer, but not significant, mean survival times than the 15 patients with AKI events: 56 ± 21 versus 45 ± 10 months. Indeed, only 25% of the entire group survived beyond 60 months.

Because the progression to CKD in AKI survivors typically occurs months after the initial AKI insult, therapeutic interventions to slow CKD progression are possibly effective also in patients who survive AKI and then progress to CKD, especially if an injury pathway that is common to CKD progression without AKI is responsible. If, however, a different pathway would be responsible, it would be useful to unravel the mechanisms and to seek specific preventive interventions in function of these.

The precise pathophysiological mechanisms of the impact of AKI on the genesis of *de novo* CKD and/or the progression of pre-existing CKD are unknown and some of the preclinical studies on this topic were recently summarized (Yang et al., 2011). A more detailed description of the molecular mechanisms involved in

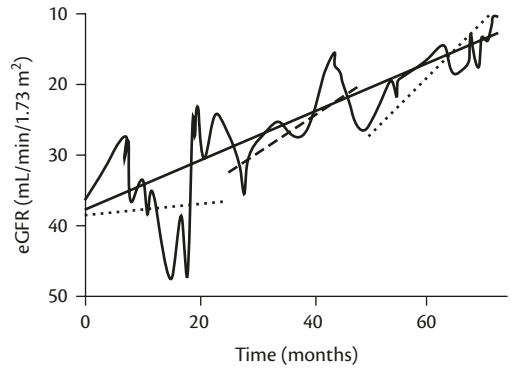

Fig. 238.3 AKI episodes and rate of decline in renal function. Serial eGFR determinations in one patient illustrate multiple episodes of AKI (solid line). These acute episodes can be obscured by best fit plots: the best fit overall slope (solid grey) is very different from that obtained in the first (dotted), second (longer dashes) or third (shorter dashes) 2-year follow-up periods.
Reproduced with permission from Kelly, K. J. and Dominguez, J. H. (2010). Rapid progression of diabetic nephropathy is linked to inflammation and episodes of acute renal failure. *Am J Nephrol*, 32(5), 469–75.

progression of AKI to CKD is given in Chapter 221. As pointed out by Levin and Stevens (2011) and Lameire et al. (2013) the evidence that even silent episodes of AKI may contribute to the development and/or progression of CKD may have considerable socioeconomic and public health consequences both in developed and emerging countries. In the latter countries, repeated episodes of AKI resulting from dehydration or infection could contribute to CKD development in susceptible individuals, because of low birth weight and poor nutrition (Jha and Chugh, 2008; Naicker et al., 2008). Furthermore, given the known association of ESRD and CKD with cardiovascular co-morbidity, it is unclear how much survival from dialysis-requiring AKI will increase also this burden in low-income countries as well as elsewhere.

Patients surviving an episode of AKI should thus not only be followed preferably by a nephrologist but should receive the same standard therapeutic management that is currently used to treat CKD patients, that is, blood pressure control, nephrotoxin avoidance, and nutritional intervention.

Based on a Veterans Affairs database the nephrology referral of patients surviving an episode of AKI and who had an eGFR < 60 mL/min/1.73 m^2 30 days after peak injury was recently investigated (Siew et al. 2011). The time to referral considering improvement in kidney function (eGFR > 60 mL/min/1.73m^2), dialysis initiation, and death as competing risks over a 12-month surveillance period was analysed. The prevalence of for AKI preadmission kidney dysfunction (baseline eGFR, < 60 mL/min/1.73 m^2) in this cohort was 60%. The overall mortality during the surveillance period was 22%. The cumulative incidence of nephrology referral was, however, only 8.5% and the severity of AKI did not affect referral rates. These data demonstrate that only a minority of at-risk survivors are referred for nephrology care after an episode of AKI. Determining how to best identify survivors of AKI who are at highest risk for complications and progression of CKD could facilitate early nephrology-based interventions.

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CHAPTER 239

Acute kidney injury in children

Alexander Fichtner and Franz Schaefer

Introduction

In recent years, acute kidney failure research has undergone a fundamental shift of paradigms. Ever since the introduction of the classic term 'acute renal failure' in 1951, renal impairment was primarily defined in the context of functional renal failure and the necessity of renal replacement therapy (RRT) (Smith, 1964). However, a growing body of evidence suggests that even small changes in kidney function profoundly impact morbidity and mortality both in adults and children (Zappetelli et al., 2009). Recently, the concept of 'acute kidney injury' (AKI) has been introduced to reflect novel insights regarding the underlying dynamic pathophysiological processes, shifting the focus from functional to structural kidney alterations (Goldstein and Chawla, 2010). This new conceptual framework, together with the increasing incidence of paediatric AKI due to challenging surgical procedures, intensive care, and invasive therapeutic interventions (Alexander, 2007) and the development of novel biomarkers to quantitate the risk of AKI early in the disease process, have led to a remarkable renaissance of AKI research in the paediatric arena.

Definition of acute kidney injury in children

As discussed in Chapter 220, a plethora of definitions of AKI has been used in the literature, but in 2004, a consensus committee suggested defining AKI in adults using a staging approach reflected in the acronym RIFLE (Risk, Injury, Failure, Loss, End-stage renal disease) (Bellomo et al., 2004). Alternative criteria were proposed by the Acute Kidney Injury Network (AKIN), taking into account the rate of decline by narrowing the timescale to 48 hours and integrating fixed serum creatinine (SCr) increases (> 0.3 mg/dL) (Mehta et al., 2007). Recently, a KDIGO guideline work group has proposed a harmonized AKI nomenclature (Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group, 2012). Moreover, the RIFLE staging system was subsequently adapted to paediatric needs, using estimated glomerular filtration rate (eGFR) values instead of SCr (Akcan-Arikan et al., 2007) (Table 239.1).

Several studies have assessed the prognostic value of these classification systems (in terms of length of hospital stay, costs, morbidity, and mortality) for paediatric patients (Alkandari et al., 2011). Similarly, as in adult studies, higher p(aediatric)RIFLE stages are associated with unfavourable outcomes (Hoste and Kellum, 2006; Plötz et al., 2008). The eGFR-based pRIFLE classification appears more sensitive in detecting mild functional impairment than the AKIN or KDIGO criteria (Zappitelli et al., 2008; Kavaz et al., 2012).

Since they are based on consecutive assessments of SCr, the RIFLE, AKIN, and KDIGO systems suffer from general disadvantages in AKI detection, particularly in children. Staging may be influenced by age and body composition, nutritional and fluid status, the integrity of muscle turnover, and by the use of diuretics. In neonates, SCr represents maternal values in the first few days of life, and levels depend on the degree of prematurity. The functional impairment follows renal tissue damage with considerable delay and calculation of eGFR formally requires steady-state conditions which are often not present in AKI. Also, absolute changes in SCr may be of limited use in the paediatric population where the SCr concentration is strongly age dependent. Also oligoanuria, the other constituent of the AKIN and pRIFLE classifications, is of limited sensitivity particularly in neonates, since up to 60% of neonatal AKI is non-oliguric (Karlowicz and Adelman, 1995).

Epidemiology of paediatric acute kidney injury

Most reported AKI incidence rates refer to AKI in hospitalized patients and vary markedly with respect to the populations investigated, the reporting area, and the AKI definition applied. The overall incidence of AKI appears to increase in developing and emerging countries. In a tertiary care centre in Thailand, the incidence of AKI increased ninefold since the period before 1995 (Vachvanichsanong et al., 2006).

In developed countries, the incidence of paediatric AKI, defined as *need for acute RRT*, is relatively stable and varies between 0.8 and 4 per 100,000 children aged < 15 years (Moghal et al., 1998; Ball and Kara, 2008). Among critically ill paediatric patients, the need for RRT is approximately 1–2% (Hui-Sickle et al., 2005).

Using the *pRIFLE criteria*, the incidence of AKI has been reported as 7% in emergency departments in the United States (Wiliams et al., 2002; Mian et al., 2011), and 4.5–10% in paediatric intensive care units (PICUs) (Bailey et al., 2007; Plötz, 2010). The risk of AKI increases sharply, up to 82%, in ventilated and vasopressor-dependent patients (Akcan-Arikan et al., 2007). Recent studies from Canada and Turkey in this population observed AKI incidences of 31–36% using RIFLE or AKIN criteria (Kavaz et al., 2012; Mammen et al., 2012).

In emerging countries, the incidence of AKI according to pRIFLE criteria in tertiary care centres is comparable to developed countries with incidences of 9% for non-critically ill and 36.1% for critically ill patients (Andreoli, 2004; Nasir et al., 2011). In rural areas, AKI is more commonly due to community-acquired disorders; two recent studies from Nigeria reported an overall AKI incidence of

Table 239.1 Definitions of acute kidney injury

	RIFLE creatinine criteria (Bellomo et al., 2004)		Paediatric RIFLE criteria (Akcan-Arikan et al., 2007)		KDIGO criteria (KDIGO Acute Kidney Injury Work Group, 2012) (modified AKIN criteria, Mehta et al., 2007)	
RIFLE/KDIGO	**Creatinine**	**Urine output**	**Estimated CCl**	**Urine output**	**Creatinine/eGFR[a]**	**Urine output**
Risk/Stage 1	SCr ≥ 1.5-fold or decrease of GFR ≥ 25%	< 0.5 mL/kg × h for 6 hours	Decrease of eGFR by 25%	< 0.5 mL/kg × hours for 8 hours	SCr increase ≥ 0.3 mg/dL within 48 hours or to 150–190% of baseline *within the prior 7 days (known or presumed)*	< 0.5 mL/kg × hours for 6–12 hours
Injury/Stage 2	SCr ≥ 2-fold or decrease of GFR ≥ 50%	< 0.5 mL/kg × hours for 12 hours	Decrease of eGFR by 50%	< 0.5 mL/kg × hours for 16 hours	SCr increase to 200–290% of baseline	< 0.5 mL/kg × hours for ≥ 12 hours
Failure/Stage 3	SCr ≥ 3-fold or SCr ≥ 4 mg/dL	< 0.3 mL/kg × hours for 24 hours or anuria for 12 hours	Decrease of estimated CCl by 75% or eGFR < 35 mL/min × 1.73m^2	< 0.3 mL/kg × hours for 24 hours or anuria for 12 hours	SCr increase to ≥ 300% of baseline or ≥ 4 mg/dL *(in patients below age of 18 years, eGFR ≤ 35 mL/min/1.73m^2) or initiation of renal replacement therapy*	< 0.3 mL/kg × hours for ≥ 24 hours or anuria for ≥ 12 hours
Loss	Persistent failure >4 weeks			Persistent failure >4 weeks		
End stage	Persistent failure >3 months			Persistent failure >3 months		

In italics = modifications from AKIN criteria; [a] estimated GFR = 0.413 × height [m]/SCr [mg/dL].

CCL = creatinine clearance; eGFR = estimated glomerular filtration rate; SCr = serum creatinine

1.7–3.1% of hospital admissions, with 80% of cases being community acquired (Esezobor et al., 2012; Olowu et al., 2012).

Aetiologies of paediatric acute kidney injury

The aetiology of AKI is conventionally stratified into pre-, intra- and postrenal causes and subclassified according to urine output (Table 239.2). Alternatively, AKI may be classified by intrinsic renal injury versus secondary renal impairment due to systemic diseases or interventions. The aetiological spectrum of paediatric AKI has changed markedly during the past few decades. In developed countries, the incidence of secondary AKI, that is, due to surgical interventions, stem cell or solid organ transplantation, drug toxicity, and sepsis increases, whereas primary renal disorders (i.e. haemolytic uraemic syndrome (HUS), glomerulonephritis) remain stable and prerenal causes have decreased. By contrast, the predominance of infectious diseases (i.e. gastroenteritis, malaria) and primary renal diseases persists in the developing world, especially in rural areas (Table 239.3).

In the following sections, we will discuss specific aspects of important aetiologies of AKI in children.

Neonatal AKI

The neonatal period is characterized by a unique combination of risk factors for AKI, including the postnatal haemodynamic changes, increased insensible fluid losses, a physiologically small fraction of cardiac output utilized for renal perfusion (fetus 2–4%; first week of life 10%; adult 20%), and a diminished capability to compensate fluid losses. The risk of volume depletion is further aggravated by the limited urine concentrating capacity of the neonatal kidney (maximum neonate: < 700 mOsm; at 1 year: 1300 mOsm). The GFR is physiologically low (mean first 3 days of life: preterm neonates 14 mL/min/1.73 m^2, term neonates 21 mL/min/1.73 m^2) and gradually increases during the first few weeks and months of life. Furthermore, SCr is an insensitive marker of AKI in the first days of life since it may still represent maternal values. In addition, AKI in neonates is often non-oliguric (up to 60%) but oliguric AKI is associated with a significant increased mortality (Karlowicz and Adelman, 1995; Agras et al., 2004).

Diagnosing AKI in this highly dynamic period is a challenging task. In remarkable anticipation and analogy of the current adult AKI definition, Gouyon and Guignard suggested early on to define any SCr > 1.5 mg/dL (133 µmol/L) for the first few days of life, and any increase by > 0.3 mg/dL (> 26.5 µmol/L) per day thereafter as the cut-off to define neonatal AKI (Gouyon and Guignard, 2000).

The diagnostic dilemmas regarding neonatal AKI have generated immense interest in applying novel biomarkers of imminent or manifest kidney injury (see below). A recent study reported significantly elevated cystatin C and reduced uromodulin and epithelial growth factor urine concentrations in neonates with AKI (Askenazi et al., 2012).

The incidence of AKI in neonates varies between 8% and 31% of all admissions to neonatal ICUs (Agras et al., 2004; Andreoli, 2009). In a survey of > 66,000 preterm neonates, SCr increased to > 1.3 mg/dL (115 µmol/L) in 15% and to > 2 mg/dL (177 µmol/L) in 2.5% (Walker et al., 2011). The mortality risk of infants with very low birth weight increases 2.4-fold when an increase of SCr by > 1 mg/dL (88.4 µmol/L) occurs (Askenazi et al., 2009; Koralkar et al., 2011).

The most common cause of AKI in neonates is perinatal asphyxia. The AKI incidence in these children ranges between 30% and 61%, depending on the AKI criteria used and the severity of the asphyxia (Chevalier et al., 1984; Aggarwal et al., 2005). Using the AKIN criteria, a retrospective study reported a 9.1% AKI incidence

Table 239.2 Major aetiologies of AKI in children

	Neonates	Paediatric patients
Prerenal	Decreased intravascular volume (insensible losses, haemorrhage—e.g. placental rupture) Circulatory failure Peripheral vasodilatation (sepsis) Pharmacologic agents	Decreased intravascular volume (gastroenteritis, haemorrhage, burns) Peripheral vasodilatation (sepsis)
Intrinsic renal	Severe hypoxic/ischaemic insult (e.g. perinatal asphyxia) Malformations: ◆ Bilateral renal hypo/dysplasia ◆ Polycystic kidney disease Vascular lesions: ◆ Renal vein thrombosis ◆ Renal artery thrombosis Drug related (incl. *in utero* exposure)	Severe hypoxic/ischaemic insult Drug related Toxin mediated: ◆ Endogenous: haemoglobin, myoglobin, urate, oxalate, tumour lysis syndrome, cytokines (sepsis) ◆ Exogenous: biological poisons, diethylene glycol, methanol, heavy metals, etc. Interstitial nephritis (drugs, idiopathic) Infections: ◆ Viral (Hanta) ◆ Pyelonephritis (bilateral or single kidney) Glomerulonephritis: ◆ Post streptococcal GN ◆ Henoch–Schönlein/IgA GN ◆ RPGN Vascular lesions ◆ Microangiopathies (incl. HUS) ◆ Renal vein thrombosis ◆ Renal artery thrombosis ◆ Hepatorenal syndrome
Post-renal	Urethral obstruction Obstruction in a solitary kidney Bilateral ureteral obstruction Bilateral ureterocoele Neurogenic bladder Extrinsic compression	Urethral obstruction Neurogenic bladder Extrinsic compression

GN = glomerulonephritis; HUS = haemolytic uraemic syndrome; RPGN = rapidly progressive glomerulonephritis.

for mild and a 56% incidence for severe forms of asphyxia (Kaur et al., 2011). Further common causes of neonatal AKI are the use of nephrotoxic drugs (cyclooxygenase inhibitors for therapy of persistent ductus arteriosus, antibiotics) and neonatal septicaemia. Also, the incidence of renal vein thrombosis is highest in this age group (2.2 per 100,000 live births).

Haemolytic uraemic syndrome in children

HUS secondary to Shiga-toxin producing *Escherichia coli* (STEC-HUS), characterized by microangiopathic haemolytic anaemia, thrombocytopenia, and AKI is the most important cause of AKI worldwide in children beyond the neonatal period and most commonly affects children at pre-school age. HUS typically accounts for 15–20% of paediatric AKI cases in developed and up to 35% in developing countries (Bailey et al., 2007; Van Biljon, 2008), with substantial regional, seasonal, and year-to-year variability. HUS is particularly common in Latin American countries; the annual incidence of HUS in Argentina is around 1 per 10,000 children aged < 5 years (Rivas et al., 2006).

Ingestion of STEC with contaminated meat, dairy products, or water causes severe haemorrhagic enterocolitis. Approximately 5–7 days after the start of gastrointestinal symptoms, 5–15% of children with STEC enterocolitis develop signs and symptoms of HUS. The key pathophysiological mechanism involves dissemination of bacterial Shiga toxin to the renal microvasculature, where it leads to swelling and apoptosis of endothelial cells. Consecutive local activation of platelets, leucocytes, and the complement and coagulation systems causes formation of occlusive thrombi in the renal arterioles and glomerular capillaries. Local platelet consumption and mechanic haemolysis lead to thrombocytopenia and severe anaemia (Bauwens et al., 2011). Between 40% and 70% of children with HUS-related AKI become oligoanuric and require RRT for an average of 7–10 days (Grisaru et al., 2011). Thrombotic microangiopathy may also occur outside the kidneys, for example, in the central nervous system (seizures, coma; 10% of patients), the myocardium (myocardial infarction; 3%), or pancreatitis.

Despite the often severe acute morbidity, the prognosis of STEC-HUS is generally favourable. More than 95% of children

Table 239.3 Distribution of main AKI causes in published paediatric cohorts

	Date (region) Reference	Cohort (patients with AKI)	AKI cause
Developed countries	1978–1998 (Virginia) Williams et al., 2002	All hospitalized patients (N = 228)	1978–1988: HUS: 38% 1988–1998: HUS: 22% Sepsis: 18% (overall) Cardiac surgery: 16% (overall) Oncology: 14% (overall)
	1999–2001 (Texas) Hui-Stickle et al., 2005	All hospitalized patients (N = 248)	HUS: 1% Sepsis: 11% Ischaemic: 21% Nephrotoxic drugs: 16% Primary renal: 7%
	2000–2001 (Canada) Bailey et al., 2007	Paediatric ICU patients (N = 44)	HUS: 18% Sepsis: 9% Cardiac surgery: 11% Oncologic: 18% Chronic renal failure: 7%
	2001–2006 (New Zealand) Ball and Kara, 2008	Paediatric ICU patients (N = 226)	HUS: 17% Sepsis: 13% Cardiac surgery: 58% Glomerulonephritis: 4%
	1994–1998 (Turkey) Bircan et al., 2000	All hospitalized patients (N = 106)	HUS: 2% ATN: 16% Glomerulonephritis: 49% Urinary tract obstruction: 20%
	2006–2007 (Turkey) Duzova et al., 2010	All hospitalized patients (N = 472)	Sepsis: 18% Ischaemic: 28% Drug: 6.5% Gastroenteritis: 8% Glomerulonephritis: 11% Urinary tract obstruction: 2%
Developing countries (rural areas)	1982–1999 (Morocco) Bourquia et al., 2002	All hospitalized patients (N = 120)	HUS: 15% Interstitial nephritis: 8% Glomerulonephritis: 51% Urinary tract obstruction: 6%
	1985–2003 (Nigeria) Anochie and Eke, 2005	All hospitalized patients (N = 211)	HUS: 3% Sepsis: 15% Gastroenteritis: 29% Malaria: 14% Glomerulonephritis: 14%
	2010–2012 (Nigeria) Esezobor et al., 2012	All hospitalized patients (N = 70)	HUS: 6% Sepsis: 25% Malaria: 11% Glomerulonephritis: 16%
	2005–2008 (India) Shah et al., 2011	All hospitalized patients (N = 180)	HUS: 2.8% Sepsis: 7.7% ATN: 42% Gastroenteritis: 18% Glomerulonephritis: 21.7%
	2010–2011 (Southern India) Krishnamurthy et al., 2013	All hospitalized patients	HUS: 4% Infections: 55% Glomerulonephritis: 17%

ATN = acute tubular necrosis; HUS = haemolytic uraemic syndrome; ICU = intensive care unit.

survive, and full functional renal recovery is observed in 80% of children. The disease does not recur, presumably due to the development of immunity.

Approximately 5–10% of HUS cases are not related to STEC infection. These atypical (aHUS) cases are mostly due to genetic or autoantibody-mediated functional alterations of the complement regulatory system leading to complement hyperactivation (Noris et al., 2012). Other causes of aHUS include hereditary abnormalities in the coenzyme Q pathway or cobalamin metabolism (Loirat and Frémeaux-Bacchi, 2011; Micheletti et al., 2011). Cases of aHUS are usually characterized by a less acute onset and/or incomplete biochemical and haematological manifestation. However, the long-term prognosis of aHUS is poor, with two-thirds of affected patients progressing to end-stage renal disease or having a fatal outcome within 1 year of the first disease manifestation (Noris and Remuzzi, 2009).

In the management of AKI in STEC-HUS, an initial fluid bolus should be administered to rule out a prerenal component related to excessive diarrhoea-related fluid losses. If unsuccessful, dialysis should swiftly be instituted to prevent fluid overload, uraemia, and hyperkalaemic episodes. The risk for the latter is particularly high in this form of AKI associated with severe haemolysis.

Antibiotic treatment aimed at eradicating STEC has not proven successful (Safdar et al., 2002) and may even be harmful (Wong et al., 2012) by stimulating Shiga toxin release. Shiga toxin-neutralizing monoclonal antibodies are currently being tested in paediatric clinical trials. The treatment and outcome of aHUS related to complement hyperactivation has recently changed profoundly by the advent of the monoclonal C5b antibody, eculizumab. Whereas the traditional approach to perform plasma exchange to eliminate mutant complement proteins and antibodies and supplement normal complement factors was of limited efficacy, complete and persistent disease remission is achieved by timely administration of eculizumab (Lapeyraque et al., 2011).

Bone marrow transplantation

Patients receiving bone marrow or stem cell transplantation are at increased risk of AKI due to the use of nephrotoxic medications, high risk of sepsis, tumour lysis syndrome, and veno-occlusive disease/hepatorenal syndrome. Furthermore, they are highly susceptible to fluid overload. The fraction of children developing AKI after bone marrow transplantation ranged between 27% and 42% in different studies (Özçakar et al., 2009; Ileri et al., 2010). Up to 50% of bone marrow transplant and 5–10% of stem cell transplant recipients reportedly require RRT (Patzer et al., 2003; Detaille et al., 2007).

Diagnosis of paediatric acute kidney injury

Clinical features

The major challenges to promptly diagnosing AKI across the paediatric age range are the lack of specific clinical signs indicating an initial renal insult, the low sensitivity of SCr as the leading diagnostic marker, and the enormous heterogeneity of the underlying causes. Hence, AKI is often first suspected based on characteristic extrarenal features of disorders commonly leading to AKI (e.g. bloody diarrhoea, a history of pharyngitis, haemoptysis, skin symptoms, etc.), or due to the presence of known risk factors for the development of AKI. (See Table 239.4.)

Table 239.4 Overview of major risk factors for paediatric AKI

Neonates	Paediatric patients
Low Apgar score	
Very low birth weight (<1500 g)	
Asphyxia	Hypoxia
Sepsis	Sepsis/infections/multiorgan failure
Persisting ductus arteriosus (incl. therapy with NSAID)	
Maternal NSAID/antibiotics/RAS antagonist intake during pregnancy	Nephrotoxic medication
Respiratory distress syndrome	Chronic kidney disease
Vascular catheterization	
Intubation	Invasive ventilation
Ionotropic support	Vasoactive medication
Phototherapy	
Cardiac surgery	Cardiac surgery

NSAID = non-steroidal anti-inflammatory drug; RAS = renin–angiotensin system.

Investigations

The initial diagnostic approach involves screening for AKI risk factors and close monitoring of SCr and urine output, the two diagnostic components of AKI (Table 239.5).

Once the diagnosis of AKI is made, sonography of the urinary tract is a rapid and non-invasive technique to make an initial assessment of the major underlying aetiology, that is, pre-, intra-, and postrenal causes of the disorder. Whereas bilateral hydronephrosis is suggestive of postrenal AKI, hyperechogenic and enlarged kidneys with poor corticomedullary differentiation indicate an intrinsic renal process. Doppler colour sonography readily reveals perfusion impairments such as in venous or arterial thrombosis, frequent causes of AKI in neonates.

The differentiation between intrinsic bona fide AKI/acute tubular necrosis (ATN) and fluid-dependent prerenal azotaemia may be more challenging. A classical biochemical marker to differentiate the aetiology of AKI is the fractional excretion of sodium, which differs in prerenal AKI (FE_{Na} < 1%) and intrinsic renal injuries (FE_{Na} 2–3%) (Espinel, 1976). However, FE_{Na} is of limited value in preterms and newborns due to their immature tubular function, in patients with primary tubular disorders, in nephrotic syndrome, and in liver cirrhosis. Also, FE_{Na} is markedly affected by diuretic treatment. The fractional excretion of urea has been suggested to be more sensitive and specific (Carvounis et al., 2002). An FE_{urea} < 35–40% reflects a prerenal hypovolaemic state whereas values >50% indicate ATN. Studies in adults showed variable diagnostic sensitivity and specificity of FE_{urea} in differentiating prerenal from intrarenal AKI (Carvounis et al., 2002; Pépin et al., 2007; Darmon et al., 2011). The largest paediatric study noted 68% sensitivity and 87% specificity for a FE_{urea} cut-off of 35%, outperforming FE_{Na} (Fahimi et al., 2009). In neonates, FE_{urea} seems to have no advantage over FE_{Na} (Jungthirapanich et al., 2010).

Additional auxiliary tools to assess fluid status in children include echocardiography, bioelectrical impedance, ultrasound of

Table 239.5 Suggested basic investigations in paediatric AKI

Suspected aetiology	Screening investigations	Additional investigations
Acute nephritis	Renal/urinary tract ultrasound incl. Doppler studies Urine sediment (+ culture) Protein:creatinine ratio Creatinine, urea, electrolytes, BGA, liver enzymes, albumin, full blood count, coagulation screening	Anti-streptolysin O and anti-DNAse B titre Complement status (CH50, APH50, C3, C3d, C4, C3 nephritic factor) IgA ANA, ds-DNA, anti-GBM, ANCA, ENA, anti-cardiolipin antibodies
Infections	CRP	Microscopy/culture/PCR/serology: *Puumala* (Hantaan); Hep B, C; HIV Pneumococcus, meningococcus Malaria Leptospirosis
HUS	Blood film, schistocytes, LDH, Haptoglobin	Shiga toxin-PCR, STEC stool culture, STEC O157 IgG/IgM antibodies Complement status Factor H, I serum levels ADAMTS13 activity Factor H autoantibodies Gene screening: CFH, CFI, MCP, C3, CFB, thrombomodulin
Rhabdomyolysis	CK, urine myoglobin	
Tumour lysis	Uric acid	
'Acute on chronic'	PTH, bone X-ray	

ANCA = antineutrophil cytoplasmic antibody; CK = creatine kinase; CRP = C-reactive protein; ENA = extractable nuclear antigen; GBM = glomerular basement membrane; LDH = lactate dehydrogenase; PTH = parathyroid hormone; STEc = Shiga toxin-producing *Escherichia coli*.

the vena cava, and real-time near-infrared spectroscopy (Hanson et al., 2009).

Biomarkers

The rise of SCr in AKI occurs at a time when renal injury is already established, limiting the efficacy of protective measures to preserve kidney function. Hence, intense research efforts have been made in recent years to identify early markers of renal injury which may improve the differential diagnosis of underlying causes, allow monitoring of responses to interventions and predict outcomes of AKI. A rapidly growing number of candidate biomarkers of imminent AKI is currently being generated by the advent of high-throughput screening technologies and their application in animal models. So far, a few of these candidates have shown usefulness in clinical studies (see also Chapter 223). Most of the compounds identified indicate cellular damage (usually tubular cell injury), but do not reflect early changes in glomerular or tubular function. Also, it should be emphasized that clinical validation studies have most commonly been performed in single centres in the post-cardiac surgery setting, where the renal insult occurs at a distinct time point and the investigated patient cohort is relatively homogeneous. When biomarkers were tested as screening tools or outcome predictors in unselected critically ill patients admitted to ICUs or emergency departments, performance results were generally less impressive. Another potential limitation of AKI biomarker research is the fact that candidate compounds are usually evaluated against a creatinine-based 'gold standard', with all the limitations listed above. Finally, the common practice of receiver operating characteristic (ROC)-area under the curve (AUC)-based comparisons of prognostic models including or excluding the biomarker of interest has been questioned on methodological grounds.

Here we will discuss AKI biomarkers which have been firmly established in clinical studies including paediatric populations.

Cystatin C

Serum cystatin C is an alternative to SCr to determine GFR. The 13 kDa protein, constantly produced by nucleated cells, is freely filtered and completely reabsorbed by tubular epithelial cells in healthy state. Serum cystatin C concentrations are apparently independent of body mass, gender, infections, and malignancies, but confounding has been reported for thyroid diseases, spina bifida, diabetic ketoacidosis, and generalized inflammation (Zaffanello et al., 2007; Cruz et al., 2011). Serum cystatin C levels are much less age dependent than those of SCr. Concentrations are higher in preterm than at-term infants and decline during the first month of life. The normal range of adults is attained soon after the first year of life. Serum cystatin C is an excellent predictor of AKI (Herget-Rosenthal et al., 2004; Zhang et al., 2011), with a maximum predictive value (AUC-ROC 0.96) when measured 10–12 hours after the initial renal insult. In children and adults undergoing cardiac surgery, serum cystatin C levels rise 36 hours earlier than those of SCr (Krawczeski et al., 2010). In neonates, serum cystatin C has the particular advantage of being independent of maternal values, unlike SCr (Cataldi et al., 1999).

Urinary cystatin C levels are generally less useful in predicting AKI than serum levels (AUC-ROC 0.64) (Koyner et al., 2008; Zhang et al., 2011); however, in neonates, where serial blood sampling is challenging, urinary cystatin C has also shown promise as a predictor of AKI (AUC-ROC 0.82) (Askenazi et al., 2012).

Neutrophil gelatinase-associated lipocalin

Neutrophil gelatinase-associated lipocalin (NGAL) is a 25 kDa iron-binding protein expressed in the loop of Henle and distal tubule. It is freely filtered by the glomerulus and almost completely reabsorbed at the proximal tubule, thus increased urinary excretion suggests proximal tubule damage (Mishra et al., 2003; Supavekin et al., 2003). The marker can be measured in serum/plasma (pNGAL) and

urine (uNGAL). In a seminal study in 71 children undergoing cardiac surgery, uNGAL sampled 2 hours post intervention predicted AKI with excellent accuracy (ROC-AUC 0.97) (Mishra, 2005). Moreover, uNGAL closely predicted the length of stay, need for RRT and mortality. Subsequent studies in paediatric and adult post-cardiac surgery patients principally confirmed the usefulness of uNGAL in predicting AKI, albeit with substantially lower discriminative power (AUC-ROC 0.71 in children, 0.67 in adults) (Parikh et al., 2011a, 2011b). Although NGAL levels tend to be confounded by septic conditions (Bagshaw et al., 2010), uNGAL displayed solid AKI predictive power across heterogeneous cohorts of critically ill children (ROC-AUC 0.78) (Zappitelli et al., 2007). Notably, pNGAL appears to predict AKI in adults but not in children (Parikh et al., 2011a).

Urinary interleukin 18

Interleukin-18 (IL-18) is a proinflammatory cytokine expressed by proximal tubular epithelial cells after an ischaemic insult and activated by the apoptotic pathway enzyme caspase-1 (Edelstein et al., 1999; Melnikov et al., 2001). In paediatric cardiac surgery patients, IL-18 exhibited good predictive value comparable to uNGAL (Krawczeski et al., 2011; Parikh et al., 2011b). IL-18 may also prove useful in predicting AKI in neonates (AUC-ROC 0.72) (Li et al., 2012). However, IL-18 is confounded by sepsis and is probably more useful in predicting the severity of emerging AKI than the occurrence of AKI per se (Washburn et al., 2008).

Urinary kidney injury molecule 1 and liver-type fatty acid binding protein

Kidney injury molecule 1 (KIM-1) is a 104 kDa transmembrane glycoprotein abundantly expressed in the proximal tubules after ischaemic or toxic AKI (Ichimura et al., 1998). A single study in children after cardiac surgery showed a high predictive power (ROC-AUC 0.83) of urinary KIM-1 measured 12 hours postoperatively for subsequent AKI development (Han et al., 2008). Studies in adults have suggested that KIM-1 levels may rise as early as 2 hours after the insult, and noted an independent association with death or need of dialysis (Liangos et al., 2007).

Liver-type fatty acid binding protein (L-FABP) is a 14 kDa protein synthesized in the liver, which localizes to proximal tubule cells (Kamijo-Ikemori et al., 2006). Urinary L-FABP 4 hours after cardiac surgery predicted AKI in paediatric patients (ROC-AUC 0.81) (Portilla et al., 2008). Like NGAL and IL-18, L-FABP appears to rise independently of AKI in septic shock (Nakamura et al., 2009).

Other promising AKI biomarkers awaiting further clinical validation in the paediatric age group include urinary nitrate (Mian et al., 2011), aprotinin (Nguyen et al., 2008), netrin 1 (Ramesh et al., 2010), interleukin 6 (Dennen et al., 2010), as well as metabolomic approaches (Beger et al., 2008).

In summary, the recent progress in AKI biomarker research holds promise that panels of indicative biomarkers, in conjunction with clinical indicators or risk stratification scores, will soon be available to accurately predict an individual child's risk of developing AKI. Yet, currently none of the novel biomarkers, alone or in combination, have found unequivocal acceptance in clinical practice for any cause of AKI. Given the significant assay costs of most candidate biomarkers, their superiority over SCr will need to be established carefully in various clinical settings to justify the one to two orders of magnitude higher cost per measurement. Once these hurdles are overcome, a subsequent, even more challenging step towards providing therapeutic benefit from biomarker research will be to develop early intervention protocols that will effectively prevent or mitigate AKI in high-risk patients (Kaplan and Wong, 2010).

Prevention of paediatric acute kidney injury

Current strategies to prevent or treat AKI are mainly based on supportive care and avoidance or removal of extrarenal risk factors. There are three principal approaches to 'renoprotective' intervention: maintenance of renal perfusion and oxygenation, avoidance of further nephrotoxicity, and treatment of the underlying cause and/or renal process. Novel preventive therapeutic approaches for AKI are under investigation and some strategies have shown promising results in animal models; however, these results could only in part be reproduced in human studies.

Loop diuretics

Numerous studies testing the use of furosemide to prevent or treat AKI in adults did not demonstrate any effect on the incidence and duration of AKI, mortality, or the requirement for RRT (Ho and Sheridan, 2006; Ho and Power, 2010). Moreover, furosemide was clearly ototoxic when administered at high doses. A recent post hoc analysis of the FACT trial, which originally evaluated a conservative versus a liberal fluid management in adult patients with acute lung injury, showed a benefit of furosemide use with respect to 2-month survival. The association was lost when adjusting for fluid balance, suggesting that the protective effect of furosemide was related to the optimization of fluid control (Grams et al., 2011). Paediatric studies showed no clear benefit of furosemide in preventing AKI in children with bone marrow transplants (Michael et al., 2004).

Theophylline

Theophylline, a xanthine derivative with non-specific adenosine receptor antagonistic properties, was shown experimentally to reverse renal vasoconstriction during hypoxic episodes in rabbits (Gouyon and Guignard, 1988). To date, theophylline is the only pharmacological compound with a clearly established preventive action in human AKI, first demonstrated in randomized clinical studies in neonates. In four independent trials in neonates with severe perinatal asphyxia, a single low-dose theophylline bolus (5–8 mg/kg) administered within the first hour of life led to a significantly greater estimated creatinine clearance (22 vs 6.5 mL/min/1.73 m^2), increased urine output, and reduced tubular damage on days 2 and 3 of life (Jenik et al., 2000; Bakr, 2005; Bhat et al., 2006; Eslami et al., 2009). Comparable results were reported for preterm neonates receiving theophylline for respiratory distress syndrome (1 mg/kg/day for 3 consecutive days) (Cattarelli et al., 2006). The KDIGO guidelines on AKI did not recommend theophylline in the prevention of contrast-induced AKI (CI-AKI) in adult patients (Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group, 2012), but a recent meta-analysis found that theophylline significantly reduced the incidence of CI-AKI and had a modest improvement on kidney function after contrast exposure in the adult general population. However, beneficial effects of theophylline were not observed in patients with high baseline creatinine values (> SCr1.5 mg/dL (133 μmol/L)) (Dai et al., 2012).

Dopamine

Dopamine binds to peripheral dopamine (D_1/D_2), alpha- and beta-adrenergic receptors. D_1 receptors are expressed in the renal

vasculature and tubular epithelia, and D_2 receptors in the glomerulus, renal nerves, and renal vascular endothelium. Dopamine at low dosage dilates the interlobular arteries and glomerular arterioles in rats, whereas higher doses reduce renal blood flow via alpha-adrenergic effects (Steinhausen et al., 1986). Likewise, low-dose dopamine (0.5–3 micrograms/kg/min) increased renal blood flow and GFR in healthy humans (Hoogenberg et al., 1998). These effects gave rise to the concept that prophylactic dopamine infusion might exert renoprotective actions in patients at risk for AKI. Unfortunately, despite increased urine output and a transient increase in GFR, no benefit with regards to AKI incidence and duration, need for RRT, or patient survival was observed in randomized clinical trials (Friedrich et al., 2005); dopamine even adversely affected clinical outcomes by causing arrhythmia, increasing myocardial oxygen demand, and compromising renal blood blow in elderly patients. In sick preterm neonates, dopamine (6 micrograms/kg/min) increases renal blood flow and urine output (Seri et al., 1998); however, in neonates under indomethacin therapy for symptomatic patent ductus arteriosus, dopamine reduces neither mortality nor the incidence of renal failure (Barrington and Brion, 2002).

Fenoldopam

Fenoldopam (a selective dopamine D_1 receptor and moderate α_2-adrenoreceptor agonist) dose-dependently increases renal blood flow and decreases systemic blood pressure in dogs (Hahn et al., 1982). Measurements in hypertensive patients confirmed these effects (Carey et al., 1984). Further studies in adults and children yielded mixed results: fenoldopam clearly reduces the risk of CI-AKI (odds ratio 0.41) in adults, but has no impact on RRT, survival, and length of ICU or hospital stay (Zangrillo et al., 2012). Consequently, fenoldopam has not been recommended by KDIGO as a preventive agent in adult AKI patients.

In critically ill children, fenoldopam increased urinary output (Moffett et al., 2008). The drug may exert dose-dependent nephroprotective efficacy in children at risk of AKI: whereas low-dose fenoldopam (0.1 micrograms/kg/min) had no impact on AKI incidence, urine output, and length of ICU stay in neonates undergoing cardiac surgery (Ricci et al., 2008), placebo-controlled administration of high-dose fenoldopam (1 micrograms/kg/min) in young infants undergoing surgery with cardiopulmonary bypass attenuated urinary cystatin C and uNGAL in the early postoperative period and reduced the risk of postoperative AKI by 62% (Ricci et al., 2011).

Management of paediatric acute kidney injury

Fluid management

The initial management of AKI traditionally involves a fluid bolus (10–20 mL/kg of crystalloid solution) to test for fluid responsiveness in case of prerenal AKI. The liberal, repetitive use of this strategy has recently been challenged by the insight that fluid overload is one of the major independent risk factors for morbidity and mortality of AKI, as demonstrated in several retrospective and prospective observational studies in children with AKI either with (Goldstein et al., 2001; Foland et al., 2004; Sutherland et al., 2010) or without RRT (Arikan et al., 2012; Askenazi et al., 2013b). The critical degree of initial fluid overload associated with increased mortality appeared to be an increase in body weight by 10–15%. Of note, a recent large-scale randomized clinical trial of fluid bolus treatment in African children with severe dehydration due to infections revealed a 45% increase in mortality associated with the use of aggressive (20–45 mL/kg) saline or albumin fluid boluses (Maitland et al., 2011).

At the current state of evidence, it appears appropriate to provide 10–20 mL/kg fluid boluses to children with suspected dehydration, the latter based, whenever available, on documented acute weight loss and biochemical indices (e.g. FE_{Na}). Fluid overload should be strictly avoided and RRT should be promptly initiated when the estimated fluid excess exceeds 10% of the estimated dry weight.

In case of fluid overload with preserved diuresis, the use of diuretics is usually recommended to achieve negative fluid balance. Conservative fluid management in AKI is limited by the need to provide adequate nutritional supply (see below). The daily maintenance total fluid input should equal urine losses plus insensible fluid losses (400 mL/m^2 body surface area plus a 12% per centigrade body temperature above 37°C), minus the desired net fluid loss. If the acceptable fluid input resulting from this equation is insufficient to provide sufficient energy intake, RRT should be initiated.

Electrolyte imbalances

Hyperkalaemia, one of the critical complications of AKI, develops due to reduced glomerular filtration and metabolic acidosis (each 0.1 unit reduction in arterial pH increases serum potassium by 0.4 mmol/L) and may be aggravated by excessive endogenous potassium release such as haemolysis, rhabdomyolysis, or tumour lysis syndrome. Hyperkalaemia should be treated aggressively when potassium increases rapidly or when serum levels exceed 6.5 mmol/L. Conservative therapy involves elimination of potassium administration via intravenous fluids and diet and administration of an exchange resin. Immediate measures to lower serum potassium include intravenous furosemide, administration by intravenous route or inhalation of beta-mimetics, calcium and dextrose-insulin infusions, and alkalizing therapy. *Hyponatraemia* in AKI is usually caused by dilution in the setting of fluid overload. Hyponatraemia due to excessive sodium losses may occur in patients with prerenal azotaemia due to severe secretory diarrhoea, in AKI related to kidney diseases with tubular dysfunction, and as a result of diuretic use. *Hypocalcaemia* may occur secondary to use of furosemide, impaired synthesis of 1,25 vitamin D by the diseased kidney, and/or severe hyperphosphataemia. *Hypernatremia* usually is the consequence of repeated buffering with sodium bicarbonate in oligoanuric patients. If persistent, all these alterations are firm indications to restore fluid and electrolyte balance by RRT.

Nutritional management

Caloric intake should be maintained at 100–130% of basal energy expenditure to avoid catabolism. Basal energy expenditure can be estimated by the Kennedy–Caldwell equation:

$$\text{Resting energy expenditure}\left(\text{kcal / day}\right) = 22 + \left(31 \times \text{weight}\left[\text{kg}\right]\right) + \left(1.16 \times \text{age}\left[\text{years}\right]\right)$$

The optimal protein intake in children with AKI is controversial. Since malnutrition is associated with increased mortality in

critically ill patients, sufficient protein should be supplied to maintain metabolic balance. Hence, nutritional protein administration should not be restricted as a means to attenuate the rise in BUN (blood urea nitrogen) associated with declining GFR. On the other hand, there is little evidence that hypercatabolism can be overcome simply by increasing protein intake to supraphysiologic levels. Hence, the nutritional protein administration should meet the recommended dietary intake appropriate for age. In patients receiving continuous renal replacement therapy (CRRT) or peritoneal dialysis (PD), additional amino acid and protein losses via the filtrate/dialysate fluid amount to 0.2–0.3 g/kg/day, which should be accounted for in the nutritional prescription. A large survey of children receiving CRRT reported an average maximum daily intake of 53, 31, and 21 kcal/kg energy and 2.4, 1.9, and 1.3 g/kg protein in patients aged < 1, 1–13, and > 13 years, respectively (Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group, 2012).

Regarding the preferred route of nutrition, enteral feeding may be problematic because of impaired gastrointestinal motility due to medications, decreased nutrient absorption secondary to bowel oedema, mechanical ventilation, and numerous other factors. However, the provision of nutrients via the gut lumen helps maintain gut integrity, decreases gut atrophy, and decreases bacterial and endotoxin translocation. Furthermore, enteral nutrition should exert protective effects on the risk of stress ulcers or bleeding. Clinical studies in adults have suggested that enteral feeding is associated with improved survival in ICU patients (Metnitz et al., 2002; Scheinkestel et al., 2003). Hence, enteral nutrition is the recommended form of nutritional support for patients with AKI. If oral feeding is not possible, tube feeding should be promptly initiated.

In catabolic patients, administration of insulin may be required to achieve appropriate utilization of glucose and amino acids. Intense insulin therapy has been applied with conflicting results in adults (for review, see Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group, 2012). In a prospective randomized controlled trial (RCT) comparing intensive insulin therapy (glycaemic targets 5–80 (2.8–4.4 mmol/L) and 70–100 mg/dL (3.9–5.5 mmol/L) for infants and children, respectively) and conventional therapy (target 180–215 mg/dL (9.9–11.8 mmol/L)) in critically ill children (mostly post cardiac surgery), strict glycaemic control reduced the length of ICU stay, the incidence of secondary infections, the need for vasoactive support, and patient mortality (Vlasselaers et al., 2009). However, the risk of severe hypoglycaemic episodes increased fivefold, arguing for judicious, closely monitored use of intense insulin therapy in hyperglycaemic critically ill children. It is recommended to adopt the preferred glycaemic target in the 110–150 mg/dL (6.1–8.3 mmol/L) range which is based on an extensive risk:benefit analysis in 26 RCTs in adult patients (Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group, 2012).

Renal replacement therapy in paediatric AKI

Indications to initiate RRT

Emergency indications for dialysis are given by life-threatening conditions such as severe hyperkalaemia, severe acidosis, overwhelming fluid overload (lung or pericardial oedema), and refractory malignant arterial hypertension.

In patients with less advanced or complicated AKI, RRT may be indicated to control the accumulation of uraemic solutes, correct fluid overload, and reverse acid–base abnormalities.

In the wider context of critical illness, dialysis may be initiated as a renal 'support' rather than 'replacement' therapy to allow administration of nutrients and drugs and maintain acid–base and electrolyte balance without concern of fluid overload.

The optimal timing of RRT initiation has been addressed in several large observational studies in adult AKI patients relating the BUN level, RIFLE stage, the degree of fluid overload, or time on ICU at start of dialysis to patient outcomes (Demirkilic et al., 2004). Taken together, these studies in adult patients revealed a trend towards lower mortality in patients with earlier initiation of RRT. In paediatric AKI, fluid overload has emerged as a relevant risk factor for mortality (Goldstein et al., 2001; Foland et al., 2004; Sutherland et al., 2010) (Table 239.8). Across the studies, AKI survivors consistently had lower fluid overload at the start of RRT than non-survivors, even when adjusting for the severity of illness, with a cut-off of 10% overload allowing the best prognostic distinction. Whereas the causal relationship between fluid overload and patient survival is not entirely clear, a randomized trial in haemodynamically stable adult patients with acute respiratory distress syndrome found a clear clinical benefit of strict fluid management avoiding fluid overload (Wiedemann et al., 2006). However, it remains to be formally demonstrated both in adults and children that fluid-driven timing of RRT initiation will effectively prevent fluid overload and translate into superior outcomes.

Choice of RRT modality

In principle, all RRT modalities can be applied successfully across the paediatric age range. As there are only a few rare modality-specific contraindications (e.g. gastroschisis or bladder exstrophy for PD), the modality selection will depend mostly on the centre-specific expertise, the patient's haemodynamic condition, and vascular access options. PD has the advantage of low cost, easy and safe catheter placement, lacking need for anticoagulation, and gentle, continuous fluid and solute removal. It can be applied even in preterm neonates, where vascular access issues limit the use of extracorporeal techniques. Intermittent and continuous haemodialysis and haemofiltration provide higher solute clearances and allow for more efficient fluid control. In recent years, technological advances have facilitated the application of extracorporeal techniques in young infants and even neonates, and have led to preferential use of CRRT in paediatric tertiary care centres as initial treatment modality (Sadowski et al., 1994; Bunchman et al., 1995; Warady and Bunchman, 2000; Symons et al., 2003, 2007; Askenazi et al., 2013a).

However, on the global scale, PD is probably still by far the most commonly used modality due to its availability in many less specialized paediatric units, particularly in emerging countries. The comparative efficacy, safety, and short- and long-term results of PD versus continuous and intermittent extracorporeal techniques are unknown since randomized trials are lacking in children and observational studies are notoriously confounded by indication bias and/or centre preference effects.

Peritoneal dialysis

For peritoneal access, surgically placed paediatric Tenckhoff catheters are generally preferred over percutaneously placed stiff acute PD catheters, due to the high complication rates of the latter. PD is

Table 239.6 Devices for acute extracorporeal treatment of children

Company	Machine	Volume neonatal tubing set (mL)	Volume paediatric tubing set (mL)	Blood flow (mL/min)	Dialysate/filtrate flow (mL/hour)
AsahiKasai	PlasautoΣ	84	120	1–400	10–12,000
Bellco	CarpeDiem	27, 33, 41		5–50	150–300
Edwards	Aquarius		64 (plus filter)	10–450	100–12,000
Fresenius	multiFiltrate	72		10–100	100–1500
Gambro	Prisma	50	90	10–180	100–4500
	Prismaflex		90	10–450	100–6000

usually started with an initial fill volume of 10 mL/kg, hourly cycles, and 2.4% dextrose and subsequently adjusted according to ultrafiltration and clearance needs. If dialysis is required for an extended period, the fill volume is gradually increased to 1000–1200 mL/m^2 (800 mL/m^2 in neonates) and a regular continuous ambulatory PD or automated PD prescription is implemented. In neonates and children with compromised liver function, bicarbonate-based PD fluid is strongly preferred due to the risk of lactic acidosis with conventional lactate-buffered solutions.

Extracorporeal therapy

The most critical factor in paediatric extracorporeal treatment is to ensure a proper vascular access. Catheter size should be adapted to body size; the minimal size of a dual-lumen catheter allowing an appropriate blood flow (> 100 mL/m^2 body surface area) is 6.5 F. Whereas the internal jugular route reportedly provides the best technique survival (Hackbarth et al., 2007), access via the femoral vein is often preferred in neonates and small infants. The subclavian route should be avoided in children at risk of chronic kidney disease (CKD) since the high rate of post-puncture stenosis may compromise future options for permanent access such as arteriovenous fistulas or grafts.

Both for intermittent and continuous extracorporeal treatments, dialysis devices adapted for paediatric use with blood, filtrate, and dialysate/substitution fluid flow rates adjustable over a wide range, highly accurate volumetric ultrafiltration control, and filters and tubing sets adapted to paediatric size should be used. The filter membrane area should approximately equate body surface area, and the total extracorporeal volume should not exceed 10–15% of the blood volume, which is 90 mL/kg in preterm neonates to 70 mL/kg in infants and older children. Red blood cell packs should be used to prime the extracorporeal system if the extracorporeal volume exceeds 10% of the blood volume. (See Tables 239.6 and 239.7.)

Both heparin and regional citrate anticoagulation protocols are now well established in paediatric RRT. Whereas both modalities confer comparable filter survival, citrate-based anticoagulation protocols clearly reduce the risk of bleeding complications (Brophy et al., 2005, Kreuzer et al., 2010).

Table 239.7 Recommended paediatric catheter sizes

Patient weight	Catheter size	Site of insertion	blood flow rates
Neonate	Double-lumen, 6.5F or 7F	Femoral artery or vein, umbilical vein	3-8 mL/kg/min
3–6 kg	Double lumen, 7F	Jugular or femoral (subclavian)	3-8 mL/kg/min
6–15 kg	Double lumen, 8F		5–12 mL/kg/min
15–30 kg	Double lumen, 9F or 10F		5–12 mL/kg/min
> 30 kg	Double lumen, 10F or 12F		3–8 mL/kg/min

Outcomes of paediatric AKI

AKI is clearly associated with increased mortality and morbidity in children; mortality rates of 17–32% have been reported for PICU populations (Plötz et al., 2008; Schneider et al., 2010). In a study applying the RIFLE score in 3400 critically ill paediatric patients, mortality risk globally was elevated fivefold in patients diagnosed with AKI; the risk increased with each RIFLE stage (Schneider et al., 2010). These findings have been confirmed in children with multiorgan failure, ARDS, stem cell transplantation, and ECMO treatment (Brophy, 2008).

Table 239.8 Initial fluid overload and outcome of paediatric CRRT

	Cohort	Outcome
Foland et al., 2004	Single-centre, PICU (N = 113) CVVH; 91% MODS	Survivors: fluid overload 9% Non-survivors: fluid overload 16%
Goldstein et al., 2005	Single-centre, PICU (N = 116) CRRT; 100% MODS	Survivors: fluid overload 14% Non-survivors: fluid overload 25% < 20% fluid overload: 58% survival > 20% fluid overload: 40% survival
Hayes et al., 2009	Single-centre, PICU (N = 76) CRRT; 83% MODS	Survivors: fluid overload 7% Non-survivors: fluid overload 22%
Sutherland et al., 2010	Multicentre, PICU (N = 297) CRRT; 79% MODS	< 10% fluid overload: 70% survival 10–20% fluid overload: 57% survival > 20% fluid overload: 34% survival

CRRT = continuous renal replacement therapy; CVVH = continuous veno-venous hemofiltration; MODS = multi-organ dysfunction syndrome; PICU = paediatric intensive care unit.

Adapted from Goldstein (2011).

Among children undergoing RRT, mortality rates typically range from 30% to 60%, with rates up to > 80% in children with multiorgan failure (Fernandez et al., 2005; Hayes et al., 2009; Askenazi et al., 2011).

The risk of developing CKD after surviving AKI has so far been addressed in a small number of studies. In adults surviving AKI, the hazard ratios to develop CKD, or ESRD are 8.8 and 3.1, respectively (Coca et al., 2012). Early paediatric studies reported incidence rates of CKD following AKI between 27% and 67%, depending on the underlying disease and the definitions of AKI and CKD applied (Georgaki-Angelaki et al., 1989; Slack et al., 2005). Among 174 paediatric AKI survivors, 9% progressed to ESRD within 3–5 years (Askenazi et al., 2006). Another study reported an overall CKD rate (according to KDOQI definition) of 10.3% among 126 PICU patients 1–3 years after AKI episodes diagnosed by AKIN criteria (Mammen et al., 2012). Long-term follow-up studies in disease-specific paediatric AKI cohorts showed 14% of patients developing CKD and 31% persistent proteinuria after haemolytic uraemic syndrome (Garg et al., 2003; Grisaru et al., 2011). Among cancer survivors, 7.5% developed CKD after AKI (Arjmandi-Rafsanjani et al., 2008).

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CHAPTER 240

Acute kidney injury in the elderly

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Introduction

Acute kidney injury (AKI) is largely a disease of the elderly patient. As described in this chapter, age-related changes in the kidney as well as the accumulated co-morbid conditions and polypharmacy associated with ageing greatly increase the susceptibility to the development of AKI. The aetiologies of AKI in the elderly patient represent the same spectrum of prerenal, intrarenal, and postrenal causes as in other age categories. However, elderly patients tend to have a higher relative risk for developing AKI due to volume depletion and urinary tract obstruction. Diagnosis of AKI can be confounded by the use of serum creatinine which has limitations in the diagnosis of AKI. The elderly patient also poses special challenges as this cohort of patients may have poorer short- and long-term outcomes, which may influence decision-making on the provision of aggressive care such as offering renal replacement therapy (RRT). These complex decisions require a careful analysis of potential outcomes as well as coordinated discussions with family members to ensure that the most thoughtful and rational treatments are offered.

Aetiology and pathogenesis of acute kidney injury in the elderly

Structural and functional renal changes with ageing

With ageing, in the absence of a specific disease, the kidney undergoes structural and functional alterations leading to a significant decrease in renal mass, functioning nephron numbers, and baseline kidney function (Choudhury et al., 2009). In aggregate, these changes lead to a decrease in renal functional reserve in times of stress and an accompanying increase in the susceptibility to AKI (summarized in Fig. 240.1 and Table 240.1).

Overall, from age 20 years to age 70 years, there is a 19% and 9% decline in kidney weights of males and females, respectively, with renal mass loss preferentially affecting the renal cortex (Tauchi et al., 1971). The number of functioning glomeruli decreases roughly in proportion with the changes in renal weight, whereas the size of the remaining glomeruli increases. The number of sclerotic glomeruli rises with advancing age, increasing from < 5% of the total glomeruli at the age of 40 years to 10–30% by the eighth decade of life (Kappel and Olsen, 1980). Tubular alterations, such as decreased number and size of tubules, increased interstitial collagen deposition, and fibrosis develop as well (Martin Sheaff, 2007; Aymanns et al., 2010; Chronopoulos et al., 2010c). Specific clinical conditions, including hypertension, diabetes mellitus, obesity, abnormal lipid levels, and vitamin D deficiency, seem to be associated with increased renal sclerosis with age (Choudhury et al., 2011).

With renal senescence, there is a variable decrease in glomerular filtration rate (GFR), according to measurement criteria, gender, race, genetic influence, dietary protein intake, and, most importantly, the presence of medical conditions which can interfere with renal function (Chronopoulos et al., 2010a, 2010b). Longitudinal studies have indeed demonstrated a significant reduction in creatinine clearance with age, beginning at age 34 years and accelerating after age 65 years. The decline in GFR is approximately 1 mL/min/1.73 m^2 per year after age 50 years (Rowe et al., 1976; Lindeman et al., 1985).

Advancing age is also associated with a decrease in effective renal plasma flow (ERPF), partly due to fibro-intimal hyperplasia and hyaline arteriosclerosis of pre-glomerular vessels (Chronopoulos et al., 2010a). This decrease in ERPF can be as much as 10% per decade of life. Moreover, ageing kidneys seem to be hypersensitive to angiotensin II and less responsive to vasodilatory mediators, such as atrial natriuretic peptide and prostacyclin (Moritoki et al., 1992; Sato et al., 1993; Jerkic et al., 2001; Chronopoulos et al., 2010a). These factors, combined with decreased nitric oxide production and increased renal vascular resistance, act to further reduce ERPF.

Renal cell repair activity also seems to decline with age, thus resulting not only in AKI after milder insults, but also AKI of longer duration. The reduced capacity of tubular regeneration in the ageing kidney seems partly due to the shortage of renal progenitor cells (Miya et al., 2012). Other contributing factors are decreased telomere length, induction of factors involved in cell-cycle regulation, such as the cyclin-dependent kinase inhibitors p16INK4A and p21 and suppression of Klotho gene, which is responsible for protecting cells from oxidative stress (Ding et al., 2001; Kuro-o, 2008), and mitochondrial dysfunction (Perico et al., 2011).

Other contributing factors to increased susceptibility to AKI in the elderly

Impaired sodium handling is one of the factors responsible for the increased susceptibility to AKI in the elderly (Chronopoulos et al., 2010a). Both less efficient sodium reabsorption in the proximal tubule and/or reduced activity of the renin–angiotensin–aldosterone system may contribute to impaired sodium conservation by the senescent kidney (Fliser, 2005). This, along with a decreased thirst mechanism, makes the elderly patient more prone to AKI-related to volume depletion. Moreover, as people age, they are prescribed an increasing number of drugs (polypharmacy) and this represents an important risk factor for AKI (Chronopoulos et al., 2010a). Both pharmacokinetics and pharmacodynamics are altered in older people (Flamenbaum, 1986), particularly in case of impaired mobility.

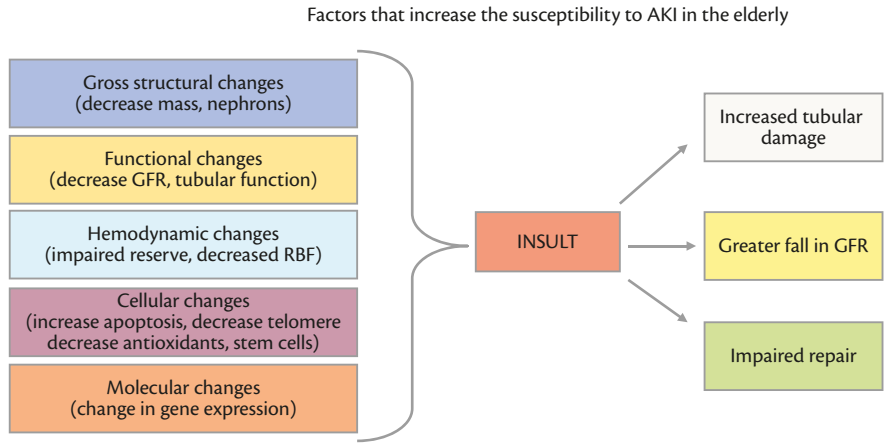

Fig. 240.1 Factors that increase susceptibility to AKI in the elderly.

The absorption of drugs in the elderly is largely unaltered, although some senescent changes take place in the gastrointestinal system, such as decreased secretion of gastric acid and gastrointestinal mobility (Chan and Michelis, 1998). However, alterations in the tissue distribution with ageing may significantly increase toxicity of different drugs. Generally, lean body mass decreases in the elderly with respect to fat body mass. Water-soluble drugs, such as aminoglycosides, digoxin, and aminophylline, therefore attain higher concentrations in the non-fat compartment. Furthermore, concomitant use of diuretics may increase plasma levels of these drugs and hence their nephrotoxic effects. On the other hand, activity of fat-soluble drugs, such as benzodiazepines, barbiturates, and phenytoin, may be prolonged due to enlargement of this reservoir. Due to the decreased production of albumin and its reduced binding activity in the elderly, the proportion of free drug increases as well as their toxicity. Finally, ageing is associated with a decrease of both hepatic drug extraction and renal excretion, with consequent prolonged drug half-life. Altogether, most pharmacokinetic changes in the elderly give rise to an increased possibility for adverse effect of any given drug, including its toxicity.

Table 240.1 Factors contributing to AKI in the elderly

Structural and functional renal changes with ageing	Other contributing factors
Decrease in number of functioning glomeruli	Impaired sodium handling
Tubular alterations	Decreased thirst mechanism
Decrease in glomerular filtration rate	Polypharmacy/drug interaction
Decrease in effective renal plasma flow	Alterations in tissue distribution of drugs
Increased sensitivity to angiotensin II	Decreased albumin production
Decreased sensitivity to vasodilatory mediators	Altered kidney and hepatic function
Decreased renal cell repair activity	
Decreased telomere length	
Altered cell-cycle regulation	
Suppression of Klotho gene	
Mitochondrial dysfunction	

Epidemiology of acute kidney injury in the elderly

Community-acquired AKI

An overall improvement in the mortality rate due to better medical care has resulted in an increase in the size of the geriatric population in both developed and developing countries (Robbins and Oholer, 1990). The probability of survival to older age has improved and the absolute number and proportion of older people is projected to increase in the next few decades. The fastest growing age cohort is made up of those aged ≥ 80 years, increasing at an estimated 3.8% per year, and projected to represent one-fifth of all older people by 2050 (United Nations, 2000) (Fig. 240.2).

Older age is associated with an increased prevalence of chronic illness and functional impairment (Song et al., 2007). Despite widely varying incidences of AKI reported in the literature (largely a reflection of differing definitions of AKI), most studies support the finding that elderly people are at higher risk for development of AKI. There is a three- to eightfold age-dependent increase in the frequency of development of community-acquired (out of hospital) AKI in patients > 60 years of age (Feest et al., 1993). Not surprisingly, the past 25 years have seen the mean age of patients with AKI increase by at least 5 years and perhaps as much as 15 years (Turney et al., 1990).

Hospital-acquired AKI

Elderly individuals need a host of diagnostic and therapeutic interventions, and hospitalization per se exposes them to complications, such as hospital-acquired AKI. In hospitalized patients, the reported incidence of AKI varies between 5% and 7% of all clinical or surgical hospitalized patients (Abernethy Lieberthal, 2002; Singri et al., 2003; Chronopoulos et al., 2010c), and the incidence in the postoperative period ranges from 0.1% to 30%, depending on the criteria used to define AKI and the type of surgery performed (Sural et al., 2000; Sear, 2005). Of the patients with this complication, nearly 1% can develop severe AKI with creatinine levels above 4 mg/dL or need for dialysis (Kohli et al., 2000; Mehta and Chertow, 2003). Despite the advances in anaesthetic, surgical, and monitoring techniques, postsurgical mortality rate can range from 20% to 80%, depending on the presence of comorbidities (Sural et al.,

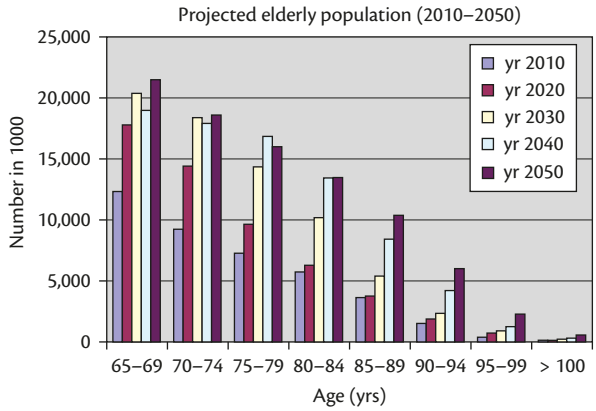

Fig. 240.2 Population trends in the elderly.

2000; Mehta and Chertow, 2003). This figure increases to almost 20 times in patients undergoing emergency procedures (Bailes, 2000).

AKI in the critical care setting

Fifty-five per cent of all American intensive care unit (ICU) beds-days are occupied by patients aged ≥ 65 years (Angus et al., 2004; Chronopoulos et al., 2010a). Of the 17,440 patients in medical and surgical ICUs from 40 institutions in the United States, the proportion of patients who were over age 65 was 48%; 25% were 65–74 years old, 17.2% were 75–84 years old, and 5.3% were >85 years old (Knaus et al., 1991). In a multicentre study, Australian New Zealand Care Society Adult Patient (ANCIZS) database researchers determined that 13% of 120,123 adult patients were aged ≥ 80 years and that the admission rate for this age group increased by 5.6% per year during the period between 2000 and 2005 (Bagshaw et al., 2009).

AKI is a common and important occurrence in the ICU setting, with a reported incidence of 1–25% depending on the population being studied and the criteria used to define AKI (Chertow et al., 1998; de Mendonca et al., 2000). AKI, which usually appears as a consequence of acute lung injury, sepsis, and trauma in ICU patients, is associated with a mortality rate of 50–70%, which has remained relatively constant over the last decades (Silvester et al., 2001).

Most studies support the statement that the elderly patient in the ICU is at higher risk for AKI. The BEST Kidney collaborators, in a prospective multicentre study on 26,269 critically ill patients with a median age of 67 years, determined that 5.7% of the patients developed severe AKI (Uchino et al., 2005). Moreover, in a recent study comparing the RIFLE (Risk, Injury, Failure, Loss, and End-stage renal disease) and AKIN (Acute Kidney Injury Network) criteria, the incidence of AKI in the first 48 hours of ICU stay ranged between 28.5% and 35.5%. The mean age of the patients was 63 years, with 25% aged > 75 years (Joannidis et al., 2009).

Clinical aspects of acute kidney injury in the elderly

Even though elderly patients often have the same clinical conditions responsible for AKI as the general population, specific differences in the incidence and in the presentation of these diseases make this group of patients unique.

Prerenal AKI is the second most common cause of AKI in the elderly after acute tubular necrosis (ATN; discussed further below), accounting for nearly a third of cases (Cheung et al., 2008). The mechanism responsible for kidney injury is a decreased renal perfusion which, in a patient with reduced renal blood flow and GFR, like the elderly, can stimulate sympathetic nervous system activity and the release of vasoconstrictor substances, in turn leading to a further reduction in GFR and, subsequently, to kidney injury. Renal hypoperfusion can develop in different clinical conditions, such as reduced cardiac output (myocardial dysfunction and pericardial disease), internal volume distribution to interstitial spaces (cirrhosis, nephrotic syndrome, sepsis, and malnutrition), and external loss of fluids with insufficient fluid replacement (vomiting, diarrhoea, bleeding, and excessive sweating due to febrile illnesses). While many of these causes can be reversed with adequate fluid replacement, others progress to ATN, especially if the insult is prolonged and severe. Dehydration and volume depletion occur frequently in the elderly, affecting nearly 1% of hospital admissions in this population (Lavizzo-Mourey et al., 1988). Being bedridden and having poor fluid oral intake are important risk factors for dehydration, often associated with significant hypernatremia which, if untreated, has a very high mortality rate (Weinberg et al., 1994).

Numerous intrarenal causes of AKI can also affect the elderly, of which ATN is probably the most common with an incidence ranging from 25% to 87% (Lameire et al., 1991; Cheung et al., 2008). Elderly patients are more susceptible to serious infections and to the development of sepsis, which often results in ATN in this population of patients. In the setting of sepsis, the development of AKI requiring dialysis has a mortality rate > 80% (Wardle, 1994). Vascular diseases, such as renal artery occlusion or thromboembolism, are often responsible for AKI in the elderly as well. They are usually associated with atherosclerosis, atrial fibrillation, or myocardial infarction. Moreover, older patients seem to have a higher incidence of antineutrophil cytoplasmic antibody and antiglomerular basement membrane-associated rapidly progressive glomerulonephritis (Preston et al., 1990). The relative risk of death is 5.3 times higher in patients aged > 60 years compared to younger patients following aggressive immunosuppressive treatment (Keller and Buttner, 1994). Finally, older patients are susceptible to developing rhabdomyolysis in the setting of acute immobilization, infectious diseases, cerebrovascular accidents, hyperosmolar state, hyponatraemia, hypernatraemia, hypothermia, and after falls.

Finally, postrenal AKI is quite frequent in the elderly and accounts for 7.9–9% of cases of AKI in patients aged > 65 and 70 years (Macias-Nunez et al., 1996; World Health Organization, 1998). The obstruction may be either intrinsic or extrinsic and can occur at any level of the urinary tract. Among the causes of lower urinary tract obstruction, the most common in males is prostatic enlargement due to benign prostatic hypertrophy or carcinoma. Benign prostatic hypertrophy is the most common neoplasm in men, affecting 50% of males aged 50 years and increasing to 90% by the ninth decade of life. A small percentage of these patients develop severe obstructive AKI, some of them progressing to irreversible renal failure, whereas others recover quite well. The second most common cause in males is urethral stricture disease, often secondary to trauma. In women, important causes of ureteral obstruction, responsible for postrenal AKI, are pelvic malignancies, such as carcinoma of the cervix and ovarian neoplasms. Lymphoma, bladder, and rectum carcinomas are frequent causes of obstructive AKI in

the geriatric population as well. An uncommon cause of postrenal AKI in the elderly is inflammatory abdominal aortic aneurysm, which can be identified through proper imaging studies.

Elderly patients are frequently subjected to medical procedures and clinical treatments which are often responsible for AKI in this population. Among the drugs commonly prescribed to older patients, non-steroidal anti-inflammatory drugs (NSAIDs), angiotensin-converting enzyme inhibitors (ACEIs), and angiotensin-receptor blockers (ARBs) are frequently associated with AKI. These agents interfere with the protective autoregulatory mechanisms which maintain renal blood flow and GFR across a wide range of blood pressures. While NSAIDs inhibit prostaglandin production, with subsequent increased vascular resistance in the afferent arteriole, ACEIs and ARBs reduce vascular resistance in the efferent arteriole, thus impairing intraglomerular pressure (Chronopoulos et al., 2010c). In states of marginal renal perfusion, such as heart failure, volume depletion, and renal artery stenosis, which are very common clinical conditions in the elderly, these drugs may lead to precipitous falls in renal blood flow and GFRs, thus resulting in ischaemic AKI (Hollenberg, 1983; Kleinknecht et al., 1987). Moreover, dehydration and volume depletion conditions can be worsened by the concomitant administration of diuretics, laxatives, and drugs that decrease appetite or the level of consciousness.

However, ATN is probably the most frequent cause of AKI in the elderly and is often associated with the use of nephrotoxic drugs, such as antibiotics, particularly aminoglycosides, immunosuppressive medications, and chemotherapeutic agents, such as ciclosporin and cisplatin. Aminoglycosides have a direct toxic effect on the epithelial tubular cells, while ciclosporin is responsible for a decrease in renal perfusion. Well-known risk factors for drug-induced ATN include age > 60 years, atherosclerotic cardiovascular disease, diabetes, pre-existing chronic kidney disease, and hypoperfusion states.

Moreover, although there are no available data on the incidence of acute interstitial nephritis in the elderly, this group of patients are likely to be at increased risk due to the large number of medications which are prescribed. Antibiotics, such as penicillins, cephalosporins fluoroquinolones, diuretics, in particular furosemide, and NSAIDs are often responsible for this syndrome in older patients. The dose of the drug administered and the duration of the treatment are determinant factors for possible regression of the kidney injury. Proton pump inhibitors, usually safe and frequently prescribed in the elderly, have been associated with acute interstitial nephritis as well (Ni et al., 2010). Recovery occurs after withdrawal of the drug, but it is often incomplete and some patients may require therapy with corticosteroids to improve kidney function (Simpson et al., 2006).

The elderly are also at increased risk of radiocontrast-induced AKI, given the high number of diagnostic and therapeutic radiographic procedures performed in this population of patients. Contrast-induced AKI is often observed after cardiac and/or peripheral vascular catheterization and revascularization. These procedures are common among the elderly due to the high prevalence of atherosclerotic and cardiovascular disease in this population. Other than age, however, other factors, such as baseline renal function, diabetes, cardiac failure, emergent procedures, and female sex, also contribute to a higher risk for contrast-induced AKI (McCullough et al., 2006). Gadolinium was previously considered to be an interesting alternative contrast agent for certain high-risk individuals, such as patients with advanced chronic renal insufficiency, patients on haemodialysis, and patients with AKI. In the light of recent information, however, particularly older gadolinium formulations should not be used as a substitute for radiocontrast in patients with acute or chronic renal failure, because of the risk of nephrogenic systemic fibrosis (Swartz et al., 2003). This consideration is especially true for older individuals in whom chronic kidney disease is prevalent.

The high prevalence of comorbidities in elderly individuals leads to an increased need for surgical procedures as well, and they account for about one-third of ATN cases in this population (Pascual et al., 1990). The incidence of AKI ranges from about 0.1% in general surgery up to 31% or more in cardiac surgery (Rosenfeld et al., 1987). Advanced age is a risk factor for AKI development in most of these settings, but factors such as emergency surgery and comorbidities are also important risk factors (Rosenfeld et al., 1987). Hypotension during and after surgery, postoperative fluid loss, and arrhythmias are commonly encountered in the elderly and in combination with impaired renal autoregulation, may induce haemodynamically mediated AKI. Postoperative period is often complicated by severe infections, which may also result in ATN (Noor and Usmani, 2008).

Challenges in the diagnosis of acute kidney injury in the elderly

Renal injury in the elderly should be identified promptly to ensure that preventative/early therapeutic strategies are implemented most effectively. In current clinical practice, a diagnosis of AKI is made on the basis of the presence of an increased serum creatinine level and/or a decreased urine output. Although these criteria have been used for years, they have many shortcomings, especially in older patients (Chronopoulos et al., 2010c).

The most important limitation of serum creatinine measurement in all patients is the delayed increase in this parameter after a renal insult. Indeed, studies have shown that changes in its value may lag behind changes in GFR by several days (Lameire and Hoste, 2004; Waikar and Bonventre, 2009). In the elderly, in particular, serum creatinine is unreliable as a precise indicator of GFR due to the fact that the daily production of creatinine is diminished because of reduced muscle mass. Consequently, the serum creatinine concentration will underestimate the decline in GFR with age (Swedko et al., 2003). Another major weakness of using serum creatinine level as a diagnostic tool is its fluctuation according to hydration status and vascular tone, regardless of renal function. This is an important consideration in older patients as they are particularly susceptible to fluid status changes, and are more likely to be on medications which affect vascular tone, such as ACEIs and ARBs. The problems associated with serum creatinine levels for AKI diagnosis are even more manifest in critically ill elderly patients, since they may be influenced by other factors, such as muscle trauma, fever, immobilization, and advanced liver disease (Lameire and Hoste, 2004). Moreover, the elderly are more susceptible to fluid accumulation, which may lead to serum creatinine dilution and, consequently, to underestimation of the severity of AKI (Macedo et al., 2010). All these conditions often lead to delayed recognition of AKI and late initiation of treatment, as unfortunately many physicians still base clinical decisions on arbitrarily determined levels

of creatinine and urea. Urine output as well cannot be considered a reliable indicator of renal injury, in the absence of an indwelling catheter.

Although not currently recommended for use in routine clinical practice, novel biomarkers such as neutrophil gelatinase-associated lipocalin (NGAL), kidney injury molecule 1 (KIM-1), interleukin 18 (IL-18), and cystatin C have been useful for the early diagnosis of AKI. With the exception of cystatin C, none of these biological markers have been specifically studied in older patients. Cystatin C is a marker of renal dysfunction in advanced age, and has been shown to be predictive of death and cardiovascular events in elderly individuals in several studies (Fliser and Ritz, 2001; Shlipak et al., 2005). Despite advances in diagnostic tools, early diagnosis of AKI in the elderly still remains a challenge.

After AKI is identified, its laboratory evaluation follows the pathophysiological scheme of investigating for prerenal, renal, and postrenal causes. Attention to the history and physical examination is critical in narrowing the differential diagnosis to potential aetiologies and to focus the work-up with specific laboratory or imaging tests. Given the high incidence of ATN and obstructive causes of AKI, urine microscopic examination and ultrasonography are mandatory. Foley catheter placement should be considered in all patients as well.

The finding of pigmented granular casts in the urine is indicative of tubular damage and supports the diagnosis of ATN, while the presence of red blood cell casts indicates glomerular involvement and warrants consideration of whether a renal biopsy should be performed (Perazella and Coca, 2012). Since the incidence of complications of renal biopsy is not significantly higher in the elderly (Rakowski and Winchester, 1986), one should not hesitate to perform this procedure, if indicated, under appropriate guidance using imaging (ultrasound or computed tomography (CT) scan). However, it is also important to consider the presence of significant glomerulosclerosis and arteriosclerosis, which may render the interpretation of histological findings more difficult.

It is always imperative to exclude a possible obstructive cause in an elderly patient presenting with AKI, especially among those with known uropathy, for example, prostatic hypertrophy or urolithiasis (Pascual et al., 1995). Prompt intervention may result in improvement or complete recovery of renal function. Ultrasonography is safe, sensitive, readily available, and has become one of the initial investigations of choice in this setting. The diagnosis of obstruction is based on a dilated collecting system filled with fluid. However, a few cases of urinary tract obstruction have been reported to be associated with minimal or no dilation of the collecting system (Gornish et al., 1990), in particular in a dehydrated patient. If ultrasonography reveals non dilated kidneys but obstructive AKI is still suspected, repeating the examination after rehydration or a duplex-Doppler sonography is probably a useful tool. Renal arterial resistance rises with obstruction of the kidneys. A resistance index > 0.7 suggests obstructive AKI and requires mandatory ureteral catheterization (Pascual et al., 1995). A radioisotope renography using mercaptoacetyltriglycine (MAG-3) can also identify functional obstruction in the absence of dilation of the collecting system.

CT may serve as an effective tool in the setting of urolithiasis, in particular for patients with inadequate ultrasonographic visualization or with unidentified cause of obstruction. This imaging tool can better assess urolithiasis and associated obstruction than plain abdominal radiographs, even though its sensitivity is lower for stones < 2 mm (Zilberman et al., 2011). CT can be also used after percutaneous nephrolithotomy to assess stone-free status and possible procedure complications (Gnessin et al., 2012).

Treatment problems

Once renal injury is established and the diagnosis is made, the only useful measures are those that prevent further deterioration in renal function or additional renal insults.

In general, the treatment of AKI in the elderly follows the same principles as for the general population (Table 240.2). This means careful attention to dosing medications, avoidance of further nephrotoxic insults, management of fluid, electrolyte, and acid–base balance, mandatory catheterization in case of obstructive AKI, and provision of adequate nutritional support. If iatrogenic AKI (nephrotoxic ATN) or acute interstitial nephritis is diagnosed, withdrawing the drugs responsible for these syndromes is imperative. In case of rapidly progressive glomerulonephritis, caution must be paid in the use of immunosuppressive agents, such as corticosteroids and cytoxic drugs, given their altered pharmacokinetics and the higher risk of opportunistic infections and complications. Particular attention must be paid to the development of signs of sepsis, which is often occult in frail elderly patients (Fontanarosa et al., 1992). Infections are often accompanied by a state of hypovolaemia, and usually require adequate fluid resuscitation as well as timely and appropriate antibiotic therapy, trying to avoid aminoglycosides or, if necessary, reduce the dose of administration.

The decision to initiate renal support therapy in the elderly with multiple comorbidities and a very poor prognosis may be difficult. This is especially true for those individuals with significant baseline renal impairment where the likelihood of renal recovery may be low. The decision to initiate dialysis in these patients requires several considerations.

First of all, owing to increased autonomic dysfunction, decreased cardiovascular reserve, and frequent comorbidities and medications, older patients are more prone to haemodynamic complications during dialysis, such as intradialytic hypotension, hypertension, and arrhythmias (Chronopoulos et al., 2010c). Older patients are also more vulnerable to bleeding problems and to neurologic

Table 240.2 Therapeutic approach to AKI

General approaches	Renal replacement therapy
Withdrawal of nephrotoxic drugs	Discuss issues comprehensively with patient and relatives, and arrive at decision for renal replacement therapy initiation collaboratively
Management of fluid balance	Consider early initiation of renal support, particularly in septic patients
Management of electrolyte and acid–base balance	Imaging-guided dialysis catheter placement, whenever possible
Early recognition and treatment of septic conditions	Monitor closely for complications
Catheterization	Intradialytic hypotension
Adequate nutritional support	Hypertension
	Arrhythmias
	Bleeding problems
	Neurologic complications

complications resulting from rapid changes in serum electrolytes and osmolarity (Bonello et al., 2009). Although it has not been studied specifically in the elderly, it has been suggested that continuous renal replacement therapy (CRRT) is associated with a more stable haemodynamic profile than intermittent dialysis in the general population, and is also associated with a reduced risk of disequilibrium syndrome owing to slower osmolality shifts, which might make this modality useful in the fragile elderly population (Hsieh and Chen, 2007). However, when choosing the type of modality, clinicians must also consider the increased risk associated with continuous anticoagulation in a population prone to bleeding, as well as the higher costs associated with CRRT. Overall, mounting experience in intermittent haemodialysis, particularly in the slow low-efficiency dialysis (SLED) modus, suggests that it is a safe and relatively well tolerated in the elderly population with AKI (Bonello et al., 2009).

Decisions regarding initiation of renal support therapy undoubtedly must be individualized, taking into consideration the particular clinical situation, the patient's and/or family's wishes, the chances for functional renal recovery, and the probability of survival. Although the information on AKI treatment available to physicians is mostly based on studies that have stratified older individuals into different groups, it has become clear that clinical management decisions should never be made on the basis of chronological age alone.

Prognosis of acute kidney injury in the elderly

Given the high incidence of AKI in the elderly, the clinical outcome in this population is of great importance. Although AKI can be fully reversible, the renal repair process also can be incomplete and result in chronically decreased kidney function. This can range from subclinical decreases in GFR to dialysis-dependent end-stage renal disease (ESRD).

Incidence rates of ESRD after AKI in the elderly differ widely among studies, ranging from < 1% to > 40% (Bhandari and Turney, 1996; Schiffl, 2006; Liano et al., 2007). A recent systematic review and meta-analysis has demonstrated that recovery of kidney function after AKI is approximately 28% less likely to occur when the patient is aged > 65 years (Schmitt et al., 2008). Whether these results are caused by effects of age on the kidney itself or the increased number of comorbidities, including baseline chronic kidney disease is still not certain. Little is known about mortality in elderly patients who experience AKI and do not require dialysis. In a prospective, multicentre study including hospitalized patients, no increased risk of death with advanced age was found (Pascual and Liano, 1998). These data are supported by an older study by Lameire et al. which also failed to show any differences in mortality or renal recovery between patients aged > 65 years and those aged 17–64 years (Lameire et al., 1987). On the contrary, the study by Ali et al. showed a significant and incremental increase in mortality risk with age and comorbidities (Ali et al., 2007).

Existing outcome data on ICU patients requiring dialysis vary widely, with reported mortality ranging from 31% to 80% because of differences between studies in terms of the definition of advanced age, treatment intensity, severity of illness, and length of follow-up. Some studies report an increased mortality risk in elderly critically ill patients with AKI (Uchino et al., 2005). Conversely, other well-conducted studies found no difference in mortality attributable to older age (Pascual and Liano, 1998). One of these studies found multiple organ dysfunction syndrome (MODS) to be an independent risk factor for increased mortality (Van Den Noortgate et al., 2003). In fact, clinical characteristics and outcomes of patients with MODS and AKI requiring RRT are very different from those of patients with chronic kidney disease who develop AKI with dialysis initiation in the ICU. Patients with MODS often have a higher acute severity of illness and short-term mortality, but lower long-term mortality because of less comorbid illness. Indeed, several studies on long-term outcomes of hospital survivors of MODS and AKI treated with RRT have documented a surprisingly low post-discharge mortality rate and an acceptable self-perceived quality of life (Gopal et al., 1997; Morgera et al., 2002). In a multicentre study, ANCIZS database researchers demonstrated which factors might be associated with lower survival in elderly patients admitted to the ICU (Bagshaw et al., 2009). Admission from a chronic care facility, co-morbid illness, non-surgical admission, greater illness severity, mechanical ventilation and longer stay in the ICU were found to be associated with lower patient survival.

More precise data about age as a prognostic factor for renal recovery both in hospitalized and ICU patients, would be crucial and could help decide whether older survivors of AKI necessitate close follow-up after discharge if they are at increased risk of ESRD.

Prevention strategies

Given the significant morbidity and mortality associated with AKI, preventive strategies are clearly important. Since the development of AKI in the elderly is in part related to structural and functional changes in the senescent kidney, a two-pronged approach to prevention may be strategic: first, to retard or attenuate age-related sclerosis and decline in GFR, thereby reducing the kidney's susceptibility to insults, and second, specific strategies to prevent or minimize insults to the kidney (Table 240.3)

A number of clinical factors, including hypertension, diabetes mellitus, obesity, abnormal lipid levels, and vitamin D deficiency, have been associated with increasing renal sclerosis with age. In addition, tissue factors such as angiotensin II, advanced glycosylation end products, and oxidative stress are associated with renal ageing. Some authors have suggested that control of blood pressure,

Table 240.3 Prevention strategies

Prevention of age-related nephropathy[a]	Prevention of acute kidney injury
Non-pharmacologic strategies	Avoidance of hypovolaemia (crystalloids)
Blood pressure control	Avoidance of nephrotoxic drugs
Lifestyle changes (diet and exercise)	Pharmacovigilance
Calorie restriction	Use of bicarbonate solutions and *N*-acetylcysteine in case of contrast media administration
Control of weight, glucose, and lipids	Early recognition of intra-abdominal hypertension
Natural antioxidants	Use of vasopressors if indicated
Pharmacologic strategies	Renal replacement therapy
Renin–angiotensin–aldosterone system antagonists	
Blood pressure control	
Vitamin D replacement therapy	

[a]Adapted from Choudhury and Levi (2011).

metabolic factors, and inflammatory processes in ageing individuals may decrease the rate of renal functional decline associated with age (Choudhury and Levi, 2011).

The key elements in any AKI prevention strategy, whenever feasible, are avoidance of hypovolaemia, avoidance of nephrotoxic agents whenever possible, including specific drugs, and iodinated contrast media (Cheung et al., 2008). If complete avoidance is not possible, then efforts should be directed towards recognizing potential drug–drug interactions, and avoiding combinations which may amplify their nephrotoxic effects, as well as the injudicious use of drugs that have the potential to cause hypovolaemia, such as diuretics and laxatives. Whenever possible, drug levels must be measured to monitor for potential nephrotoxicity.

Some specific preventive therapies for contrast-induced AKI have been proven effective, such as adequate hydration and the use of the smallest possible amount of a low-osmolal or iso-osmolal non-ionic contrast agent. Although other measures for preventing contrast-induced AKI, such as the use of bicarbonate solutions for hydration instead of 0.9% saline, and supplementation with *N*-acetylcysteine, are probably effective, conflicting data exist in the literature (Ellis and Cohan, 2009).

Although intra-abdominal hypertension is most often seen in ICU, it can sometimes be encountered in the wards, particularly in patients who have undergone abdominal surgery. Of particular relevance to the elderly, advanced age is a major risk factor for the development of Ogilvie syndrome (acute colonic pseudo-obstruction), and cases of this syndrome are increasingly being described as a complication occurring after total hip replacement and hip arthroplasty (Tezval et al., 2009). Clinicians should be aware that increases in intra-abdominal pressure can exert a negative impact on renal function long before the overt abdominal compartment syndrome has developed (Bagshaw et al., 2008).

With regards to the ICU in particular, two groups have published consensus statements on AKI prevention (Brochard et al., 2010; Joannidis et al., 2010). According to the Working Group for Nephrology, several measures are required to prevent AKI in ICU patients (Joannidis et al., 2010). Prompt resuscitation of the circulation with special attention to adequate hydration is recommended, as well as maintaining adequate blood pressure using vasopressors agents. Specific vasodilators under strict haemodynamic control and isotonic salt solutions might be used in case of emergency procedures administering contrast media. Periprocedural haemofiltration may be performed in patients with severe chronic renal insufficiency undergoing coronary intervention. Also a recent international consensus conference suggested an adequate volume repletion to prevent AKI in ICU patients, even though correction of fluid deficit will not always prevent renal failure (Brochard et al., 2010). Fluid resuscitation with crystalloids is effective and safe, and it is preferred to hyper-oncotic solutions, due to their possible negative effect on kidney function. RRT is a life-sustaining intervention that can provide a bridge to renal recovery. Although no method has proven to be superior, careful management is essential for improving outcome.

Summary

AKI in the elderly patient is a relatively common occurrence. The aetiologies of AKI in this population include prerenal, intrarenal, and postrenal causes with ATN and obstructive causes being the most common. The elderly kidney is predisposed to AKI due to molecular, cellular, structural, and functional changes associated with ageing itself as well as age-related comorbidities. Once AKI is established, elderly patients may have a similar prognosis to younger cohorts but this area requires further study. However, in those elderly patients with multiple co-morbid conditions who develop AKI in the setting of a critical illness, the decision to provide aggressive support such as dialysis requires careful and thoughtful decision-making. As our knowledge of ageing increases, it might be possible to devise specific strategies to protect the ageing kidney from insults. However, as for now, prevention relies on meticulous care to avoid nephrotoxins, maintain intravascular volume status, and to monitor urine output and renal function.

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CHAPTER 241

Acute kidney injury in the tropics

Vivekanand Jha

Introduction

The tropical zone is the part of earth between the latitudes 23° north–23° south, where the sun is directly overhead at least once during the solar year. The tropical climate is characterized by the presence of high year-round temperatures and the absence of winter frost. The rainfall varies from very high throughout the year in tropical rainforests to very low in the deserts of Africa and the Middle East. Currently approximately 40% of the world population lives in the tropics; the proportion is likely to grow to 60% by 2060 as a result of high birth rate and migration (United Nations, Department of Economic and Social Affairs, 2010).

The current average gross national product per capita of the temperate zone is 4.5 times that of the tropical zone. In 1820, the tropical zone gross domestic product per capita was 70% that of the temperate zone, but fell to 25% by 1992. The average annual growth rate in the temperate zones during this period was 1.4% per year, compared with the 0.9% per year in the tropical region. The national per capita income exhibits a consistent increase from the low equatorial tropical latitudes to the high latitudes, both in the Northern and Southern hemispheres. Of the 30 economies classified as high income by the World Bank, only two small regions (Singapore and Hong Kong) are in the tropical region (Bloom and Sachs, 1998; Sachs, 2001).

The disease burden including the spectrum of acute kidney injury (AKI) in tropical countries is heavily influenced by local climatic and economic conditions, and is fundamentally different from that seen in the hospitals of affluent countries in temperate climates (Fig. 241.1). AKI is encountered in already hospitalized, usually elderly patients with multiorgan disease, or after surgical or diagnostic interventions, often due to iatrogenic factors (hospital-acquired AKI) in the non-tropical hospitals (Jha et al., 1992). The major burden of AKI in tropical countries, however, is constituted by previously healthy, relatively young individuals who have developed AKI as a result of factors encountered in their environment and present to hospitals with established AKI (community-acquired AKI) (Kaufman et al., 1991; Jha and Chugh, 2008; Daher et al., 2012; Kaul et al., 2012). In contrast to the multifactorial origin of hospital-acquired AKI, the aetiology of tropical community-acquired AKI is usually due to a single cause, typically an infection, exposure to an environmental toxin, envenomation by snakes or insects, or obstetric complications (Daher et al., 2012; Kaul et al., 2012; Jha and Parameswaran, 2013).

Many conditions that cause AKI in the tropics are related to public health problems (Schoolwerth et al., 2006). The ecosystem around water plays a major role in many causes. Ambient temperature affects the availability and quality of water. High tropical temperatures increase the evaporation of surface water and transpiration through plant surfaces. This combined loss, known as evapo-transpiration, leads to water scarcity. Tropical soil is highly fragile (Tiessen et al., 1997), high temperature and heavy precipitation lead to leaching of minerals and organic compounds into flowing water, which is used for day-to-day activities. Water-logging leads to contamination of grain in the field and supports growth of infectious microorganisms. The final result is a continued high prevalence of water-borne diseases, many of which lead to AKI. Spread by direct transmission such as aerosols is also more likely in the tropics because of overcrowding and poor living conditions (Jha and Parameswaran, 2013).

Tropical ecosystems also favour the growth of other life forms, pests, and parasites. Low temperatures and freezing winter months are crucial in killing parasites and pests in the temperate climate. High temperature, wet weather, and salinity favour the growth of the disease-carrying animal reservoirs, vectors, and organisms that survive outside the human host, thereby favouring the transmission of both vector and water-borne diseases.

The tropical vector-borne diseases are difficult to control. In the 1950s and 1960s, vector eradication relied on the use of chemical insecticides. However, concerns about negative impacts on ecosystems (e.g. depletion of biodiversity), adverse acute as well as long-term human health effects of exposures, and risk of development of vector resistance led to an abandonment of this strategy (<http://www.who.int/heli/risks/vectors/malariacontrol/en/index.html>). This has been replaced by the newer 'integrated vector management', which requires more resources for implementation. Finally, tropical rains also affect the behaviour of venomous snakes. Flooding of the burrows in which they live forces them to come to the surface, especially in the fields at times when large numbers of workers are in the fields for planting or harvesting crops, leading to a spike in the number of bite victims. Seasonal variation in snake envenomation is seen throughout the tropics (Chugh, 1989; Rodrigues Sgrignolli et al., 2011).

Global warming and climate change are expected to affect availability of clean air, safe drinking water, and sufficient food. Diarrhoeal diseases, malnutrition, and vector borne infections, major preventable causes of AKI and deaths in the tropics, are highly climate-sensitive and are expected to worsen as the climate changes.

The impact of high disease burden is worsened by poverty, which further undermines health. The poor are exposed to greater personal and environmental health risks, are less well nourished, have less information, and are less able to access healthcare. Cultural reasons disproportionately restrict access to healthcare to certain

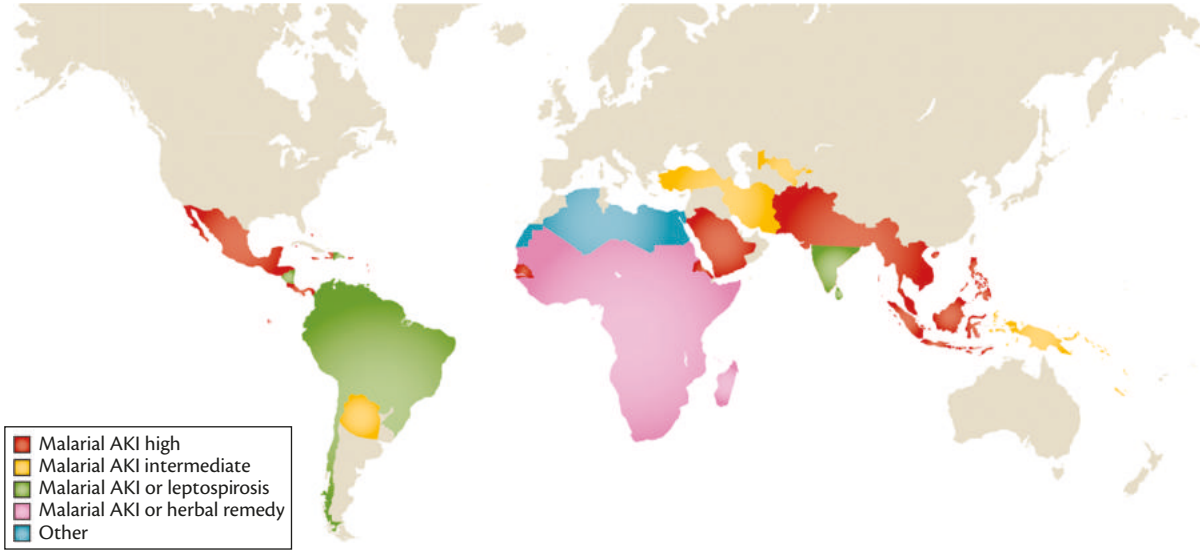

Fig. 241.1 Prevalence estimates of different causes of community-acquired acute kidney injury in the tropical zone.
From Jha and Parameswaran (2013).

sections of the societies, for example, women and children. Tropical societies are characterized by high fertility and high mortality (Sachs, 2001). The high number of children increase the workforce, but at the cost of fewer resources per child, fewer opportunities for primary and higher education, and lack of access to primary healthcare. Poverty and lack of appropriate regulations increase the risk of encounter with environmental and industrial toxins that can cause AKI.

The combined effect of high disease burden and economic underdevelopment in the tropics is reflected in lower life expectancy and higher infant and maternal mortality. Even after correcting for the level of income, the infant mortality in temperate zones is 52% lower and the life expectancy 8% higher in the non-temperate zones (Sachs, 2001). Healthcare systems in large parts of tropics are underdeveloped; specialized care is scarce and distributed unevenly. For cultural reasons, access to healthcare can be disproportionately restricted in certain sectors of society, for example, women and children. Poor access, suspicion of modern medical systems, high costs, and spiritual and cultural beliefs result in reliance on traditional medical systems. Many indigenous tropical remedies contribute to development or exacerbation of AKI (Jha et al., 1992; Chertow et al., 2005). Reliance on non-traditional systems of medical care contributes to delayed presentation, often with life-threatening complications in those with already established AKI.

Conversely, illness reduces productivity and household savings, lowers learning ability, and leads to a diminished quality of life, thereby perpetuating or even increasing poverty (Jha and Chugh, 2008). The poorer tropical societies lag behind countries of the temperate zone in scientific and technological innovation, and are unable to devise solutions for their health problems. Economic considerations prevent transposition of technological solutions appropriate for the more affluent countries. This is evident while providing renal replacement therapy (RRT) for AKI: technologically complex and expensive treatments like continuous renal replacement therapies (CRRTs) are eschewed in favour of cheaper and less demanding peritoneal dialysis.

Epidemiology of acute kidney injury in the tropics

It is difficult to form a consolidated view of epidemiology of AKI in the tropical countries because of a lack of appropriately designed large studies. Most published reports are from single centres, usually referral hospitals in urban centres, and may not reflect the true characteristics of AKI, especially from rural areas. Many patients who develop AKI in remote areas do not even manage to reach urban hospitals. Further, studies have used different denominators to calculate incidence, such as the number of hospital admissions or discharges or population served, making comparisons difficult (Abraham et al., 1989; Jha et al., 1992; Seedat and Nathoo, 1993; Thomas et al., 2000; Al-Homrany, 2003; Vukusich et al., 2004). Finally, most studies were published prior to the formulation of a uniform definition of AKI, making comparisons difficult. The reported incidence of AKI in the tropical countries ranges from 0.31 per thousand discharges (Vukusich et al., 2004) to 7.9 per thousand admissions (Noronha et al., 1997). Most of these studies did not differentiate between hospital-acquired or community-acquired AKI. About 0.1–0.25% of all admissions in Asian hospitals are for management of AKI (Aggarwal et al., 2007). AKI is recognized as the most commonly encountered renal emergency in these countries (Chugh et al., 1989; Jayakumar et al., 2006).

A unique demographic characteristic in the AKI population of the tropical countries is that they are younger than those reported elsewhere. In the West, the median age of patients with AKI has increased from 41 years in the 1950s to 61 years in the 1980s (Turney et al., 1990). In contrast, the average age of patients dialysed for AKI in India was 34.3 years (Jha and Parameswaran, 2013). Data from other tropical countries also reveal similar findings (Bamgboye et al., 1993; Seedat and Nathoo, 1993; Firmat et al., 1994; Zewdu, 1994). Most affected individuals do not have pre-existing comorbidities like hypertension, diabetes or chronic kidney disease (CKD), characteristically found in subjects with hospital-acquired AKI.

Aetiology of tropical acute kidney injury

The main causes of AKI encountered in tropical countries are shown in Table 241.1. Some of the causes have been well characterized and studied, whereas for others, the numbers are small and only a temporal association determines the cause-and-effect relationship.

It is difficult to provide a reliable estimate of the relative importance of various causes of tropical AKI, as this varies from region to region. For example, diarrhoeal diseases, falciparum malaria, leptospirosis, typhus, and envenomation are the major causes of AKI in South Asia, whereas malaria and indigenous herbal remedy-induced AKI are prevalent in Africa. The literature from Latin America is sparse, but suggests that leptospirosis, envenomation, and obstetric causes are responsible for the majority of AKI. In older studies of AKI from tropical countries, the causes were divided into medical, surgical, and obstetric categories (Fig. 241.2).

Table 241.1 Important causes of acute kidney injury in the tropics

Infections	Malaria
	Leptospirosis
	Haemorrhagic fever with renal syndrome
	Zygomycosis
	Diarrhoeal diseases
	Scrub typhus
	Dengue fever
	Melioidosis
	Typhoid
	Chlamydia
	Legionnaire disease
	Epidemic Lift Valley fever
Plant toxins	*Callilepis laureola* (impila)
	Djenkol beans
	Marking nut
	Mushroom poisoning
	Cleistanthus collinus poisoning
	Tripterygium wilfordii
Animal poisons	Snake bites
	Wasp, hornet, and bee stings
	Spider bite
	Jellyfish sting
	Scorpion sting
	Carp gallbladder or bile
Chemical nephrotoxins	Ethylene glycol
	Paraquat
	Ethylene dibromide
	Copper sulphate
	Chromic acid
Other causes	Intravascular haemolysis due to glucose 6-phosphate dehydrogenase deficiency
	Obstetrical ARF
	Heat stroke
	Natural disasters

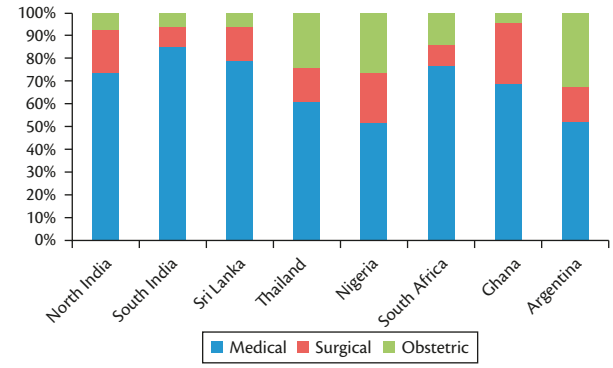

Fig. 241.2 Relative contribution of medical, surgical, and obstetric causes of acute kidney injury in different tropical countries.

The epidemiology had changed over the years with a progressive decline in obstetric and diarrhoeal AKI as a result of improved maternal care and widespread use of oral rehydration solution. Data from a large hospital showed a decline in the incidence of obstetric AKI from 22% in the 1970s to 8% in the 1990s ($P < 0.001$), whereas the surgical cases increased from 11% in the 1960s to >30% in the 1990s ($P < 0.001$) (Chugh et al., 1989). However, in contrast to the developed countries of the tropical climate where AKI due to these causes have virtually disappeared, they continue to be encountered, albeit in reduced proportions. Even within the medical group, the aetiological factors leading to development of AKI in the tropical countries cannot be compared with those in the developed countries and have changed over time (Fig. 241.3). Diarrhoeal diseases, intravascular haemolysis due to glucose 6-phosphate dehydrogenase deficiency, copper sulphate poisoning, snake bites, and insect stings, which together constitute > 40% of cases of AKI in India, are distinctly rare in Western countries (Chugh et al., 1978c, 1989, 2005).

As more patients present to tertiary hospitals because of improving economic conditions, the absolute number of patients with AKI has gone up. In a single hospital, the number of cases of severe AKI requiring dialysis showed a steady increase from 131 cases in 1992 to 1202 in the 2009. This reflects an increasing awareness of

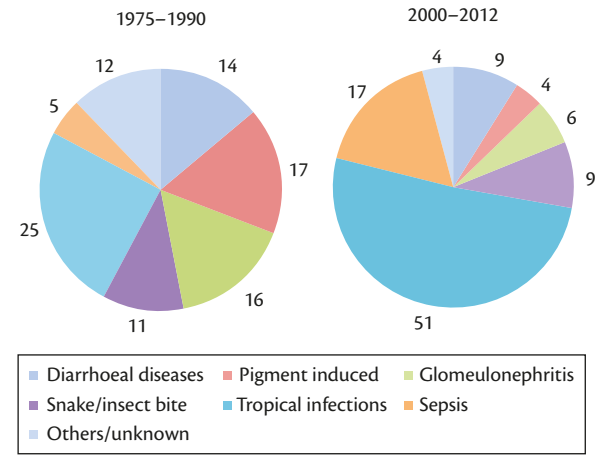

Fig. 241.3 Medical causes of acute kidney injury in a tropical hospital over two different time periods. (Jha, unpublished data).

the condition in primary health centres, leading to more frequent referral to dialysis units (V. Jha, unpublished data).

Pathophysiology of tropical acute kidney injury

The pathogenesis of tropical AKI depends on the cause. Leptospirosis causes AKI as a result of direct invasion leading to local inflammatory reaction with cellular proliferation and infiltration. Toxicity to several renal compartments can cause AKI. These include membrane components of leptospires, carp raw bile, toxic mushroom, and cottonseed oil, which exhibit tubular toxicity. Russell's viper venom and pit-viper venom are toxic to the vascular and glomerular endothelium and renal tubules (Sitprija and Boonpucknavig, 1983; Ratcliffe et al., 1989).

AKI following snake bites and insect stings can be caused through indirect pathways, such as myoglobin (rhabdomyolysis), haemoglobin (haemolysis), bile acids, oxygen free radicals, enzymes like phospholipases and proteases, and complement products (Mahasandana et al., 1980; Sitprija and Boonpucknavig, 1989; Chugh and Sakhuja, 1990; Sitprija et al., 1990; Zager, 1991). Direct endothelial injury as a result of interaction between erythrocytes parasitized by falciparum malaria and microvascular endothelium (cytoadherence) is well recognized.

Certain plant chemicals get excreted in urine and precipitate in the concentrated and acidic urine of the distal tubules. Examples are djekolic acid crystals in AKI following ingestion of Djenkol beans and oxalate crystals in AKI from star fruit juice and *Averrhoa bilimbi* (Irumban Puli) juice (Bakul et al., 2013).

A number of tropical infections and toxins produce haemodynamic alterations similar to those observed in sepsis (Barsoum et al., 2007), including generalized arterial vasodilatation with reduction in systemic vascular resistance, with secondary activation of the neurohumoral axis, sympathetic activation, activation of renin–angiotensin–aldosterone axis and non-osmotic release of vasopressin. Release of these mediators results in intrarenal vasoconstriction, leading to AKI (Schrier and Wang, 2004; Lameire et al., 2005).

Hypovolaemia is observed in severe infections due to increased vascular permeability and fluid loss from intravascular compartment. Diarrhoeal diseases and dengue haemorrhagic fever are common causes of severe hypovolaemia in the tropics.

Dialysis for acute kidney injury in the tropics

Haemodialysis is available in most tropical countries with the exception of some parts of sub-Saharan Africa, but the facilities are concentrated in urban centres and overwhelmed by the huge patient load. Being less technology intensive, peritoneal dialysis is used widely and has been shown to be equivalent to more expensive CRRT modalities (Gabriel et al., 2008; George et al., 2011). This modality is perhaps the only form of dialysis possible in remote areas (Mohandas and Chellapandian, 2004) and in small children (Kohli et al., 1995).

The impact of tropical acute kidney injury

The main victims of AKI in the tropical region are the young, active members of the societies, often the primary breadwinners of the family. Hospitalization for management of AKI leads to 'catastrophic' or 'impoverishing' health expenditure (defined as expenditures that endanger a household's ability to maintain its customary standard of living, and has been set between 5% and 20% of total household income) (Xu et al., 2003).

In addition to the high mortality, patients who survive an episode of AKI may not enjoy complete health (Ponte et al., 2008). Amongst a cohort of children with AKI discharged from a public sector hospital in India, Sinha et al. (2009) found proteinuria, hypertension, haematuria, or reduced glomerular filtration rate in 32% at 6 months and 38% after 10 years. Snake bite-induced AKI, high peak creatinine, and prolonged oliguria were associated with adverse outcomes. Late presentation is a risk factor for future development of CKD (Coca et al., 2012). Once again, the high prevalence and the relative youth of the population add to the growing burden of CKD.

Many of the specific causes of tropical AKI are discussed in other chapters. The infectious causes are covered in chapters in Section 8, and the obstetric causes in Chapter 250. The remaining portion of this chapter discusses some specific causes not described elsewhere in the book.

Intravascular haemolysis and glucose 6-phosphate dehydrogenase deficiency

Glucose 6-phosphate dehydrogenase (G6PD) is a key enzyme that protects erythrocytes from oxidant stresses. Reduction in activity leads to haemolysis and AKI in some ethnic populations in tropical countries. In India, G6PD deficiency is the commonest cause of clinically significant intravascular haemolysis, leading to AKI in about 5–10% of cases (Chugh et al., 1977b, 1978c; Sarkar et al., 1993).

The incidence of G6PD deficiency varies from 2.2% to 15% in various ethnic groups in India (Jolly et al., 1972), 13% in Saudi Arabia (Gelpi, 1965), 15% in East Africa (Allison, 1960), 20% in Nigeria (Gilles and Ikeme, 1960), and 62% in Kurdish Jews (Szeinberg, 1973). The gene for G6PD is located on the X chromosome. All males inherit the abnormal gene from their mothers who act as the carriers. Because of the inactivation of one of the two X chromosomes, the heterozygote female carriers have a subpopulation of red blood cells that are not deficient, and do not develop clinically significant haemolysis.

Clinical features

Haemolytic crisis usually develops within hours of exposure to the oxidant stress to the erythrocytes, most commonly by drugs, toxins, or infections. Commonly incriminated drugs include primaquine, sulphonamides, acetylsalicylic acid, nitrofurantoin, nalidixic acid, furazolidone, niridazole, doxorubicin, and phenazopyridine. Accidental ingestion of toxic compounds such as naphthalene balls and severe metabolic acidosis of any aetiology can also precipitate haemolytic episodes. Infections that can precipitate haemolysis include viral hepatitis, rickettsia, typhoid, and urinary tract infection.

The clinical manifestations include passage of dark (cola) coloured urine and a sudden drop in haemoglobin. In some forms of G6PD deficiency, the enzyme activity is least in the senescent red blood cells, which are rapidly destroyed. The haemolysis abates following this crisis, as the residual population of young erythrocytes

is able to deal with the continued oxidant stress. AKI is oliguric in the vast majority (Chugh et al., 1977b; Sarkar et al., 1993). Patients with additional risk factors such as dehydration and septicaemia and those taking other nephrotoxic agents are more likely to develop renal dysfunction.

Diagnosis

The diagnosis should be considered in any individual who develops AKI following an acute haemolytic episode, and the patient should be thoroughly questioned about any possible exposure to oxidant agents. A sudden drop in haematocrit, along with a rise in plasma-free haemoglobin, unconjugated hyperbilirubinaemia, and decline in plasma haptoglobin supports the diagnosis. Estimation of G6PD level in the erythrocytes by the fluorescent spot test establishes the presence of enzyme deficiency. A false-negative test may be seen during a haemolytic episode when the surviving population consists of younger erythrocytes with normal enzyme activity. It may therefore be necessary to repeat the test after the patient has recovered from the acute haemolytic episode.

Pathology

Renal histology shows features of acute tubular necrosis (ATN). The tubules may contain pigmented haemoglobin casts. Acute cortical necrosis has also been reported in rare instances (Chugh et al., 1994).

Pathogenesis

G6PD is a key enzyme of the hexose monophosphate shunt, responsible for regeneration of reduced glutathione that protects the sulphydryl (-SH) groups of haemoglobin and the erythrocyte membrane from oxidation. The oxidized haemoglobin precipitates within the red blood cells, forming Heinz bodies, resulting in haemolysis. A number of mutations in the G6PD gene give rise to variants with varying degrees of enzyme activity. The Mediterranean variant, prevalent in the Indian population, is an unstable enzyme with a very low activity, and patients with this variant exhibit a chronic anaemia. The A- variant, commonly encountered in other parts of the world, has a more stable activity. Patients with either form develop acute haemolytic episodes following oxidant stress (Beutler, 1991).

The exact mechanism of development of renal lesions following haemoglobinuria is not clear. The finding of pigment casts lends support to the hypothesis of intratubular obstruction by local precipitation of haemoglobin in acid urine. However, the development of renal insufficiency following haemoglobinaemia is unpredictable. It is not necessary for large quantities of haemoglobin to be released in the systemic circulation for development of AKI. The equivalent of 100 mL of erythrocytes, when lysed and released into human circulation, can lead to AKI (Jaenike, 1966). The severity of AKI depends upon concomitant systemic abnormalities such as volume depletion or acidosis. Haemoglobin dissociates into nephrotoxic ferrihaemate in the acidic environment of the distal nephron (Garcia et al., 1981). Braun et al. (1970), using an *in vitro* model to assess the effects of haem pigment on renal function, demonstrated the nephrotoxicity of ferrihaemate in acid urine. Other by-products of the haemolytic process, possibly the red blood cell wall or cytoplasmic constituents, could also be nephrotoxic.

Snakebite

Snakebite is an occupational hazard in the rural areas of the tropics. Of the 2700 species of snakes recognized worldwide, only 450 are venomous and are distributed mainly in the tropical and subtropical regions (Sakhuja and Chugh, 1989). According to the World Health Organization, the global annual mortality from snake bite is around 40,000, of which 23% of deaths occur in West Africa, 10% in India, and 20% in South America. Venomous snakes are classified into four families: Viperidae, which includes Russell's viper, *Echis carinatus* (saw-scaled viper), puff adder, pit viper, and rattlesnakes; Elapidae, which includes kraits, cobras, mambas, and coral snakes; Colubridae, of which the boomslang is a prominent species; and Hydrophidae or the sea-snakes.

Renal lesions have been reported following bites by all snakes except elapids. AKI is the most frequent clinically important effect of envenomation on the kidneys (Furtado and Lester, 1968; Lakier and Fritz, 1969; Sitprija et al., 1974; Sitprija and Boonpucknavig, 1979; Chugh et al., 1984; Chugh, 1989).

Information on the precise incidence of snakebite-induced AKI in different geographical regions is lacking, but largely depends upon the distribution of viperine snakes. The incidence following *E. carinatus* or Russell's viper bites in India varies from 13% to 32% (Verma et al., 1982; Chugh et al., 1984; Mathew and Rajaratnam, 1987). The reported incidence from other countries varies between 1% and 27% (Efrati and Raif, 1953; Visuvaratnam et al., 1970; Warrell et al., 1977; Sitprija and Boonpucknavig, 1979; Ramachandran, 1994).

Clinical features

Depending upon the dose injected, the presentation may vary from mild local symptoms to extensive systemic manifestations. Pain and swelling of the bitten part appear within a few minutes and may be followed by blister formation and ecchymosis. Bleeding, the major symptom of systemic poisoning, is seen in 65% of cases. This may take the form of persistent local ooze from the site of the bite, or bleeding into other organs, and may be severe enough to produce shock. The blood is incoagulable in patients with severe systemic envenomation. Sea-snake bites cause myonecrosis, resulting in severe myalgia and weakness.

The first indication of AKI is the reduction in urine volume, which may develop within a few hours of the bite (Sitprija et al., 1974; Chugh et al., 1975a, 1984). About half the cases give a history of passage of cola-coloured urine. Non-oliguric AKI is seen in < 10% of cases. Patients with severe bleeding, disseminated intravascular coagulation, or secondary sepsis may present with hypotension. Life-threatening hyperkalaemia necessitating immediate dialysis may develop in those with intravascular haemolysis. Oliguria usually lasts for 4–15 days, and its persistence indicates acute cortical necrosis (Chugh, 1989).

Investigations show coagulopathy, with intense hypofibrinogenaemia, reduction of factors V, X, and XIIIA, protein C, and antithrombin C. Depletion of factor V, X, and fibrinogen and elevation of fibrin degradation products become apparent early. Leucocytosis and elevated haematocrit due to haemoconcentration may be seen.

Management

Besides local wound care, early administration of antivenom is vital in those with evidence of envenomation as manifested by

incoagulable blood, spontaneous systemic bleeding, intravascular haemolysis, local swelling involving more than two segments of the bitten limb, and a serum fibrinogen degradation product concentration > 80 micrograms/mL (> 80 mg/L) in those reporting within 2 hours of the bite. Knowledge of the offending snake species allows administration of monovalent antivenom wherever this is available. Immunodiagnostic techniques are helpful in the easy and rapid identification of the venom antigen (Reid, 1983). ELISA has been used extensively in the rural areas of Thailand for this purpose. The currently available test, however, is not quick enough for the clinicians. Moreover, only polyvalent antivenom is available in many tropical countries and so precise identification of the snake is not essential for management. Indian studies have recommended initial administration of 20–100 mL, followed by repeat dosage of 25–50 mL every 4–6 hours until the effects of systemic envenoming disappear. A simple way to monitor the efficacy is by monitoring whole blood clotting time three to four times every day. Coagulability is generally restored within 6 hours of an adequate dose. The test must be monitored for at least 3 more days, as delayed absorption of the venom can lead to recurrence of the coagulopathy (Warrell et al., 1976). Where available, immunoassays permit serial estimation of venom levels, which guides antivenom administration. In sea-snake envenomation, patients require from 100 to 1000 units of *Enhydrina schistosa* antivenom (Reid, 1975). Other therapeutic measures include replacement of blood loss with fresh blood or plasma, maintenance of electrolyte balance, administration of tetanus immunoglobulin, and treatment of pyogenic infection with antibiotics. Increasing fluid intake, as well as rendering the urine alkaline early in the course, may prevent renal damage in patients with intravascular haemolysis. The prognosis is good in patients who present before major systemic complications develop, and who receive adequate doses of antivenom. The overall mortality rate is about 30% (Chugh et al., 1984).

Pathology

On gross examination, the kidneys are normal or slightly enlarged, and may show petechial haemorrhages. Light microscopy shows ATN in 70–80% of patients (Chugh, 1989). The tubules are lined by flattened epithelium and the lumina contain desquamated cells and hyaline or pigment casts. Varying degrees of interstitial oedema, inflammatory cell infiltration with eosinophils, mast cells, and hyperplastic fibroblasts, and scattered areas of haemorrhage may be seen (Date and Shastry, 1982). Electron microscopy reveals dense intracytoplasmic bodies representing degenerated organelles. Sitprija and Boonpucknavig (1977) demonstrated electron-dense mesangial deposits in patients bitten by cobras and green pit vipers. Other lesions include acute cortical necrosis, acute interstitial nephritis, necrotizing vasculitis involving interlobular arteries, and occasionally crescentic glomerulonephritis (Seedat et al., 1974; Sitprija et al., 1982). Acute cortical necrosis carries the worst prognosis and is seen in about 20–25% of AKI cases following Russel's viper and *E. carinatus* bites (Chugh et al., 1984).

Pathogenesis

The pathogenetic mechanisms that lead to AKI include direct nephrotoxicity of venom, hypovolaemia, haemolysis, myoglobinuria, and disseminated intravascular coagulation.

The kidney is particularly vulnerable to the direct cytotoxic effects of the snake venom because of its high blood flow rate and the capacity to concentrate these substances (Harding and Welch, 1980). Rats injected with the venoms of *Bothrops jararaca, Agkistrodon piscivorus*, and rattlesnake developed increased excretion of tubular enzymes and histopathological changes of ATN (Raab and Kaiser, 1966; Schmidt et al., 1976; Burdmann et al., 1993). Ratcliffe et al. (1989) showed a dose-dependent decrease in inulin clearance in the isolated perfused rat kidney following administration of Russell's viper venom. Willinger et al. (1995) showed that Russell's viper venom causes extensive destruction of the glomerular filter, lysis of vessel wall, and epithelial cell injury in all segments of the tubule in experimental animals. However, the occurrence of these lesions has not been confirmed by all workers (Chugh et al., 1984). Pernow et al. (1989) have shown that the structure of some of the snake venoms, including the sarapotoxin of the Israeli burrowing asp, is similar to the potent vasoconstrictor, endothelin-I. Vasculotoxic factors have been isolated from the venoms of several snakes, including *E. carinatus, Vipera palastinae, Agkistrodon halys, B. jararaca*, and Habu snake. Studies using the Habu snake venom have shown development of mesangiolysis followed by proliferation of mesangial cells and extracapillary proliferation (Morita et al., 1978; Morita and Churg, 1983).

Hypotension and circulatory collapse secondary to bleeding, depression of the medullary vasomotor centre or the myocardium, arteriolar dilatation, and increased vascular permeability, as shown with crotalids (Mebs, 1970; Minton, 1971), *Vipera palastinae* and *Bitis arietans* contribute to AKI. Intravascular haemolysis has been observed following bites by Russell's viper and *E. carinatus* bites in humans and experimental animals (Chugh et al., 1975a; Chugh and Singhal, 1981). The haemolysis results from the action of phospholipase A2, and a basic protein called 'direct lytic factor'. Phospholipase A2 forms 70% of the venom content of Russell's viper and acts on plasma lecithin, leading to the production of haemolytic lysolecithin (Condrea et al., 1964; Chugh et al., 1975a). Microangiopathic haemolytic anaemia has been recorded following *Agkistrodon rhodostoma* (Rubenberg et al., 1967), Russell's viper (Chugh et al., 1975a), puff adder (Warrell et al., 1975), and gwardar (Harris et al., 1976) bites and may be of pathogenetic importance in the development of AKI. Bites by sea-snakes produce severe muscle necrosis and the resulting myoglobinuria, especially in the presence of other factors such as dehydration and acidosis, can give rise to AKI.

Disseminated intravascular coagulation has been observed following viper bites in experimental animals as well as humans. Infusion of Russell's viper or *E. carinatus* venom into rhesus monkeys is followed by development of disseminated intravascular coagulation within 2 hours (Lakier and Fritz, 1969; Sitprija et al., 1974; Warrell et al., 1977; Chugh, 1989). The procoagulant factors in the venom activate factors V and X, and the subsequent activation of the coagulation cascade leads to rapid thrombin formation. The fibrinolytic activity is either due to direct action of the venom or a physiological response to fibrin deposition. Phospholipase A2 also leads to platelet aggregation. The demonstration of fibrin thrombi in the renal microvasculature, both in clinical and experimental studies, confirms the role of disseminated intravascular coagulation in the genesis of renal lesions (Chugh et al., 1975a, 1984).

There are differences between venoms of snakes from different geographic regions. This may partly explain the poor efficacy of antivenoms that are used in areas distant from source of immunizing venoms.

Bee, wasp, and hornet stings and spider bites

Honeybees, yellow jackets, hornets, and paper wasps, stinging insects belonging to the order Hymenoptera, are found in most tropical countries. An isolated sting by these insects may be followed by no more than a local allergic reaction. A large dose of the venom, leading to systemic symptoms may be injected when an individual is attacked by a swarm of insects (Chugh et al., 1976a; Sakhuja et al., 1988; Sert et al., 1993). These include vomiting, diarrhoea, hypotension, loss of consciousness, and occasionally AKI. Patients with AKI have been reported to receive hundreds of stings. AKI following bee or hornet stings is secondary to haemolysis, rhabdomyolysis, or both (Munoz-Arizpe et al., 1992; Sert et al., 1993). Haemolysis results from the direct action of a basic protein fraction and melittin in these venoms, and indirectly by phospholipase A (Joshua and Ishay, 1973; Haberman, 1977). Rhabdomyolysis has been attributed to polypeptides, histamine, serotonin, and acetylcholine present in hornet and wasp venoms (Venters et al., 1961). Sandbank et al. (1973) have postulated a direct nephrotoxic role of these venoms based on evidence obtained from their experimental studies. Renal biopsy invariably reveals ATN. Sometimes stings by a single insect can cause AKI secondary to haemolytic uraemic syndrome (Kumar et al., 2013). In contrast to bees and wasps, a single spider bite may introduce enough venom to produce AKI (Muehrcke, 1969, pp. 190–1), especially in children. Venom of the spider *Sicarius* causes disseminated intravascular coagulation and AKI (Kibukamusoke et al., 1984).

Glomerulonephritis

Various forms of rapidly progressive glomerulonephritis and post-infectious glomerulonephritis constitute about 10% of all cases of AKI seen in the tropics. The incidence of AKI associated with the post-infectious forms of glomerulonephritis has declined in the Western countries to about one-tenth of that observed in the 1950s (Case Records of the Massachusetts General Hospital, 1995). However, it continues to be a significant cause of AKI, especially in the paediatric population, in the tropical countries. The other forms of rapidly progressive glomerulonephritides giving rise to AKI are similar to those seen in the temperate zone and are discussed elsewhere (see Section 3 of this book).

Acute kidney injury secondary to herbs and toxins

The spectrum of toxin exposure in the tropical climate is substantially different from that seen in the rest of the world. Toxins may be of chemical or plant origin. Exposure may be accidental, either as an occupational hazard or when a toxic substance is mistaken for some non-toxic agent, whereas many are consumed with a suicidal or homicidal intent. The true incidence remains largely uncertain because of the non-specific nature of the structural and functional abnormalities. A good history is pivotal to the diagnosis, and exposure to prescription and non-prescription drugs, herbal remedies, industrial chemicals, fertilizers, paints, alcohol, or other forms of potentially contaminated intoxicants should be asked about. Traditional medicines form a special class of nephrotoxins encountered in the developing countries. In many cultures, these agents are obtained from a traditional healer or a witch-doctor, a person with considerable authority who also acts as a spiritual leader, historian, herbalist, and exorcist. The popularity of these healers is directly related to a combination of ignorance, poverty, lack of medical facilities in rural areas of the tropics, lax legislation, and widespread belief in indigenous systems of medicine (Gold, 1980; Joubert, 1982; Joubert and Sebata, 1982; Jha and Rathi, 2008). The indications for taking such medicines range from minor ones like constipation, impotence, and menstrual disorders to serious disorders like cancer and renal failure. Many preparations are well known to be abortifacients. Great importance is attached to regular bowel movement in many tropical societies, and a number of these substances induce vomiting and/or diarrhoea, often to the point of producing hypotension and AKI.

Poisonings with traditional medicines is an important cause of mortality in many African countries. In a Pretoria hospital, 86.58% of all deaths from acute poisoning were due to traditional medicines administered by traditional healers. At least eight remedies were associated with haematuria and AKI (Joubert, 1982). About a quarter of all AKI due to medical causes seen over a 2-year period at the University of Nairobi, Kenya were related to the use of herbal remedies (Otieno et al., 1991). In another series from Africa (Seedat, 1978), one-third of 150 cases with AKI were due to a herbal medication. Similar figures have been reported from several other African hospitals (Lowenthal et al., 1974; Buchanan and Cane et al., 1976). Personal communications with nephrologists in several tropical countries suggest that the incidence is much higher than what is commonly reported. In addition to oral route, many of these substances are administered as enemas. The enemas consist of mixture of herbs, barks, roots, leaves, and bulbs, and are administered through a truncated cow's horn or hollow reed. Increasing urbanization and industrialization have brought in the use of potent chemicals, for example, paint thinners, turpentine, chloroxylenol, ginger, pepper, soap, vinegar, copper sulphate, and potassium permanganate. AKI has been reported following the use of tribal enemas (Dunn et al., 1991).

Callilepis laureola (impila) poisoning

Callilepis laureola, a herb with tuberous rootstock, grows in South Africa, Zambia, Zaire, Zimbabwe, and neighbouring countries. An extract of the tubers is used as a traditional remedy for various illnesses. The extract is taken orally or given as an enema or douche. According to some estimates, impila is used by > 50% of the population in Natal, and poisoning is amongst the commonest causes of AKI in the Black population of South Africa (Wainwright and Schonland, 1977; Seedat, 1978; Seedat and Nathoo 1993).

Clinical features

Toxic symptoms occur in < 24 hours in 40% and within a few days in 72% of the patients (Wainwright and Schonland, 1977; Seedat, 1978; Watson et al., 1979). The early clinical manifestations are gastrointestinal symptoms, including abdominal pain and vomiting. Hypoglycaemia is invariable and leads to the alteration of consciousness and convulsion. Patients with severe poisoning may show abnormal liver function and even frank jaundice. Renal

failure usually precedes hepatic dysfunction. The toxic effects are more severe in children. Treatment is supportive. Correction of hypoglycaemia and volume and electrolyte replacement must be instituted. The mortality rate is > 50%.

Pathology and pathogenesis

Renal histological lesions are those of ATN (Wainwright and Schonland, 1977). Interstitial oedema with dense interstitial infiltration is common. The precise mechanism of renal failure is not clear. Direct nephrotoxicity is a possibility. An alkaloid in the tuber of the plant, atractyloside, is believed to have nephrotoxic and hypoglycaemic effects (Wainwright and Schonland, 1977). The presence of this compound can be confirmed by several assays in patients with impila poisoning (Bye et al., 1990; Laurens et al., 2001). It has been shown to inhibit oxidative phosphorylation in experimental studies (Bye et al., 1990). Gastrointestinal upset leading to volume depletion resulting in renal ischaemia may also contribute to the renal dysfunction.

Djenkol bean poisoning

The djenkol (jering) trees (*Pithecolobium lobatum* and *Pithecolobium jiringa*, Family Mimosaceae) grow in Indonesia, Malaysia, Southern Thailand, and Myanmar. Considered a local delicacy, djenkol beans are consumed raw or in fried or roasted form. Raw djenkol beans consumed in large amounts can cause poisoning, especially if associated with low fluid intake (Reimann and Sukaton, 1956; Areekul and Kirdudom, 1977; Eiam-Ong et al., 1989; H'ng et al., 1991; Sesagothy et al., 1995). AKI has been reported most commonly from Java and Sumatra in Indonesia and Malaysia.

Clinical features

The symptoms of poisoning (djenkolism) may occur immediately after ingestion of beans or as late as 36 hours after consumption, and include dysuria, lumbar and lower abdominal pain, hypertension, haematuria, and oligoanuria (Reimann and Sukaton, 1956; Eiam-Ong et al., 1989). Urinalysis shows the presence of protein and microscopy shows erythrocytes, epithelial cells, and needle-like crystals of djenkolic acid. The majority of victims recover within a few days. A great variation has been noted in individual susceptibility to the toxic effects of this bean. Toxicity may be caused by a single bean in one individual, while it may take 20 beans to cause poisoning in another.

Management

High fluid intake and alkalinization of urine helps in dissolving the crystals. Occasional cases may need irrigation of bladder or renal pelvis with alkaline solution. Djenkolism may be prevented by pre-treatment of the beans by boiling or consumption of small amounts of the raw beans with liberal fluid intake.

Pathogenesis

The bean contains djenkolic acid, ($C_{11}H_{23}N_3S_3O_6$), a sulphur-rich cysteine thioacetal of formaldehyde, which forms needle-like crystals in concentrated acid urine, causing obstruction of renal tubules. The crystals may act as a nidus for stone formation (Areekul et al., 1978). In animal experiments, continuous intravenous infusion of djenkolic acid decreases the glomerular filtration rate and renal plasma flow in a dose-dependent fashion (S. Eiam-Ong and V. Sitprija, unpublished data). ATN is the dominant lesion in these animals, with crystals observed in only a few (Areekul et al., 1976).

Other plants

Several plants are used as traditional medicines, and may cause renal failure through their indirect side effects (Table 241.2). There is no scientific evidence of a direct nephrotoxicity. Since vomiting and diarrhoea are frequently observed following consumption of these medicinal plants, AKI could be attributed to volume depletion.

Copper sulphate poisoning

AKI following the ingestion of copper sulphate has been reported from the Indian subcontinent (Wahal et al., 1963; Chuttani et al., 1965; Chugh et al., 1977a). The extensive use of copper sulphate in the leather industry, its low cost, and easy availability are the main reasons for its usage as a mode of suicide amongst those of poor socioeconomic groups. The incidence has shown a significant decline in the past two decades (Chugh et al., 1989). Another form of copper sulphate poisoning has been reported from Nigeria where ingestion of 'holy water' given by spiritual leaders was followed by intravascular haemolysis and AKI. Chemical analysis of the green water showed a very high copper content (Sontz and Schweiger, 1995).

Clinical features

Symptoms appear within minutes of ingestion, and consist of a metallic taste, excessive salivation, burning retrosternal and epigastric pain, nausea, and repeated vomiting. The vomitus is blue-green in colour and turns deep blue on addition of ammonium hydroxide, allowing it to be differentiated from bile. Diarrhoea, haematemesis, and melaena follow. In severe cases, jaundice, hypotension, convulsions, and coma may develop (Chuttani et al., 1965; Chugh et al., 1977a; Sontz and Schweiger, 1995). Acute pancreatitis, myoglobinuria, and methaemoglobinaemia have also been reported (Chugh et al., 1975b, 1977a). Renal failure is seen in 20–25% of cases and is invariably oliguric (Wahal et al., 1963; Chuttani et al., 1965). Physical examination reveals mild icterus and extensive oropharyngeal ulceration. Death may occur in the acute phase from gastrointestinal bleeding or hepatic or renal failure. In patients who survive this phase, diuresis ensues after 7–10 days and is followed by gradual recovery.

Management

Gastric lavage should be done using 1% potassium ferrocyanide solution, which leads to formation of insoluble cupric ferrocyanide. Egg white or milk can be administered as an antidote. Emesis should not be tried. An upper gastrointestinal endoscopy is necessary to determine the degree and extent of ulceration. Volume deficit should be corrected with crystalloids and patients with haemolysis should receive blood transfusions. The hyperkalaemia is often severe and sustained because of the ongoing haemolysis and requires early and frequent dialysis.

Pathogenesis

Direct nephrotoxicity, copper-induced haemolysis and fluid loss appear to be the main pathogenetic factors for development of AKI

Table 241.2 Plant nephrotoxins causing acute kidney injury reported from tropical countries

Plant	Reported from	Active molecule	Renal manifestations	Other manifestations
Amanita phalloides (deathcap), *A. virosa* (destroying angel)	Many countries	Phallotoxin, amatoxin	ATN	Diarrhoea, jaundice
Catha edulis (khat leaf)	East Africa, Arab peninsula	S-cathione, ephedrine	ATN	Hepatotoxicity
Cleistanthus collinus (Oduvan)	India	Cleistanthin A and B, collinusin, diphylline	AKI	Hypotension, hypokalaemia, arrhythmia
Colchicum autumnale (meadow saffron)	Turkey	Colchicine	ATN	Haemorrhagic gastroenteritis, muscle paralysis, respiratory failure
Crotalaria laburnifolia (Bird flower)	Zimbabwe, Sri Lanka	Pyrrolizidine alkaloids	ATN, HRS	Hepatic veno-occlusive disease, pulmonary injury, thrombocytopenia
Dioscorea quartiniana (yam)	Africa, Asia	Dioscorine, dioscin	ATN	Convulsions
Euphorbia metabelensis (spurge)	Zimbabwe	Irritant chemicals in plant latex	ATN	Thrombocytopenia
Larrea tridentate (chaparral)	Chile, South Africa	Nordihydroguaiaretic acid, s-quinone	Renal cysts, Renal cell carcinoma	Hepatic failure
Propolis	Brazil	Unknown	AIN	Contact dermatitis
Rhizoma rhei	Hong Kong	Anthraquinones (Emodin, Aloe-Emodin)	AIN	None
Securidacea longepedunculata (violet tree, wild wisteria)	Congo, Zambia, Zimbabwe	Methylsalicylate, securinine, saponins	ATN	Vomiting, diarrhoea
Sutherlandia frufesces (cancer brush), Dodonaea angustifolia	South Africa	Unknown	AIN	Pulmonary embolism
Takeout roumia	Morocco, Sudan	Paraphenylenediamine	ATN	Rhabdomyolysis
Taxus celebia (Chinese yew)	Asia	Flavonoid	ATN, AIN	Hepatitis, haemolysis, DIC
Thevetia peruviana (yellow oleander)	India, Sri Lanka	Cardiac glycosides	ATN	Liver failure, cardiac arrhythmias
Tripterygium wilfordii Hook F (Thunder god vine)	Taiwan	Triptolide	ATN	Diarrhoea, shock
Uncara tomentosa (Cat's claw)	Peru	Alkaloids, flavonols	AIN	Diarrhoea, hypotension, bruising, bleeding gums

AIN = acute interstitial nephritis; AKI = acute kidney injury; ATN = acute tubular necrosis; HRS = hepatorenal syndrome.

Adapted from Jha, V. (2010). Renal diseases in the tropics. In D. A. Warrell, T. M. Cox, and J. D. Firth (eds.) *Oxford Textbook of Medicine* (5th ed.), pp. 4082–95. Oxford: Oxford University Press.

(Metz, 1969; Chugh et al., 1977a). High copper concentrations can produce a considerable oxidant stress and can cause haemolysis through interference with the activity of a variety of enzymes, such as Na-K ATPase, glucose 6-phosphate dehydrogenase, glutathione reductase, and catalase. In experimental animals, copper sulphate has been shown to produce direct toxic damage to the proximal tubules.

Pathology

Renal histology usually shows ATN. There is extensive necrosis of the proximal tubules with marked interstitial oedema. Pigmented haemoglobin casts may be noted in patients with intravascular haemolysis. Acute cortical necrosis has been seen rarely.

Heat stroke

Heat stroke occurs when body thermal regulatory mechanism is unable to dissipate an adequate amount of heat, leading to a rise in body temperature. The exact incidence of heat stroke is not known, but a significant number of cases are observed in summer months in tropical areas with high ambient temperatures and high relative humidity (Shibolet et al., 1967; Sanguangvong et al., 1988). The condition affects mainly elderly individuals living in poorly ventilated places (Levine, 1969), but can develop in healthy adults after heavy physical exertion in a hot and humid environment (Schrier et al., 1967).

The characteristic features are hyperpyrexia, hyperventilation, nausea, vomiting, cramps, ataxia, incoherent speech, followed by loss of consciousness, hypotension, and vascular collapse. As the syndrome progresses, oliguric renal failure may develop. Laboratory data show haemoconcentration, hypernatraemia, hypocalcaemia, and elevated transaminases, aldolase, and creatine phosphokinase. Haemolysis, myoglobinuria, and disseminated intravascular coagulation are seen in severe cases. Urinalysis reveals high specific gravity, proteinuria, red blood cells, and granular and erythrocyte casts. Presence of multiorgan failure indicates a poor prognosis.

Hyperkalaemia is often striking because of associated rhabdomyolysis. Renal function usually shows a complete recovery.

The pathogenesis is multifactorial, with hypovolaemia, hypotension, myoglobinuria, and disseminated intravascular coagulation contributing to the development of renal failure. Extreme hyperthermia may directly damage renal tubular cells. The pathology shows ATN.

Management consists of rapid cooling by any method with continuous monitoring of temperature. Rehydration should be instituted with care because the fluid requirement in most patients is only 1000–1200 mL. The central venous pressure should be monitored to guide fluid therapy if hypotension persists despite successful cooling.

Hypothermia

Hypothermia is defined as a central core temperature of 35°C or less. Cases of hypothermia are encountered mainly in the poor, homeless, and destitute during winter months (Reuler, 1978). With the onset of hypothermia, there is a decrease in the oxidative tubular activity and sensitivity to antidiuretic hormone. This results in a reduced sodium and water reabsorption and increase in urine flow. AKI has been reported rarely (Sandhu et al., 1992) and probably is a consequence of hypovolaemia, hypotension, rhabdomyolysis, or acute pancreatitis. Management includes the institution of adequate supportive measures and both external and core rewarming. Peritoneal or haemodialysis using warm dialysate (43–44°C) has been used successfully for this purpose even in patients without renal failure (Lash et al., 1967; Pickering et al., 1977). External warming alone may precipitate hypovolaemia. Renal biopsy shows ATN (Sandhu et al., 1992).

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CHAPTER 242

Acute kidney injury and hantavirus disease

Jan Clement

Epidemiology of haemorrhagic fever with renal syndrome

Epidemics of a then unknown but serious infectious renal illness, called 'trench nephritis', were rampant in the rat-infested trenches of World War I on both sides of the front ('Néphrite de guerre', 'Feldnephritis'), and already > 100 years ago, were supposed to be caused by 'a filtrable agent', a former denomination of 'a virus' (Clement, 2003a). The disease was rediscovered by Western medicine and documented by renal biopsies > 60 years ago during another armed conflict, the Korean War (1951–1953) (Clement, 2003a). Nevertheless, haemorrhagic fever with renal syndrome (HFRS) remains worldwide probably the most underestimated form of acute kidney injury (AKI), despite overwhelming evidence of its global ubiquity. Indeed, recent global reviews of AKI describe prerenal azotaemia as the leading cause of AKI, followed by acute tubular necrosis (ATN), as the major cause of intrinsic AKI, and to a lesser degree acute tubulointerstitial nephritis (ATIN). ATIN is nowadays considered as mainly caused by drugs, antibiotics, and non-steroidal anti-inflammatory drugs (NSAIDs) in particular (Lameire et al., 2005; Bellomo et al., 2012; Lameire et al., 2013; Prakash et al., 2013). However, HFRS, or even hantaviral diseases (HTVDs) as a whole, should definitely be added to this list, since it is a frequent and particular form of viral ATIN (Lähdevirta, 1971; Lähdevirta et al., 1978; van Ypersele et al., 1986; Ferluga and Vizjak, 2008; Lordemann et al., 2009), deserving more attention in the literature. Indeed, HFRS, and even the renal participation in the American so-called hantavirus pulmonary syndrome (HPS) has distinctive clinical, laboratory, and pathogenic features that sets it apart from most, if not all, other ATIN forms. Moreover, virtually all HTVD cases eventually end up in hospital, where they often develop further complications, potentially leading to a skewed diagnosis of so-called hospital-acquired AKI (HAAKI), thereby worldwide blurring the demarcation line between community-acquired AKI (CAAKI) and HAAKI. Hantavirus is a truly cosmopolite virus with obvious renal tropism, highly endemic in many areas of the world, and particularly in the Old World, making it, together with leptospirosis, the most global zoonosis. A recent estimate of HFRS incidence worldwide is 150,000–200,000 cases yearly, of which > 90% are localized in the Far East (Clement et al., 2007, 2010a). Moreover, HFRS is, with leptospirosis, the only AKI (and ATIN) form, which can occur in massive epidemics, involving thousands of cases in the Far East and hundreds of cases in Russia and Europe. In China alone, a grand total of > 1.4 million HFRS cases have been reported up to 2010, with > 46,000 registered deaths, corresponding with a a fatality rate of 3.29%. The record year was 1986, with 115,985 confirmed cases, or an all-high incidence of 11.08/100,000, and 2561 (2.2%) deaths (Liu et al., 2011). In Europe and European Russia, > 225,000 HFRS (mostly the milder nephropathia epidemica (NE)) cases have been registered so far, with > 75% of these in European Russia. In the 1978–1992 period alone, a total of 65,906 cases have been registered in the European part of Russia. In some peak years, Russia witnessed > 10,000 cases/year, for example, 11,413 in 1985 (World Health Organization, 1993). Registered HFRS numbers in Western Europe also show epidemic proportions (e.g. 3259 in Finland in 2008, and 2824 in Germany in 2012), probably as a result of global warming (Clement et al., 2010a, 2011a; Krüger et al., 2013). The total of reported HFRS cases from 23 European countries (except France and the United Kingdom however) was 4529 in 2008, and 4200 in 2010 (European Centre for Disease Prevention and Control, 2013, pp. 142–5). Up to now, these impressive and ever increasing figures are apparently never taken into account for calculating and discussing global AKI or even CAAKI in developed or developing countries (Clement et al., 2013b). Nevertheless, already in the clinical description of the very first (1985–1986) NE cases in Belgium and France, totalling 76, van Ypersele de Strihou et al. noted AKI in all cases, with peak serum creatinine values between 142 and 1575 μmol/L (van Ypersele de Strihou et al., 1986). In subsequent HFRS series, AKI was reported in up to 94% (Lee and van der Groen, 1989; Mustonen et al., 1994). In a clinical analysis of 55 cases of the first reported NE outbreak in Belgium (1993), a peak serum creatinine of > 1.2 mg (> 105 μmol/L) was noted in 84% of cases, whereas a peak value of > 4.5 mg% (> 400 μmol/L) was reached in 32% of cases (Colson et al., 1995). Finland, with its population of 5.3 million, is now for HFRS (exclusively NE) the most endemic country in the world, with a total of 22,681 registered NE cases between 1995 and 2008 (annual average incidence 31/100,000) of which 52% had to be hospitalized, good for 50,000 hospital days (Makary et al., 2010; Vaheri et al., 2013). Thus, with an estimated true incidence of at least 6000 *Puumala virus* (PUUV) infections/year, Finland equals or surpasses, with one single 'emerging' CAAKI, the reported mean incidence given for all other AKI forms combined, HAAKI included, in most other Western countries (Lameire et al., 2005, 2013; Bellomo et al., 2012). Moreover, NE is now the most prevalent serious febrile condition in Finland, after influenza (Makary et al., 2010). In Germany, and

since the record year 2012 (2824 cases), HTVD is now among the five most common notifiable viral diseases (Krüger et al., 2013), and is thus rapidly becoming the single most cause of CAAKI in this Western country, and lately perhaps of AKI altogether, just like in Finland.

HFRS, or at least its European PUUV-induced form NE, should thus not be considered as an esoteric rare disease, but is still under evaluated and/or often missed, even in West-Europe (Krüger et al., 2013). In an early (1985–1986) and globally the most important sero-epidemiological study performed in 21,435 healthy Belgian civilian and military blood donors, immunofluorescent assay (IFA) screening with the Korean hantavirus prototype *Hantaan virus* (HTNV) and/or with the European prototype PUUV yielded 287 immunoglobulin (Ig)-G positives, or a prevalence of 1.33%. A renal staging in 64 PUUV-IgG positives revealed no abnormalities, and no elevated blood pressure. Moreover, none of these study subjects recalled a prior hospital admission for AKI (Clement and van der Groen, 1987). In more endemic countries like Finland and northern Sweden, the average IgG seroprevalence is about 5% (Ahlm et al., 1994; Jonsson et al., 2010). However, comparing NE incidence (recorded over 14 years) with IFA IgG PUUV-antibody prevalence in a highly endemic area of Sweden, the IgG antibody prevalence rate in the oldest age groups (> 60 years) appeared to be 14–20 times higher than the accumulated life-risk of being hospitalized with registered NE for men and women, respectively. This observation proves that the vast majority of PUUV infections and their transient renal involvement passes unnoticed, or is misinterpreted as a 'bad flu' (Niklasson et al., 1987).

In temperate Europe, beechnuts are the staple food for bank voles, and so-called mast years with heavy beechnut production in autumn may facilitate higher winter survival and earlier winter breeding, resulting in a bank vole populations 10–20 times the norm, inducing local NE outbreaks (Clement et al., 2009, 2010a). Hypothesized for the first time after the 1993 Franco-Belgian NE outbreak (Clement et al. 1994), 3- to 2-yearly 'mast years' appeared significantly linked to NE peaks exactly each time 1 year later in Belgium (Clement et al., 2009), France (Clement et al., 2010a), and Germany (Clement et al., 2011b). The summer of 2003 was by far the hottest summer ever recorded so far in Europe, and induced in autumn 2004 a very large mast production in Belgium, France, and Germany, leading 1 year later (2005) to the then highest joint NE peak (> 1000 cases) ever registered for these three countries combined (Clement et al., 2011b). This 'mast hypothesis' explains why (humid) regions with a dense beech coverage in West Europe are also areas highly endemic for NE: a rare example of tree ecology having an impact on a kidney disease, and a phenomenon which can be studied by satellite monitoring combined with climatic data gathering (Barrios et al., 2010; Amirpour Haredasht et al., 2012), and which is even predictable by a so-called multiple input–single output (MISO) mathematical model (Amirpour Haredasht et al., 2011). (Some aspects on the general epidemiology, as well as virology and mode of disease transmission, are discussed in Chapter 188.)

Clinical features

It is now clear that all symptoms typical for HFRS and HPS are both caused by vascular leakage, the degree of which, however, is extremely variable, depending not only on the species of the infecting hantavirus, but also substantially on the immunological response of the human host itself (Maes et al., 2004, 2006). Moreover, it should be realized that about 85% of PUUV infections are very mild or subclinical (Ahlm et al., 1994; Clement et al., 2007), thus very often leading to a missed diagnosis. To a lesser degree, the same rule may apply also to the other, more severe hantaviral pathogens.

Aspecific flu-like presenting symptoms are followed within days by (unapparent) laboratory signs, and eventually later by clinical signs, indicating a renal involvement. Signs of (transient) other multiorgan involvement (lung, liver, heart, etc.) are not exceptional but are all transient, if the patient survives. Fever is present in 100% of all HFRS cases, followed by headache (85–100%), myalgia (>90%), backache (82–95%), abdominal pain (64–92%), and nausea (61–91%) (van Ypersele de Strihou et al.,1986; Lee and van der Groen, 1989; Settergren, 2000; Jonsson et al., 2010). The so-called three pains of HTVD, headache, orbital pain, and lumbar pain, are rarely seen together in other AKI forms, and even in other acute infections (Clement et al., 2007). Lumbalgia, caused by stretching of the renal capsule due to renal swelling, can be unilateral, and so severe as to evoke, together with the haematuria, a renal colic (van Ypersele de Strihou et al., 1986). In exceptionally severe NE cases, the renal swelling can be so intense that spontaneous 'internal rupture' with perinephric haemorrhage ensues (Clement et al., 2001). Pain and tenderness in the upper right quadrant of the abdomen can be caused by (transient) acalculous cholecystitis (Keyaerts et al., 2004), but may also suggest an acute appendicitis, in view of the fever, leucocytosis, and high C-reactive protein (CRP). Initial and heavy, but transient proteinuria (94–100%) and haematuria (58–85%) are the first subsequent signs of renal involvement, confirmed by oliguria in 37–70% of HFRS cases (van Ypersele de Strihou et al., 1986; Lee, 1989; Mustonen et al., 1994; Settergren, 2000; Jonsson et al., 2010). Proteinuria is an early and constant sign in all hantavirus infections, even in the New World cases of HPS, which have not the kidney, but the lung as main target organ. In fact, proteinuria as presenting symptom has been noted in up to 100% of South American HPS cases (Enria et al., 2000; Peters and Khan, 2002). The degree of proteinuria in NE can be extremely high, up to 30 g/L. Despite this, a full-blown nephrotic syndrome never develops, since spontaneous remittance mostly within weeks without sequelae and with a normal blood pressure is the rule (Mäkelä et al., 2000; Settergren, 2000; Miettinen et al., 2006; Rabb and Colvin, 2007).

Thrombocytopenia is an early and very reliable sign, found in 52–78% of HFRS cases (as in most American HPS cases), but probably reaches > 90% if assessed early enough after the onset of symptoms (Lee and van der Groen , 1989; Colson et al., 1995; Jonsson et al., 2010). A case presenting without early proteinuria and without early thrombocytopenia is probably not a hantavirus case. Moreover, the degree of thrombocytopenia is a severity index, and a further drop in the number of platelets during the clinical course is heralding very often a further decline in renal function, whereas the opposite is also true (Rasche et al., 2004). These varying degrees of (transient) renal functional impairment are however only the tip of the iceberg in all Old World hantavirus infections, since even non-hospitalized cases often show substantial but temporary rises in serum creatinine, as is apparent in medical files of general practitioners in hyperendemic regions (Jan Clement, personal observation).

Although very common (70%) and unique so far to hantavirus infections, diverse ocular abnormalities are often missed, but form a specific and early clinical sign, particularly well documented in NE. In a prospective study, reduced visual acuity was noted in up to 87% of cases, due to acute myopia, mainly as a result of oedematous thickening of the lens. Intra-ocular pressure is often lowered, but exceptionally the opposite, that is, acute glaucoma can occur, even as a presenting urgent sign (Hautala et al., 2011). Periorbital oedema is also very characteristic. Conjunctival suffusion as a haemorrhagic sign ('the red eye symptom') is much less present in NE than it is in *Seoul virus* (SEOV) (23%), or in HTNV infections (79%) (Lee and van der Groen, 1989). Relative bradycardia is another typical but often overlooked sign, consisting of a slow pulse frequency (< 60 beats/min), despite high fever on admission, present in up to one-third of NE cases (van Ypersele de Strihou et al.,1986; Colson et al., 1995). It is not clear why acute myopia and relative bradycardia are so far never mentioned in American HPS series.

Despite the theoretical notion that hantaviruses are the only 'viral haemorrhagic fever' (VHF) pathogens present in the entire northern hemisphere, haemorrhagic symptoms are rare (≤ 20%) and minor in NE (petechiae, nose bleeding, etc.), in contrast to the more severe forms induced by HTNV and/or *Dobrava-Belgrade virus* (DOBV) in the Far East, respectively in the Balkans, where severe haemorrhagic complications and shock often lead to death (Lee and van der Groen, 1989). Haemorrhagic necrosis of the pituitary gland (Sheehan's syndrome), of the adrenals, and of the right cardiac atrium have been described as complications in severe HTNV-induced infections, but are extremely rare in NE.

Investigations

Every patient suspected of having a hantavirus infection should at admission undergo not only the classical routine blood examinations, but also thorough and repeated urine examinations and ultrasound (US) imaging of the abdomen. A clinical suspicion of HFRS can only be secured by serologic tests, nowadays mainly and preferentially based on specific IgG and particularly IgM enzyme-linked immunosorbent assay (ELISA), bearing in mind that diagnostic IgM-positivity can take more than a week to develop, particularly and somewhat paradoxically in the most severe cases, where it can even remain totally negative. Given the propensity of serological cross-reactions, determination for academic purposes of the exact species of infecting hantaviruses is only possible by specialized confirmation tests, such as RT-PCR on acute serum or cumbersome neutralization tests on convalescent serum (Maes et al., 2004, 2009a).

Inflammatory lab anomalies such as elevated erythrocyte sedimentation rate, CRP, lactate dehydrogenase (LDH), and white blood cell count reach high levels suggestive rather for a severe bacterial than for a viral condition (van Ypersele de Strihou et al.1986; Mustonen et al., 1994; Settergren, 2000). CRP levels > 100 mg/L are a severity index, and are highly unusual in other viral infections. A typical haematological anomaly on a simple blood smear on admission is the 'diagnostic triad', consisting of (very) high leucocytosis with a left shift and multiple immature forms, presence of immunoblasts, and thrombocytopenia (Hjelle et al., 1995; Koster et al., 2001). Bacterial infections and/or sepsis, with marked neutrophilia and thrombocytopenia, can perfectly mimic severe HFRS, but show toxic granulation and Döhle bodies, which are typically absent in HTVD (Koster et al., 2001). In severe cases, raised haematocrit and low serum albumin are indicative of haemoconcentration by capillary leakage (see Chapter 188). Hyponatraemia and (borderline) hypokalaemia are often noted (Mustonen et al. 1994; Clement et al., 2007; Gizzi et al., 2013). Hyponatraemia ≤ 130 mmol/L is often a severity index. In contrast with the rapidly evolving AKI, the rarity of pronounced hyperkalaemia is striking, even in the most severe forms. This is explained by the presence of proximal tubular reabsorption dysfunction (contributing to the hyponatraemia), resulting in increased distal sodium delivery and increased sodium-potassium exchange by the intact distal tubule. In NE, serum potassium levels are elevated only in cases with concomitant rhabdomyolysis (which is rare) or with intravascular micro-angiopathic haemolysis (which is exceptional) (Keyaerts et al., 2004).

Serum lipids on the acute sample can show the so-called lipid paradox as already noted in earlier NE cases (Hory et al., 1988; Mustonen et al., 1994; Colson et al., 1995; Keyaerts et al., 2004; Maes et al., 2006), in Asian HFRS (Cho et al., 2008), and in American hantavirus cases (Jan Clement, unpublished observations). This 'lipid paradox' consists of the combination of a low total (and particularly high-density lipoprotein) cholesterol, in striking contrast to a very high level of triglycerides. This very transient phenomenon is probably caused by the 'cytokine storm' (see Chapter 188). Although low cholesterol levels are admittedly encountered in other severe infections, such as malaria and leptospirosis, the unusual combination with fasting hypertriglyceridaemia seems rather specific for acute hantavirus infections, and allows a quick first-step diagnostic approach.

Haematuria, which can occur only microscopically, together with frank proteinuria, gives a first but important clue to the diagnosis. Proteinuria can be sudden and massive, is always non-selective, and disappears again completely within weeks. Such early and important proteinuria, which is rarely if ever seen in other acute infections, excludes practically all other ATIN forms (Michel and Kelly, 1998). In the largest so far and recent study of biopsy-proven ATIN, only 10 out of 468 cases (2.1%) had nephrotic proteinuria, and 107/468 (22.8%) had proteinuria > 1.5 g/day, but HFRS was not considered as a diagnostic possibility (Goicoechea et al., 2013). Moreover, urine microscopy might reveal pigmented, coarsely epithelial cell casts, characteristic for tubular injury, but dysmorphic red blood cells (RBCs) and RBC casts, suggestive for acute glomerulonephritis, have not been described in HFRS, as they are extremely rare in other ATIN forms as well (Michel and Kelly, 1998).

Useful in cases not yet on diuretics, and reinforcing a clinical suspicion of ATIN, may be a fractional excretion of urinary sodium ($FEUNa^+$) of > 1%, despite the fact that the patient is often dehydrated on admission, due to prolonged vomiting and/or diarrhoea. US examination of the abdomen (and preferably also of the lower thorax) can exclude a postrenal origin of oliguria, often reveals third-space fluid accumulation (pleural effusion, ascites, pericarditis, and/or a perirenal fluid rim), and often also confirms organomegaly of liver, spleen, and particularly of the kidneys. A longitudinal kidney diameter of ≥ 13 cm proves renal swelling by intensive interstitial oedema (van Ypersele et al., 1986; Paakkala and Mustonen, 2007). The latter is recognizable as an echodensity, comparable to, or even higher than that of the liver, with

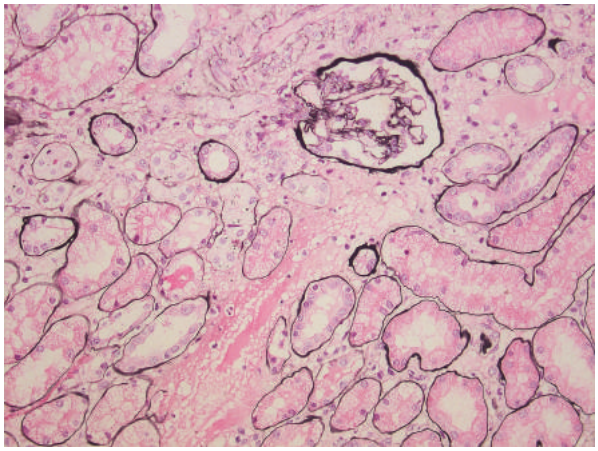

Fig. 242.1 A 'typical' kidney biopsy with AKI caused by *Puumala virus* (PUUV) infection. The most striking anomaly is diffuse interstitial oedema, that focally (at 7 hours) has a haemorrhagic aspect. In the interstitial space a sparse infiltrate of mononuclear cells is present. Epithelium of the cortical tubules is often swollen and vacuolized, but frank acute tubular necrosis is absent. The glomerulus is completely normal. (Silver methenamine stain, original magnification ×200.) Courtesy of Professor E. Lerut, MD, A-Path, University Hospital Leuven, Belgium.

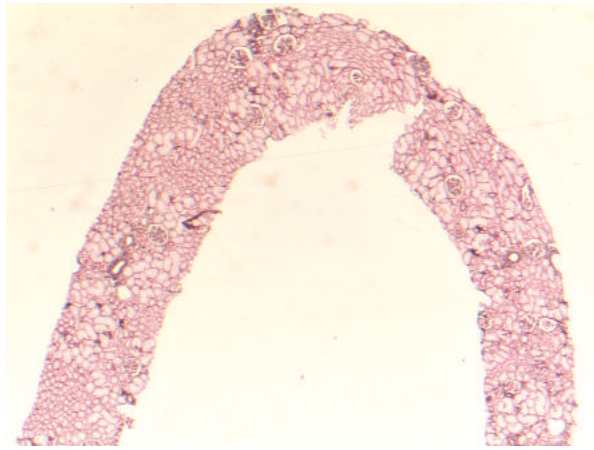

Fig. 242.2 Entire cortical kidney biopsy (silver methenamine stain, original magnification ×25) for initially unexplained multiorgan failure, including AKI with nephrotic-range proteinuria. The only striking anomaly is groups of dilated cortical tubuli with sometimes flattened epithelium. Interstitial oedema is very mild, and mononuclear cell infiltrate is virtually absent. Glomeruli appear all normal. Interstitial haemorrhages, pathognomonic for hantavirus nephropathy, are totally absent. However, these lesions are often confined to the medulla and the cortico-medullary junction, both lacking here. Final diagnosis was serologically and biomolecularly (positive RT-PCR)-confirmed *Puumala virus* (PUUV) infection. Courtesy of Professor E. Lerut, MD, A-Path, University Hospital Leuven, Belgium, and Professor M. Praet, MD, A-Path, University Hospital Ghent, Belgium.

poor cortico-medullary differentiation and often a swollen cortex. However, since interstitial oedema is a rapidly changing phenomenon in hantaviral disease, renal US findings are only relevant for the day of examination itself. More rarely, acalculous cholecystitis, with oedematous thickening of the gallbladder wall to > 5 mm, is also discovered (Keyaerts et al., 2004).

Given the relatively high specificity of all these clinical and laboratory anomalies, a kidney biopsy, not devoid of risks in thrombocytopenic patients, is rarely if ever required as the next diagnostic procedure (Settergren, 2000; Clement et al., 2007), in contrast with the generally accepted recommendations for most other ATIN forms, for which it is still considered as the 'gold standard' (Michel and Kelly, 1998; Goicoechea et al., 2013). Moreover, the clinician is struck by the paucity of lesions on kidney biopsy, which can entirely be normal, except for a slight interstitial oedema, sometimes accompanied by a patchy monocellular infiltrate with mainly CD8+ T lymphocytes, and, rather exceptionally, by the typical interstitial microhaemorrhages (Fig. 242.1), often present at the cortico-medullary junction. If present however, these interstitial microhaemorrhages are diagnostic for HFRS (Lähdevirta et al., 1978; van Ypersele et al., 1986; Ferluga and Vizjak, 2008). Except for sometimes mild mesangial hypercellularity, glomeruli are always normal, as is the vasculature (Figs 242.2 and 242.3). Immunofluorescent or electron microscopy examinations are negative, normal, or non-contributive (Lähdevirta, 1971; van Ypersele et al., 1986; Ferluga and Vizjak, 2008). As in most proteinuric glomerular diseases, effacement of podocyte foot processes in 20–30% of the capillary loops may be visualized in HFRS cases with nephrotic-range proteinuria. A flattened and vacuolated proximal tubular epithelium with poorly differentiated or even absent brush border may be seen, but almost never full-blown tubular necrosis (Fig. 242.1). In summary, the paradox of an almost normal renal biopsy in a rapidly progressive AKI should alert the puzzled nephrologist to the possibility of HFRS (Clement et al., 2011c).

Pathogenesis of the renal dysfunction

While temporary disassembling of cell-to-cell contacts in the glomerular endothelium (Krautkrämer et al., 2011) might explain the often massive proteinuria characteristic for impending HFRS, it cannot explain the temporary loss of kidney function, even with oligo-or anuria, often occurring later in the clinical course. Since interstitial oedema is a constant finding in all HTVD forms, it is tempting to speculate that it might also constitute the key of temporary AKI: intense parenchymal oedema might augment the intrarenal tissue pressure in a kidney contained in its capsule (causing intense lumbalgia) to a pressure so high that filtration function is stopped by a purely mechanical form of transient obstruction, which is relieved rapidly once the degree of oedema starts to diminish. This hypothesis could explain the rapid onset and equally rapid self-remittance without sequels of this particular AKI form, and seems to be confirmed by the fact that the degree of parenchymal swelling was found to correlate with the severity of the clinical course in NE cases (Paakkala and Mustonen, 2007). Moreover, orphan drugs which can be life-saving for hereditary angio-oedema, like the bradykinin receptor antagonist icatibant (see 'Treatment and outcome'), might also appear very beneficial in HTVD, due to their extremely rapid action on inflammatory oedema.

Differential diagnosis

Patients with fever and myalgia and/or backache are often prescribed antibiotics and/or NSAID, and when AKI ensues a few days later, drug-induced renal toxicity is often suspected (van Ypersele de Strihou et al., 1986; Rabb and Colvin, 2007). However, hyperkalaemia instead of hypokalaemia often develops after (prolonged)

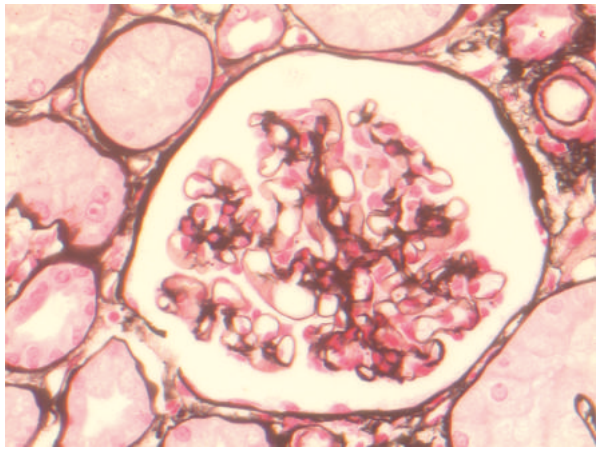

Fig. 242.3 Glomerulus in detail (silver methenamine stain, original magnification ×400) of the same PUUV patient as in Fig. 242.2. There are no lesions in the glomerular tuft, or in Bowman's capsule. Immunofluorescence and electron microscopic studies (not shown) were completely normal. These negative findings in a case of massive proteinuria and RIFLE stage 3 AKI, both of rapid onset and of rapid self-remittance (as in all hantavirus AKI forms), strongly suggest a functional, rather than an anatomical, lesion, linked to the patient's immunoresponse (see text). This temporary functional deficit, most probably of the endothelial barrier function, could also explain the total absence of renal sequels after spontaneous remittance.

Courtesy of Professor E. Lerut, MD, A-Path, University Hospital Leuven, Belgium, and Professor M. Praet, MD, A-Path, University Hospital Ghent, Belgium.

NSAID use, and diagnostic eosinophilia and eosinophiluria or typical eosinophilic interstitial infiltrates on kidney biopsy are often lacking, even in drug-induced ATIN (Michel and Kelly, 1998). Moreover, initial thrombocytopenia and proteinuria, the serum lipid perturbations, elevated CRP and LDH, which can all be quite marked in HFRS, do not fit with the diagnosis of drug-induced ATIN as the sole explanation of all these concomitant anomalies. Although HFRS has become the most frequent form of infectious ATIN in Europe and probably also in Asia, the suddenness of massive proteinuria, followed by the very rapid pace of decline (and subsequent spontaneous restoration) of renal function, are phenomena setting it apart from all other ATIN presentations. Even more confusing is the fact that significant proteinuria has been described as typical for ATIN following NSAIDs, whereas a nephrotic syndrome, sometimes labelled as 'idiosyncratic', has been linked to minimal change disease (MCD) after NSAIDs, often coexisting with ATIN (Rabb and Colvin, 2007). However, MCD associated with NSAID is mostly characterized by slow and progressive renal function deterioration, quite in contrast with HFRS. One wonders if at least some of these so-called drug complications are in fact not missed HFRS cases, treated with NSAIDs (van Ypersele de Strihou et al., 1986), a hypothesis extremely easy to check even years post factum, since specific anti-hantaviral IgG are presumed to remain life-long (Clement et al., 1987; Settergren, 2000).

HFRS cases can exceptionally present all laboratory signs of haemolytic anaemia, including the presence of schistocytes, evoking in the light of AKI with thrombocytopenia, the possibility of haemolytic uraemic syndrome (HUS). If plasma exchange is consequently installed as treatment, this can even result in false-negative IgM hantavirus serology (Keyaerts et al., 2004). Moreover, more severe hantavirus species such as DOBV can induce clustered cases of bloody diarrhoea or at least guaiac-positive stool, reinforcing the false impression of abdominal pain due to enterohaemorrhagic *Escherichia coli* infection, followed by HUS. Finally, some recently defined serious complications of pregnancy have acronyms comprising a series of anomalies that all can occur similarly in HFRS, such as AFLP (acute fatty liver of pregnancy), and particularly HELLP (haemolysis, elevated liver enzymes, low platelets), moreover often accompanied by varying degrees of oedema, proteinuria, and AKI. Still more confusing, these syndromes can start with (mild) fever, abdominal pains, flu-like symptoms, and even with troubled vision, a symptom hitherto considered as specific for HFRS heralding subsequent AKI (see 'Clinical features'). In AFLP and HELLP, prompt delivery is often considered the gold standard for saving both mother and child, but is rarely if ever indicated for HFRS during pregnancy (Macé et al., 2013). Early and urgent recognition is therefore mandatory, preferably based on clinical differences rather than on time-consuming hantaviral serology (which can initially be negative, see 'Differential diagnosis'). Arterial hypertension, hyperuricaemia, and hypoglycaemia are rarely present in HFRS, whereas massive new-onset proteinuria, hyponatraemia, hypokalaemia, and the 'lipid paradox' are not characteristic for AFLP or HELLP (Clement et al., 2013a).

Rat bite fever (RBF) is another rat-borne, worldwide zoonosis that is often forgotten in the differential diagnosis of fever and general malaise after a rat contact. RBF is caused by a bacterium, *Streptobacillus moniliformis*, occurs most often after a rat-bite or ingesting food contaminated by rats, and can lead to a rash, arthropathy, and multiple abscesses, all symptoms rare or absent in hantavirus infections (Clement et al., 2003).

The only other VHF prevalent in Europe is Crimean–Congo haemorrhagic fever (CCHF), often occurring also in localized outbreaks, but confined so far to the Balkan Peninsula and Russia. Other infections starting with fever and thrombocytopenia, and followed by AKI, are dengue haemorrhagic fever and most rickettsioses, in particular scrub typhus, which can also occur in clusters after open field activities, just like HFRS (Lee and Van der Groen, 1989) (see Chapters 189 and 193). Scrub typhus is only prevalent in South-East Asia, and is often marked by the presence of a black eschar. In contrast, another zoonosis, leptospirosis, remains the great mimicker in virtually all aspects, including kidney biopsies, but is present worldwide, and is also (mainly) rodent-borne (see Chapter 191). More exceptional differential diagnoses of causes of haemorrhagic interstitial nephritis are discussed by Lordemann et al. (2009).

Treatment and outcome

The case fatality rate is nowadays 0.1–0.3% for PUUV infections, 1% for SEOV, 5–10% for HTNV, up to 15% for DOBV, but is still as high as 35% or even higher for American HPS cases, where heart and lungs are the main target organs (Jonsson et al., 2010). Of note, the morbid prognosis of global AKI with a case fatality rate > 50%, the increased mortality associated with multiorgan involvement or even small rises of serum creatinine, the little improvement in mortality despite significant advances in supportive care, and finally the association of AKI with later development of chronic kidney disease, are all elements confirmed in other in-hospital AKI forms (Lameire et al. 2005, 2013; Bellomo et al. 2012), but are not applicable to HFRS worldwide (Clement et al. 2007, 2013b). If the

HFRS (or HPS) patient survives, rapid restoration to normal renal function without sequelae is the rule, as proven in many isolated case reports or clinical series (van Ypersele de Strihou et al., 1986; Clement and van der Groen, 1987; Kim et al., 1989; Settergren, 2000; Schütt et al. 2004; Lordemann et al. 2009). Finnish follow-up studies of NE cases, confirmed that kidney function, proteinuria, and blood pressure were all within normal limits, consecutively 5 (Mäkelä et al 2000) and 10 years (Miettinen et al. 2006) after PUUV infection. In fact, the same excellent long-term prognosis had already been demonstrated much earlier in Finland (i.e. before the aetiological agent was even known), and confirmed on follow-up renal biopsies (Lähdevirta et al. 1978). Renal recovery is always heralded by a prolonged period of polyuria and nocturia during weeks, or even months, due to a diminished renal concentrating capacity.

Treatment is purely supportive, but may necessitate admission to an intensive care unit (ICU), including renal replacement therapy (RRT), mechanical ventilation, or even extracorporeal membrane oxygenation. Whenever possible, potentially nephrotoxic drugs such as NSAIDs, iodine-containing contrast products, and even antibiotics are to be avoided. Paracetamol is preferred over aspirin as painkiller, in view of the haemorrhagic diathesis. If acute glaucoma is the first reason for an urgent hospitalization, classic treatment with oral or intravenous (IV) acetazolamide, and/or colloids IV are to be avoided, since the former is contraindicated in renal impairment, and the latter can precipitate mild acute lung insufficiency into frank pulmonary oedema, particularly in an oliguric patient. In contrast with prerenal AKI, fear of dehydration after abundant vomiting, and/or fear of renal insult after instauration of NSAIDs, should not lead to overzealous administration of IV fluids in a patient whose main problem on admission is vascular hyperpermeability. This overhydration can result in widespread interstitial oedema, also often including pulmonary oedema, but is accompanied by a normal or even low central venous pressure (Clement et al., 1994a; Colson et al., 1995). On the other hand, and later in the clinical course, lung and generalized tissue oedema, with substantial weight gain of up to 7 kg in a few days, could incorrectly be interpreted as fluid overload, prompting increased use of diuretics, which may further decrease renal arterial blood flow, particularly in HFRS (and HPS), where endovascular volume is already greatly reduced by capillary leakage.

Further caution is warranted for unnecessary and potentially hazardous interventions, such as renal and other biopsies (see 'Investigations'), and even most forms of RRT. For instance, acute dialysis may be started by the attending clinician, not familiar with HFRS, in view of a rapid daily rise of serum creatinine as a 'pre-emptive' measure, often before a weekend. However, a true uraemic state is almost never reached, due to the short course of HFRS, while other classic indications for acute RRT, such as serious hyperkalaemia, are often lacking (see 'Investigations'). The most encountered indication for acute RRT is hypervolaemia or diffuse oedema, which in fact may often be avoided by careful fluid balance monitoring in an oliguric patient. Except perhaps for the treatment of disseminated intravascular coagulation, occurring only in severe hantavirus infections, platelet transfusion is never indicated, even in cases with extreme thrombocytopenia, given the preserved reactivity of the normal bone marrow (Keyaerts et al., 2004). At first sight, paradoxically for a so-called renal syndrome, the single most important intervention in severe hantavirus infections may be mechanical lung ventilation, together with cardio-supportive measures in ICUs, since acute pulmonary oedema and heart failure can be life-threatening (Clement et al., 1994; Colson et al., 1995; Schütt et al., 2004; Johnsson et al., 2010; Rasmuson et al., 2011; Gizzi et al., 2013). Conversely, in 10% of American so-called pulmonary syndromes caused by *Andes virus* (ANDV), dialysis was deemed necessary as acute treatment (Enria et al., 2000; Peters and Khan, 2002), proving again that acronyms such as HFRS and HPS are illogical, and should better be replaced by the general denominator 'hantavirus disease' (HTVD), fulfilling at least part of Koch's postulate (Clement et al., 2012).

There is at present no convincing study showing benefits of corticosteroids in hantavirus infections, although in other situations these drugs are often considered a prime indication for life-threatening pulmonary or renal oedema, particularly in ATIN. On the contrary, a large retrospective study to evaluate the supposed beneficial effect of steroids in biopsy-proven ATIN, found no major beneficial effect in 60 cases, not even the often-cited 'hastening of recovery' (Clarkson et al., 2004). Speed of recovery due to therapeutics is difficult to assess in a condition like HFRS, where spontaneous and rapid self-remittance is the rule.

Except for the RNA-inhibitory antiviral drug ribavirin, a nucleoside analogue, there is no causative treatment for hantavirus infections. However, ribavirin is not widely available and should be given only intravenously and early in the clinical course. These considerations mean that IV ribavirin remains limited to quickly recognized (e.g. during an epidemic) and severe forms of the disease, where the clinician cannot afford to wait for serological results for the diagnosis and where the potential benefits of this medication to its non-negligible side effects have been outweighed. In practice, this is applicable only for epidemics of severe HTNV disease in Korea and particularly in China, where encouraging results have been obtained (Huggins et al., 1991). However, in a limited field study of HPS in the United States, no convincing beneficial effect could be demonstrated with IV ribavirin (Mertz et al., 2004). Very recently, however, a spectacular remission within days was obtained in a moribund patient with NE and severe capillary leakage syndrome after one single dose of a bradykinin receptor antagonist, icatibant, given as a salvage medication (Antonen et al., 2013). However, this encouraging result has to be confirmed in formal clinical trials.

So far, the only current prophylaxis consists in reduced exposure to rodents and their aerosolized excreta, and, perhaps unexpectedly, a tobacco stop. Indeed, after the first (1999) European case–control study following a NE outbreak in Belgium, smoking appeared bearing a significant odds ratio (OR) for infection of 9.1 (95% confidence interval (CI) 2.6–31.2; P = 0.0004), second only to the well-known risk factor of wood-cutting in the forest, with OR 15.5 (95% CI 2.0–119.6; P = 0.008) (Van Loock et al. 1999; Clement et al., 2010b). This surprising finding was later confirmed by an extensive Finnish case–control study (Vapalahti et al., 2010), and a US case–control study is currently underway to explore if this conclusion is also valid for American HPS. Hantaviruses enter the human host via the lower respiratory tract, and it seems conceivable that chronic damage by smoking might facilitate this viral entry. Moreover, the Belgian study showed that NE patients smoked significantly more than their non-infected controls, suggesting an additional risk for infection in heavy smokers (Van Loock et al. 1999; Clement et al., 2010b)

At least three inactivated vaccines, based respectively on purified suckling mouse brains, golden hamster kidney cells, or Mongolian gerbil kidney cells, have been developed in Korea and/or China, and proved effective for local use. However, none of these vaccines have been licensed by the World Health Organization (Maes et al. 2009b). Genetically manipulated and particularly mixed PUUV and HTNV DNA vaccines are underway.

Conclusion

Recent retrospective pluri-annual analyses of very large cohorts of hospitalized patients indicated a rise of incidence, but a decreased fatality rate of AKI (see Chapters 220 and 237). However, most of these studies were carried out in hospitals in the United States, where the HFRS incidence is very low, in contrast to the Far East, where yearly tens of thousands of HFRS cases are registered, and to Europe, where for more than a decade HFRS has clearly been on the rise, perhaps as an effect of global warming. Moreover, HFRS is a peculiar and often very localized form of CAAKI, which should never be considered as an in-hospital complication. It is recommended that in future analysis of data on global AKI this emerging but underestimated form of kidney disease should be better taken into account (Clement et al., 2013b).

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CHAPTER 243

Community-acquired pneumonia and acute kidney injury

Norbert Lameire

It is known that in one-half of the patients hospitalized for community-acquired pneumonia (CAP), severe sepsis develops, with non-pulmonary organ dysfunction developing in more than one-third and septic shock in 4.5% (Dremsizov et al., 2006). Some years ago it was found that acute kidney injury (AKI) was common in CAP even in patients who appeared to have an uncomplicated course of CAP and where AKI was observed in one-quarter of them (Murugan et al., 2010). Remarkably, the overall 34% incidence of AKI in patients with CAP is very similar to that reported for a general population of critically ill patients. In general, patients with AKI compared to those without AKI were older, had more co-morbidity, and had higher biomarker concentrations (interleukin 6, tumour necrosis factor, D-dimer) even among patients without severe sepsis. The risk of death associated with AKI varied when assessed by Gray's survival model and after adjusting for differences in age, gender, ethnicity, and co-morbidity. This risk was significantly higher immediately after hospitalization but gradually fell over time in the overall cohort and in those with non-severe pneumonia. A significantly higher risk of death was also present in patients with CAP who were never admitted to an intensive care unit.

In patients with severe sepsis, AKI occurred in those who also had evidence of greater activation of inflammatory, coagulation, and fibrinolysis pathways. Among the patients with less severe CAP, AKI was associated with modest but significant differences in immune and fibrinolysis activation.

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CHAPTER 244

Acute kidney injury in severe sepsis

John Prowle and Rinaldo Bellomo

Epidemiology

Sepsis and septic shock remain the most important cause of acute kidney injury (AKI) in critically ill patients and account for > 50% of cases of AKI in the intensive care unit (ICU) (Uchino et al., 2005) (Box 244.1). Septic AKI (S-AKI) can be defined by the presence of consensus criteria for AKI (Bellomo et al., 2004), consensus criteria for sepsis (Bone et al., 1992), and the absence of other obvious, non-sepsis related, causes of AKI.

S-AKI probably occurs in somewhere between 15% and 20% of all ICU admissions and severe S-AKI, necessitating renal replacement therapy (RRT), occurs in approximately 2–3% of all ICU patients (Bagshaw et al., 2007b). Its mortality varies according to severity of AKI, reaching > 50% in patients receiving acute RRT (Palevsky et al., 2008).

Clinical features

As a clinical syndrome, clinical features of S-AKI can be quite varied. The focus of infection can be anywhere in the body, intra-abdominal or pulmonary, soft tissue or systemic, due to endocarditis or to an abscess in a solid organ. Whatever the cause of sepsis, the patient is frequently critically ill, requiring mechanical ventilation, invasive monitoring, and/or vasopressor support. In this setting, the kidney is seen to rapidly lose function with oliguria often progressing to anuria, rapidly rising serum urea and creatinine, and development of hyperkalaemia and metabolic acidosis.

Investigations

After the taking of a relevant clinical history and performing a full examination, investigations are typically directed to determining the nature of the infection and its source. These include blood tests to help confirm the presence of infection and of associated organ injury and other appropriate microbiological and imaging investigations. Ultrasonography of the kidney should be performed to exclude urinary tract obstruction and possible pyelonephritis. It also helps assess the renal size and parenchyma and provides some information on the presence of chronic kidney disease. A variety of textbooks suggest that it is possible to use urinary tests to distinguish acute tubular necrosis (structural injury) from so-called prerenal AKI (functional injury). As we shall see, such distinction may not be clear-cut in the clinical evolution of S-AKI and, experimentally, urine biochemistry was not a reliable indicator of renal perfusion in a S-AKI model (Langenberg et al., 2006a). Similarly, in a systematic review of the value of such tests in humans, there was significant lack of data and a wide variety of findings in septic ARF (Bagshaw et al., 2006). All of these observations strongly support the concept that, in S-AKI, biochemical analysis of urine is not diagnostically accurate, prognostically valuable, or clinically useful (Hall et al., 2011). In this regard, emerging urinary biomarkers of kidney injury may prove more valuable (Bagshaw et al., 2007a). Additionally, the presence of urinary tubular epithelial cells and granular tubular casts may predict severity and progression of S-AKI reflecting the presence of structural tubular injury (Perazella et al., 2010).

Aetiology and pathogenesis

Both sepsis and AKI are heterogeneous clinical syndromes and the pathogenesis of AKI in sepsis is likely to vary between individuals. Furthermore, conventional biochemical tests of kidney function such as serum creatinine fail to accurately distinguish the nature and extent of parenchymal kidney injury in these patients. Lastly renal biopsy is rarely performed in S-AKI and there is a marked lack of histopathological evidence to guide our understanding of this condition. It is not surprising, therefore, that our understanding of septic human AKI has advanced little in the last 50 years. To overcome such limitations, animal models of AKI have been developed that enable more sophisticated and invasive measurements to be made. Unfortunately, these animal models have been largely based on ischaemia-reperfusion or nephrotoxin-induced injury and such models may not be directly relevant to the pathogenesis of S-AKI (Heyman et al., 2002).

A major paradigm, which has been derived from observations in animals and humans with *hypo*dynamic shock (including haemorrhagic, cardiogenic or even unresuscitated septic shock), is that AKI is caused by renal ischaemia leading to renal tubular cell injury and death. This construct implies that restoration of adequate renal blood flow (RBF) should be the primary means of renal protection in critically ill patients. However, in human sepsis, AKI is most often observed in the context of hyperdynamic septic shock. In this setting, the importance of reduced RBF in the pathogenesis of AKI remains controversial and evidence exists that RBF may be little altered or even increased above normal in conditions where S-AKI arises. Accordingly, the dogma that most AKI (including S-AKI) is 'ischaemic' remains inadequately tested.

Box 244.1 Most common causes or triggers for the development of acute kidney injury in critically ill patients[a]

◆ Sepsis or septic shock	47.4%
◆ Major cardiovascular surgery	23.2%
◆ Cardiogenic shock	26.9%
◆ Hypovolaemia	25.5%
◆ Major gastrointestinal surgery	11.4%
◆ Drug toxicity	19.0%
◆ Hepatorenal syndrome	5.7%
◆ Obstructive uropathy	2.7%
◆ Other factors	12.8%

[a]NB: more than one cause/trigger can apply to a given patient.

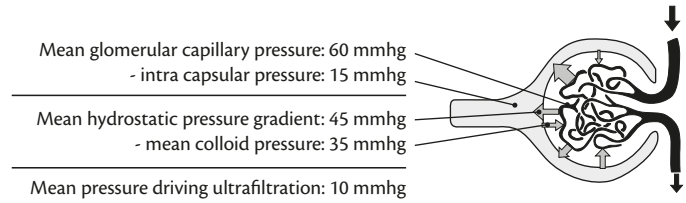

Fig. 244.1 Factors determining ultrafiltration in the glomerulus pressures are approximation as direct measurements would be difficult to perform in humans. Only a small net pressure gradient is required to cause normal glomerular filtration, thus relatively small changes in glomerular and capsular pressures can have large effects on ultrafiltration and a number of different mechanisms can contribute to loss of GFR in AKI (see Table 244.1).

In several experimental studies of S-AKI, global RBF declines after induction of sepsis or endotoxaemia (Kikeri et al., 1986). This results not only in a reduction in glomerular filtration rate (GFR) but also, if hypoperfusion is severe and prolonged, in metabolic deterioration and diminished cellular contents of high-energy phosphates, possibly causing cell death and established AKI. On the other hand, other studies have found that the renal circulation participates in the systemic vasodilatation seen during severe sepsis/septic shock, so that RBF does not diminish, but S-AKI develops. Thus S-AKI, at least in the first 6–48 hours may develop not in the setting of renal hypoperfusion, but in the setting of maintained and even increased renal perfusion.

Several experimental and human studies support the notion of maintained RBF in sepsis (Ravikant and Lucas, 1977). In eight critically ill patients, AKI occurred despite normal values of RBF (Brenner et al., 1990). Observations in hyperdynamic models of sepsis may be more relevant to human septic shock because such patients typically show a hyperdynamic state. Indeed the reason why the results of experimental studies are different in terms of renal perfusion may be mostly related to the state of the systemic circulation (hypodynamic or hyperdynamic state). In fact, the consistent observation is that, once an experimental hyperdynamic state exists, global renal hypoperfusion/ischaemia is not the norm.

A comprehensive review of 160 original animal studies found that only a minority reported both cardiac output and RBF. In these studies, changes in RBF depended very much on the model. However, once the model was hyperdynamic (high cardiac output), RBF was *either preserved or increased.* On multivariate analysis cardiac output was the only significant predictor of RBF (Langenberg et al., 2005).

In a sheep model of severe sepsis, induced by intravenous administration of live *Escherichia coli* which simulated sepsis syndrome as seen in man, once hyperdynamic sepsis was initiated, RBF was repeatedly and consistently increased often by > 100% (Langenberg et al., 2006b, 2007). Such renal hyperaemia is associated with renal vasodilatation but also oliguria and decreased creatinine clearance (AKI). Thus, *in the short term* (6 hours), AKI can occur in the setting of renal hyperaemia and *renal vasodilatation*. To understand how the triad of renal vasodilatation, renal hyperaemia, and loss of GFR can occur simultaneously, one needs to consider the haemodynamic principles responsible for the simultaneous control of renal vascular tone, RBF, and GFR, and the key role played by the glomerular arterioles in the control of intrarenal haemodynamics and glomerular ultrafiltration (Fig. 244.1).

It is possible that, even though there is preserved or increased global RBF in S-AKI, internal redistribution of blood flow favouring the cortex may occur, so that ischaemia at the cortico-medullary junction would then mediate tubular injury and S-AKI. However, no evidence exists to confirm this mechanism in hyperdynamic sepsis using technology that allows continued measurement of medullary and cortical blood flow over time. In an investigation using Doppler flowmetry to monitor medullary and cortical flow in septic sheep (Di Giantomasso et al., 2003) and found that both flows remained unchanged and that the administration of vasopressor therapy (norepinephrine) induced a significant increase in both. These observations suggest that, at least in the early phases of severe sepsis, the loss of GFR may be mediated by glomerular haemodynamic changes rather than tubular ischaemic injury and that tubular injury if and when it occurs may not be directly related to global changes in blood flow. Finally, the functionally favourable modification of this state by vasoconstrictor/vasopressor therapy further challenges the widely held view of what is optimal renal resuscitation in S-AKI.

It is important to note that the above finding discussed relate only to *a short-term model of S-AKI* (6 hours). It is unknown whether RBF remains elevated if hyperdynamic sepsis is sustained for a longer period. However, a longer-term model (48 hours) of S-AKI achieved by the continuous intravenous infusion of live *E. coli* at a dose carrying limited lethality (20%) (Langenberg et al., 2006b) found that cardiac output increased threefold over time and that *RBF increased at almost exactly the same rate as mirror image of the cardiac output.* This increase in RBF could be fully accounted for by renal vasodilatation. As RBF increased by 300%, however, urinary output progressively declined to near anuria and creatinine clearance (a marker for GFR) decreased by 80%. The serum creatinine increased fourfold. Clearly, these animals had developed severe S-AKI with distinct loss of GFR in the setting of pronounced hyperaemia. Interestingly, during this 48-hour period all markers of tubular function available (urinary sodium excretion, fractional excretion of sodium, and fractional urea excretion) indicated preservation of tubular function providing further evidence that (as would be logical) GFR was lost not because of tubular events, but because of glomerulus-related events.

Studies of recovery from such severe S-AKI displayed the same changes seen during sepsis but in reverse (Langenberg et al., 2007).

Table 244.1 Factors that can mediate a fall in GFR during AKI

Abnormality	Physiological effect	Consequence
Low systemic blood pressure	Low glomerular hydrostatic pressure	Decreased glomerular filtration
Afferent arteriole vasoconstriction		
Efferent arteriole vasodilatation		
Renal interstitial oedema	High intracapsular pressure	
Extrinsic compression		
Tubular obstruction		
Failure of downstream tubular reabsorption		
Low renal plasma flow	Rapid rise in oncotic pressure	

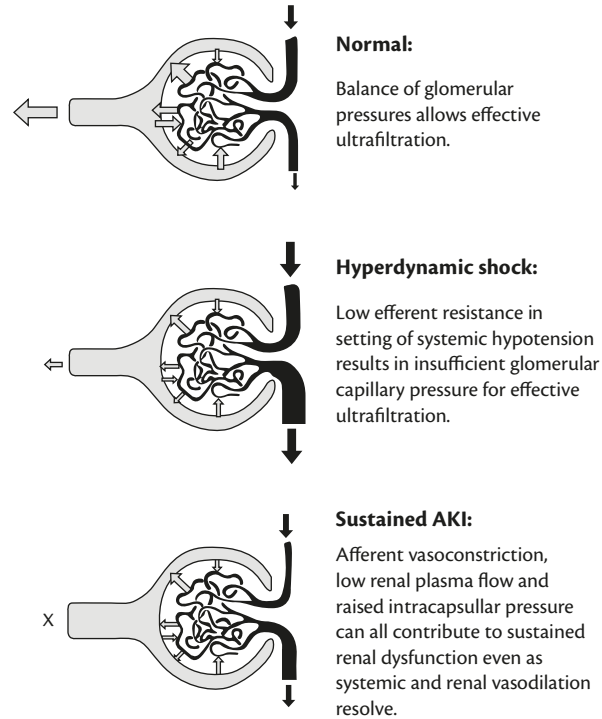

Fig. 244.2 Glomerular haemodynamics and ultrafiltration in the normal state (A), during AKI in early hyperdynamic shock (B), and during established AKI with partial resolution of systemic vasodilation.

RBF returned to normal over 48 hours as did renal vascular resistance. The information obtained from this model and the information obtained from the short-term model of S-AKI provides further support for the notion that *oliguric AKI can develop in the presence of marked hyperaemia and renal vasodilatation.*

It is useful to reflect that GFR is dependent upon the pressure gradient that drives ultrafiltration across the glomerular membrane, the ultrafiltration gradient (Fig. 244.1), and consequently the pathological mechanisms that can cause GFR to fall (Table 244.1). The ultrafiltration gradient is driven by the glomerular capillary pressure (Gcp) determined by the relationship between the resistance of the afferent and efferent glomerular arterioles, the vessels which control inflow and outflow from the glomerulus. It is opposed by oncotic pressure and the Bowman's space hydrostatic pressure. For RBF to increase and renal vascular resistance to decrease, both the efferent and afferent arterioles *must dilate*. Although such dilatation can account for the hyperaemia and renal vasodilatation, it cannot explain the loss of GFR. If the afferent arteriole dilated, with no change in the efferent arteriole, then GFR might be expected to increase because the Gcp would inevitably increase. Thus, for Gcp to decrease, the efferent arterioles must also dilate. However, this is still insufficient to explain what has been reported in hyperdynamic experimental animals. If such postulated efferent arteriolar vasodilatation simply maintained the normal relationship between afferent and efferent arteriolar tone, Gcp would be increased by the increased flow and GFR would increase. There is, therefore, a physiologically logical mechanism by which RBF can increase, renal vasodilatation can also occur and, simultaneously, Gcp and GFR can decrease: simultaneous dilatation of both arterioles but with greater efferent than afferent dilatation (Fig. 244.2B). This would be a physiological state similar to that seen with the administration of angiotensin-converting enzyme inhibitors and characterized by afferent vasodilatation (mild to moderate) and even greater (marked) efferent arteriolar vasodilatation

If this physiological paradigm were true, then administration of an agent which acts as a preferential efferent arteriolar vasoconstrictor should deliver the following physiological consequences: decreased RBF, renal vasoconstriction, and increased urinary output and GFR. Such an agent exists: angiotensin II (Ang II). In controlled animal studies comparing intravenous infusion of Ang II with placebo in the setting of experimental S-AKI (Wan et al., 2009) urinary output increased dramatically as did creatinine clearance, while RBF decreased and renal vasoconstriction developed.

Other studies support the view that preferential efferent arteriolar vasoconstriction might improve GFR. Some evidence exists, for example, that arginine vasopressin (AVP) causes calcium release from intracellular stores, which in turn contributes to the contractile response of both afferent and efferent arterioles. However, such response is more prominent in the efferent arteriole (Fallet et al., 2005) and appears to lead to increases in Gcp. If this paradigm were correct, one might expect that the infusion of AVP would improve urine output and creatinine clearance in sepsis. Indeed, this is what can be seen in models of S-AKI where AVP significantly increased creatinine clearance with no change in RBF (Di Giantomasso et al., 2006). More importantly, this is what was shown by the Vasopressin and Septic Shock Trial (VASST) investigators in a post hoc analysis (Gordon et al., 2010) of the evolution of AKI in the 464 patients that were part of a multicentre, double-blind randomized controlled trial (RCT) of AVP in septic shock (Russell et al., 2008). In at-risk patients, AVP infusion was associated with a decreased progression to failure and a lower risk of use of RRT.

It is also possible that intrarenal shunting also contributes to loss of GFR. Such shunting can affect GFR if peri-glomerular vessels or other anatomical channels existed that can literally shunt blood away from the glomerulus. Such vessels have been reported in the past (Casellas and Mimran, 1981) and have been recently identified by others (Molitoris and Sandoval, 2011); however, the contribution, if any, to the pathogenesis of S-AKI remains uncertain.

Furthermore, as new models of S-AKI are developed, evidence has emerged that even in the setting of hyperdynamic sepsis, AKI can develop in presence of a variety of systemic and regional haemodynamic states (Benes et al., 2011) and that knowledge of systemic haemodynamics does not assist in predicting the renal haemodynamic phenotype.

Finally while early S-AKI can be accompanied by elevated RBF in the early stages, clinical measurements of RBF in *established* AKI of varied causes including sepsis have been associated with very variable, but generally reduced RBF (Prowle et al., 2009). Similarly, measurement of RBF in 10 patients with established S-AKI, nine requiring RRT, demonstrated RBF was consistently reduced *as a fraction of cardiac output*, so that in hyperdynamic shock, RBF was normal or somewhat elevated (but lower than would be expected given very large cardiac output) while in haemodynamically stable patients, RBF was reduced (Prowle et al., 2012). Furthermore measurements of GFR in established AKI seem to correlate very poorly with RBF (Prowle et al., 2010b, 2012). Preferential constriction of the afferent arteriole may cause this elevation in renal vascular resistance and can occur within the kidney as a response to tubular injury (Singh and Okusa, 2011); significantly this will result in a disproportionately large fall in GFR as it reduces Gcp and RBF (Fig. 244.2C). Collectively these finding suggest that, in established AKI, renal vascular resistance is relatively increased, but that this may be a later occurrence that sustains AKI even when systemic vasodilatation has resolved, rather than an initiating event in AKI. In addition to this mechanism, elevated Bowman's space pressure and elevated venous pressure may also contribute to reduction in ultrafiltration gradient in sustained AKI (Fig. 244.2C) (Sharfuddin and Molitoris, 2011; Singh and Okusa, 2011).

If S-AKI can occur in the absence of global renal ischaemia, while experimental subtotal (90%) renal ischaemia can occur without being followed by AKI (Saotome et al., 2010), it seems unlikely an ischaemia reperfusion model is sufficient to explain clinical S-AKI. What processes then mediate the structural renal injury that leads to sustained AKI after the resolution of initial haemodynamic changes? Furthermore, what is the nature of this structural renal pathology? Classical histopathological descriptions of acute tubular necrosis in AKI are largely derived from historical reports of AKI in occurring in the context of crush injury, protracted shock, or nephrotoxin exposure (Oliver et al., 1951; Langenberg et al., 2008). Subsequent studies of the histopathology S-AKI failed to demonstrate such severe tubular pathology (Langenberg et al., 2008) although tubular cell detachment from basement membrane, loss of tubular brush border, and tubular cellular apoptosis have been observed in patients with AKI (Lerolle et al., 2010). It appears that, rather than extensive frank necrosis, de-differentiation of renal tubular cells, breakdown of cell–cell adhesion, and loss of polarized cell-membrane expression of ion channels (Kwon et al., 1999) are processes by which kidney dysfunction can arise in AKI. In more severe cases, this de-differentiation can culminate in cell death by apoptosis. Such processes are accompanied by leucocytic infiltrates (Lerolle et al., 2010) and appear to have much in common with cellular injury occurring in other organs during septic shock (Cinel and Opal, 2009). It seems likely that local inflammatory responses, endothelial activation and microcirculatory dysfunction are the important mediators of cellular injury in S-AKI rather than whole-organ changes in oxygen delivery. The kidney may thus be an organ uniquely sensitive to the inflammatory processes that underlie multiorgan dysfunction in sepsis and S-AKI an expression of this systemic pathology.

Sepsis is characterized by the release of a vast array of inflammatory cytokines, arachidonate metabolites, vasoactive substances, thrombogenic agents and other biologically active mediators. A large body of experimental data suggests that these various mediators and neuro-endocrine mechanisms might be involved in the pathogenesis of organ dysfunction in sepsis (Marshall et al., 2003).

For example, tumour necrosis factor alpha (TNFα) plays a major role in the pathogenesis of Gram-negative septic shock, mediating a broad spectrum of host responses to endotoxaemia. Soluble TNF receptor p55 (TNFsRp55)-based neutralization of TNFα, achieves protection against lipopolysaccharide (LPS)-induced AKI in wild-type mice (Knotek et al., 2001). With pre-treatment using TNFsRp55, GFR decreased only by 30%, as compared with a 75% decrease without TNFα neutralization. LPS-induced AKI can be attributed to TNFα acting directly on its receptor, TNFR1, in the kidney. Mice deficient in TNF receptor are resistant to LPS-induced AKI, have less tubular apoptosis, and fewer infiltrating neutrophils. TNF receptor-positive kidneys transplanted in TNF receptor knockout mice develop LPS-induced renal failure, TNF receptor-negative kidney implanted in TNF-positive mice do not. Thus, TNFα seems to be an important direct mediator of S-AKI. These observations suggest that haemodynamic factors do not operate in isolation.

Apoptosis, is a form of cell death that is mediated by a genetically determined biochemical pathway and characterized morphologically by cell shrinkage, plasma membrane blebbing, chromatin condensation, and nuclear fragmentation. Cells can die by one of two pathways: *necrosis* or *apoptosis*. Necrosis results from severe ATP depletion. Such depletion leads to rapid uncoordinated collapse of cellular homeostasis. Apoptosis is an energy-requiring and genetically directed process.

There is now good evidence to show that human renal tubular cells die by apoptosis as well as necrosis in experimental models of renal injury. The endothelial cells can undergo apoptosis in response of variety of stimuli, especially immune mediated cell injury via TNFα and Fas ligand.

Apoptosis of tubular cells by inflammatory cytokines and LPS is a possible mechanism of renal dysfunction in endotoxaemia (Jo et al., 2002). If high-dose TNFα was added to cultured kidney proximal tubular cells, there is increased expression of Fas mRNA, the Fas-associated death domain (FADD) protein, as well as increased DNA fragmentation. TNFα and LPS elicit apoptotic cell death of cultured bovine glomerular endothelial cells, which is time and concentration dependent (Messmer et al., 1999). Their effect was characterized by an increase in pro-apoptotic proteins and a decrease in anti-apoptotic proteins such as Bcl-xL.

Injury in other organs can contribute to S-AKI. In a fascinating series of studies, experimental and clinical acute respiratory distress syndrome (ARDS) was associated with kidney injury while lung-protective low-tidal volume ventilation protected the kidney from injury (Imai et al., 2003). Using a rabbit model of ARDS, animals randomized to an injurious ventilator strategy had increased epithelial cell apoptosis in the kidney as well as the small intestine. Furthermore, such animals had evidence of renal dysfunction. When renal cells were incubated *in vitro* with plasma from rabbits exposed to an injurious ventilator strategy apoptosis of such cells was induced and was markedly greater than seen with exposure to control plasma. These investigators hypothesized that Fas ligand

might be responsible for these changes and used Fas-Ig (a fusion protein which blocks soluble Fas ligand) to test this hypothesis. They found that Fas ligand blockade attenuated *in vitro* apoptosis of renal cells. To further confirm such association, they obtained plasma from patients enrolled in a previous ARDS study comparing low-tidal volume ventilation to traditional tidal volume ventilation and found that there was a significant correlation between Fas ligand levels in plasma and serum creatinine. Given that the vast majority of patients with ARDS have sepsis, these observations are highly relevant to S-AKI and highlight yet another pathway potentially responsible for AKI in the setting of sepsis.

Treatment and outcome

The principles of management of established S-AKI are the treatment or removal of its cause and the maintenance of physiological homeostasis while recovery takes place. Avoidance of secondary renal injury from further haemodynamic instability, nosocomial infections, and/or nephrotoxin exposure is particularly important in determining the speed and extent of renal recovery. Many elements of therapy in S-AKI form part of the general supportive management of critical illness including nutrition, appropriate transfusion management, stress ulcer prophylaxis, and assiduous attention to the prevention of infection, particularly in the insertion and care of intravascular catheters. In addition, drug therapy must be adjusted to take into account the effect of the decreased clearances associated with loss of renal function and for those provided by any RRT provided.

Haemodynamic management is a particularly important, but controversial issue in the management of S-AKI. While patients tend to have high cardiac outputs, insensible or distributive fluid losses are common and fluid resuscitation is often required acutely. However, clinicians should be careful to minimize fluid inputs to those required to maintain adequate cardiac output as fluid administration and capillary leak frequently lead to generalized tissue oedema, particularly in the context of oliguria. As fluid overload has been associated with adverse outcomes in AKI (Prowle et al., 2010a), cardiac output monitoring should be used to guide appropriate fluid management in the sickest patients. Targeting of supra-normal levels of cardiac output with haemodynamic therapies has been shown to worsen outcomes in critical illness (Hayes et al., 1994), however, *early* use of protocolized haemodynamic management, targeting measures of *normal* cardiac output has been associated with improved survival and less organ dysfunction in sepsis (Rivers et al., 2001), including incidence of S-AKI (Lin et al., 2006). Optimal composition of fluid therapy is a complex and contentious topic. High-molecular-weight, hyperoncotic starch solutions have been shown to increase the incidence and severity of AKI in septic shock (Brunkhorst et al., 2008) and should not be used, otherwise high-quality evidence to guide choice of fluid composition in sepsis is lacking.

Vasopressor therapy is commonly employed in hyperdynamic septic shock. While vasoconstrictors were historically regarded of potential harm to an ischaemic kidney, most available evidence favours moderate vasopressor use in vasodilatory shock. Use of norepinephrine has been shown to improve RBF and GFR in experimental models of S-AKI (Anderson et al., 1981; Bellomo et al., 1999) and restoration of urine output in clinical septic shock complicated by oliguria (Martin et al., 1993). It appears that systemic vasoconstrictors have a larger positive effect in raising renal perfusion pressure by increasing systemic blood pressure than a negative effect by increasing renal vascular resistance, an effect that may in any case be mitigated by reduction in renal sympathetic tone as systemic blood pressure is restored. Increasing mean arterial pressure up to 75 mmHg has been shown to increased renal oxygen delivery and GFR in human AKI (Redfors et al., 2011) and persistently lower blood pressure has been associated with persistence or worsening of AKI in the context of sepsis (Badin et al., 2011). Consideration should be given to a patient's baseline blood pressure when selecting blood pressure targets, relative hypotension in comparison to patient-normal blood pressure has been associated with development of AKI in hospital (Liu et al., 2009), suggesting blood pressure targets might need to be higher in the chronically hypertensive. Importantly, while vasopressors therapy should not be the sole therapy for hypotension in the context of low cardiac output, when cardiac output is normal or high, vasopressors appear to be more efficacious and less harmful than continued fluid resuscitation for vasodilatory shock.

Complications such as encephalopathy, pericarditis, myopathy, neuropathy, electrolyte disturbances, or other major electrolyte, fluid, or metabolic derangement are more specific to advanced renal dysfunction and must be anticipated and prevented. Their prevention may include several measures, which vary in complexity from fluid restriction to the initiation of extracorporeal RRT.

Hyperkalaemia (> 6 mmol/L) may be emergently treated with insulin and dextrose administration, the infusion of bicarbonate if acidosis is present, nebulized salbutamol, or all of these together. If the serum potassium is > 7 mmol/L or electrocardiographic signs of hyperkalaemia appear, calcium (usually as calcium gluconate) should also be administered. However, it must be emphasized that the above measures are *temporizing actions* and unless hyperkalaemia can be rapidly corrected by resolution of acidosis and sustained improvement in renal function, RRT should be promptly instituted. Metabolic acidosis is almost always present, but in its own right is only a specific indication for RRT when severe and refractory. Fluid overload can sometimes be prevented by the use of loop diuretics in patients with preserved urine output, however, their use doesn't appear to alter clinical outcomes from AKI in the ICU (Uchino et al., 2004) and may delay specific therapy (Mehta et al., 2002). Importantly, not only is fluid overload associated with the occurrence of AKI (Payen et al., 2008), its presence in patients with AKI has been associated with significantly decreased survival (Payen et al., 2008; Bouchard et al., 2009). If the patient is oliguric, often the only way to avoid fluid overload is to institute RRT at an early stage in anticipation of fluid balance requirements and given the adverse effects of fluid overload there is much to recommend such an expectant approach. Marked azotaemia ([urea] > 30 mmol/L or [creatinine] > 300 μmol/L) is undesirable and should probably be treated with RRT unless recovery is imminent or already under way and a return towards normal values is expected within 24–48 hours. It is recognized however, that no RCTs exist to define the ideal time for intervention with artificial renal support.

Renal replacement therapy

In some patients, S-AKI is severe enough to require RRT. No single set criteria exists to justify such intervention. Despite controversy about the best time to start RRT, the general trend in most

Box 244.2 Modern criteria for the initiation of renal replacement therapy in the ICU[a]

- Anuria (no urine output for 6 hours)
- Oliguria (urine output < 200 mL/12 hours)
- [blood urea nitrogen] > 80 mg/dL or urea > 30 mmol/L
- [Creatinine] > 300/L mmol/L
- [K^+] > 6.5 mmol/L or rapidly rising
- Pulmonary oedema unresponsive to diuretics
- Uncompensated metabolic acidosis (pH < 7.1)
- Uraemic complications (encephalopathy/myopathy/neuropathy/pericarditis)

[a]If one criterion is present, RRT should be considered. If two criteria are simultaneously present, RRT is strongly recommended.

developed countries, especially in critically ill patients, has been to start such therapy earlier in the course of the patient's illness (Box 244.2). This approach is supported by indirect observational evidence. Once a decision is made to begin acute RRT, several forms of RRT are available: continuous RRT (CRRT), intermittent haemodialysis (IHD) or slow extended dialysis (SLED), and peritoneal dialysis (PD). Because of its clearance limitations, difficulty with fluid removal, and complications, PD is rarely used in adults in developed countries.

There continues to be much controversy whether intermittent or continuous RRT should be used. No suitably powered RCTs have been performed to address this issue. The relatively small to medium-sized studies performed, however, do not suggest a difference in patient survival. Nevertheless, evidence exists that use of IHD is associated with more positive fluid balances (Bouchard et al., 2009) and greater haemodynamic instability (Palevsky et al., 2008) than CRRT when used for treatment of AKI in the ICU.

Once RRT is applied there is uncertainty about the appropriate intensity of treatment, especially in critically ill patients. Two large, multicentre randomized controlled studies of RRT intensity have been now been completed: the ATN study (Palevsky et al., 2008) and the RENAL study (Bellomo et al., 2009). These two studies are the largest studies of AKI ever conducted and included a substantial number of patients with S-AKI. They did not show a benefit from increasing the intensity of RRT and, in aggregate, suggest that, in current practice, the *delivered* dose of RRT should be equivalent to 20–25 mL/kg/hour. This observation is important because in routine clinical practice dose delivered is typically 20% less than that prescribed, suggesting that *prescribed* dose of CRRT should be approximately 30 mL/kg/hour.

Another important implication of the ATN and RENAL studies is that CRRT is the current standard of care for critically ill patients with S-AKI requiring RRT who are also receiving vasopressor support. Such patients were allocated to either CRRT or SLED in the ATN trial because the participating centres considered it inappropriate for them to be treated with IHD. In fact, essentially all these patients received CRRT. Of course, all such patients received CRRT in RENAL. Thus, by academic consensus, CRRT has now been become the standard of care in haemodynamically unstable S-AKI patients. A final key observation of the ATN and RENAL trials pertains to the difference in renal recovery to dialysis independence. Such recovery was much greater in the RENAL trial (essentially exclusive use of CRRT) than in the ATN trial (substantial use of IHD in addition to CRRT) suggesting that the use of CRRT might facilitate renal recovery.

Prognosis

The mortality of S-AKI in general remains high with the ATN trial reporting a mortality of close to 55% and the RENAL trial reporting a mortality of close to 40%. In addition, several large epidemiological studies have recently linked AKI with the later development of chronic kidney disease, end-stage kidney disease, and mortality (Coca et al., 2009). These observations suggest that even a short episode of AKI may contribute to long-term organ and patient morbidity and mortality. Whether this increased risk reflects the effect of AKI itself or whether AKI acts as a marker which identifies more vulnerable patient remains unclear.

Conclusions

Our understanding of the pathogenesis of S-AKI is limited. Although haemodynamic factors might play a role in the loss of GFR during sepsis, they may not act through the induction of renal ischaemia. S-AKI may be a unique form of AKI where non-haemodynamic mechanisms of cell injury are likely to be at work, which are immunological/toxic/inflammatory in nature and which may affect the vasculature as well as tubular cells. Among these mechanisms, apoptosis may be important. It is possible that, as evidence accumulates, the paradigms currently used to explain S-AKI will shift from ischaemia and vasoconstriction to hyperaemia and vasodilatation and from acute tubular necrosis to either acute tubular apoptosis or simply tubular cell dysfunction. If this were to happen, our therapeutic approaches will also be profoundly altered.

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CHAPTER 245

Cardiovascular surgery and acute kidney injury

Jeremiah R. Brown and Chirag R. Parikh

Introduction

Over the last decade, cardiac surgery-associated acute kidney injury (AKI) has been recognized as a frequent adverse event following cardiac surgery (Brown et al., 2006, 2010a; Lassnigg et al., 2008; Hobson et al., 2009). In this clinical context and others, AKI has been strongly associated with increased morbidity, mortality, and length of hospitalization (Brown et al., 2006, 2010a; Lassnigg et al., 2008; Waikar et al., 2008; Hobson et al., 2009). These adverse events that accompany AKI have been shown to be directly proportional to the magnitude of the peak rise in serum creatinine (Bihorac et al., 2009; Hobson et al., 2009) and the duration of AKI (Brown et al., 2010a; Coca et al., 2010). On average, each hospital-acquired AKI event costs the hospital approximately $7500 (Chertow et al., 2005), making AKI a costly complication and a target for prevention in hospitalized patients around the world.

Defining acute kidney injury

Commonly used definitions for AKI in cardiac surgery have included the Society for Thoracic Surgeons (STS) criteria, the Acute Dialysis Quality Initiative Workgroup for Risk, Injury, Failure, Loss, and End-stage kidney disease (RIFLE) criteria (Bellomo et al., 2004), and more recently consensus has focused on adoption of the Acute Kidney Injury Network (AKIN) (Mehta et al., 2010) definition (Table 245.1). The RIFLE and AKIN definitions include tiers to quantify the severity of AKI based on the highest postoperative serum creatinine. The duration of AKI using the AKIN definition has also been evaluated as a more sensitive and specific measure of AKI severity after general surgery (Coca et al., 2010) and cardiac surgery (Brown et al., 2010a). Trends in AKI, using the AKIN definition, have remained constant over the past decade ranging from 18% to 42% of patients undergoing coronary artery bypass graph surgery (CABG), valve, or CABG with valve surgery (Fig. 245.1). The highest incidence of AKI is found in the combined CABG/valve procedures, likely due to extended cardiopulmonary bypass pump times with paralleled hypoperfusion and reduced oxygen saturation delivery to critical organs including the brain and kidneys. In cardiac surgery, even small changes in serum creatinine have been associated with poor survivorship (Brown et al., 2006). Survival is also significantly lower among patients that develop longer durations of AKI (Brown and O'Connor, 2010).

Progression of acute kidney injury to renal failure

AKI after cardiac surgery has been associated with more rapid progression to incident chronic kidney disease (CKD), progressive CKD, and renal failure (dialysis or kidney transplant). Ishani et al. demonstrate the progression from normal renal function prior to cardiac surgery to the development of CKD (estimated glomerular filtration rate (eGFR) < 60 mL/min/m^2) and the progression of CKD patients to a higher CKD stage (e.g. stage 3 to 4 or 4 to 5) in the years that followed stratified by the percentage change in serum creatinine from prior to surgery to post-surgery (Ishani et al., 2011). Ishani and colleagues reported on the progression from small changes in serum creatinine to incident CKD and progressive CKD; it is important to note that cardiac surgery patients with a ≥ 50% rise in serum creatinine, which constitutes AKI, progressed more quickly to incident CKD and had more rapid progression of CKD than patients without elevations in serum creatinine or mild elevations in serum creatinine that would not meet the criteria for AKI. This evidence suggests that there is a direct correlation between the degree of acute injury to the kidneys during the perioperative period and long-term progression of worsening renal function. Others have confirmed this phenomenon in other patient populations, demonstrating the increased risk of progression to end-stage renal disease (ESRD) and mortality (Amdur et al., 2009; Ishani et al., 2009; James et al., 2011). Therefore, patients developing perioperative AKI are at risk for progressing towards worsening renal function and should be monitored following the perioperative period to prevent unnoticed rapid progression to renal failure.

Acute kidney injury and mortality

The Northern New England Cardiovascular Disease Study Group (NNECDSG, <http://www.nnecdsg.org>) has reported on the poor survivorship associated with perioperative changes in serum creatinine (Brown et al., 2006) and longer durations of AKI (Brown and O'Connor, 2010). The early findings demonstrated that subtle changes in serum creatinine were directly proportional to increased 90-day mortality (Brown et al., 2006). The association between AKIN states of AKI and survival is consistent with the earlier reports of changes in serum creatinine (Fig. 245.2). More recently, NNECDSG AKI researchers and TRIBE-AKI investigators jointly evaluated the role of the duration of AKI as a marker for AKI severity and

Table 245.1 Classification of AKI

	Dialysis	Serum creatinine (SCr)	eGFR	Urine output
STS	Dialysis	SCr increase > 2.0 and 2× most recent preoperative		
RIFLE				
Risk		SCr increase by 1.5× (50%) from baseline	GFR decrease of > 25%	< 0.5 mL/kg/hour for 6 hours
Injury		SCr increase 2× (100%) from baseline	GFR decrease by > 50%	< 0.5 mL/kg/hour for 12 hours
Failure		Increase in SCr by 3× (200%) from baseline, or SCr ≥ 4mg/dL	GFR decrease by > 75%	< 0.3 mL/kg/hour or anuria for 12 hours
Loss	Persistent need for renal replacement > 4 weeks			
ESRD	Renal replacement therapy > 3 months			
AKIN				
Stage 1		Increase in SCr by ≥ 0.3 mg/dL or increase by 1.5–2× from baseline		Urinary output < 0.5 mL/kg/hour for 6 hours
Stage 2		Increase in SCr > 2–3× from baseline		Urinary output < 0.5 mL/kg/hour for > 12 hours
Stage 3	Dialysis	Increase in SCr by > 3× from baseline or absolute SCr ≥ 4 mg/dL, with an acute increase of ≥ 0.5 mg/dL		Urine output < 0.3 mL/kg/hour for 24 hours or anuria for 12 hours

AKIN = Acute Kidney Injury Network; eGFR estimate glomerular filtration rate; RIFLE = Risk Injury Failure Loss End Stage Renal Disease; SCr = Serum Creatinine; STS = Society of Thoracic Surgeons.

demonstrated the proportionality associated with longer durations of AKI and worse survival (Fig. 245.3). These Kaplan–Meier survival plots demonstrate the severe consequences patients face with the development of AKI and moderate or severe AKI.

Predicting acute kidney injury and acute kidney injury duration

A number of investigators have sought to develop risk models for renal failure and/or AKI. Most of the prediction modelling efforts have investigated the ability of patient and procedural risk factors to predict the occurrence of renal failure (Chertow et al., 1997; Thakar et al., 2005; Mehta et al., 2006; Wijeysundera et al., 2007). These models have also performed well for predicting severe AKI using the STS definition of AKI, defined as a 2.0 mg/dL or twofold increase in serum creatinine or new dialysis (Thakar et al., 2005; Mehta et al., 2006; Wijeysundera et al., 2007; Englberger et al., 2010). Yet, other investigators have developed models in predicting immediate postoperative declines in creatinine clearance or eGFR (Aronson et al., 2007; Brown et al., 2007; Palomba et al.,

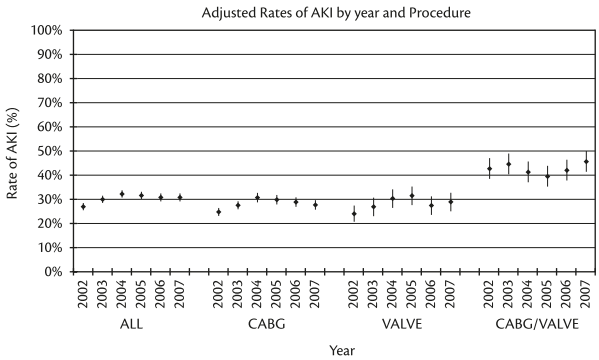

Fig. 245.1 Adjusted rates of acute kidney injury with 95% confidence intervals by year and type of cardiac surgery. All surgery includes coronary artery bypass graft (CABG), valve, or CABG/valve. Rates of AKI have remained constant over time ranging between 25% and 45%.

From the Northern New England Cardiovascular Disease Study Group (unpublished data).

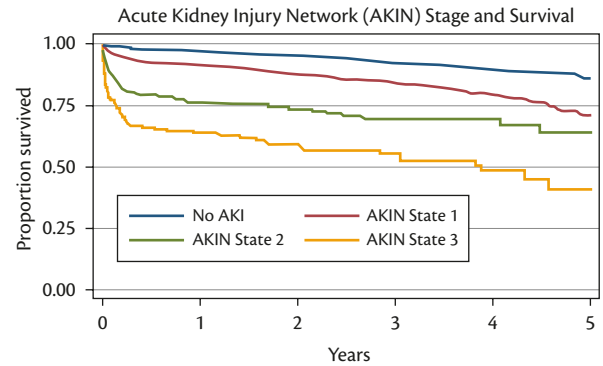

Fig. 245.2 Kaplan–Meier survival graph for cardiac surgery patients by acute kidney injury network (AKIN) stage: no AKI (blue), AKIN stage 1 (red), AKIN stage 2 (green), and AKIN stage 3 or renal failure (yellow).

From the Northern New England Cardiovascular Disease Study Group (unpublished data).

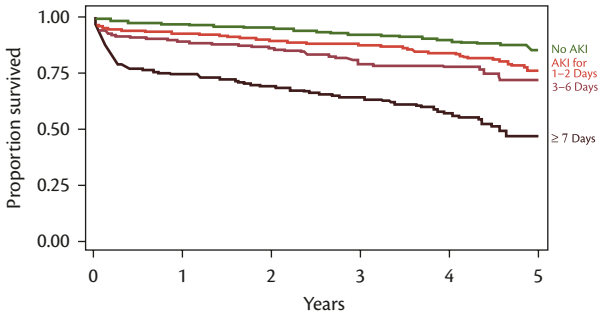

Fig. 245.3 Kaplan–Meier survival graphs by duration of acute kidney injury (AKI) after cardiac surgery: No AKI, AKI lasting 1–2 days, AKI lasting 3–6 days, and AKI lasting 7 or more days.

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2007). One example included the NNECDSG's approach to predict at least a 30 mL/min/m^2 drop in eGFR among patients with normal or near normal renal function (eGFR ≥ 60 mL/min/m^2) (Brown et al., 2007). Recent investigations have incorporated additional perioperative risk factors from the procedure and complications from the procedure as an attempt to improve the prediction of AKI of duration of AKI. The various risk factors utilized in the prediction modelling for renal failure and AKI. Major similarities amongst the models include age, gender, baseline renal function, heart failure, diabetes, use of an intra-aortic balloon pump, and duration on cardiopulmonary bypass (Table 245.2) (Huen and Parikh, 2012).

Another approach to predicting the severity of AKI focused on predicting the length of time, or duration, of the acute injury. The duration of AKI was modelled to predict the average projected number of days a patient may sustain AKI and is published as an online risk calculator (<http://yale.edu/tribeaki/aki_duration_calc.html>). This can be a useful way to determine a patient's risk and length, or duration, or AKI after cardiac surgery. If the duration is projected to be > 3 days, a nephrology consult on admission to the ICU may be helpful in preventing the onset of AKI and minimize the duration.

Novel biomarkers and acute kidney injury prediction

Novel biomarkers have the ability to improve our prediction of AKI events and provide earlier detection. Several biomarkers have been rigorously investigated including plasma cystatin C, urinary neutrophil gelatinase-associated lipocalin (NGAL), urinary interleukin 18 (IL-18), *N*-acetyl-B-(D)-glucosaminidase (NAG), alpha-1 microglobulin, albuminuria, and urinary kidney injury molecule 1 (KIM-1) (Liangos et al., 2009; Parikh et al., 2011a, 2011b; Shlipak et al., 2011). The TRIBE-AKI Consortium released evidence that supports the use of serum creatinine and cystatin C in determining risk of AKI prior to cardiac surgery (Fig. 245.4); this was found to be true among all patients and more so for predicting severe AKI (Shlipak et al., 2011). In adult cardiac surgery, TRIBE also demonstrated the clinical utility of postoperative kidney biomarkers, including plasma NGAL and urinary IL-18 and NGAL (Fig. 245.5). They reported that urinary IL-18 had superior prediction for AKI over plasma or urinary NGAL (Fig. 245.6) (Parikh et al., 2011a). In paediatric heart surgery, urinary IL-18 and urinary NGAL were both superior to plasma NGAL or serum creatinine (Parikh et al., 2011b). A small study of 103 subjects by Liangos and colleagues reported KIM-1, NAG, NGAL, and IL-18 significantly predicted AKI at 2 hours after cardiopulmonary bypass; however, after adjustment for the preoperative Cleveland Clinic Foundation score for AKI and/or cardiopulmonary bypass time, only KIM-1 remained statistically significant (Liangos et al., 2009;). Albuminuria is a predictive marker for the development of AKI (Hsu et al., 2008; Grams et al., 2010; James et al., 2010; Huang et al., 2011; Tonelli et al., 2011). An increase in the ratio between urinary albumin and creatinine has been demonstrated to improve preoperative risk prediction of AKI suggesting the addition of albuminuria to preoperative risk assessment for AKI (Huang et al., 2011; Coca et al., 2012). KIM-1 and other markers such as L-type fatty acid binding protein and alpha-1 microglobulin need further large-scale clinical trial investigations.

Recent studies by the TRIBE-AKI consortium have incorporated novel methods to evaluate the improved predictive ability of these biomarkers when added to patient and clinical risk factor models (Parikh et al., 2011a, 2011b; Shlipak et al., 2011). These methods have included the net reclassification index (NRI) and incremental discrimination improvement index (IDI) (Pencina et al., 2008). Investigations have demonstrated that the NRI and IDI indexes provide better evaluation of the prediction modelling over calculating the difference between two areas under the receiver operating curve (Pencina et al., 2008). Future studies evaluating the predictive utility of kidney biomarkers for AKI assessment should incorporate these methods to evaluate their contribution above and beyond patient and clinical factors alone.

Mechanism and risk factors for acute kidney injury

AKI is postulated to result from various patient and procedural factors (Fig. 245.7). Patient factors include many of the risk factors used in the prediction modelling described previously (age, gender, baseline renal function, heart failure, and diabetes). Preoperative anaemia (haemoglobin < 14 g/dL) has also been shown to have an inverse relationship with AKI, where by each successive drop in haemoglobin under 14 g/dL increases the risk of postoperative AKI by 23% for haemoglobin between 12 and 13.9 g/dL, by 63% for haemoglobin 10–11.9 g/dL, and by 99% for haemoglobin < 10 g/dL (Karkouti et al., 2009).

Before the patient arrives at the operating room for cardiac surgery, it is most likely the patient has had a recent angiography, or cardiac catheterization. These procedures usually use small amounts of low-osmolar or iso-osmolar contrast, however sometimes an ad hoc angioplasty (percutaneous coronary intervention (PCI)) is performed and stents implanted in the coronary arteries to re-establish or sustain blood flow. During a PCI, larger, and potentially dangerous, volumes of contrast dye are injected to visualize the coronary arteries for the deployment of the devices and stents. It is during this time that patients are likely to develop contrast-induced AKI resulting from acute tubular necrosis and oxidative stress (see Chapter 246). It has been shown that there is a direct relationship between the dose of contrast and AKI (Marenzi et al., 2009; Brown et al., 2010b). Fig. 245.8 shows the dose–response of exceeding a tailored safe dose of contrast and incidence of contrast-induced AKI (Brown et al., 2010b). Others have demonstrated there is direct

Table 245.2 Variables included in the models

	Variable	CICSS	Cleveland	STS	SRI	McSPI	AKICS	NNECDSG
Demographics	Age			X		X	X	X
	Gender		X					X
	Race			X				
Clinical	Preoperative renal insufficiency	X	X	X	X	X	X	
	Prior heart surgery	X	X	X	X			X
	Advanced NYHA	X		X			X	
	Congestive heart failure		X			X		X
	Decreased ejection fraction		X		X			
	Cardiomegaly	X						
	Pulse pressure					X		
	Hypertension							X
	PVD/CVD	X						X
	COPD/chronic lung disease		X	X				
	Diabetes mellitus		X	X	X			X
	Preoperative capillary glucose>140						X	
	MI within last 3 weeks			X				
	Prior MI					X		
	Reoperation							
	Preoperative IABP	X	X		X			X
	Emergent surgery		X		X			
	Cardiogenic shock			X				
	Preoperative WBC > 12,000							X
Surgery type	Valvular surgery	X	X	X				
	CAPG + valve		X	X			X	
	Other cardiac procedures		X		X			
Inoperative	Increased CPB time					X	X	
	> 2 inotropes					X		
	Intraoperative IABP					X		
Postoperative	CVP > 14 cmH_2O						X	
	Low cardiac output						X	

CAPG = coronary artery bypass graft; COPD = chronic obstructive pulmonary disease; CPB = cardiopulmonary bypass; CVD = cardiovascular disease; CVP = central venous pressure; IABP = intra-aortic balloon pump; MI = myocardial infarction; NYHA = New York Heart Association Functional Classification; PVD = peripheral vascular disease; WBC = white blood cell count.

relationship between the timing of the cardiac catheterization and cardiac surgery, whereby the risk of AKI is higher among patients undergoing cardiac surgery within 24 hours of a cardiac catheterization (Del Duca et al., 2007; Ranucci et al., 2008; Hennessy et al., 2010; Medalion et al., 2010) with direct ties to the amount of contrast used (Hennessy et al., 2010; Medalion et al., 2010). Recent evidence also demonstrates that if the cardiac catheterization was conducted during the same admission as cardiac surgery (including in-patient transfers), the risk of AKI is increased by 54% (Kramer et al., 2010).

Operative risk factors for acute kidney injury

There are several operative factors that should be considered. Cardiopulmonary bypass (pump time) contributes to the development of AKI (Brown et al., 2006; Karkouti et al., 2009). Off-pump cardiac surgery has been shown to reduce the incidence of AKI (Kuss et al., 2010; Park et al., 2010); however, caution should be taken to only incorporate off-pump cardiac surgery as a protective measure against AKI among proficient off-pump surgeons and

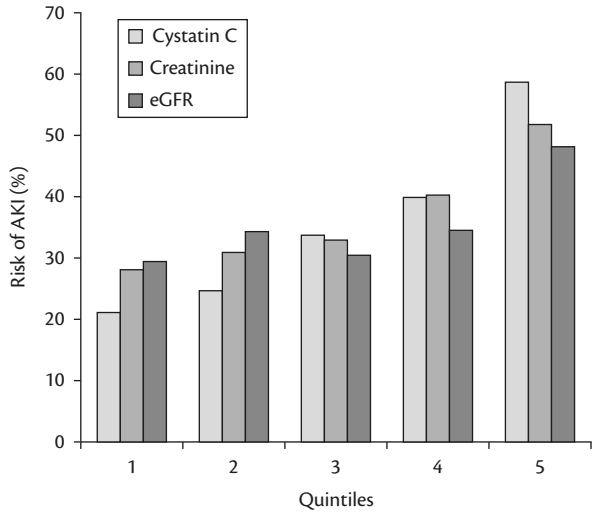

Fig. 245.4 Risk of acute kidney injury (AKI) by quintiles of serum cystatin C (left, light grey), serum creatinine (middle, dark grey), and estimated glomerular filtration rate based on serum creatinine (eGFR-Cr, right black).
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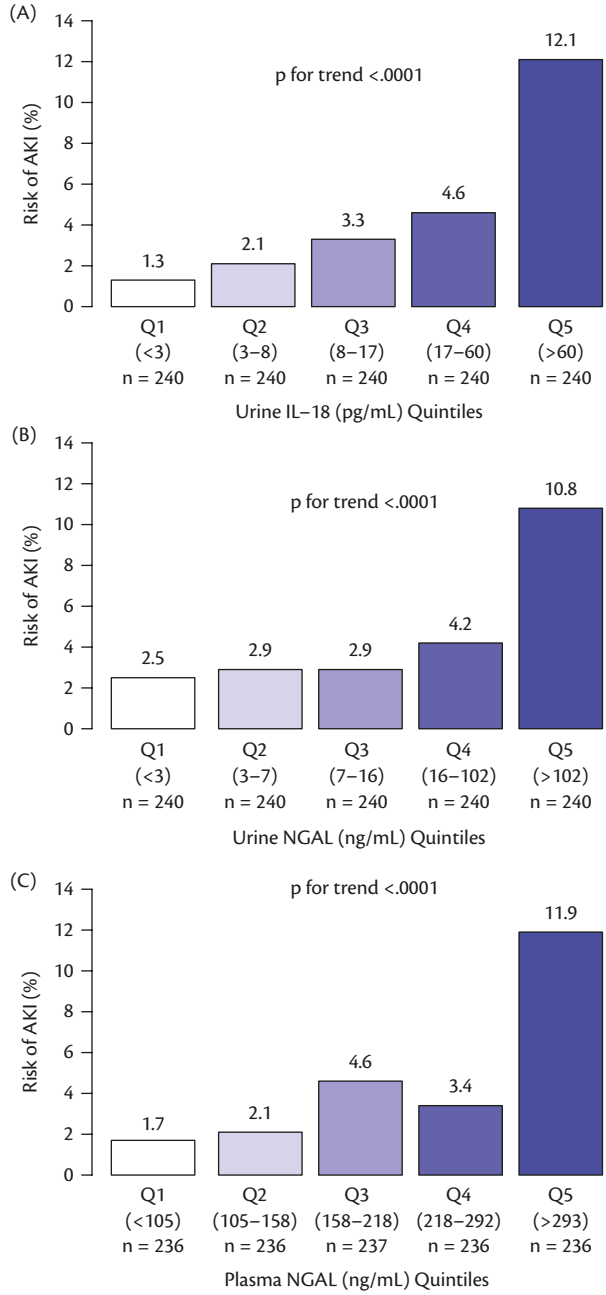

Fig. 245.5 Adult cardiac surgery risk of acute kidney injury (AKI) by quintiles of urine interleukin-18 (A), urinary neutrophil gelatinase-associated lipocalin (NGAL) (B), and plasma NGAL (C).
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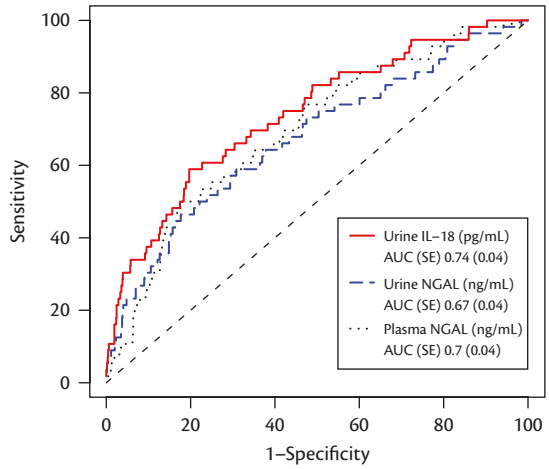
the risk–benefit should be weighed against the risk of incomplete revascularization and bleeding (Puskas et al., 2004). During cardiopulmonary bypass, gaseous or particulate emboli, renal ischaemia from hypoperfusion of the kidneys, and myoglobinuria and free haemoglobinuria are proposed causes of AKI (Grocott, 2006). It is thought that the cardiopulmonary bypass pump may result in an imbalance in O_2 supply due to low haematocrit and the need for O_2 by the kidneys. When the O_2 is < 260 mL/min/m^2 it can increase lactate levels and increase the risk of AKI. O_2 delivery can be optimized by coupling the pump flow with the haematocrit (Ranucci et al., 2005, 2010; Ranucci, 2007). To counteract these causes, cardiac surgeons and perfusionists have worked together to improve cardiopulmonary bypass management through temperature and blood pressure management, development of mechanisms and filtering devices to reduce gaseous microemboli, optimize O_2 delivery through improving the flow rate, haemoglobin levels, and haemodilution (Grocott, 2006).

The number of perioperative packed red blood cells (pRBCs) has a direct linear dose–response to the risk of developing AKI. Stored red blood cells have been shown to deteriorate after being frozen and stored for weeks at a lime. It has been demonstrated that these red blood cells develop specula and lose the biconcave disc shape causing inflexibility to travel through the capillaries, resulting in capillary damage and reduced microcirculation (Walter et al., 1999). Others have shown that patients receiving newer blood (pRBCs stored for ≤ 14 days) had significantly better survival and a lower incidence of renal failure than patients receiving pRBC transfusions that were stored for > 14 days (Koch et al., 2008). A similar effect was reported in paediatric cardiac surgery for AKI whereby AKI was reduced by 4.4% (Ranucci et al., 2010).

Prevention of acute kidney injury

A recent systematic review summarized the interventions to prevent AKI that have been evaluated with mixed efficacy in cardiac surgery. Interventions have included anti-inflammatory (*N*-acetylcysteine, glutathione, fenoldopam, leucodepletion, aspirin, dexamethasone, and methylprednisolone), natriuretics/diuretics (nesiritide, atrial natriuretic peptide (ANP), furosemide, urodilatin, and mannitol), vasodilators (prostaglandin E_1, diltiazem, dopexamine, dopamine, mannitol, fenoldopam, angiotensin-converting enzyme inhibitor, sodium nitroprusside, theophylline, and prostacyclin), operative techniques (mostly off-pump), prophylactic continuous veno-venous haemodiafiltration or renal replacement therapy, and other strategies (albumin, insulin, clonidine, and volume expansion) (Park et al., 2010). Park and colleagues concluded that most of



	5th Quintile				
	Cut point	Sensitivity	Specificity	LR+	LR–
Urine IL–18 (pg/mL)	60	54%	82%	3	0.56
Urine NGAL (ng/mL)	102	46%	81%	2.42	0.67
Plasma NGAL (ng/mL)	293	50%	82%	2.78	0.61

Fig. 245.6 Adult cardiac surgery receiver operating characteristic curve for acute kidney injury (AKI) for urinary interleukin 18 (red), urinary neutrophil gelatinase-associated lipocalin (NGAL) (blue), and plasma NGAL (black).
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the prophylactic strategies conducted prior to cardiac surgery were protective against AKI; these included ANP/nesiritide, fenoldopam, and dopamine (Park et al., 2010).

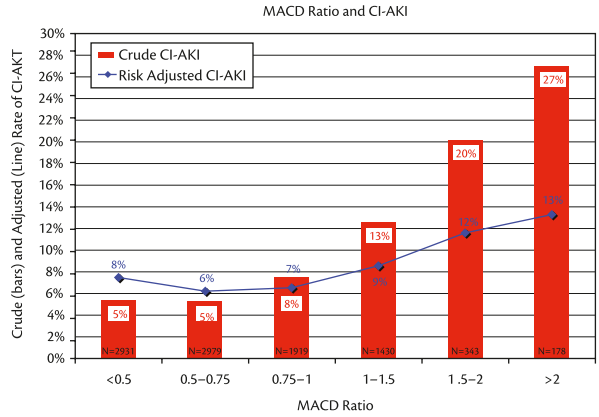

Fig. 245.8 Contrast-induced acute kidney injury (CI-AKI) after percutaneous coronary intervention (PCI) stratified by the calculated ratios of contrast volume to the predicted maximum acceptable contrast dose (MACD) are plotted by the crude (red bars) and risk-adjusted (blue diamonds).
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Ischaemic preconditioning prior to cardiac surgery may be an alternative prophylactic method to reduce AKI through preconditioning a remote site in the body (arm or leg) to reduced blood flow which may reduce reperfusion injury and AKI (Ali et al., 2007; Zimmerman et al., 2011). Zimmerman and colleagues demonstrated in a small single-centre randomized trial that ischaemic preconditioning resulting in an absolute risk reduction of 0.27 (12 vs 28 AKI events, P = 0.004) and resulted in lower rates of sustained AKI at 2 or more days (Zimmerman et al., 2011). It is likely

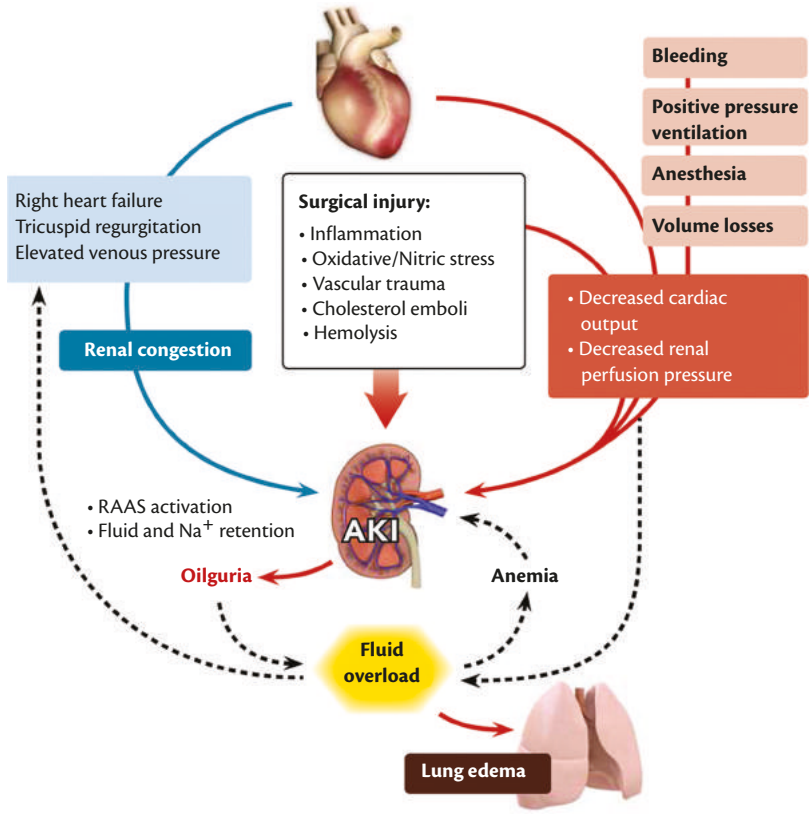

Fig. 245.7 Illustration of the medical and surgical interventions associated with the development of acute kidney injury.

that simple ischaemic preconditioning methods could be incorporated at the time of entry to the operating room and may not only assist in AKI event reduction but also reduce myocardial reperfusion injury.

Quality improvement efforts to reduce acute kidney injury

Above, we summarized the clinical research that has sought to mitigate AKI in the context of cardiac surgery. Some of these interventions have demonstrated consistency in prevention, while others either need more investigation or the development of new strategies. Most of these efforts have focused around modifying or discontinuing potentially nephrotoxic medication or exposure to nephrotoxins, such as radiocontrast dye. McCoy and colleagues reported on the single-centre use of a computerized medication safety tool designed for patients developing AKI. Through the use of this automated intervention tool, 52.6% of the time potentially nephrotoxic medications were halted or modified within 24 hours of an acute increase in serum creatinine qualifying as AKI; a 49% improvement prior to the intervention (McCoy et al., 2010). Additional simple and sophisticated process tools should be developed by multidisciplinary teams to study the problem of AKI. When doing so, teams should identify targets for intervention, test those interventions, evaluate their effectiveness, and re-design continually. Such microsystem-level improvement efforts are known as PDSA cycles of change (Plan-Do-Study-Act) (Batalden et al., 2003; Nelson et al., 2008).

Conclusions

In this chapter we have discussed the mortality, subsequent healthcare costs, utilization, and morbidity that follows subtle changes in serum creatinine known as AKI in the perioperative setting of cardiac surgery. The field has come a long way from 10 years ago when subtle changes in serum creatinine were often ignored to the current volume of research and dedication that has identified and sought solutions for the patient safety issues surrounding cardiac surgery-associated AKI. In the near future, novel kidney injury biomarkers and risk tools will be available to identify early signs of AKI and acute tubular necrosis and hopefully matched with aggressive tools for medication adjustment and injury-specific tools to mitigate AKI and its subsequent morbidity and mortality.

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CHAPTER 246

Contrast-induced acute kidney injury

Douglas Stewart, Gaurav Shah, Jeremiah R. Brown, and Peter A. McCullough

Minimizing kidney injury in the setting of cardiovascular disease

The association between chronic kidney disease (CKD) and an increased incidence of cardiovascular disease has been well established. The United States has seen an exponential increase in diagnoses of diabetes, obesity, and hypertension in the last 10–15 years (McCullough et al., 2011). Patients with these illnesses subsequently are subject to accelerated renal and cardiovascular insults that rarely result in immediate death or urgent need for dialysis, but are associated with prolonged hospital stays, increased cost, and increased in-hospital and long-term morbidity and mortality (Solomon and Deray, 2006).

Rising numbers of interventional procedures spanning throughout all fields of medicine have respectively increased patients' exposure to intravascular iodinated contrast media in the last 10 years. The incidence of contrast-induced acute kidney injury (CI-AKI) ranges between 0.6% and 2.3%, with even higher numbers for the patient population with underlying cardiovascular pathology (Gleeson and Bulugahapitiya, 2004; McCullough and Soman, 2005; Solomon and Deray, 2006). Dialysis as an unfortunate complication of CI-AKI results in 0.3–0.7% of patients with approximately half of those individuals requiring permanent renal replacement therapy for the rest of their lives (Solomon, 2005). Risks of morbidity and mortality rise, both in hospital and at 1 year, in patients who develop CI-AKI followed by a more rapid progression of CKD (Solomon, 2005).

Definition of contrast-induced acute kidney injury

CI-AKI is an important complication after the intravascular administration of iodinated contrast as discussed above (Nash et al., 2002; Gleeson and Bulugahapitiya, 2004; McCullough and Soman, 2005). The definition of CI-AKI implies impairment in renal filtration function occurring within 48–72 hours after the procedure, in the absence of alternative aetiologies. Past clinical trials have suggested that a rise in serum creatinine of 0.5 mg/dL or a 25% increase from the baseline value indicates occurrence of CI-AKI (Barrett et al., 1992; Solomon, 2005). Serum creatinine concentrations generally peak on day 2 or 3 after contrast exposure and typically return to baseline values within 2 weeks (Solomon, 2005). In 2007, the Acute Kidney Injury Network (AKIN) and in 2012 the Kidney Diseases improving Global Outcomes Expert Group (Lameire, and Kellum, 2013) proposed the definition of a rise in serum creatinine ≥ 0.3 mg/dL with oliguria (< 0.5 mL/kg/hour for > 6 hours), which is compatible with the older definitions. It is expected that in addition to this signal of reduced filtration function, markers of acute tubular injury in the blood and urine will be used to establish a diagnosis of CI-AKI in the near future.

General consensus statements concerning CI-AKI agreed upon by multidisciplinary panels (McCullough et al., 2006) have surfaced in the past 10 years. These statements, available in published literature, deal with the issues of screening, risk stratification, high-risk scenarios, and reasonable preventive measures. Fortunately, the frequency of CI-AKI has decreased over the past decade from a general incidence of approximately 15% to approximately 7% of patients (Bartholomew et al., 2004). Explanations for this decreased incidence despite an increase in the pool of patients at risk include greater awareness of the problem, more liberal use of intravenous fluids to prevent volume depletion, reduction in the quantity of contrast used, and the shift from higher to lower osmolar contrast agents. In addition, smaller catheters are now used with guidewire techniques that may reduce the frequency of subclinical atheroembolism which could contribute to the syndrome. At the time of writing this chapter, there are no approved diagnostic tests, preventive therapies, or specific treatments for CI-AKI.

Pathophysiologic mechanisms

Exact underlying mechanisms of CI-AKI are unclear; however, several accepted concepts are described in the literature and continue to be sources of scientific investigation. A reduced number of functioning nephrons manifested by clinical CKD must be present as an underlying 'injured' substrate, for the development of CI-AKI as recognized by a rise in serum creatinine (Bartholomew et al., 2004; Persson et al., 2005). In patients with CKD, identified by an estimated glomerular filtration rate (eGFR) < 60 mL/min, there is a considerable loss of nephron units over the course of chronic disease, such as hypertension and diabetes. Residual renal function in this subset of patients is vulnerable to further decline with additional insults (sepsis, intravascular iodinated contrast, cardiopulmonary bypass, nephrotoxic medications, and atheroembolism). Contrast agents promote nephrotoxicity by two major mechanisms: (1) vasoconstriction and ischaemic injury, and (2) direct chemotoxicity to renal

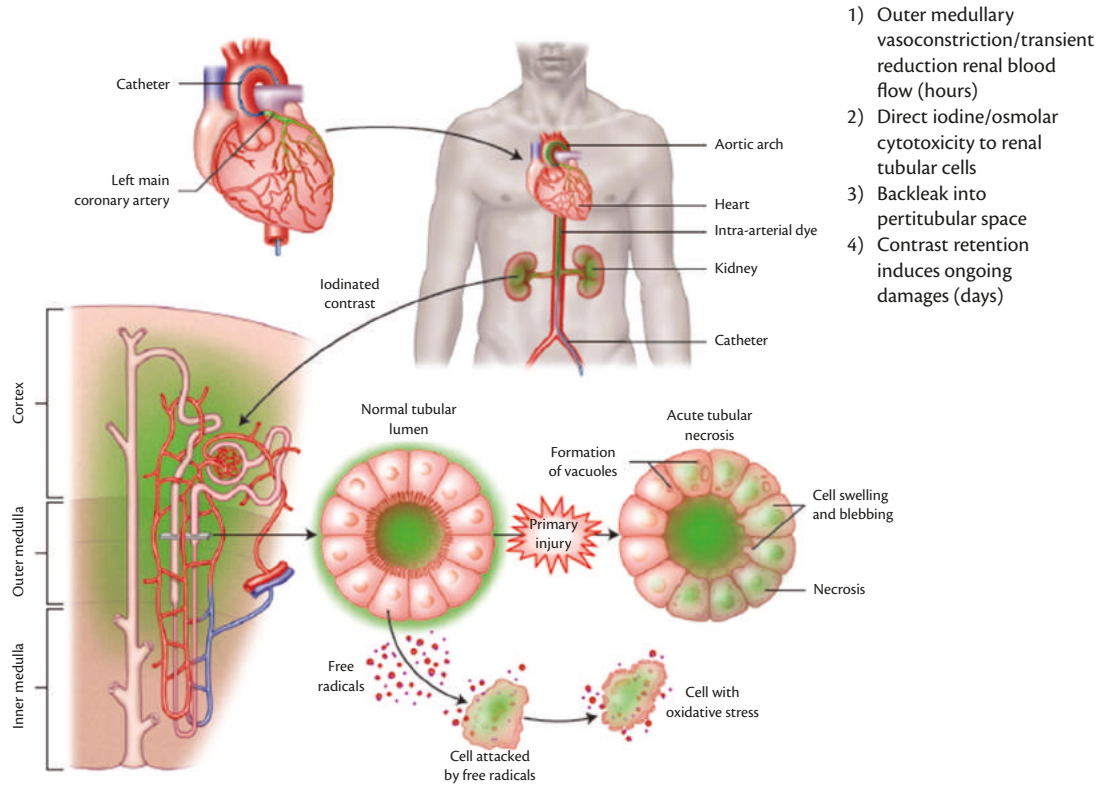

Fig. 246.1 Pathophysiology of contrast-induced AKI demonstrating in the presence of a reduced nephron mass, the remaining nephrons are vulnerable to injury. Iodinated contrast, after causing a brief (minutes) period of vasodilation, cause sustained (hours) intrarenal vasoconstriction and ischaemic injury. Proximal renal tubular cells have a high-capacitance system for managing solute and water that takes up iodinated contrast into the cells and causes direct cytotoxicity, release of catalytic iron, and intracellular oxidative injury by reactions catalysed by iron. If a sufficient mass of nephron units are affected, then a recognizable rise in serum creatinine will occur. Reproduced with permission from Brown, J. R. and McCullough, P. A. (2012). *Contrast Nephropathy and Kidney Injury, Textbook of Cardiovascular Intervention*. New York: Springer Publishing Company.

tubular cells (Persson et al., 2005). Several mechanisms of insult collide to create a 'perfect storm'. Superimposed acute vasoconstriction caused by the release of adenosine, endothelin, and other renal vasoconstrictors triggered by iodinated contrast (Fig. 246.1) provides initial damage to tubular cells predisposing to further injury (Brown and McCullough, 2012). Global reductions in renal blood flow last for several hours and are promoted by the extravasation of contrast from the urinary space in the loop of Henle into the peritubular plexus of arterioles and venules where it promotes local vasoconstriction and further tubular ischaemia. The proximal renal tubular cells have high-capacitance fluid and solute mechanisms that pump contrast and urinary solute into the cytosol of the cells.

There are considerable differences in oxygen tension in the kidney due to the gradients of regional blood flow necessary for the complex movement of sodium and water. The outer cortex has approximately five times the oxygen tension of the outer medulla. Thus the outer medulla, which is the cross-section of the kidney corresponding to the loop of Henle, is the vulnerable zone in most forms of AKI. Conversely, the glomerulus in the cortex is spared and explaining why haematuria is not seen in CI-AKI. In the setting of vasoconstriction, the descending and ascending limbs of the loop of Henle experience hypoxic damage in the outer and deeper portions of the medulla (Persson et al., 2005; Solomon and Dauerman, 2010). By increasing renal vascular resistance, addition of contrast media aggravates hypoxic response (Solomon and Deray, 2006). Another factor hypothesized, but not well understood, involves the increased oxygen demand due primarily to work overload in the remaining functioning tubular cells. A combination of transient increases in eGFR and osmotic diuresis lead to larger uptake of NaCl in distal nephron segments. Agmon et al. demonstrated that by shifting medullary flow within the kidney, contrast exposure may cause increased oxygen demand (Agmon et al., 1994).

After a very brief increase in renal blood flow, via the above mechanisms, there is an overall approximate 50% sustained reduction in renal blood flow lasting for several hours. There is concentration of iodinated contrast in the renal tubules, collecting ducts, and peritubular space resulting in a persistent nephrogram on fluoroscopy or repeated X-rays (plain film or computed tomography (CT)). This nephrogram, representing iodinated contrast in the peritubular and interstitial space, can last for up to 8 days after the original contrast administration in patients with severely reduced renal filtration at baseline (Fig. 246.2). This stasis of contrast in the kidney allows for direct cellular injury and death of renal tubular cells and explains the variability in the rise in serum creatinine over the ensuing days.

The specific cytotoxic effects of contrast agents have been demonstrated and involve direct chemotoxicity and release of catalytic iron from cellular organelles which is necessary to generate superoxide radicals that propagate local oxidative tissue injury and cell death (Persson et al., 2005). Many reactions involved in oxidative

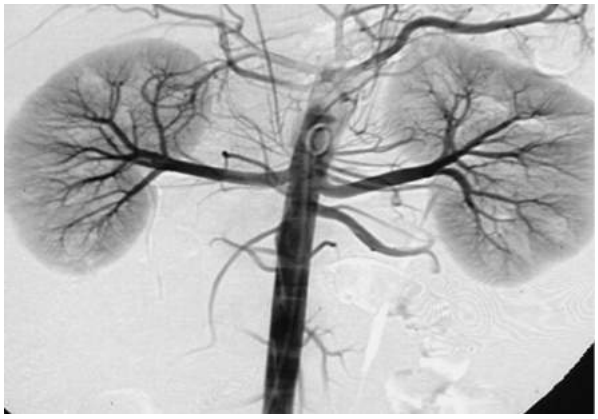

Fig. 246.2 Normal nephrogram during aortography using digital subtraction angiography. When the renal parenchyma is radiographically visible > 2 hours later, then a persistent nephrogram is identified and the patient can be expected to develop CI-AKI.

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stress are dependent on sources of intracellular labile iron, including the cytochrome P450 chain and mitochondria. The generation of oxygen free radicals occurs even under normal conditions, but levels may increase exponentially as tissue succumbs to oxidative stress in the form of hydrogen peroxide and the hydroxyl radical, both of which are capable of destroying cell membranes and enabling cell-to-cell death. This deleterious process is dependent on catalytic iron which can be found in the blood and urine of patients with CI-AKI, and thus, the labile forms of iron (Fe^{2+} and Fe^{3+}) are being considered as future therapeutic targets in CI-AKI. Any superimposed insult such as sustained hypotension in the catheterization laboratory, microshowers of atheroembolic material from catheter exchanges, the use of intra-aortic balloon counterpulsation (IABP), sepsis, or a bleeding complication can amplify the injury processes occurring in the kidney.

The degree of cytotoxicity to renal tubular cells is directly related to the length of exposure those cells have to iodinated contrast, hence, the importance of high urinary flow rates before, during, and after contrast procedures to reduce contrast dwell time. Previous studies have demonstrated that contrast media may induce apoptosis. The effects upon intercellular junction overture and epithelial cell surfaces are mechanisms essential for normal electrolyte reabsorption, and may be yet another key mechanism leading to toxic effects of contrast administration.

Risk stratification

Identification of patients at risk for CI-AKI can help guide prophylactic treatment to prevent post-procedural complications. Cardiac catheterization laboratories have some form of screening tool to estimate renal function for patients exposed to contrast media. The most commonly used tool is measurement of the serum creatinine. However, this may not be adequate to account for several factors including age, sex, and weight of the patient. Estimation of the creatinine clearance using the Cockcroft–Gault equation or the eGFR using the Modification of Diet in Renal Disease (MDRD) equation is more accurate in identifying patient populations with CKD. It has been suggested that an eGFR of < 60 mL/min is considered to be a risk factor for CI-AKI (Kagan and Sheikh-Hamad, 2010; Laville and Juillard, 2010). Patients with CKD with other co-morbid conditions such as diabetes mellitus (Laville and Juillard, 2010) are at further increased risk of developing CI-AKI. Advanced age (>65 years) and female sex (Sidhu et al., 2008; Laville and Juillard, 2010) are also identifiable risk factors. In addition, there have been reports of increased risk of AKI in patients with metabolic syndrome, impaired fasting glucose, obesity, and hyperuricaemia (Toprak, 2007).

Categories of contrast media

Contrast media can be categorized according to osmolality (high-osmolal (HOCM) ~2000 mOsm/kg, low-osmolal (LOCM) 600–800 mOsm/kg, and isosmolal (IOCM) 290 mOsm/kg) with decreasing levels of renal toxicity according to these classifications. The American College of Cardiology (ACC)/American Heart Association (AHA) guidelines for the management of acute coronary syndrome patients with CKD listed the use of IOCM as a class I, level of evidence A recommendation. The use of IOCM is also recommended in renal dialysis patients to minimize the chances of volume overload and complications prior to the next dialysis session. Most other societies concur with these recommendations for intra-arterial administration and allow the use of LOCM in lower risk patients and intravenous administration.

Contrast volume is an important predictor of CI-AKI. Even small volumes (~30 mL) of contrast medium can have adverse effects on renal function in patients at particularly high risk (Manske et al., 1990). As a general rule, the volume of contrast received should not exceed twice the baseline level of eGFR in mL (Laskey et al., 2007). This means that for patients with significant CKD, reasonable goals would be < 30 mL for diagnostic cardiac catheterization and < 100 mL for percutaneous intervention (PCI), CT, and other intravascular studies.

The risk of CI-AKI is generally higher following intra-arterial than after intravenous injection (Campbell et al., 1990; Moore et al., 1992). However, in CT studies, where a comparatively large volume of contrast medium is given as a compact intravenous (80–120 mL) bolus rather than an infusion, the risk of CI-AKI may be increased (Fig. 246.3).

Finally, it is believed that serial exposures of contrast and subsequent administration in the setting of AKI further worsens renal function and may be more likely to cause persistent renal dysfunction. This is particularly true when a persistent nephrogram is present, and iodinated contrast is still present within the kidneys. Therefore, when faced with the option, a limited diagnostic catheterization and PCI (ad hoc PCI) in the same setting is favoured over a diagnostic catheterization and then a scheduled PCI within 10 days. The same concept applies for diagnostic followed by interventional radiologic procedures. It should be noted that there are no published sources of comparative data on this topic.

Intravenous volume expansion

Volume expansion and treatment of dehydration has a well-established role in prevention of CI-AKI, although few studies address this theme directly. Expansion of blood volume with intravenous fluid improves renal blood flow, increases glomerular filtration, and very importantly, increases urine flow, which

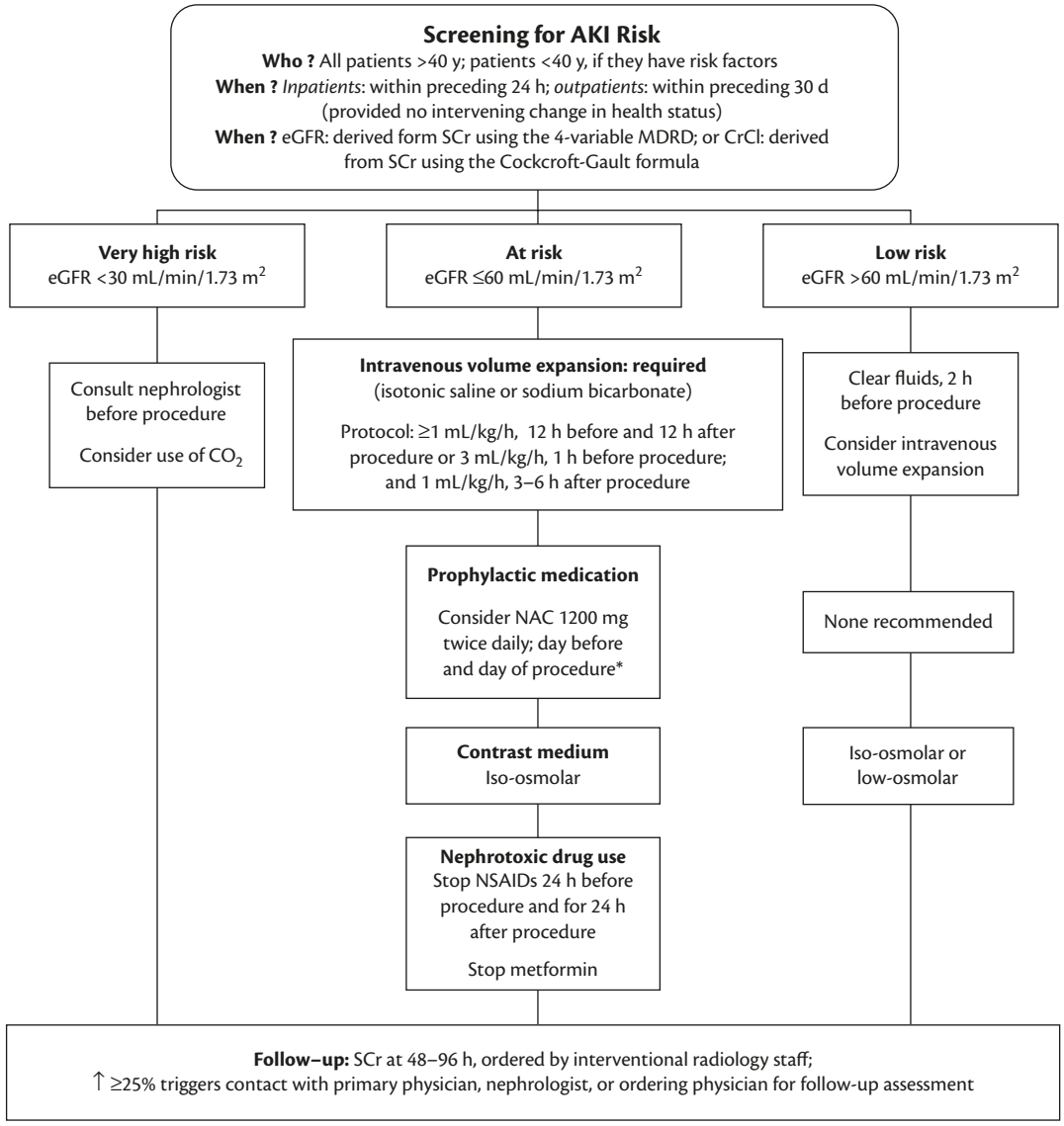

Fig. 246.3 Protocol for diagnostic computed tomography risk defined according to American College of Radiology criteria. *The evidence for a useful effect of N-acetyl cysteine (NAC) is weak (see text). AKI = acute kidney injury; CKD = chronic kidney disease; CM = contrast medium; CrCl = creatinine clearance; eGFR = estimated glomerular filtration rate; MDRD = Modification of Diet in Renal Disease; NSAIDs = non-steroidal anti-inflammatory drugs.

probably reduces the duration of toxic contrast exposure to the kidneys. There are limited data on the most appropriate choice of intravenous fluid, but the evidence indicates that isotonic crystalloid (saline or bicarbonate solution) is probably more effective than half-normal saline (Mueller et al., 2002). Theoretically, alkalinization of the urine and interstitial spaces with sodium bicarbonate would slow oxidative stress reactions, and thus, could be protective in various forms of CI-AKI. However, additional confirmatory trials with sodium bicarbonate (Merten et al., 2004) are needed since the largest trial to date (A Randomized Controlled Trial for the Prevention of Contrast Induced Nephropathy with Sodium Bicarbonate vs. Sodium Chloride in Patients Undergoing Coronary Angiography (MEENA trial)) showed no benefit of sodium bicarbonate over normal saline (Brar et al., 2008). A trial evaluating intravenous volume expanders suggests that administering a combination of normal saline solution plus sodium bicarbonate (intravenously 1 hour before and continuing for 6 hours afterwards) versus isotonic normal saline alone also has showed no benefit of added sodium bicarbonate (Ali Vasheghani-Farahani et al., 2010). Klima and Christ (2012) published a multicentre randomized trial in 258 subjects and found no difference between normal saline and sodium bicarbonate as the fluid administered on the rates of CI-AKI. Of interest, sodium bicarbonate (166 mEq/L) 3 mL/kg IV over 20 minutes before the procedure plus sodium bicarbonate orally (500 mg per 10 kg) was non-inferior to sodium bicarbonate (166 mEq/L) 3 mL/kg for 1 hour before and 1 mL/kg/hour for 6 hours after the procedure.

There is also no clear evidence to guide the choice of the optimal rate and duration of infusion. However, good urine output (> 150 mL/hour) in the 6 hours after the procedure has been associated

with reduced rates of CI-AKI in one study (Stevens et al., 1999). Conversely, oliguria (urine volume < 0.5 mL/kg/hour for 6 hours) in the face of intravenous hydration can be a sign of CI-AKI and is part of the AKIN definition of AKI discussed earlier. This is also consistent with the initial guidelines for AKI proposed by the Kidney Disease International Global Outcomes organization. Since only about 25% of intravenously administered isotonic crystalloid remains in the vascular space, in order to achieve a urine flow rate of at least 150 mL/hour, ≥ 1.0–1.5 mL/kg/hour of intravenous fluid has to be administered for 3–12 hours pre- and 6–12 hours post contrast exposure.

Dialysis and haemofiltration

Iodinated contrast is water soluble and removed by dialysis, but there is no clinical evidence that prophylactic dialysis reduces the risk of CI-AKI, even when carried out within 1 hour or simultaneously with contrast administration. Haemofiltration, however, performed 6 hours before and 12–18 hours after contrast deserves consideration given reports of reduced mortality and need for haemodialysis in the post-procedure period in very high-risk patients (serum creatinine of 3.0–4.0 mg/dL, eGFR 15–20 mL/min) (Marenzi et al., 2003, 2006). Specialists should be aware that haemofiltration calls for a 5000 IU heparin bolus before initiation followed by a continuous heparin infusion of 500–1000 IU/hour through the inflow side of the catheter. At the time of the cardiac procedure, the haemofiltration treatment should be stopped, and the circuit temporarily filled with a saline solution and short-circuited to exclude the patient without interruption of the flow.

Preventive measures

There are no currently approved pharmacological agents for the prevention of CI-AKI. Specific past strategies aimed at prevention of CI-AKI have focused on reversing, the effects of vasoconstriction (pre-hydration, fenoldopam, theophylline), improvement in nephron flow (loop diuretics), or protection against oxygen free radical damage (*N*-acetylcysteine (NAC), urinary alkalinization with bicarbonate solution). With iodinated contrast, the pharmacological agents tested in small trials that deserve further evaluation include the antioxidants ascorbic acid and NAC, statins, aminophylline/theophylline, and prostaglandin E_1. Although commonly administered, NAC has not been consistently shown to be effective. To date, 11 meta-analyses have been published on this subject, and seven of these reports found a net benefit for NAC in the prevention of CI-AKI. However, a review by Bagshaw et al. (2006) found marked heterogeneity in study results in 10 of the 11 meta-analyses. Importantly, only in those trials where NAC reduced serum creatinine below baseline values because of decreased skeletal muscle production did renal injury rates appear to be reduced. Thus, NAC may falsely lower serum creatinine and not fundamentally protect against CI-AKI, although others have demonstrated that NAC given in the absence of contrast does not falsely lower serum creatinine (Rehman et al., 2008). However, NAC as an antioxidant has been shown to lower rates of CI-AKI and mortality after primary PCI in one trial (Marenzi et al., 2006). Dosing of NAC has varied in the trials; however, the most successful approach has been with 1200 mg orally twice daily on the day before and after the procedure (Briguori et al., 2007). Moreover, the largest study on NAC, the Acetylcysteine for the Prevention of Contrast-Induced nephropathy (ACT) trial, showed no benefit of NAC for the prevention of CI-AKI (The ACT Investigators, 2011). This study randomized > 2300 patients undergoing angiographic procedures with at least one risk factor (age > 70, renal failure, diabetes mellitus, heart failure, or hypotension) of AKI to acetylcysteine versus placebo. There was no difference in AKI or mortality and need for haemodialysis at 30 days between the two groups. The incidence of CI-AKI (primary endpoint) was 12.7% in the acetylcysteine group and 12.7% in the control group (relative risk, 1.00; 95% confidence interval, 0.81–1.25; P = 0.97).

Numerous trials and studies have attempted to evaluate the effects after administration of isotonic normal saline, sodium bicarbonate solution, or a combination of the two. Unfortunately, the heterogeneity of study results has left the medical community confused. Clinicians should continue to treat patients on a case-by-case basis with the understanding that no definitive therapy has significantly proven any benefit. Further studies are needed to identify an effective prophylactic therapy or strategy in addition to hydration with isotonic normal saline.

The vast majority of cardiovascular patients should be on statin therapy with a common low-density lipoprotein cholesterol (LDL-C) target of < 70 mg/dL. It has been demonstrated that patients continued on statins during cardiovascular procedures including PCI and coronary artery bypass graft have lower rates of CI-AKI (Khanal et al., 2005). Small randomized trials published to date support this concept as well (Chello et al., 2007; McCullough and Rocher, 2007). Preservation of endothelial function at the level of the glomerulus and reductions in systemic inflammatory factors are postulated mechanisms by which statins may have renoprotective effects (McCullough and Rocher, 2007).

Nephrotoxic drugs including non-steroidal anti-inflammatory agents, gentamicin, amphotericin, and ciclosporin should be discontinued 72 hours prior to contrast exposure if possible. In addition, metformin should be withheld to minimize the risk of lactic acidosis should CI-AKI develop. The general consensus in current recommendations by medical societies including ACC/AHA/Society for Cardiovascular Angiography and Interventions, Royal College of Radiologists and the American Diabetes Association, is to withhold metformin for 24–48 hours prior to the procedure (based on renal dysfunction) and withhold drug 48 hours after a cardiac catheterization (Khurana and Malik, 2010).

Biomarkers for contrast-induced acute kidney injury

Several serum and urinary biomarkers have been suggested as potential tools used to predict CI-AKI in patients exposed to contrast media. One of the promising biomarkers available clinically is cystatin C (Laville and Juillard, 2010). It has been suggested that cystatin C is a more sensitive early marker than serum creatinine in identification of patients with CI-AKI, especially patients with diabetes (Pucci et al., 2007; Laville and Juillard, 2010). Furthermore, it appears to be less influenced by non-renal factors such as patients' nutritional status and body mass index. Another biomarker, neutrophil gelatinase-associated lipocalin (NGAL), is a member of the lipocalin family and is readily excreted and detected in blood urine. This is a natural siderophore which is produced in response to the release of catalytic or unbound iron.

NGAL works to bind labile iron, and thus, limit the degree of oxidative damage occurring at the tissue level. Produced by leucocytes and many somatic cells, NGAL is induced in the human kidney distal cortical tubules and secreted in blood and urine, in response to nephrotoxic and ischaemic injuries such as exposure to iodinated contrast. Thus, whole-blood and/or urinary NGAL represents an early, sensitive, biomarker for CI-AKI which is now available for use in several countries (Nickolas et al., 2008; Laville and Juillard, 2010). Other biomarkers under investigation include L-fatty acid binding protein (commercially available in Japan), kidney injury molecule 1, interleukin 18, and glutathione S-transferase (Laville and Juillard, 2010). Further studies are required to validate these biomarkers. The implementation of these biomarkers as point-of-care testing tools to identify at-risk patients will require significant technological advances to expedite results and guide appropriate therapy.

Follow-up

Vigilant follow-up of patients at risk for CI-AKI is essential in effort to closely monitor and treat patients who develop renal failure after contrast exposure. For practical purposes, an increase in serum creatinine of ≥ 0.3 mg/dL from baseline is considered CI-AKI (Mehran, 2007). Since accumulation of serum creatinine is a relatively slow process, CI-AKI based solely on this value may not become apparent until 72 hours after contrast exposure. Other available serum and urinary biomarkers, such as cystatin C (Pucci et al., 2007; Laville and Juillard, 2010; Solomon and Dauerman, 2010) and NGAL (Nickolas et al., 2008; Laville and Juillard, 2010; Solomon and Dauerman, 2010) can allow earlier detection (< 24 hours) after contrast exposure (Solomon and Dauerman, 2010). For optimal patient safety, it is recommended to obtain a follow-up serum creatinine 48–72 hours after contrast exposure. If the serum creatinine is elevation, additional follow-up will be needed until renal function normalizes or referral to a nephrologist.

Future therapeutic directions

Future approaches include large planned studies of oral and intravenous antioxidants (including a moderate labile iron chelator, deferiprone) and intrarenal infusions of renal vasodilators (fenoldopam, natriuretic peptides) using flow-directed catheters. Trials examining the effects of using forced hydration with a balancing pump causing marked elevations of urine output, thereby reducing the transit time of iodinated contrast in the renal tubules, are underway. Novel, hopefully less toxic forms of radio-opaque contrast agents are a source of future interest and development. The medical community awaits more definitive, unbiased results of future, large clinical trials to help guide safer and more effective strategies for CKD patients at risk for CI-AKI.

Conclusion

CI-AKI is predictable and is partially preventable. Reasonable steps should be taken to minimize risk. Novel diagnostic and therapeutic approaches are needed to manage the ever-increasing numbers of patients undergoing interventions using iodinated contrast media (McCullough, 2008).

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CHAPTER 247

Renal failure in cirrhosis: pathogenesis, diagnosis, and treatment

Vicente Arroyo, Mónica Guevara, and Javier Fernández

Introduction

Patients with cirrhosis frequently develop renal failure of different causes including hypovolaemia, infections, parenchymal renal diseases, nephrotoxicity, and hepatorenal syndrome (HRS). HRS is the most characteristic renal failure in cirrhosis and is considered the most severe complication in these patients. Patients with type 1 and type 2 HRS have a mean survival time of a few weeks and months after the onset of renal failure, respectively. The poor prognosis of HRS has led to the introduction of serum creatinine (SCr) in the process of allocation of liver transplantation in order to reduce mortality on the waiting list.

During the last decade, great advances have been made concerning the mechanism, prevention, and treatment of HRS in cirrhosis. In this chapter we discuss these issues and briefly review other types of renal failure in cirrhosis.

Concept of hepatorenal syndrome

HRS is a functional renal failure that develops in patients with advanced cirrhosis as a consequence of a severe reduction in renal perfusion (Epstein et al., 1970, 1977) (see also chapter 169). There is good evidence suggesting the functional nature of HRS. Renal histology is normal or, if not, the lesions do not justify the reduction in glomerular filtration rate (GFR) (Salomon and Zak, 1966). The kidneys of cirrhotic patients with HRS function normally when transplanted to patients with chronic renal failure (Koppel et al., 1969). Finally, HRS may reverse following treatment with vasoconstrictors and albumin or liver transplantation (Guevara et al., 1998c; Hadengue et al., 1998; Le Moine et al., 1998; Angeli et al., 1999; Gulberg et al., 1999; Uriz et al., 2000; Duvoux et al., 2002; Halimi et al., 2002; Moreau et al., 2002; Ortega et al., 2002; Sanyal et al., 2003; Alessandria et al., 2007; Martin-Llahi et al., 2008; Neri et al., 2008). HRS occurs in the setting of a severe impairment of circulatory function characterized by arterial hypotension and homeostatic activation of the renin–angiotensin system, sympathetic nervous system, and antidiuretic hormone. However, in the splanchnic circulation, there is arterial vasodilation (Henriksen et al., 1986, 1992), while in contrast, there is vasoconstriction *in most extrasplanchnic territories* including the kidneys. Recent studies have shown that circulatory failure in HRS is also associated with impairment in cardiac function (Ruiz-del-Arbol et al., 2003, 2005; Krag et al., 2010).

There are two types of HRS. Type 2 HRS is characterized by moderate and steady renal failure (average SCr 2 mg/dL (176 μmol/L)) (Salerno et al., 2007). The main feature of patients with type 2 HRS is refractory ascites due to poor response to diuretics. Refractory ascites can also be observed in patients with cirrhosis without HRS. In fact, 60–70% of patients with refractory ascites do not have HRS. These patients also present significant, but less severe reduction of GFR. Mean survival time after onset of type 2 HRS is 6 months.

Type 1 HRS is characterized by acute and rapidly progressive renal failure (average peak of SCr 4 mg/dL (352 μmol/L)). The rate of progression of renal failure arbitrarily used to define HRS type 1 has been set as a 100% increase of SCr reaching a level > 2.5 mg/dL (220 μmol/L) in < 2 weeks (Arroyo et al., 1996; Salerno et al., 2007). The probability of survival of patients with type 1 HRS is only 2–3 weeks. Type 1 HRS usually occurs in close temporal relationship with a precipitating event, mainly spontaneous bacterial peritonitis (SBP) (Toledo et al., 1993; Follo et al., 1994). Other infections are less frequently associated with HRS (Terra et al., 2005; Fasolato et al., 2007). Viral, alcoholic, toxic, or ischaemic hepatitis superimposed on cirrhosis, gastrointestinal bleeding, and major surgical procedures are other precipitating events. There are patients with type 1 HRS, however, in whom a precipitating event cannot be identified. Transient episodes of spontaneous bacteraemia due to translocation of bacteria from the intestinal lumen to the systemic circulation, as well as translocation of bacterial products (endotoxin) are frequent in cirrhosis and may act as precipitating factors (Such et al., 2002; Frances et al., 2007a, 2007b, 2008). Conversely, bacterial infection or other precipitating events may occasionally be associated with the development of type 2 HRS. Therefore, it is the progression of circulatory failure and not the existence of a precipitating event that determines the type of HRS. Type 2 HRS and hyponatraemia are risk factors to develop type 1 HRS.

There is now evidence that type 1 HRS is part of a complex syndrome, acute-on-chronic liver failure (ACLF), characterized by multiorgan and/or system failure (kidneys, liver, brain, heart, peripheral circulation, gut, lungs, adrenal glands, defensive mechanisms against infections). The mechanism of ACLF has been related to a systemic inflammatory response syndrome, activation

of cytokines, nitric oxide, and other mediators, acute deterioration of systemic circulation, and organ failure (Wasmuth et al., 2005; Xing et al., 2007; Duseja et al., 2010; Novelli et al., 2010).

Type 2 hepatorenal syndrome is the extreme expression of an impairment of the circulatory function in cirrhosis

Changes in circulatory and renal function during the course of the disease

A reduction of the renal ability to excrete sodium and free water and a decrease in renal perfusion and GFR are the most relevant functional abnormalities in cirrhosis (Eisenmenger 1952; Schroeder et al., 1970; Schroeder et al., 1976; Arroyo et al., 1983; Epstein et al., 1985; Wasmuth et al., 2005; Duseja et al., 2010; Novelli et al., 2010). The main consequence of the reduced ability to excrete sodium in cirrhosis is the development of sodium retention and ascites, which occurs when the sodium excretion decreases below the sodium intake. The renal ability to excrete free water is reduced in most patients with cirrhosis and ascites. Dilutional hyponatraemia (arbitrarily defined as a serum sodium concentration < 130 mEq/L) develops when free water clearance is severely reduced. Finally, the main consequence of the impaired renal perfusion and GFR is type 2 HRS, which is defined as a GFR of < 40 mL/min (or a SCr > 1.5 mg/dL (> 133 μmol/L)), in the absence of any other potential cause of renal failure (Arroyo et al., 1996). Sodium retention, dilutional hyponatraemia, and HRS appear at different times during the evolution of the disease and correlate closely with the degree of the deterioration of circulatory function. Therefore, although the clinical course of cirrhosis represents a continuum from compensated cirrhosis to type 2 HRS, different phases in the clinical course of cirrhosis representing different degrees of circulatory dysfunction with distinct prognostic and therapeutic implications can be identified according to renal function.

Phase 1: a hyperdynamic circulation maintains cirrhotic patients without ascites for many years despite the progression of portal hypertension

Once cirrhosis has developed and if its cause remains active (i.e. continuous alcohol intake or persistent viral infection), there is progressive increase in portal pressure which is associated with a progressive splanchnic arterial vasodilation. Splanchnic arterial vasodilation is a relevant feature in portal hypertension (Schrier et al., 1988) and increases portal venous inflow and maintains thus the progression of portal hypertension despite the development of a collateral circulation. On the other hand, it is associated with important changes in circulatory function.

In the early stage of cirrhosis, when the disease is still compensated (no ascites), splanchnic arterial vasodilation is not associated with an impaired systemic circulatory function because of an increase in plasma volume and cardiac output. The increase in plasma volume refills the dilated arterial and venous vascular beds. The increase in cardiac output is related with an increase in cardiac inotropic and chronotropic functions. In this phase, patients present portal hypertension, increased cardiac output, reduced peripheral vascular resistance, normal mean arterial pressure, normal renal perfusion, normal GFR, and free water clearance allowing the excretion of the ingested sodium (Fig. 247.1). Plasma renin activity, plasma norepinephrine (noradrenaline), and antidiuretic hormone concentrations are normal indicating a lack of activation

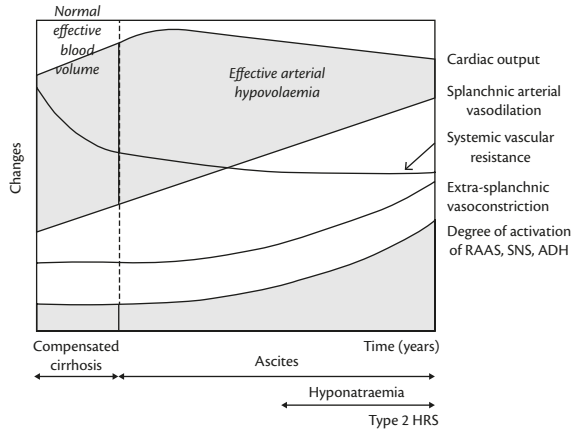

Fig. 247.1 Pathogenesis of circulatory and renal dysfunction in cirrhosis. ADH = antidiuretic hormone; HRS = hepatorenal syndrome; RAAS = renin–angiotensin–aldosterone system; SNS = sympathetic nervous system.

of the renin–angiotensin–aldosterone system, and of the sympathetic nervous system and a normal antidiuretic hormone release. However, these patients already present subtle abnormalities in renal sodium excretion (Wilkinson et al., 1979b; La et al., 1992; Rector et al., 1993). For example, they show a reduced natriuretic response to the acute intravenous (IV) administration of sodium chloride and may not be able to escape from the sodium retaining effect of mineralocorticoids. Abnormal natriuretic response to changes in posture is another relevant feature in this phase of the disease. Compared to normal subjects, urinary sodium excretion is reduced in the upright and increased in the supine posture (Fernandez-Cruz et al., 1985; Salerno et al., 1990; Bernardi et al., 1993).

Phase 2: the onset of sodium retention and ascites formation develops in cirrhosis in the absence of activation of the renin–angiotensin–aldosterone and sympathetic nervous systems

With the progression of the disease, there comes a moment when patients are unable to excrete their regular sodium intake. Sodium is then retained together with water and the fluid accumulates in the abdominal cavity as ascites. Urinary sodium excretion, although reduced, is usually higher than 10 mEq/day and in some cases it is > 50–90 mEq/day, meaning that a negative sodium balance and, therefore, the loss of ascites, may only be achieved by reducing the dietary sodium intake. In this phase, patients present higher portal pressure than when the disease was compensated. Renal perfusion, GFR, the renal ability to excrete free water, plasma renin activity, and the plasma concentrations of renin, norepinephrine, and antidiuretic hormone are still normal (Fig. 247.1) (Arroyo et al., 1983). The sodium retention is, therefore, unrelated to activation of the renin–aldosterone and the sympathetic nervous systems, the two most important antinatriuretic systems so far identified. The plasma levels of atrial natriuretic peptide, brain natriuretic peptide, and natriuretic hormone are increased in these patients, indicating that sodium retention is also unrelated to a reduced synthesis of endogenous natriuretic peptides. It has been suggested that the circulatory dysfunction in this phase, although greater than in compensated cirrhosis, is

not intense enough to stimulate the sympathetic nervous activity and the renin–angiotensin–aldosterone systems. However, in this phase a still unknown, extremely sensitive, sodium-retaining mechanism (renal or extrarenal) would be activated. Studies assessing systemic haemodynamics have clearly shown the presence of a hyperdynamic circulation with high cardiac output, low peripheral vascular resistance, and hypervolaemia.

Phase 3: the activation of the endogenous vasoconstrictor systems is associated with intense sodium retention but preserved renal perfusion, GFR, and renal ability to excrete free water, due to an increased renal synthesis of prostaglandins

When sodium retention is intense (urinary sodium excretion <10 mEq/day), the plasma renin activity and the plasma concentrations of aldosterone and norepinephrine are invariably increased (Fig. 247.1) (Arroyo et al., 1983), and aldosterone increases sodium reabsorption in the distal nephron. The renal sympathetic nervous activity stimulates sodium reabsorption in the proximal tubule and loop of Henle. Thus, sodium retention in these patients is due to increased sodium reabsorption in the entire nephron.

The plasma volume and peripheral vascular resistance do not differ from the previous phase. These features are compatible with an increased splanchnic arterial vasodilation, compensated by vasoconstriction in extra-splanchnic organs due to the increased activity of the sympathetic nervous and renin–angiotensin systems. In fact, renal, cerebral, and muscular blood flows in cirrhosis are reduced and correlate inversely with plasma renin activity and norepinephrine concentrations (Maroto et al., 1993; Sacerdoti et al., 1993; Platt et al., 1994; Guevara et al., 1998a). The most interesting feature is that cardiac output in patients in phase 3, although higher than in normal subjects, is lower than in patients in phase 2, indicating that the progression of circulatory dysfunction from phase 2 to phase 3 and the activation of the endogenous vasoconstrictor systems are due not only to an increase in splanchnic arterial vasodilation but also to a decrease in cardiac output (Ruiz-del-Arbol et al., 2005). Arterial pressure in this phase is critically dependent on the increased activity of the renin–angiotensin system, the sympathetic nervous system, and antidiuretic hormone; the administration of drugs that interfere with these systems (losartan, angiotensin-converting enzyme inhibitors, clonidine, V_1 vasopressin antagonists) may precipitate arterial hypotension (Daskalopoulos et al., 1987; Schneider et al., 1999).

Although angiotensin II, norepinephrine, and vasopressin are powerful renal vasoconstrictors, renal perfusion and GFR are normal or only moderately reduced in this phase because their effects on the renal circulation are antagonized by intrarenal vasodilator mechanisms, particularly prostaglandins and nitric oxide (Laffi et al., 1986; Martin et al., 1998; Moore, 1999; Garcia-Estan et al., 2002; Spahr et al., 2002; Grange and Amiot, 2004). In this phase of cirrhosis, renal perfusion and GFR are critically dependent on the renal production of prostaglandins, and severe renal failure may develop if renal prostaglandins are inhibited with non-steroidal anti-inflammatory drugs (NSAIDs) (Boyer et al., 1979; Ackerman et al., 2002).

The renal ability to excrete free water is reduced due to the high circulating plasma levels of antidiuretic hormone. However, only a few patients have significant hyponatraemia because the effect of antidiuretic hormone is partially inhibited by the increased renal production of prostaglandin E_2.

Phase 4: dilutional hyponatraemia develops when the renal ability to excrete free water is severely reduced

It is accepted that the lower normal limit of serum sodium concentration is 135 mEq/L. Approximately 50% of cirrhotic patients hospitalized with ascites present a serum sodium concentration below this level (Angeli et al., 2006). According to the International Ascites Club, clinically significant dilutional hyponatraemia is considered when serum sodium concentration is ≤ 130 mEq/L (Gines et al., 1998).

Patients in this phase present with severe portal hypertension, a normal or only slightly increased cardiac output, and reduced peripheral vascular resistance. The plasma levels of renin, norepinephrine, and antidiuretic hormone are higher and renal perfusion and GFR lower than in phase 3. Serum creatinine may be normal or only moderately increased (< 1.5 mg/dL or 133 μmol/L). However, it is important to recognize that in this stage of decompensated cirrhosis muscle mass is low and SCr is thus a poor marker of GFR. Many patients with hyponatraemia and SCr < 1.5 mg/dL or 133 μmol/L have a GFR < 40 mL/min, which is the cut off level that defines type 2 HRS. The renal ability to excrete free water after an oral or intravenous water load of 1.5 L, which is approximately 10 mL/min in healthy subjects is < 1 mL/min in patients with significant hyponatraemia, and some patients are even unable to dilute the urine (Fig. 247.2).

Chronic significant dilutional hyponatraemia in cirrhosis produces a depletion of brain osmolytes, mainly myo-inositol, and predisposes to brain oedema and hepatic encephalopathy (Fig. 247.3) (Restuccia et al., 2004a). In fact, the main predictor of hepatic encephalopathy in cirrhosis is hyponatraemia (Riggio et al., 2008; Guevara et al., 2009).

Phase 5: development of type 2 HRS in cirrhosis represents the extreme expression of circulatory dysfunction

Type 2 HRS is a functional renal failure secondary to an intense renal hypoperfusion. It is characterized by intense reduction of GFR (SCr between 1.5 to 2.5 mg/dL (133–221 μmol/L))

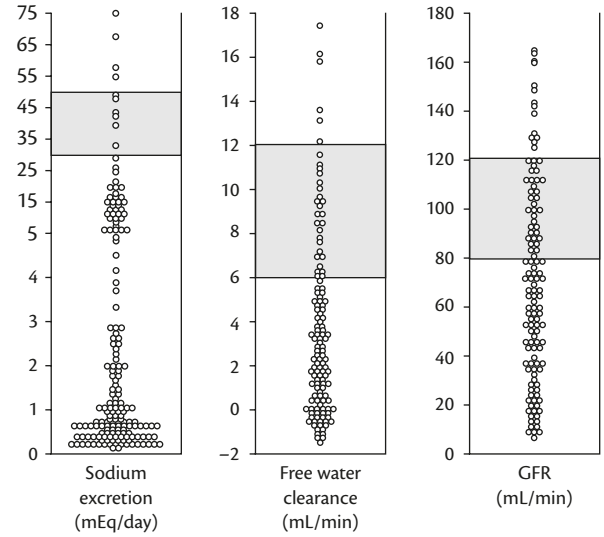

Fig. 247.2 Sodium excretion, free water clearance, and glomerular filtration rate (GFR) in a large series of patients with cirrhosis. Shadow areas represent normal values.

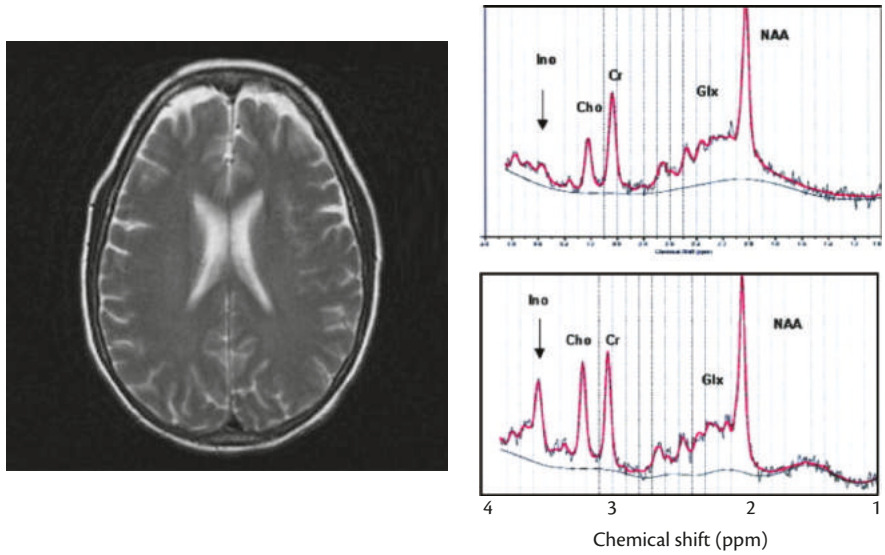

Fig. 247.3 Representative 1H-MRS spectra (magnetic resonance spectroscopy) from a healthy subject (upper spectra) and a patient with cirrhosis and hyponatraemia (low spectra). Note the reduction in myo-inositol (Ino) and choline (Cho) peaks in patients with cirrhosis and hyponatraemia, compared with peaks in the healthy subject.

From Effects of dilutional hyponatremia on brain organic osmolytes and water content in patients with cirrhosis, Tea Restuccia, Beatriz Gómez-Ansón, Mónica Guevara, Carlo Alessandria, Aldo Torre, M. Elena Alayrach, Carlos Terra, Marta Martín, Magda Castellví, Lorena Rami, Aitor Sainz, Pere Ginès, Vicente Arroyo, *Hepatology*, pp. 1613–1622, Copyright © 2004 John Wiley and Sons.

in the absence of other potential causes of renal failure. The International Ascites Club considers that SCr should be > 1.5 mg/dL (133 μmol/L) or a GFR < 40 mL/min for the diagnosis of HRS (Arroyo et al., 1996). However, many patients with a GFR < 40 mL/min have a SCr < 1.5 mg/dL (< 133 μmol/L). Therefore the frequency of type 2 HRS is underestimated when only SCr is used in the clinical evaluation.

Type 2 HRS develops in very advanced phases of cirrhosis in the setting of an intense deterioration of circulatory function (Fig. 247.1). Patients with type 2 HRS present arterial hypotension with very high plasma levels of renin, norepinephrine, and antidiuretic hormone. The vascular resistance in these patients is increased not only in the kidneys, but also in the brain, muscle, and skin, indicating a generalized arterial vasoconstriction to compensate an intense splanchnic arterial vasodilation. Renal failure in type 2 HRS is probably due to the extreme overactivity of the endogenous vasoconstrictor systems that overcomes the intrarenal vasodilatory mechanisms. The cardiac output in patients with type 2 HRS is lower than in patients with ascites but normal SCr (Ruiz-del-Arbol et al., 2005). A significant number of these patients present a normal or even reduced cardiac output, indicating the disappearance of the hyperdynamic circulation. Circulatory dysfunction causing type 2 HRS is therefore related to progression of both the splanchnic arterial vasodilation and the impairment in cardiac function.

The sodium retention is very intense in patients with type 2 HRS and is due to a reduced filtered load of sodium and a marked increased sodium reabsorption in the proximal tubule. The delivery of sodium to the distal nephron, the site of action of most diuretics, is very low, explaining that most of these patients do not respond to diuretics and present with refractory ascites. Free water clearance is also markedly reduced and most patients present with significant hyponatraemia (Fig. 247.2). The prognosis of these patients is very poor because type 2 HRS represents the latest phase of the disease.

Mechanism and key factors associated with type 2 hepatorenal syndrome

Splanchnic arterial vasodilation

Splanchnic arterial vasodilation in cirrhosis is thought to be due to an increased local release of vasodilatory substances secondary to portal hypertension. Nitric oxide has been the most intensely studied mediator but other mediators such as calcitonin gene-related peptide, substance P, carbon monoxide, and endogenous cannabinoids may also be involved (Gupta et al., 1992; Hori et al., 1996; Uriz et al., 2002; De Las et al., 2003; Reichenbach et al., 2010). Translocation of bacteria or bacterial products from the intestinal lumen to the intestinal extracellular space and lymphatic system, which is related to intestinal bacterial overgrowth and increased permeability of the mucosa, is probably an important mechanism in this process. A local inflammatory reaction, activation of cytokines, and stimulation of inducible nitric oxide synthase develops as a consequence of this feature leading to an increased nitric oxide synthesis in the vascular endothelium and arterial vasodilation. The observation that selective intestinal decontamination with oral norfloxacin, which reduces bacterial overgrowth and translocation, improves the circulatory function and suppresses plasma renin activity in patients with cirrhosis and ascites supports this contention (Gines et al., 1990; Soriano et al., 1991; Llovet et al., 1997; Novella et al., 1997). Also the demonstration that the hyperdynamic circulation of cirrhosis disappears following nitric oxide inhibition is compatible with this observation. Evidence has been presented that nitric oxide release into the splanchnic circulation in cirrhosis could also be mediated by neuronal nitric oxide synthase (Gupta et al., 1992; Fernandez-Rodriguez et al., 1995; Martin et al., 1998; Grange and Amiot, 2004). The endogenous cannabinoid system is also involved in the circulatory

dysfunction in cirrhosis (Ros et al., 2002). Finally, an intense process of vascular remodelling with increased angiogenesis in the splanchnic circulation, secondary to local activation of proangiogenic factors is also present (Fernandez-Varo et al., 2003; Morales-Ruiz et al., 2005).

Due to the release of local vasodilators and vascular neoformation, the splanchnic circulation is resistant to the vasoconstrictor effect of angiotensin II, catecholamines, and vasopressin. Therefore, the haemodynamic effect of the splanchnic arterial vasodilation that spontaneously develops in cirrhosis or of any other complication leading to deterioration of the effective arterial blood volume (diuretics, infection) cannot be compensated by splanchnic arterial vasoconstriction, the main vascular compartment regulating arterial pressure in normal subjects, but only by increasing vascular resistance in extrasplanchnic organs, particularly the kidneys. This is probably the reason of the high frequency of renal functional impairment in cirrhosis.

Reduction in cardiac output: role of cirrhotic cardiomyopathy

The cardiac response to splanchnic arterial vasodilation in cirrhosis has for many years, been considered as qualitatively homogeneous in all patients and in all phases of the disease. This is because most haemodynamic studies in cirrhosis have been performed in non-azotaemic patients with and without ascites and their findings were extended to the entire population of decompensated cirrhosis. Based on these studies, it was assumed that type 2 HRS is the extreme expression of the arterial vasodilation present in these patients. However, in the few studies assessing cardiovascular function in patients with type 2 HRS and/or refractory ascites, cardiac output was found to be significantly reduced compared to patients without HRS (Ruiz-del-Arbol et al., 2005; Krag et al., 2010) These findings indicate that two mechanisms, splanchnic arterial vasodilation and decrease in cardiac output, are the reasons of the renal impairment.

This contention has been more clearly demonstrated in a longitudinal study of 66 non-azotaemic cirrhotics with tense ascites (Ruiz-del-Arbol et al., 2005). Forty per cent of the patients developed HRS during follow-up. These patients were studied at inclusion and following the development of HRS. In the initial study, those patients who went on to develop HRS had significantly lower mean arterial pressure and cardiac output, and significantly higher plasma renin activity and norepinephrine concentrations compared with those who did not develop HRS (Table 247.1). Moreover, patients who developed HRS, but not patients without the syndrome, experienced a further decrease in arterial pressure and cardiac output and increase in renin and norepinephrine without changes in peripheral vascular resistance (Table 247.1). These findings are in agreement with the previous studies and support the concept that HRS occurs in the setting of aggravation of arterial vasodilation and decrease in cardiac output. In this study, basal increased plasma renin activity and reduced cardiac output were found to be the only independent predictors of HRS development and survival, a feature also observed recently by Krag et al. (2010).

Response to arterial hypotension is abnormal in patients with cirrhosis. In healthy subjects, arterial hypotension is associated with activation of the renin–angiotensin and sympathetic nervous systems which act at two levels. In the systemic circulation they produce arterial vasoconstriction and increase in systemic vascular resistance. In the heart they increase pulse rate, left ventricular contractility, and cardiac output. However, in these hypotensive cirrhotic patients, cardiac output and the heart rate do not increase (Ruiz-del-Arbol et al., 2005). This failure in cardiac inotropic and chronotropic functions is also observed during the spontaneous impairment in circulatory function leading to the development of type 2 HRS.

Cirrhotic cardiomyopathy, a syndrome characterized by impaired contractile responsiveness to stress (physical exercise or pharmacological stress with vasoconstrictors) and/or altered diastolic

Table 247.1 Renal function tests, cardiovascular function, plasma renin activity, and norepinephrine concentrations in patients who did not develop hepatorenal syndrome (group A) and baseline and follow-up measurements in patients who presented with hepatorenal syndrome (group B)

	Group A (n = 39)	Group B (n = 27)	
	Baseline	**Baseline**	**Follow-up**
Child–Turcotte–Pugh score (points)	9.7 ± 1.3	9.9 ± 1.3	10.8 ± 2.1†
MELD score (points)	13.7 ± 4.0	15.8 ± 4.6	25.7 ± 6.8††††
Serum creatinine (mg/dL)	0.85 ± 0.18	1.05 ± 0.26***	3.03 ± 1.49††††
Serum sodium (mmol/L)	134.5 ± 4.8	132.6 ± 4.6	127.0 ± 5.1††††
Urinary sodium (mmol/L)	17.4 ± 18.9	7.0 ± 6.1***	4.0 ± 4.5†
MAP (mmHg)	88 ± 9	83 ± 9*	75 ± 7††††
HR (bpm)	87 ± 15	85 ± 13	82 ± 14
RAP (mmHg)	6.7 ± 2.5	6.9 ± 2.6	5.7 ± 2.2†
PAP (mmHg)	15.2 ± 3.8	14.3 ± 4.3	12.8 ± 2.8††
PCWP (mmHg)	9.2 ± 3.2	9.2 ± 2.6	7.5 ± 2.6††††
CO (L/min)	7.2 ± 1.8	6.0 ± 1.2**	5.4 ± 1.5†††
SVR (dyn.s/cm^{-5})	962.0 ± 256.4	1,058.6 ± 265.6	1,096.1 ± 327.6
Stroke volume (mL/beat)	85.2 ± 17.0	73.2 ± 18.9*	65.3 ± 18.8†
Stroke work (gm-m)	91.3 ± 17.9	75.3 ± 22.9**	62.7 ± 21.3††††
Left ventricular stroke work (gm-m)	140.0 ± 32.6	114.2 ± 43.5*	88.5 ± 32.3††††
Plasma renin activity (ng/mL/ h)	3.1 ± 2.3	9.9 ± 5.2****	17.5 ± 11.4††††
Plasma aldosterone (ng/dL)	32.0 ± 30.7	130.5 ± 69.4***	202.5 ± 130.0††††
Plasma norepinephrine (pg/mL)	221.6 ± 68.2	571.1 ± 241.1****	965.0 ± 502.5††††

CO = cardiac output; HR = heart rate; MAP = mean arterial pressure; PRA = plasma renin activity; SVR = systemic vascular resistance.

*P < 0.05; **P < 0.01; ***P < 0.005; ****P < 0.001 with respect to baseline values of group A.

†P < 0.05; ††P < 0.01; †††P < 0 .005; ††††P < 0 .001 with respect to baseline values of group B.

The absence of significant changes in systemic vascular resistance between groups is compatible with peripheral arterial vasodilation compensated by the vasoconstrictor effect of the renin–angiotensin and the sympathetic nervous systems.

From Ruiz del Arbol, L. et al. (2005). Circulatory function and hepatorenal syndrome in cirrhosis 1. *Hepatology*, 42, 439–47.

function with electrophysiological abnormalities (prolongation of QT interval and altered electromechanical coupling) that develops in parallel with liver failure, could play a key role in the impaired cardiac response to arterial vasodilation. Interestingly, many of the factors thought to be important in the pathogenesis of splanchnic arterial vasodilation are also potential mechanisms of cirrhotic cardiomyopathy (Liu et al., 2006; Lee et al., 2007).

Impairment of blood perfusion in the kidney and extrarenal organs

For many years HRS has been considered as the result of a combination of liver and renal failure, with liver failure being the initial event and renal failure the consequence and it was thought that the poor prognosis of patients with HRS was more the consequence of liver failure with renal failure playing only a minor role. During the last few years, however, increasing evidence suggests that HRS is a much more complex syndrome affecting organs other than the liver and the kidney. Moreover systemic circulatory dysfunction associated with HRS not only impairs the intrarenal circulation but also the intrahepatic circulation thus creating vicious circles that may contribute to the progression of hepatic failure. The systemic circulatory dysfunction in cirrhosis, therefore, plays a key role in the pathogenesis of liver failure.

Renal hypoperfusion

The pathophysiology of renal hypoperfusion in type 2 HRS is multifactorial. Since renal perfusion in cirrhosis correlates inversely with the activity of the renin–angiotensin and sympathetic nervous systems (Schroeder et al., 1970; Saito et al., 1978; Wilkinson et al., 1979a; Arroyo et al., 1981; Epstein et al., 1985; Nicholls et al., 1985; Parelon et al., 1985; Bernardi et al., 1993; Gerbes et al., 1993; DiBona et al., 1996), HRS is thought to be related to the extreme stimulation of these systems. The urinary excretion of prostaglandin E_2, 6-keto prostaglandin F1α (a prostacyclin metabolite), and kallikrein is decreased in patients with HRS, which is compatible with a reduced renal production of these vasodilatory substances (Gentilini et al., 1983; Solomon et al., 1988; Yuki et al., 1991). Renal failure in HRS is, therefore, the consequence of an imbalance between the activity of the systemic vasoconstrictor systems and the local production of vasodilators within the kidney. Once renal hypoperfusion in HRS develops, it could be amplified by the stimulation of intrarenal vasoconstrictors. For example, renal ischaemia increases the generation of angiotensin II by the juxtaglomerular apparatus but also the production of adenosine which, in addition of being a renal vasoconstrictor, potentiates the vascular effect of angiotensin II, and the synthesis of endothelin. Other intrarenal vasoconstrictors that have been implicated in HRS are leukotrienes and F2-isoprostanes (Huber et al., 1989; Uemura et al., 1994). Renal vasoconstriction in HRS is, therefore, the consequence of the simultaneous effect of numerous vasoactive mechanisms on the intrarenal circulation.

The cutaneous, muscular, and cerebral blood perfusions are reduced in patients with HRS

Brachial and femoral blood flows are markedly reduced in patients with HRS indicating a vasoconstriction in the cutaneous and muscular arterial vascular beds (Maroto et al., 1993). The resistive index in the mean cerebral artery is also increased indicating cerebral vasoconstriction (Guevara et al., 1998a) (Fig. 247.4). The degree of vasoconstriction in these vascular territories in decompensated cirrhosis (patients with ascites with and without type 2 HRS) correlates directly with the degree of renal vasoconstriction and with the plasma levels of renin. Impairment in circulatory function in cirrhosis is therefore associated with generalized non-splanchnic arterial vasoconstriction.

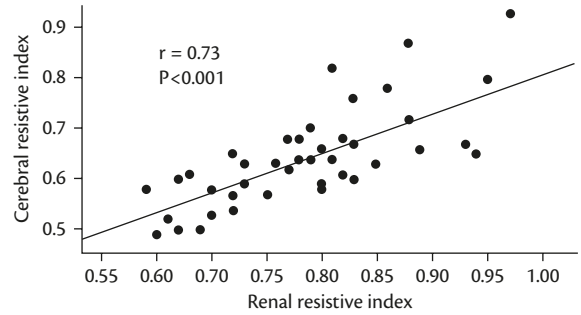

Fig. 247.4 Relationship between the renal resistive index and the resistive index in the middle cerebral artery in a group of patients with cirrhosis.
From Increased cerebrovascular resistance in cirrhotic patients with ascites, Mónica Guevara, Concepción Bru, Pere Ginès, Gloria Fernández-Esparrach, Pau Sort, Ramón Bataller, Wladimiro Jiménez, Vicente Arroyo, Juan Rodés, *Hepatology*, pp. 39–44, Copyright © 2003 John Wiley and Sons.

Hepatic encephalopathy is common in patients with HRS. There are many possible mechanisms of this complication, including liver failure, dilutional hyponatraemia, and the precipitating event of HRS. Cerebral vasoconstriction, however, could be an additional factor. In fact, cerebral blood flow is lower in patients with hepatic encephalopathy than in those without this complication.

Intrahepatic vasoconstriction

Angiotensin II, norepinephrine, and vasopressin have powerful effects on the intrahepatic circulation. They produce arterial vasoconstriction, increase the intrahepatic resistance to the portal venous flow and portal pressure, and reduce splanchnic blood flow. In patients with cirrhosis this vasoconstrictor effect is enhanced due to reduced synthesis of nitric oxide in the hepatic circulation (Rockey and Chung, 1998). It is thus not surprising that the stimulation of the endogenous vasoactive systems in HRS is associated with aggravation of portal hypertension and reduction in hepatic blood flow (Ariyan et al., 1975; Arroyo et al., 2005).

Adrenal dysfunction and systemic circulatory function in cirrhosis

Adrenal dysfunction associated with liver failure was first described in patients with acute liver failure and with cirrhosis and severe sepsis or septic shock (Fernandez et al., 2006; Tsai et al., 2006). In patients with cirrhosis and severe infections the incidence of relative adrenal insufficiency ranges between 60% and 80%. Subsequent studies have reported a 30–40% incidence in patients with decompensated cirrhosis and ascites.

A close relationship exists between adrenal insufficiency and HRS in patients with severe infection. Other features associated with adrenal insufficiency were severe liver failure, arterial hypotension, and vasopressor dependency. In patients with decompensated liver disease without infection, adrenal dysfunction is associated with

lower arterial pressure, higher activation of the sympathetic nervous system, and dilutional hyponatraemia, Since normal adrenal function is essential for an adequate response of the arterial circulation to endogenous vasoconstrictors, adrenal insufficiency could be an important mechanism of the associated circulatory dysfunction and could be related to the development of HRS in patients with decompensated cirrhosis or with severe bacterial infections.

The mechanism of adrenal dysfunction in cirrhosis is unknown. Patients with relative adrenal insufficiency have decreased levels of high-density lipoprotein (HDL) cholesterol which correlate with the severity of the disease. Given that the adrenal gland is unable to store cholesterol and that HDL cholesterol is the dominant precursor of cortisol, reduced cholesterol substrate synthesis by the liver may play a contributory role in the adrenal dysfunction in cirrhosis. Elevated levels of proinflammatory cytokines inhibit the adrenocorticotrophic hormone (ACTH) response to corticotropin-releasing hormone and the release of cortisol in response to ACTH. This mechanism may explain the high prevalence of adrenal dysfunction in cirrhotic patients with bacterial infections and its relatively high frequency in decompensated non-infected cirrhotics, in whom elevated circulating levels of proinflammatory cytokines are also present.

Clinical features and mechanism of type 1 hepatorenal syndrome: the role of bacterial infections

Clinical features

There is at present no specific study of the natural history of type 1 HRS and the current knowledge on this syndrome is based on clinical experience, on studies of complications associated with the syndrome, particularly bacterial infections, or on therapeutic studies. There are also few investigations of the mechanism of this syndrome, but there has been information sufficient to design new therapeutic procedures based on the pathophysiology.

The frequency of type 1 HRS is much lower than that of type 2 HRS. The incidence of type 1 HRS has decreased markedly during the last two decades due to an improved management of complications of cirrhosis, particularly bacterial infections, ascites, and gastrointestinal bleeding. Liver transplantation has also significantly reduced the number of patients developing the syndrome. Type 1 HRS may develop in patients with compensated cirrhosis. However this is rare and always occurs after a major precipitating event such as severe acute toxic, viral, or alcoholic hepatitis, complicated major surgical procedure, liver resection, and severe sepsis. In most cases, type 1 HRS occurs in patients with advanced cirrhosis. In fact severe circulatory dysfunction as manifested by normal or only moderately increased cardiac output and intense activation of the renin–angiotensin and sympathetic nervous system, dilutional hyponatraemia and increased SCr (≥ 1.3 mg/dL (≥115 μmol/L) or more) are the most important predictive factors of type 1 HRS (Gines et al., 1993). The isolated development of type 1 HRS is exceptional. In most patients there is simultaneously acute deterioration of liver function with jaundice and coagulopathy and impaired cerebral function (hepatic encephalopathy). As indicated previously, a significant number of patients present with relative adrenal insufficiency and there are studies showing that development of type 1 HRS occurs in the setting of a severe impairment in circulatory function with decrease in arterial pressure and cardiac output and intense stimulation of the renin–angiotensin and sympathetic nervous systems besides also an immune paralysis. There are no specific studies on respiratory function in these patients but it is clear that type 1 HRS is associated with multiorgan and/or multisystem failure. In most cases, type 1 HRS occurs in close chronological relation to a precipitating event with bacterial infections being by far the most frequent precipitating event. It is important to note that an apparently uncomplicated SBP can precipitate type 1 HRS if it occurs in patients with risk factors. Early diagnosis and treatment of bacterial infections is thus essential to prevent the syndrome. Other precipitating events are acute hepatitis (viral, toxic, or alcoholic), major surgical interventions, severe gastrointestinal haemorrhage, or large-volume paracentesis without albumin infusion. The contribution of the bacterial infections that frequently complicate these events could be of major importance. Finally, an undetermined percentage of patients with type 1 HRS do not show a clear precipitating event. Episodes of transient bacteraemia have been proposed as a potential precipitating mechanism of type 1 HRS in these patients.

If untreated, patients with type 1 HRS die within days after the onset of the syndrome. In some patients, the cause of death is a combination of the precipitating event and the impairment in circulatory, renal, liver, and cerebral function. Hospital-acquired bacterial infection after the onset of the syndrome, frequently due to multiresistant bacteria, is a common terminal event in patients with type 1 HRS.

Renal failure associated with infection in cirrhosis

Forty per cent of patients with cirrhosis and SBP develop renal failure despite rapid resolution of the infection with antibiotics. In 30% renal failure is transient, in 25% it follows a steady course (type 2 HRS), and in 45% a rapidly progressive renal failure (type 1 HRS) develops (Follo et al., 1994). The prevalence of steady or progressive renal failure in other types of infection is significantly lower. Fasolato et al. detected progressive renal failure in 15% of patients with acute pyelonephritis, but not in patients with pneumonia or cellulitis (Fasolato et al., 2007). Patients with spontaneous bacteraemia, urinary tract infection, cellulitis, and pneumonia responding to antibiotics develop only transient renal failure and progressive renal failure was only observed in patients not responding to antibiotic treatment (Terra et al., 2005) It appears thus that although renal failure is particularly frequent in SBP it may also develop in other types of bacterial infections.

The mechanism by which SBP, an infection that responds rapidly to antibiotic treatment in most cases, is associated with such a high incidence of renal failure is related to two features. First, there is an exaggerated inflammatory response to sepsis in decompensated cirrhosis with ascites. Doses of endotoxin that do not produce changes in systemic haemodynamics in healthy rats induce arterial hypotension and a 100 times higher increment in plasma cytokines (tumour necrosis factor and interleukin 6) in cirrhotic rats with ascites (Sugano, 1992; Heller et al., 2000). In human cirrhosis the increase in the plasma levels of cytokines after sepsis is 20 times higher and more prolonged in time than in non-cirrhotic subjects. The second feature is that cirrhotic patients with ascites already present a severe impairment in systemic and renal haemodynamics and this predisposes to further deterioration of circulatory function and renal failure. The observation that patients with increased

SCr or dilutional hyponatraemia prior to infection and an intense inflammatory response (high concentration of polymorphonuclear leucocytes and cytokines in ascitic fluid) to an infection are at high risk of developing renal failure after SBP, and that this risk can be dramatically reduced by volume expansion with intravenous (IV) albumin at the diagnosis of the infection, is in agreement with this contention (Navasa et al., 1998; Sort et al., 1999).

Mechanism of type 1 HRS

There is only one sequential study assessing the circulatory changes related to type 1 HRS (Ruiz-del-Arbol et al., 2003). Systemic and hepatic haemodynamics were measured in 23 patients with SBP at diagnosis of infection and following SBP resolution. The time interval between both studies was 7 days. Eight of the 23 patients developed type 1 HRS. Plasma renin activity and plasma norepinephrine concentrations at diagnosis of infection were significantly higher and cardiac output significantly lower in the patients developing type 1 HRS compared with those not developing renal failure (Table 247.2). Development of type 1 HRS was associated with a significant decrease in mean arterial pressure and a marked stimulation of the renin–angiotensin and sympathetic nervous systems indicating severe impairment in effective arterial blood volume. Peripheral vascular resistance did not change, which is consistent with a progression of the arterial vasodilation that is not detected due to the vasoconstrictor effect of angiotensin II and norepinephrine. A marked decrease in cardiac output was observed in all cases and in some it reached values below normal limits. Interestingly no significant changes were observed in heart rate despite the marked activation of the sympathetic nervous activity. In patients not developing renal failure, no significant changes were observed in arterial pressure, plasma renin and norepinephrine levels, and cardiac output. Marked changes were also observed in hepatic haemodynamics in the patients developing type 1HRS. A marked increase in portal pressure and reduction in hepatic blood flow were observed in all cases with type 1 HRS indicating an intense intrahepatic vasoconstriction.

These results indicate that circulatory dysfunction in type 1 HRS, like in type 2 HRS, is due to both an increase in arterial vasodilation and a decrease in cardiac function. The differences between type 1 and type 2 HRS are, therefore, a matter of progression and intensity. Whereas changes in circulatory function leading to type 2 HRS are slowly progressive, the onset is acute and the course very rapid in type 1 HRS leading to severe renal failure in a short period of time. There are also rapid changes in hepatic haemodynamics with a marked fall of hepatic perfusion, which may explain the impairment in liver function observed in association with the renal failure. The mechanism of this rapid and severe impairment in circulatory function is not well known but it could be related to a systemic inflammatory reaction.

Renal failure in type 1 HRS rarely develops as an isolated feature in patients with decompensated cirrhosis. In general, patients also develop acute deterioration of liver function with jaundice, coagulopathy, and encephalopathy. All these features together with the impairment in cardiocirculatory function, adrenal insufficiency and immune paralysis and nosocomial bacterial infections form a new and poorly studied syndrome, known as 'acute-on-chronic liver failure' (ACLF). It constitutes, together with hepatocellular carcinoma, the main cause of death in decompensated cirrhosis. Circulatory dysfunction is probably the core of the syndrome with the rest of the organ and/or systems failure secondary events.

Table 247.2 Cardiovascular function and plasma renin activity and norepinephrine concentrations in patients who did and did not develop type 1 HRS following spontaneous bacterial peritonitis

	Type 1 HRS (n = 8)		No HRS (n = 15)	
	At SBP diagnosis	SBP resolution	At SBP diagnosis	SBP resolution
MAP (mmHg)	83 ± 7	73 ± 8[b]	83 ± 10	83 ± 8
PRA (ng/mL/h)	18.4 ± 11.2[a]	28.3 ± 12.4[b]	3.9 ± 3.6	2.8 ± 3.6
Norepinephrine (pg/mL)	797 ± 226[a]	1290 ± 415[b]	315 ± 172	317 ± 195
SVR (dyn.s/cm^{-5})	1137 ± 220[a]	1268 ± 320	893 ± 196	968 ± 226
CO (L/min)	5.7 ± 0.9[a]	4.6 ± 0.7[b]	7.4 ± 1.9	6.8 ± 2.0
HR (bpm)	93 ± 13	87 ± 9	87 ± 16	79 ± 16

Time elapsed between studies was < 7 days.

CO = cardiac output; HR = heart rate; MAP = mean arterial pressure; PRA = plasma renin activity; SVR = systemic vascular resistance.

[a]Significantly different compared to values at SBP diagnosis in the No HRS group.

[b]Significantly different compared to values at SBP diagnosis.

From Ruiz del Arbol, L. et al. (2003). Systemic, renal, and hepatic hemodynamic derangement in cirrhotic patients with spontaneous bacterial peritonitis. *Hepatology*, 38(5), 1210–18.

ACLF precipitated by infections is probably caused by an exaggerated inflammatory response syndrome, with high circulating levels of cytokines and release of mediators that accentuate the arterial vasodilation and impair cardiac function. Severe vasoconstriction and blood supply to the peripheral organs as well as local inflammatory reactions are probably the mechanisms of other organ/system failure. Several vicious circles explain the rapid progression of the syndrome. Circulatory function increases portal hypertension, reduces liver perfusion, and impairs liver function and this further deteriorates systemic haemodynamics. Relative adrenal insufficiency reduces the vascular effect of endogenous vasoconstrictor systems and this further deteriorates circulatory function. Finally, the activation of the sympathetic nervous system and the release of norepinephrine at the intestinal level are known to increase intestinal permeability and impair the antibacterial activity of the lymphocytes and macrophages in the intestinal wall (Worlicek et al., 2010). Norepinephrine is also released into the intestinal lumen and favours bacterial overgrowth and adherence to the intestinal mucosa. All these events increase translocation of viable bacteria and/or of bacterial products from the intestinal lumen into the lymphatics and systemic circulation, potentiating the inflammatory reaction and organ failure. The mechanism of ACLF related to other precipitating events is unknown, although it may probably be similar.

Other types of renal failure in cirrhosis

Nephrotoxicity

Renal perfusion and GFR in patients with cirrhosis and ascites are maintained by an increased renal synthesis of vasodilator

prostaglandins (PGI_2 and PGE_2). These compounds antagonize the renal effects of angiotensin II, catecholamines, and vasopressin. NSAIDs, which inhibit prostaglandin synthesis, cause a profound reduction in renal blood flow and provoke renal failure in a high number of these patients (Boyer et al., 1979; Claria et al., 2005), illustrating that vasodilator prostaglandins have a relevant role in maintaining renal haemodynamics in patients with cirrhosis and ascites. Nephrotoxicity due to NSAIDs in cirrhosis depends on the activation of the renin–angiotensin and sympathetic nervous systems. It is frequent and severe in patients with advanced cirrhosis and tense ascites, rare in patients with moderate ascites, and exceptional in patients with compensated cirrhosis.

Patients with cirrhosis are also at risk of developing aminoglycoside nephrotoxicity. In one study in infected cirrhotic patients treated with cefalotin plus an aminoglycoside using urinary β_2 microglobulin as marker of tubular damage, the prevalence of acute tubular necrosis (ATN) was 30% (Cabrera et al., 2001). It is unknown if patients with cirrhosis are prone to develop nephrotoxicity by other drugs. One study found, however, a very low incidence of contrast media-induced acute kidney injury (AKI) in these patients (Guevara et al., 2004).

Intravascular volume losses

In patients with cirrhosis and upper gastrointestinal bleeding, the prevalence of renal failure is 11% (Cardenas et al., 2001). Risk factors are severity of blood losses (prevalence in patients with and without hypovolaemic shock: 60% vs 5%) and degree of liver failure (prevalence in Child–Pugh C and A–B score patients: 29% vs 3%). A significant number of patients with renal failure after bleeding recover renal function following volume repletion. This feature suggests prerenal 'functional' AKI. However, in other patients renal failure persists or progresses despite resolution of the bleeding episode. In these cases, renal failure may be due to tubular damage or HRS.

Renal failure occurs in 30% of cirrhotic patients treated with diuretics and two types have been identified (Salerno et al., 2007). The first occurs in patients who continue diuretic treatment after the complete mobilization and disappearance of ascites. Such patients may develop dehydration, hypovolaemia, and renal impairment.

The second type of diuretic-induced renal failure is observed in patients who still have even tense ascites. Reabsorption of ascites occurs through a rich plexus of terminal lymphatics (lymphatic lacunae) on the lower surface of the diaphragm which are connected through lymphatic vessels in the anterior thoracic wall to the thoracic duct and the systemic circulation (Leak and Rahil, 1978). These diaphragmatic lymphatic systems open directly into the peritoneal cavity by intercellular gaps and stomas. The periodic respiratory movements of the diaphragm are important in the passage of ascites into the lymphatic system and the general circulation. During inspiration, intercellular gaps and stomata close, intraperitoneal pressure is increased, and lacunae are emptied centrally through the combined effect of local compression, and increased intra-abdominal and reduced intrathoracic pressures. During expiration, the gaps and stomas are opened and free communication is re-established (Yoffey, 1970). Reabsorption of ascites is a rate-limited phenomenon. The average fractional reabsorption rate of radiolabelled albumin from the peritoneal cavity into the general circulation in cirrhotics with ascites has been estimated as 1.27% of the intraperitoneal protein mass per hour, corresponding with a rate of ascitic fluid reabsorption of 1.4 L in 24 hours (Henriksen et al., 1980). The rate of reabsorption of ascitic fluid varies markedly from patient to patient and may range from 0.5 to 5.5 L in 24 hours (Henriksen et al., 1980). Although the rate of ascites formation has not been measured, these data indicate that the net passage of fluid into the intravascular compartment is very low in many patients with cirrhosis and ascites. If the increase in urine volume induced by diuretics in a patient with ascites overcomes the maximum reabsorption capacity of the abdominal fluid, hypovolaemia and renal failure develops. Diuretic-induced renal failure does not progress to severe renal impairment because the diuretic response decreases when renal function is moderately impaired. This also explains why diuretic-induced renal failure is always reversible after diuretic withdrawal or after expansion of the plasma volume.

Drugs used in the prevention and treatment of variceal bleeding

For many years, propranolol has been the most extensively drug used to prevent variceal bleeding and rebleeding, and has been considered safe in patients with ascites since it did not show significant effects on renal function (Rector and Reynolds 1984). However, two recent studies have cast some doubts about this concept (Serste et al., 2010, 2011). Patients treated with propranolol admitted to hospital with refractory ascites recover their diuretic response after discontinuation of the β-blocker. On the other hand, albumin was unable to prevent paracentesis-induced circulatory dysfunction in patients with tense ascites treated with propranolol; however, albumin recovers its efficacy following propranolol withdrawal.

The acute and chronic administration of isosorbide 5-mononitrate alone, which is also used for the primary and secondary prevention of variceal bleeding, impairs renal function in patients with cirrhosis and ascites (Salmeron et al., 1993). The effect of the combination of propranolol and nitrates on renal function, however, is more controversial. Some studies have shown an impairment in renal function (Vorobioff et al., 1993; Morillas et al., 1994), whereas others have not (Morillas et al., 1994; Merkel et al., 1995).

Reports on the renal effects of somatostatin, a drug used for the treatment of acute variceal bleeding, are conflicting. One study showed a significant decrease in GFR, sodium excretion, and free water clearance during the acute infusion of somatostatin (Gines et al., 1992), but another showed an increase in urine volume and creatinine clearance in patients with ascites who received octreotide (its synthetic analogue) (Mountokalakis et al., 1988). Moreover, the long-acting release form of octreotide failed to show any change in creatinine clearance or sodium excretion in cirrhotic patients with ascites (Ottesen et al., 2001).

Prazosin, an α1-adrenergic blocker, and the new angiotensin II receptor blockers (losartan, irbesartan) are other drugs which have been investigated as possible treatments for portal hypertension. They reduce portal pressure by decreasing intrahepatic vascular resistance. Long-term administration of prazosin to patients with compensated cirrhosis caused vasodilation of the systemic circulation and arterial hypotension, which led to ascites formation in a significant number of patients (Albillos et al., 1995). These effects were not observed when prazosin was given in combination with propranolol (Albillos et al., 1998). In patients with ascites, angiotensin II receptor blockers may induce a marked decrease in arterial pressure and renal failure (Gonzalez-Abraldes et al., 2001; Schepke et al., 2001).

Carvedilol, a non-selective β-blocker with mild intrinsic anti-α_1-adrenergic activity has been used to reduce portal pressure in cirrhosis. It is more effective than propranolol or nadolol in decreasing portal pressure. The potential adverse effect of this drug on renal function has not been explored.

In summary, drugs that produce arterial vasodilation (nitrates and α-adrenergic and angiotensin II antagonists) should be given with caution to patients with cirrhosis and portal hypertension because they may impair renal function.

Glomerulonephritis in liver diseases

Immunoglobulin A (IgA) nephropathy associated with liver disease is the most frequently encountered secondary form of IgA nephropathy (Newell, 1987). The pathogenesis is related to an inability to remove IgA-containing complexes by Kupffer cells in the liver, which in turn predispose to deposition of IgA in the kidney. In fact, IgA deposition in the skin and liver (hepatic sinusoids) make this hypothesis plausible. Although it is preferentially observed in patients with alcoholic liver disease it can be seen in other types of liver disease. Despite the high frequency of glomerular IgA deposits in advanced liver disease, most patients are asymptomatic. Patients may present with microscopic haematuria, mild proteinuria, and a mild degree of renal impairment. Light microscopy findings are very similar to those of patients with primary IgA nephropathy. These include mesangial hypercellularity and an increase in mesangial matrix. At present, several therapies (angiotensin-converting enzyme inhibitors, corticosteroids, immunosuppressive agents, IV immunoglobulin, and fish oil) have been advocated to improve the course of progressive IgA nephropathy. However, there are no specific studies assessing therapy for patients with liver disease-associated IgA nephropathy.

Patients with viral hepatitis, in particular hepatitis C (HCV), are at risk of developing essential mixed cryoglobulinaemia (EMC) (Agnello et al., 1992). The prevalence of EMC is high (41.5%) in patients with chronic liver disease. When considering independent causes, HCV prevalence is higher (54.3%) than HBV (15%) or other causes of chronic liver disease (32%), however, these numbers vary according to geographical location (Lunel and Musset, 1998b). EMC is a disorder in which mixed cryoglobulins (polyclonal immunoglobulin, IgG, and a monoclonal rheumatoid factor, IgM) precipitate at cool temperature and cause a constellation of clinical findings characterized by arthritis, purpura, peripheral neuropathy, weakness, glomerulonephritis, and manifestations of vasculitis. There are three types of cryoglobulinaemia—types I, II, and III; the strongest association with viral hepatitis is with type II. The pathogenesis is complex and it is unclear why cryoglobulins are produced and which antigen triggers their production. In cases associated with HCV infection, the virus RNA may be the triggering agent since it has been found in high concentrations in the cryoprecipitate (Agnello et al., 1992; Lunel and Musset, 1998b). Another hypothesis is related to the release of a putative antigen from injured hepatocytes or its production by Kupffer cells contributing to immunoglobulin formation. In addition, a decreased clearance of cryoglobulins due to liver dysfunction may lead to cryoglobulinaemia and its subsequent deposition in the kidney, skin, and other tissues. The diagnosis of EMC is typically made from the history, the presence of skin lesions, low complement levels, and demonstration of circulating cryoglobulins. Although the majority of patients with hepatitis C have type II-associated cryoglobulinaemia, 30–40% do not have detectable circulating cryoglobulins at presentation (Johnson et al., 1993). About 20% have signs or symptoms of chronic liver disease, but 75% have compensated cirrhosis or only mild elevations of serum transaminases (Johnson et al., 1994). Liver biopsy in these cases demonstrates chronic hepatitis or cirrhosis (Lunel and Musset, 1998a). Patients with cryoglobulinaemic glomerulonephritis usually present with proteinuria, microscopic haematuria, and mild renal insufficiency. The major clinical manifestations of EMC include palpable purpura (which is a form of vasculitis), arthralgias, lymphadenopathies, constitutional symptoms, and peripheral neuropathy. Nearly 40% will have signs consistent with extrarenal manifestations of cryoglobulinaemia. Approximately 20% of patients have nephrotic-range proteinuria and in 25% of patients an acute nephritic syndrome with rapid deterioration of renal function may develop. In the majority of patients renal function will remain stable and few will require renal replacement therapy. Laboratory features include the presence of low complement (low CH50, C4, and C3), mild elevation of serum creatinine, and presence of circulating cryoglobulins. Renal biopsy reveals a mesangiocapillary pattern of glomerulonephritis.

In the last years, several studies have evaluated specifically the treatment of cryoglobulinaemic renal disease in the setting of HCV chronic liver disease (Johnson et al., 1994; Beddhu et al., 2002; Sabry et al., 2002; Alric et al., 2004; Fabrizi et al., 2008; Feng et al., 2012). However the number of patients included in each study is low. Since hepatitis C is the inciting event for this type of nephropathy, therapy has been directed towards eliminating the virus. In cryoglobulinaemic glomerulonephritis, α-1 interferon therapy for 6 months or longer reduced proteinuria by 50%, but serum creatinine did not significantly improve (Johnson et al., 1994). Another controlled study of α-2 interferon reported an improvement in serum creatinine in 60% of patients and a better outcome was observed in those that cleared the virus; however, renal disease returned upon discontinuation of therapy (Misiani et al., 1994). In both studies clinical improvement occurred regardless whether viraemia was suppressed or not. This might be explained by the previous duration of viraemia, the genotype of HCV, or variation of the host immune response. A recent meta-analysis evaluated 225 patients with HCV-associated glomerulonephritis treated with antiviral therapy (Feng et al., 2012). The main conclusion was that antiviral treatment based on interferon-α and ribavirin can decrease protein excretion or creatinine levels in patients with chronic kidney disease (CKD) associated with HCV. The improvement in protein excretion following antiviral therapy was linked to HCV RNA clearance as the treatment effect was greater in patients achieving sustained virological response compared to those who did not achieve this.

In patients with more severe glomerulonephritis estimated by nephrotic-range proteinuria and/or rapidly progressive kidney failure and/or acute flare of cryoglobulinaemia treatment with 3 days of IV prednisone followed by oral prednisone or cyclophosphamide has been suggested. Plasma exchange in conjunction with corticosteroids and cyclophosphamide should also be considered as the initial treatment for patients with acute severe renal disease. In this last group of patients, rituximab has been given with encouraging results. However, further randomized controlled trials are needed to evaluate this treatment (Fabrizi et al., 2008).

Diagnosis of hepatorenal syndrome

The clinical diagnosis of renal failure in cirrhosis is based on serum levels of creatinine and/or blood urea nitrogen, both poor markers of GFR (Fig. 247.5) (Caregaro et al., 1994). The usefulness of other estimators of GFR such as serum cystatin C needs to be explored in these patients. Renal failure in cirrhosis is arbitrarily defined as a serum creatinine > 1.5 mg/dL (> 133 μmol/L), although it is well known that below this level patients may have severe reduction of GFR (Fig. 247.5). The most accepted criteria for the diagnosis of HRS are those proposed by the International Ascites Club which are based on the exclusion of other types of renal failure such as parenchymal renal disease (no haematuria or proteinuria, normal renal echography), ATN (no shock or treatment with nephrotoxic drugs), or hypovolaemia (no improvement of renal function after the expansion of plasma volume with saline solution or albumin) (Box 247.1) (Arroyo et al., 1996; Salerno et al., 2007). However, this is an oversimplification of the problem. Renal failure in the context of haematuria or proteinuria, or of treatment with potentially nephrotoxic drugs or shock may also be HRS (Arroyo et al., 1996; Guevara and Arroyo, 2011)

The most important differential diagnosis of renal failure in cirrhosis is between type 1 HRS and ATN because they require rapid therapeutic decisions with different treatments. The parameters traditionally used to differentiate ATN from functional renal failure (urinary sodium excretion and urinary to plasma osmolality ratio) are of no value in patients with cirrhosis and ascites (Schrier, 2011). On the other hand, granular casts may be found in the urinary sediment in both HRS and ATN and the diagnostic value of tubular epithelial cells casts has never been studied. There are few investigations assessing markers of tubular damage in cirrhosis. The urinary β_2 microglobulin was shown to be useful in the diagnosis of aminoglycoside nephrotoxicity (Cabrera et al., 1982). β_2 microglobulin is filtered by the glomerulus and almost completely reabsorbed in the proximal tubule. In ATN due to aminoglycoside there is necrosis in the proximal tubule and a marked increase in β_2 microglobulin concentration in the urine. Other urinary *bio*-markers such as, gamma-glutamyl transpeptidase, transaminases, liver-type fatty acid binding protein (L-FABP), interleukin-18 (IL-18), and kidney injury molecule-1 (KIM-1) (Malyszko, 2010) have not been evaluated in the differential diagnosis between type 1 HRS and ATN. Two recent studies suggest that neutrophil gelatinase-associated lipocalin (NGAL) might be useful in differentiating HRS and ATN in cirrhotic patients. Patients with impaired kidney function had higher urinary NGAL levels compared to patients with and without ascites. Patients with ATN had urinary NGAL levels markedly higher compared to patients with prerenal azotaemia due to volume depletion, CKD, and HRS. Among HRS patients, the highest values were found in HRS associated with infections, followed by classical (non-associated with active infections) type 1 and type 2 HRS. Differences in urinary NGAL (uNGAL) levels between classical type 1 HRS and ATN on the one hand and classical type 1 HRS and CKD and prerenal azotaemia on the other were statistically significant (Fagundes et al., 2012). In the second study, including 187 cirrhotic patients, 17 (14%) had prerenal azotaemia, 20 (17%) had HRS, and 15 (13%) had ATN (Verna et al., 2012). Patients with HRS had uNGAL levels intermediate between prerenal azotaemia and ATN In addition, in both studies uNGAL predicts short-term mortality. Urinary levels of NGAL may thus be useful in the differential diagnosis of impairment of kidney function in cirrhosis. Further studies are needed to confirm these promising results.

Treatment of type 1 hepatorenal syndrome

Vasoconstrictors and albumin

Intravenous terlipressin combined with albumin infusion is the treatment of choice of type 1 HRS (Gines et al., 2010). Numerous pilot studies have shown that it induces reversal of type 1 HRS (decrease in SCr < 1.5 mg/dL (< 133 μmol/L)) in 40–60% of patients (Hadengue et al., 1998; Le Moine et al., 1998; Uriz et al., 2000; Halimi et al., 2002; Ortega et al., 2002; Moreau and Lebrec, 2006; Alessandria et al., 2007; Martin-Llahi et al., 2008; Neri et al., 2008; Sanyal et al., 2008) and moderate increase in patient survival. These features have been recently confirmed in two prospective randomized controlled trials comparing terlipressin plus albumin versus albumin alone. The American study was blinded

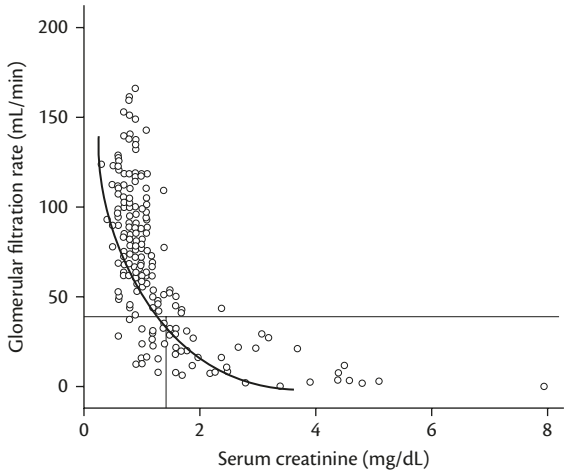

Fig. 247.5 Relationship between glomerular filtration rate and serum creatinine in a group of patients with cirrhosis. Note that there is a group of patients with low glomerular filtration rate and normal serum creatinine.

Box 247.1 Diagnostic criteria of hepatorenal syndrome according to the International Ascites Club

1. Cirrhosis with ascites.
2. Serum creatinine > 133 μmol/L (1.5 mg/dL).
3. No improvement of serum creatinine (decrease to a level of 133 μmol/L or less) after at least 2 days of diuretic withdrawal and volume expansion with albumin. The recommended dose of albumin is 1 g/kg of body weight per day up to a maximum of 100 g/day.
4. Absence of shock.
5. No current or recent treatment with nephrotoxic drugs.
6. Absence of parenchymal kidney disease as indicated by proteinuria > 500 mg/day, microhaematuria (> 50 red blood cells per high power field) and/or abnormal renal ultrasonography.

and the Spanish trial was unblended (Martin-Llahi et al., 2008; Sanyal et al., 2008). Reversal of HRS was observed in approximately 40% of patients in the therapeutic arms and in < 20% in the control arms. Both studies were unable to detect differences in survival but they confirmed increased survival in patients showing reversal of HRS. A recent meta-analysis confirms that terlipressin plus albumin prolongs short-term survival in type 1 HRS (Gluud et al., 2010). Response to therapy is characterized by a slow and sustained reduction in SCr and improvement in systemic haemodynamics as reflected by marked suppression of the plasma levels of renin and norepinephrine (Fig. 247.6). This is associated with an increase in arterial pressure, urine volume, and serum sodium concentration. Median time to reversal of HRS is 7 days and depends on pre-treatment SCr, the time being shorter in patients with lower baseline concentration. Following discontinuation of treatment HRS recurs in < 20% of patients but reversal of HRS (long-lasting in most cases) can be obtained after retreatment with the same therapeutic schedule. Some patients on the waiting list for liver transplantation may require continuous treatment with terlipressin and albumin because of repeated HRS recurrence after stopping treatment (Fig. 247.7) (Piano et al., 2011).

Treatment of type 1 HRS with albumin alone or with terlipressin alone is associated with reversal of HRS in < 20% of cases. Both components of the treatment are therefore important. Terlipressin acts through its vasoconstrictor effect. Albumin was initially given as plasma expander, to increase venous return and cardiac output. However, the effect of albumin is much more complex. Albumin in cirrhosis has arterial vasoconstrictor effects (Fernandez et al., 2005) and improves left ventricular contractibility and cardiac output. The capacity of albumin to bind and inactivate nitric oxide, oxygen radicals, and other mediators could be related to these effects (Oettl et al., 2008; Jalan et al., 2009; Arroyo and Fernandez, 2011).

Reasons why 40–60% of patients with HRS do not respond to pharmacological treatment are probably multifactorial. Preliminary data indicate that the continuous infusion of terlipressin can increase the probability of reversal of HRS up to 75% (Angeli and Morando, 2010) suggesting that the way of drug administration could be an important factor. On the other hand, patients with HRS and very high SCr levels (5–7 mg/dL (440–620 μmol/L)) usually do not respond to terlipressin (Boyer et al., 2011). Early treatment could also be a second important factor for a positive response. Finally, in other cases the mechanism of renal failure may not be HRS but rather an intrarenal disease (i.e. ATN).

In our centre, terlipressin dosage is started at 0.5 mg/4 hours. If SCr does not decrease by > 30% in 3 days, the dose is doubled. The maximal recommended dose of terlipressin is 12 mg/day. Albumin should be given with a priming dose of 1 g/kg of body weight followed by 20–40 g/day. It is advisable to monitor central venous pressure. In patients responding to therapy, treatment should be kept until normalization of SCr (< 1.5 mg/dL (< 133 μmol/L)). Complications associated with terlipressin therapy are related to its vasoconstrictor effect and include ischaemic events in skin, tongue, fingers, intestines, and heart. They are infrequent and reverse after terlipressin withdrawal. Dilutional hyponatraemia improves in patients responding to treatment. Preliminary data also suggest that the incidence of side effects is lower when terlipressin is given as continuous infusion (Angeli et al., 2009; Angeli and Morando, 2010). Factors associated with reversal of HRS are serum bilirubin < 10mg/dL and increase in mean arterial pressure > 5 mmHg. Treatment response was 100% in patients with both predictors, 53% in patients with serum bilirubin < 10mg/dL, 25% in patients with increase in mean arterial pressure, and only 10% in the remaining patients (Nazar et al., 2010). Terlipressin is not approved in the United States and Canada as treatment of HRS.

Norepinephrine is also effective in type 1 HRS. There are two small randomized controlled trials showing that this vasoactive drug may be as effective as terlipressin (Angeli et al., 1999; Duvoux et al., 2002; Sharma et al., 2006; Alessandria et al., 2007). Midodrine, an oral vasoconstrictor with α-adrenergic effect, plus

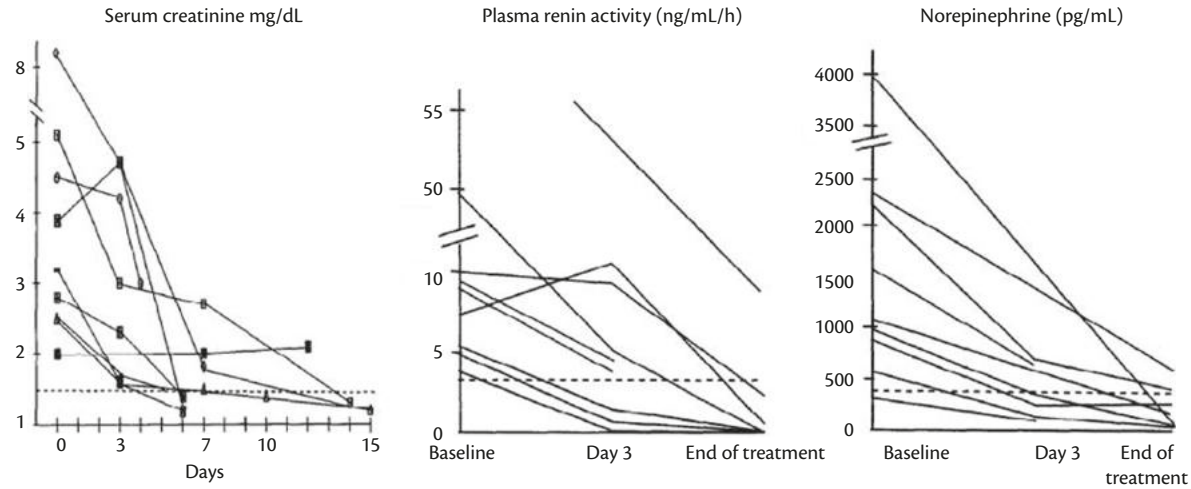

Fig. 247.6 Changes in serum creatinine, plasma renin activity, and norepinephrine concentrations in patients with hepatorenal syndrome treated with terlipressin and albumin.

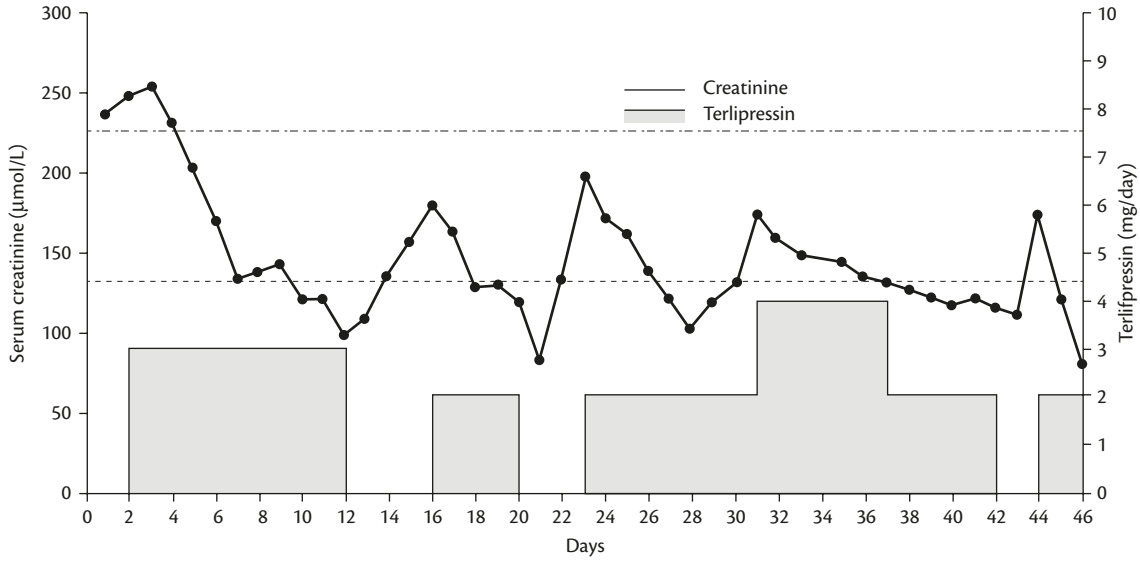

Fig. 247.7 Relationship between values of serum creatinine and treatment with terlipressin and albumin in one patient with hepatorenal syndrome. The daily dose of terlipressin is indicated in the right axis. Albumin was administered at the dose of 20–40 g/day for the duration of treatment with terlipressin. Dotted line indicates a 133 µmol/L value of serum creatinine. Dashed line indicates a 226 µmol/L value of serum creatinine.

From Piano, S. et al. (2011). Continuous recurrence of type 1 hepatorenal syndrome and long-term treatment with terlipressin and albumin: a new exception to MELD score in the allocation system to liver transplantation? *J Hepatol*, 55, 491–6.

octreotide, a somatostatin analogue, in combination with albumin, has been demonstrated to improve renal function in patients with HRS in studies with low number of patients (Angeli et al., 1999; Wong et al., 2004; Esrailian et al., 2007; Skagen et al., 2009), but, this treatment is less effective than the combination of terlipressin plus albumin (Cavallin et al., 2011).

Transjugular intrahepatic portosystemic shunt

Three pilot studies have evaluated transjugular intrahepatic portosystemic shunt (TIPS) in patients with type 1 HRS and relatively preserved hepatic function (Child–Pugh score < 12) (Guevara et al., 1998b; Brensing et al., 2000; Wong et al., 2004). They showed reversal of HRS and survival over 3 months in approximately 50% of cases. Hepatic encephalopathy was a common event following the procedure but it responded easily to medical therapy in most cases. TIPS *could thus be* an alternative treatment of type 1 HRS in patients without response to terlipressin plus albumin.

Renal replacement therapy and albumin dialysis

Both haemodialysis and continuous haemofiltration have been used to treat patients with cirrhosis and AKI (Keller et al., 1995; Capling and Bastani, 2004), but information is very scant and in most studies type 1 HRS was not differentiated from ATN. There are numerous pilot studies suggesting that albumin dialysis (MARS or Prometheus systems) may have beneficial effects in patients with type 1 HRS. Three large randomized controlled trials have so far been performed (Hassanein et al., 2007; Bañares et al., 2010; Rifai et al., 2010). In the Hassanein et al. study, albumin dialysis with the MARS system was found to be more effective than standard medical therapy in the management of patients with grade III–IV hepatic encephalopathy. Most patients had severe HRS and the treatment was found to be safe. The two other trials compared albumin dialysis with standard medical therapy in patients with type 1 HRS (MARS) or with type 1 and 2 HRS (Prometheus). Significant beneficial effect on hepatic encephalopathy was observed in the MARS study, but not on survival. In the Prometheus trial no effect on survival was observed in the whole group, but a significant improvement was observed in type 1 HRS patients. The administered dosage of dialysis was very low in both studies (six sessions of 6 hours in 21 days). Further studies are clearly needed to ascertain any potential role of albumin dialysis in type 1 HRS,

Treatment of type 2 hepatorenal syndrome

Transjugular intrahepatic portosystemic shunt

Five trials comparing TIPS versus therapeutic/large-volume paracentesis in patients with refractory and/or recurrent ascites have so far been published (Gines et al., 1991; Lebrec et al., 1996; Gerbes et al., 1998; Sanyal et al., 2003; Salerno et al., 2004). Unfortunately, very few of these patients had HRS and data from these trials are not valid for the evaluation of TIPS in patients with type 2 HRS. There are only two pilot studies specifically assessing TIPS in type 2 HRS (Brensing et al., 2000; Testino et al., 2003). Reversal of HRS and significant control of ascites were obtained in most patients. More than 50% of cases developed hepatic encephalopathy after TIPS. Seventy per cent of patients were alive after 1 year of follow-up. The mechanism of improvement of renal function in type 2 HRS after TIPS insertion has not been specifically investigated. The reduction of portal hypertension leading to a decrease in the degree of splanchnic arterial vasodilation and to an improvement in systemic haemodynamics is probably the main pathogenic mechanism involved. TIPS thus appears to be effective in reversing type 2 HRS. Randomized controlled trials using the recently introduced covered stents, with lower incidence of shunt malfunction, are required to ascertain the role of TIPS in the management of patients with type 2 HRS.

Vasoconstrictors and albumin

There are few data on the effect of terlipressin plus albumin in patients with type 2 HRS (Alessandria et al., 2002; Martin-Llahi et al., 2008). Reversal of HRS was obtained in most cases but a high prevalence (> 50%) of recurrence after stopping treatment has been described.

Liver transplantation and hepatorenal syndrome

Liver transplantation is the treatment of choice in patients with advanced cirrhosis, including those with type 1 and type 2 HRS (Gonwa et al., 1991, 2006; Nair et al., 2002; Restuccia et al., 2004b). The haemodynamic and neurohormonal abnormalities associated with HRS disappear within the first month after liver transplantation with a normal ability to excrete sodium and free water. However, these patients with HRS have more complications, spend more days in the intensive care unit, and have a higher in-hospital mortality rate than transplanted patients without HRS. The long-term survival of patients with HRS who undergo liver transplantation however is good, with a 3-year survival of 60%. This survival rate is only slightly reduced compared to that of transplantation in patients without HRS (Gonwa et al., 1991). The main problem of liver transplantation in type 1 HRS is its applicability. Due to their extremely short survival, most patients die before transplantation. The introduction of the MELD score for listing has partially solved the problem since patients with HRS are generally allocated the first places of the waiting list. Treatment of HRS with vasoconstrictors and albumin improves survival in the group of patients with response to treatment, increasing the number of patients reaching liver transplantation. Reversal of HRS before transplantation may decrease early morbidity after transplantation but there are conflicting data on survival (Restuccia et al., 2004b; Rice et al., 2011).

Prevention of hepatorenal syndrome

Three randomized controlled studies have shown that HRS can be prevented in specific clinical settings. The administration of albumin (1.5 g/kg IV at infection diagnosis and 1 g/kg IV 48 hours later) to cirrhotic patients with SBP markedly reduced the incidence of type 1 HRS (10% vs 33%), hospital mortality rate (10% vs 29%), and the 3-month mortality rate (22% vs 41) (Sort et al., 1999). Primary prophylaxis of SBP using long-term selective intestinal decontamination with oral norfloxacin in patients with low ascitic fluid protein concentration (<15 g/L) and severe liver failure (Child–Pugh score ≥ 9 with serum bilirubin > 3 mg/dL) or renal failure (SCr ≥ 1.2 mg/dL (≥ 106 μmol/L) or serum sodium ≤130 mEq/L) was associated with a significant decrease in 1-year probability of development of SBP (7% vs 61%) and type 1 HRS (28% vs 41%) and with a significant increase in the 3-month and 1-year survival (94% vs 62% and 60% vs 48%, respectively) (Fernandez et al., 2007). Finally, the administration of the tumour necrosis factor inhibitor, pentoxifylline (400 mg, three times a day) to patients with severe acute alcoholic hepatitis superimposed on cirrhosis reduced the occurrence of HRS (8% in the pentoxifylline group vs 35% in the placebo group) and the hospital mortality (24% vs 46%, respectively) (Akriviadis et al., 2000).

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CHAPTER 248

Acute kidney injury in heart failure

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Introduction

The incidence of heart failure (HF) has been steadily increasing and will further increase due to the ageing of the general population and the availability of better treatment. One to two per cent of the adult population in developed countries is affected by HF, and the prevalence rises to > 10% among persons aged older than 70 (Mosterd and Hoes, 2007; McMurray et al., 2012). HF often coexists with other comorbidities, which are the main determinants of prognosis. The coexistence of renal and cardiac disease can be today defined as cardiorenal syndrome (CRS). The definition of CRS was proposed by the Acute Dialysis Quality Initiative (ADQI) to describe 'disorders of the heart and kidneys whereby acute or chronic dysfunction in one organ may induce acute or chronic dysfunction of the other' (Ronco et al., 2010). CRS is classified into five subtypes, considering which organ is affected first and whether it is affected acutely or chronically (Table 248.1).

According to the ADQI definition, acute worsening of heart function leading to acute kidney injury (AKI) is currently defined as CRS type 1. Acute decompensated heart failure (ADHF), acute coronary syndrome (ACS), cardiogenic shock (CS), and cardiac surgery-associated low cardiac output syndrome (CS-LCO) are the cardiac events that might result in AKI (Bagshaw et al., 2010).

Several studies that describe the epidemiology of CRS type 1 have used the general and non-standardized term 'worsening renal function' (WRF) to define the acute change in kidney function. Considering this non-uniform definition, the incidence of AKI/WRF varies between 25–33% and 9–19% in ADHF and ACS respectively. This broad range in incidence is also attributable to the different timeframe used to ascertain renal impairment (Cruz, 2013). Inconsistent definitions for AKI during HF limit standardization of data and make epidemiologic studies difficult. Therefore, international guidelines currently recommend the use of a consensus definition (Risk, Injury, Failure, Loss, and End-stage renal disease (RIFLE), Acute Kidney Injury Network (AKIN)) to identify AKI. The timeframe used to recognize CRS type 1 should be limited to the period in which a direct pathophysiological linkage between HF and AKI is presumed. Considering that > 90% of all WRF occurs within the first week after hospital admission, an ideal 'ascertainment time' to consider AKI secondary to HF is 7 days (Bagshaw et al., 2010).

Given the high prevalence of chronic diseases in the population at risk for HF, four subtypes of CRS type 1 can be identified: (1) acute heart failure (AHF) leading to *de novo* AKI, (2) AHF leading to acute on chronic kidney injury, (3) acute on chronic HF leading to AKI, and (4) acute on chronic HF leading to acute on chronic kidney injury (Ronco et al., 2012).

CRS type 1 is associated with poor clinical outcomes, hospital readmission, and increased healthcare expenditure (Bagshaw et al., 2010; Cruz and Bagshaw, 2010). The risk of death seems to be proportional to the severity of AKI; however, even small and transient changes in serum creatinine (SCr) appear to influence the risk (Gottlieb et al., 2002; Logeart et al., 2008). Moreover, patients with end-stage renal disease have an increased risk of progression. The pre-existence of chronic conditions such as chronic HF or chronic kidney disease (CKD) are independent risks for poor outcomes (Hillege et al., 2000; Nohria et al., 2008).

Pathophysiology of heart failure

HF is defined as 'an abnormality of cardiac structure or function leading to failure of the heart to deliver oxygen at a rate commensurate with the requirements of the metabolizing tissues' (McMurray et al., 2012).

During AHF, arterial underfilling and venous congestion can both be partially responsible for AKI. Renin–angiotensin–aldosterone system (RAAS), sympathetic nervous system (SNS), and non-osmotic arginine vasopressin (AVP) release are the neurohormonal adaptive mechanisms, mainly acting through salt-water retention and vasoconstriction. The adaptive response soon becomes maladaptive, establishing the 'vicious cycle' responsible for the clinical features of the CRS type 1.

Drugs usually administered during HF, such as diuretics, angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs), can also contribute to kidney dysfunction. They are responsible for the renal haemodynamic changes, which in turn may precipitate AKI. Radio-contrast media (CM) exposure, especially intra-arterial (IA), can also be an additional factor leading to AKI.

Recently, the role of inflammation in the progression of HF has been investigated. It may play a role not only in distant organ damage, such as AKI, but also in further damaging cardiomyocytes.

Neurohormonal activation

Systemic hypoperfusion consequent to reduction in cardiac output results in neurohormonal activation. This condition simulates intravascular volume depletion, in response to which baroreceptors activate adaptive mechanisms. RAAS, activation of SNS, and

Table 248.1 Cardiorenal syndrome classification

CRS type 1	*AHF leading to AKI* Acute cardiac events: ACS, ADHF, CS, CS-LCO. AKI defined according to RIFLE/AKIN criteria
CRS type 2	*Chronic heart disease leading to CKD* Chronic heart failure according to the ESC or ACCF/AHA guidelines. CKD defined according to KDOQI/KDIGO guidelines
CRS type 3	*AKI leading to acute cardiac dysfunction* Acute renal events: cardiac surgery-associated AKI, AKI after major non-cardiac surgery, contrast-induced AKI (CI-AKI), other drug-induced nephropathies, and rhabdomyolysis. Acute cardiac dysfunction: AHF/ADHF as a consequence of volume overload, arrhythmias secondary to abnormalities in electrolytes and acid-base metabolism, depressed myocardial contractility because of the effect of uraemic toxins, myocardial ischaemia.
CRS type 4	*CKD leading to chronic cardiac dysfunction* CKD defined according to KDOQI/KDIGO guidelines Chronic cardiac dysfunction: LV remodelling, diastolic and systolic dysfunction, cardiomyopathy, CAD
CRS type 5	*Systemic condition leading to both heart and renal dysfunction* e.g. sepsis, diabetes, amyloidosis

ACCF = American College of Cardiology Foundation; ADHF = acute decompensated heart failure; AHA = American Heart Association; AHF = acute heart failure; AKI = acute kidney injury; CAD = coronary artery disease; CKD = chronic kidney disease; CS = cardiogenic shock; CS-LCP = cardiac surgery-low cardiac output; ESC = European Society of Cardiology; KDIGO = Kidney Disease: Improving Global Outcomes; KDOQI = Kidney Disease Outcomes Quality Initiative; LV = left ventricular;

non-osmotic release of AVP are the main humoral effectors; they mainly mediate water and salt retention and increase in peripheral vascular resistances. Angiotensin II (ATII) accounts for 60% of the aldosterone release and can itself stimulate sodium reabsorption in the proximal tubular cells. Moreover, ATII is a potent systemic vasoconstrictor and a stimulator of the SNS. Both these effectors act synergistically, increasing systemic vascular resistance to compensate for the initial decrease in ejection fraction (EF). Sympathetic stimulation contributes to sodium reabsorption, both directly and indirectly through a positive feedback on the juxtaglomerular apparatus, which finally increases renin release. ATII, aldosterone, and SNS also have a long-term trophic effect on cardiomyocytes and renal tubular cells, promoting cell hypertrophy, apoptosis, and tissue fibrosis (Burns and Thomas, 2011).

Non-osmotic release of AVP is an appropriate response to intravascular hypovolaemic state, which is a stronger stimulus than the osmotic on AVP release. The clinical implication of this physiologic mechanism is the development of hyponatraemia due to both diuretic therapy and free-water retention caused by AVP. The action of AVP on principal cells of collecting ducts is mediated by V_2 receptors located on the basolateral membrane. The interaction between AVP and V_2 receptors induce the expression of the water channels aquaporin 2 (AQP2) on the apical membrane, thus increasing collecting duct free-water permeability. Moreover, AVP also leads to vasoconstriction and cardiac hypertrophy through the V_{1a} receptor. Recently, V_2-receptor antagonists have been investigated for the treatment of AHF (Schrier, 2008; Schrier et al., 2009).

Venous congestion

Venous congestion, occurring during HF, is one of the haemodynamic determinants of CRS (Gnanaraj et al., 2013). Central venous pressure (CVP) and jugular venous pressure (JVP) were both found to be associated with impaired renal function (Mullens et al., 2009; Guglin et al., 2011). This effect seems to be related to the increased pressure in renal veins which is back transmitted by the increased CVP. Animal experimental data showed that increased renal venous pressure decreases renal blood flow (RBF) and glomerular filtration rate (GFR) through a vasoconstriction of afferent and efferent arterioles (Dilley et al., 1983).

Moreover, RBF is determined by the abdominal perfusion pressure which is inversely related to intra-abdominal pressure (IAP). The normal IAP is < 5–7 mmHg and it increases in the presence of venous congestion and visceral oedema. Elevation of IAP was present in 60% of patients admitted for ADHF. It was associated with worse renal function at baseline while its reduction was strongly correlated with the improvement of kidney function (Mullens et al., 2008).

Drugs

Many drugs commonly prescribed for the treatment of AHF can also contribute to further damage of kidney function. Patients with AHF are in a narrow therapeutic management window.

Diuretics are the cornerstone in the treatment of AHF (Aspromonte et al., 2011b). These agents may resolve congestion providing a rapid relief from symptoms, but overdiuresis can cause arterial underfilling and worse kidney function. Drugs acting on RAAS, such as ACEIs and ARBs, are included in the protocol of management of HF and often administered chronically together with diuretics. These agents have proven efficacy in improvement of outcomes in stabilized HF, however they have to be avoided during CRS type 1 and only after clinical stabilization can they cautiously be titrated (Hillege et al., 2000). During AHF, renal perfusion is strictly dependent on neurohormonal activation, which maintains GFR through vasoconstriction of both afferent and efferent arteriole. Blocking this compensatory mechanism may decrease GFR and therefore lead to CRS type 1.

This is mostly important in conditions where renal reserve is impaired, such as previous kidney injuries or with ageing (Chronopoulos et al., 2010). In such conditions GFR can be normal, due to overworking of residual functional nephrons whose activity is strictly dependent on constant activation of RAAS. The ability to response to an extra stimulus would require a further activation of RAAS to maintain GFR that these nephrons cannot achieve.

Nephrotoxic exposure

The contribution of nephrotoxic medications to development of AKI has an important role in all hospitalized patients and it is even more relevant in the setting of AHF where kidney is more vulnerable because of the haemodynamic impairment. Generally, patients with AHF can be exposed to all types of nephrotoxic medications such as antibiotics, non-steroid anti-inflammatory drugs (NSAIDs), CM, etc. In particular, CM exposure is frequent in patient with AHF, especially for those admitted with ACS who require percutaneous coronary interventions (PCI).

In the last years, the risk score for CI-AKI post PCI was developed focusing on the cumulative effect of multiple non-modifiable and

modifiable risk factors (Mehran et al., 2004; Mehran and Nikolsky, 2006). Volume of CM is considered a modifiable risk factor, but there is no recommendation about the minimum 'safe' dose since every dose should be nephrotoxic in a high-risk patient. Even if the route of administration was not included in the prognostic score system, some data support a higher risk of AKI after IA administration above the level of the renal arteries than after intravenous (IV) administration (Stacul et al., 2011). Moreover, IA administration requires a higher dose of CM than IV and the risk of cholesterol embolism is increased (Stratta et al., 2012).

Inflammation

Immune-mediated mechanisms have also been implicated in the development of CRS type 1 (Gullestad and Aukrust, 2005; Frantz et al., 2007). Abnormality in balance between inflammatory and anti-inflammatory cytokines suggests the existence of immune dysregulation in patients with HF (Aukrust et al., 1999). The inflammation is a consequence of ischaemic cell damage related to hypoperfusion and it is further amplified after reperfusion. Moreover, during AHF, blood flow is shunted away from the splanchnic region to preserve perfusion in the brain, heart, and kidney. Gut ischaemia can be responsible for paracellular absorption of lipopolysaccharide (LPS) and systemic endotoxaemia may occur as a consequence (Ronco et al., 2012).

Inflammation seems to be more than just an accompanying feature during HF since it may have a role in organ damage and in particular in AKI (Friedewald and Rabb, 2004; Cantaluppi et al., 2012). Recently, it has been demonstrated that plasma-induced apoptosis, capsase 3 and 8 activities, and interleukin (IL)-6 levels were significantly higher in CRS type 1 patients when compared to healthy controls and to patients with AHF but without renal impairment (Virzi et al., 2012a, 2012b). However, the specific role of these cytokines in the causation of AKI in the setting of AHF remains to be elucidated.

Inflammation also appears to play a role in fluid redistribution increasing the vascular permeability and interfering with the mechanism of lymphatic reabsorption (Cotter et al., 2008). Inflammation can therefore concur to the pathogenesis not only of pulmonary and peripheral oedema, but also of kidney interstitial oedema which can contribute to reduction in GFR.

Management of heart failure

Prevention

CRS type 1 is the final effect of interaction between complex pathogenic factors and once it begins, it is difficult to abort. Considering the implication on outcomes and the difficulty in interrupting the 'vicious circle', prevention of CRS type 1 is the main issue in clinical practice (McCullough et al., 2010; Cruz, 2013).

In CRS type 1, the cardiac event is primal and the preventive approach is aimed at reducing the risk of acute decompensation. One-third of the patients hospitalized for AHF have *de novo* AHF precipitated by pneumonia, hypertension, atrial fibrillation, or acute cardiac ischaemia. The remaining two-thirds have chronic HF which acutely decompensates usually because of non-compliance with diet restriction or with medications. Preventive strategies in the first group include implementation of lifestyle modifications and optimization of blood pressure control through drugs that block RAAS or beta-adrenergic blockers (McCullough et al., 2010).

The administration of ACEIs or ARBs has been shown to improve outcomes in HF, however in patients with a reduced renal reserve they can be responsible for a decline of GFR. In this case, a decrease of GFR can even be protective in the long term (Ruggenenti and Remuzzi, 2012). In fact, the reduction of the glomerular intracapillary pressure as a consequence of RAAS blocking reduces proteinuria, which in turn reduces the risk of glomerulosclerosis (Apperloo et al., 1997). Current guidelines consistently recommend continuing treatment with ACEIs or ARBs if the GFR decline over 4 months is < 30% from baseline. However, a persistent progressive increase in SCr should be cautiously evaluated and any cause of renal hypoperfusion, such as AHF, should be excluded.

Hence, administration of drugs that block RAAS in patients with stable HF and CKD (CRS type 4) is not contraindicated but close monitoring of renal function is necessary. Prompt withdrawn is recommended if AHF or any other cause of volume depletion is suspected.

Patients admitted for AHF have a high risk of developing CI-AKI especially in the setting of ACS when the IA CM administration is not avoidable. Prevention strategies such as adequate IV volume expansion with either sodium chloride or sodium bicarbonate solution are strongly recommended. However, adequate fluid loading is not easily achievable in patients with AHF, because of fluid overload. *N*-acetylcysteine can have an additive preventive effect in addition to adequate IV fluid loading.

Even if 60–70% of CM is removed by a single session of haemodialysis (HD), studies which investigated the preventive role of HD or haemofiltration (HF) showed an uncertain benefit, and indeed prophylactic HD appears to be associated with a higher incidence of CI-AKI (Cruz et al., 2012b). Therefore, neither HD nor HF are recommended to prevent CI-AKI (Fliser et al., 2012).

Another mainstay of prevention is recognition of patients at risk of developing CRS type 1 (Cruz, 2013). Prognostic scores for AKI in AHF (Forman et al., 2004), after PCI (Mehran et al., 2004) and after cardio-surgery (Thakar et al., 2005) exist. In addition to scoring systems, renal biomarkers could be useful to predict the risk of AKI. Increased levels of molecules involved in tubular damage might precede a reduction in GFR. This condition, known as subclinical AKI, may or may not evolve into AKI (Haase et al., 2012). Currently, neutrophil gelatinase-associated lipocalin (NGAL), serum cystatin C, urinary IL-18, and urinary kidney injury molecule 1 (KIM-1) are the most promising biomarkers in the early diagnosis of AKI (Cruz et al., 2011, 2012a).

Treatment

Standard evidence-based guidelines currently exist for management of both AHF (McMurray et al., 2012) and AKI (Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group, 2012). However, there are no specific recommendations for the treatment of CRS type 1. Diuretics, inotropic agents, vasopressors, vasodilators, and mechanical devices can all be used in AHF according to the clinical presentation. Management of patients with CRS type 1 should be different from the standard treatment of HF since many drugs used in AHF can further compromise renal function. Vasodilators such as nitroglycerine and nitroprusside can exacerbate renal injury by precipitating hypotension. In particular, a significant deterioration in renal function with nesiritide has been described (Sackner-Bernstein et al., 2005).

In the setting of AHF, mechanical circulatory support (MCS) may be used as a 'bridge to decision' to achieve haemodynamic stability. The expected effect on kidney function is related to the improvement in haemodynamics, though the risk of renal damage secondary to the side effect of MCS, such as haemolysis, should also be taken into account (Mao et al., 2013).

Diuretics

Diuretics are an essential component of the treatment of AHF since they promote natriuresis and reduce volume overload leading to relief from symptoms. Aggressive diuresis may be necessary to achieve clinical outcome, but overdiuresis can possibly lead to hypovolaemia and precipitate CRS type 1. Therefore, the diuretics dose should be modulated according to the patient's volume status. Biomarker-guided therapy and the use of bioelectric impedance vector analysis (BIVA) to assess hydration status could be helpful to monitor diuretic therapy and avoid unwanted iatrogenic complications during the treatment of AHF (Aspromonte et al., 2011a, 2012). In particular, brain natriuretic peptide (BNP) and its precursor pre-NT-BNP are increased in conditions of fluid overload. Their natriuretic effect is impaired because of the reduced amount of sodium that reaches the collecting ducts as a consequence of increased proximal reabsorption. Even if a high level of natriuretic peptides (NPs) can be a consequence of reduced renal clearance, monitoring of NPs can be helpful in assessment of changes in volume status and target diuretic therapy (McCullough et al., 2010).

In the setting of AHF, IV loop diuretics such as furosemide should be preferred because of their fast action. Their diuretic effect appears after 30–60 minutes, however clinical improvement of dyspnoea can occur even faster because of their vasoactive effect. IV administration is suggested because pharmacokinetics is more predictable since oral absorption can range between 10% and 100% and in AHF it is slower (Brater, 1998).

The optimal regimen for diuretic dose is unclear regarding both mode of administration and dosing. Intermittent administration can lead to salt retention during the interval in which the plasmatic concentration is low, the so-called rebound sodium retention (Ellison, 2001). This is important especially in conditions of renal impairment where the ability of the kidney to clear a diuretic is prolonged and the true pharmacokinetics are less predictable.

Diuretic dose should be individualized to the clinical response. In patients with severe AHF, renal responsiveness to loop diuretics may be decreased so that the natriuretic response is reduced and delayed compared to normal subjects. In this setting, more frequent or continuous administration can increase diuretic effect. In patients with CKD in which less diuretic reaches the site of action, a higher dose is necessary to obtain relevant diuretic response, but the natriuretic effect is not delayed (Brater, 1998).

A high dose of diuretics has been found to be associated with adverse clinical outcomes including AKI, progression of HF, and death in multiple studies (Bagshaw et al., 2010; Cruz and Bagshaw, 2010); however, the possibility of a greater severity of illness, as a major confounder, should also be considered. In fact, severe AHF may require a higher dose of diuretics with the aim of overcoming diuretic resistance. Many factors seem to contribute to diuretic resistance, and when it is established it may be difficult to reverse (Elliso, 2001). Chronic use of furosemide can cause hypertrophy and hyperplasia of distal tubular cells (thiazide sensitive) secondary to the increased delivery of distal sodium (so-called braking phenomenon); however, in the setting of AHF, the increased sodium reabsorption at proximal tubular cells secondary to neurohormonal (early breaking) activation also plays a determinant role (Aspromonte et al., 2011b). Hyponatraemia and hypoalbuminaemia can also have an additive effect.

A recent randomized controlled trial that compared continuous infusion of furosemide versus bolus injection and low dose (equal to pre-existing oral dose) versus high dose (2.5 times the pre-existing oral dose) did not find any significant difference in patients' global assessment of symptoms. High dose resulted in greater net fluid loss, weight loss, and relief from dyspnoea after 72 hours, but at the expense of a significant more frequent transient AKI. However, there was no difference in SCr or in clinical outcome after 60 days from randomization (Felker et al., 2011).

Thiazides and potassium-sparing diuretics can be used in addition to the loop diuretics, to antagonize the late breaking effect (McMurray et al., 2012); however, both of them are almost ineffective when severe renal impairment is present. Metolazone is an exception because it retains its efficacy in patients with renal insufficiency (Paton and Kane, 1977; Ernst and Moser, 2009). When the combination of loop diuretic and thiazide is used, close monitoring of electrolytes is required because of the risk of hypokalaemia.

Recently a non-selective, oral V_2 receptor antagonist (tolvaptan) was investigated in patients hospitalized for symptomatic HF. It was administrated in addition to the standard therapy and even if no effect on long-term mortality and HF-related morbidity was found, it showed promising results in term of short-term outcomes. A greater reduction in body weight at first and seventh day, in pedal oedema, and in patients' assessment of dyspnoea at first day, was achieved in the treated group at the cost of an increase in nuisance events (thirst and dry mouth) (Gheorghiade et al., 2007). Currently tolvaptan is approved in the United States for the treatment of hyponatraemia in HF, in cirrhosis, and in the syndrome of inappropriate antidiuretic hormone secretion, while in Europe it is allowed only for the last indication. No data are available about its effect with renal impaired function.

Ultrafiltration

Recently great interest was given to the use of ultrafiltration (UF) as initial therapy in AHF. The theoretic advantage of UF is that fluid overload is treated by a slow, continuous, and controlled fluid removal rather than by a rapid, intermittent, and uncontrolled way such as with diuretic therapy. As a consequence, neurohormonal activation could be better controlled as well as electrolyte balance and acid–base metabolism. Application of this technology has been limited by the need for high flow rates, large extracorporeal blood volumes, and large-bore central venous catheters. A modified UF device, with a blood flow adjustable between 10 and 40 mL/min and total extracorporeal blood volume of 33 mL, has overcome these limitations (Jaski et al., 2003). Although potentially attractive, the results regarding the superiority of UF compared to diuretics are still controversial.

In the UNLOAD (Ultrafiltration versus Intravenous Diuretics for Patients Hospitalized for Acute Decompensated Congestive Heart Failure) trial, UF produced a greater weight and fluid loss and resulted in lower HF rehospitalization rates compared to IV diuretics (Costanzo et al., 2007). No SCr differences were observed between the groups.

Recently the results from CARESS-HF (Cardiorenal Rescue Study in acute decompensated Heart Failure) study were published. In this study, patients with AKI related to AHF (but SCr < 3.5 mg/dL) were randomized to receive UF or pharmacologic therapy including continuous IV diuretic with the addition of metolazone and vasoactive therapy if necessary. Change in body weight was similar in the two groups after 96 hours although UF was associated with higher adverse events, including kidney failure, bleeding complications, and IV catheter-related complications (Bart et al., 2012). At this time there is no clear evidence that UF provides 'diuretic-sparing' benefit and the only indication for UF is in patients unresponsive or resistant to diuretic therapy (McMurray et al., 2012).

Summary

AKI occurs commonly in the setting of AHF, and is termed CRS type 1. It is associated with adverse clinical outcomes, including increased mortality, rehospitalization, and increased healthcare expenditures. Multiple pathophysiologic mechanisms have been implicated, including neurohormonal activation, venous congestion, inflammation, effects of pharmacologic therapy for HF (RAAS antagonists and diuretics), and nephrotoxic exposure. Prevention is of paramount importance, consisting of avoiding acute decompensation of chronic HF, and, among patients already presenting with AHF, prompt recognition of those at increased risk for AKI. Among patients with established AKI, diuretics remain the cornerstone of therapy. IV administration by bolus or continuous infusion appears to be equally efficacious. Biomarkers and bioelectrical impedance analysis can be helpful in estimating the real volume overload and may be useful to predict and avoid AKI. The role of UF remains controversial, and it is currently recommended only for diuretic-resistant patients.

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CHAPTER 249

Acute kidney injury in pulmonary diseases

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Introduction

Acute kidney injury (AKI) and acute lung injury (ALI) often complicate the course of hospitalized patients particularly in the intensive care unit (ICU) setting. AKI develops in up to 36–67% of critically ill patients depending on the definition used (Mehta et al., 2002; Uchino et al., 2005; Ostermann and Chang, 2007). In a large, systemized prospective cohort study, AKI was accompanied by respiratory failure in more than half of the patients, even those who did not require dialysis (Mehta et al., 2004). Furthermore, the relationship between kidney and lung injury has been further described in the Beginning and Ending Supportive Therapy for the Kidney (BEST) study (Uchino et al., 2005) and other recent observational studies (Medve et al., 2011; Piccinni et al., 2011). While one disorder may precede the other, they are particularly problematic when they coexist. Recently, several studies have shown that patients with AKI are more likely to be ventilated than patients without AKI and they have impaired ability to wean from the ventilator (Metnitz et al., 2002; Vieira et al., 2007; Waikar et al., 2007). The high mortality of 40–60% in critically ill AKI patients (Uchino et al., 2005; Bagshaw et al., 2007) is further worsened when there is combined AKI and acute respiratory failure, and may approach 80% (Chertow et al., 1995; Mehta et al., 2002). These findings highlight the importance of recognition and management of AKI in patients with lung dysfunction. In this chapter we provide a concise review of the literature and discuss the implications of these findings for managing patients.

Epidemiology

Alterations in renal function in lung diseases

AKI can complicate the course of patients with lung disorders; however, until recently, evidence was sparse regarding the incidence and prevalence of this disorder. Murugan et al. (2010) reported overall a 34% incidence of AKI in patients with community-acquired pneumonia (CAP), and they found that even in those who appeared to have an uncomplicated course, AKI developed in around one-quarter of patients. While it is well recognized that AKI accompanies ALI, there is only indirect evidence of the prevalence of AKI in ALI. Data from the Fluid and Catheter Treatment Trial (FACTT) showed that 10–14% of ALI patients received renal replacement therapy with an average of 11 days of renal support (Wiedemann et al., 2006). Since a mainstay of management of ALI is mechanical ventilation, renal dysfunction in this setting is influenced by the effects of ventilation (Drury et al., 1947; Uchino et al., 2005). In addition, recent reports have highlighted the importance of small changes in serum creatinine associated with high mortality in ventilated patients (Nin et al., 2010). Information on the incidence of AKI in chronic obstructive pulmonary disease (COPD) is similarly poorly described although it is commonly seen with a variety of comorbidities such as hypertension, ischaemic heart disease, diabetes mellitus, and chronic kidney disease (CKD) (Terzano et al., 2010). Besides CKD, several renal disorders including fluid overload, hypercapnia-induced renal dysfunction, and decreased renovascular resistance are reported (Sharkey et al., 1999; de Leeuw and Dees, 2003; Hemlin et al., 2007) but have not been directly linked to AKI. It is currently unclear whether exacerbations of COPD requiring antibiotic therapy or the associated pulmonary hypertension are risk factors for AKI and ultimately contribute to CKD. Evidence from cystic fibrosis (Ratjen and Doring, 2003) suggests that repeated and persistent pulmonary infection especially due to *Pseudomonas aeruginosa* (Cystic Fibrosis Foundation Patient Registry, 2011) precludes the survivors with cystic fibrosis to receive repeated courses of intravenous aminoglycoside antibiotics for exacerbations over their lifetime (Al-Aloul et al., 2005). Besides aminoglycoside-induced AKI (Bertenshaw et al., 2007; Bockenhauer et al., 2009), a recently reported study indicated that adults with cystic fibrosis have a CKD prevalence of 2.3% and this elevated risk is related with increased prevalence of diabetes in this population (Quon et al., 2011). There is evidence that in patients with COPD with right ventricular failure, the renin–angiotensin–aldosterone axis is stimulated (Anand et al., 1992). In addition to this mechanism, elevated $PaCO_2$ and hypoxaemia associated with hypercapnia also leads to sodium retention (Reihman et al., 1985; Palange, 1998). Elevated plasma volume has been demonstrated in patients with pulmonary arterial hypertension and found to be associated with poor outcome (James et al., 2003). Recently, a retrospective study of 105 pulmonary arterial hypertension patients with acute right-sided heart failure showed an AKI incidence of 32% and increased mortality in patients with AKI (Haddad et al., 2011). In summary, available evidence suggests that AKI is common in patients with acute and chronic lung dysfunction, however the natural history and course of this disorder is not well described.

Alterations in lung function in patients with kidney disease

Alterations in lung function in the setting of AKI have been recognized to span a spectrum of states ranging from the 'uraemic lung'

to changes in lung diffusion capacity. Bass and Singer (1950) suggested that the lung could be injured during AKI as AKI patients showed abnormal chest X-rays postulated to be secondary to 'increased permeability of pulmonary capillaries'. Since then, many researchers have reported on lung injury associated with kidney injury (Hopps and Wissler, 1955; Bleyl et al., 1981). In dialysis patients, there are diverse reports about the lung function including decreased or increased diffusion capacity of the lung for carbon monoxide (DLCO), small airway disease, and elevated exhaled H_2O_2 (Bush and Gabriel, 1991; Tkacova et al., 1993; Karacan et al., 2004; Rysz et al., 2007). In 1985, Lee carried out an electron microscopic observation of chronic uraemic lungs in six uraemic patients and found the epithelial cell damage varied from oedematous swelling to total disruption. The interstitial changes included focal accumulation of oedema fluid, patchy fibrosis, and increased cellularity. Particularly interesting were the altered alveolo-capillary basement membranes which showed irregular thickening, lamination, and fragmentation (Lee, 1985). Experimental evidence suggests organ cross-talk wherein renal ischaemia reperfusion injury can lead to increased pulmonary capillary permeability.

Volume accumulation and overload from a decline in renal function and aggressive fluid resuscitation can additionally contribute to increased pulmonary dysfunction without direct lung injury which has been termed pseudo-ARDS (Schrier, 2010).

Simultaneous kidney and lung involvement

Several illnesses that involve kidney and lung simultaneously are listed in Table 249.1. The timing and sequence of each organ involvement can vary considerably depending on the underlying events. For instance, in sepsis the primary source can result in the lung (pneumonia) or the kidney (urosepsis) being the initial organ involved. Systemic disorders (lupus, ANCA-positive vasculitis) can additionally present as a single organ involvement or both. Secondary effects of increased intra-abdominal pressure can affect both the kidneys and lungs and are often unrecognized. Table 249.1 summarizes the various interactions of the kidney and lung.

Pathophysiology

Experimental evidence of kidney–lung interactions

Over the last two decades, our understanding of the pathophysiology and mechanisms of kidney–lung interactions has been enhanced by several experimental models. In general, changes in kidney function in the setting of lung disease have been attributed to the effects of deranged pulmonary physiology and the secondary effects of mechanical ventilation. As discussed earlier, it is likely that the changes in kidney function are a net result of a variety of factors acting in concert over time.

Lung to kidney (including the effects of mechanical ventilation)

The experimental studies which reveal the pathophysiology of kidney injury in the setting of lung diseases are summarized in Table 249.2 and described further.

Table 249.1 Clinical evidence of kidney–lung interaction and underlying pathophysiology

Kidney to lung	Lung to kidney	Kidney and lung simultaneously
Observational studies PICARD, BEST Historic studies including autopsy studies		Goodpasture syndrome
Increased permeability of pulmonary capillaries (Bass and Singer, 1950)	ARDS network studies ALI studies	ANCA-associated vasculitis Wegener granulomatosis Microscopic polyangiitis Churg–Strauss syndrome
Pulmonary oedema rich in protein (Hopps and Wissler, 1955)		Lupus nephritis with lung involvement
Alveolocapillary damage and the subsequent plasmatic leakage (Bleyl et al., 1981)		Sepsis (Luce, 1987) Abdominal compartment syndrome
Pathogenesis		
Established kidney disease (CKD)	**Established lung disease**	**Lung–kidney**
Pre-dialysis Epithelial, interstitial, basement membrane damage (Lee, 1985)	*COPD*	*Goodpastures* anti-GBM antibodies to NC1 domain of the alpha-3 chain of type IV collagen *ANCA + GN* Acute or rapidly progressive glomerulonephritis that is typically associated with crescent formation and concomitant pulmonary haemorrhage
	Fluid overload (de Leeuw and Dees, 2003) CKD (Terzano et al., 2010)	Pauci-immune small vessel vasculitis
	Hypercapnia-induced renal dysfunction (Hemlin et al., 2007)	Immune complex disease

(*Continued*)

Table 249.1 Continued

Kidney to lung	Lung to kidney	Kidney and lung simultaneously
Dialysis patients	In hypoxaemic patients, renovascular resistance decreased when hyperoxaemia was induced. This fall in renovascular resistance was reversed with the addition of carbon dioxide (Sharkey et al., 1999). *Cystic fibrosis* Aminoglycosides-induced AKI (Bertenshaw et al., 2007; Bockenhauer et al., 2009) CKD (Quon et al., 2011) *Pulmonary hypertension*	*Sepsis* Acute tubular necrosis Interstitial and alveolar oedema *ACS:* AKI induced by elevated renal parenchymal and renal vein pressure (Mohmand and Goldfarb, 2011) Sodium and water retention (Bloomfield et al., 1997) Mechanical effect by displacing the diaphragm cranially leads to increased peak airway pressure, compressive atelectasis, decreased lung compliance and reduced lung volumes (Obeid et al., 1995, Pelosi et al., 2007).
Decreased DLCO (Bush and Gabriel, 1991)		
Increased DLCO and decreased PImax and PEmax (Karacan et al., 2004)		
Small airway disease (Tkacova et al., 1993) Elevated exhaled H2O2 in HD patients with cellulose membrane (Rysz et al., 2007)		
	Volume overload (Palange, 1998, Reihman et al., 1985) AKI (Haddad et al., 2011)	
New-onset kidney disease (AKI)	**New-onset lung disease**	
Impaired ability to wean from the ventilator (Vieira et al., 2007) Patients with AKI are twice as likely to need mechanical ventilation as patients without AKI (Waikar et al., 2007)	*Pneumonia* Acute kidney injury is common among patients with pneumonia regardless of severity of lung disease and is associated with higher immune response and an increased risk of death (Murugan et al., 2010)	
The requirement for mechanical ventilation is even higher for AKI patients requiring renal replacement therapy (Metnitz et al., 2002)	*ALI* 10–14% of ALI patients received renal replacement therapy (Wiedemann et al., 2006)	
	Mechanical ventilation 30-minute periods of continuous positive pressure breathing reduced renal function by 20–50% (Drury et al., 1947)	
	AKI develops as a component of multi-organ system dysfunction (Uchino et al., 2005)	
	Early and small changes in serum creatinine concentrations are associated with mortality (Nin et al., 2010)	

AKI = acute kidney injury; ANCA = antineutrophil cytoplasmic antibody; ARDS = acute respiratory distress syndrome; CKD = chronic kidney disease; COPD = chronic obstructive pulmonary disease; DLCO = diffusion capacity of the lung for carbon monoxide; HD = haemodialysis; PEmax = static expiratory pressure; PImax = static inspiratory pressure; GBM = glomerular basement membrane; NC1 = non=collagenous 1.

Hypoxaemia and hypercapnia

Many studies about the interactions between kidney function and hypoxaemia show that increased diuresis and natriuresis occur in response to acute hypoxaemia (Vidiendal Olsen et al., 1998; Hildebrandt et al., 2000). Haemoconcentration and decrease in sodium reabsorption might be adaptive mechanisms of oxygen transport and consumption. The effect of hypercapnia on renal blood flow (RBF) has been well documented. Acute hypercapnia reduces RBF and causes renal vasoconstriction (Sharkey et al., 1999). In addition, transient hypercapnic stress causes exaggerated and prolonged elevation of renal interstitial norepinephrine (noradrenaline) levels (Sobajima et al., 2011). Hotter et al. reported that exposure to simulated ischaemic atmosphere, but not to low O_2 or high CO_2 alone, induced cell apoptosis in a renal tubular epithelial LLC-PK1 cell culture model of ischaemia-reperfusion injury. They suggested that ischaemia-induced apoptosis *in vivo* would be dependent on the natural, joint action of hypoxia and hypercapnia (Hotter et al., 2004).

Haemodynamic changes

Haemodynamic changes following mechanical ventilation have been implicated as potential mechanisms for kidney dysfunction. Increased intrathoracic pressure associated with positive pressure ventilation (PPV) decreases venous return to the heart (preload) and results in decreased cardiac output. PPV affects both left ventricular geometry and pulmonary vascular volume and resistance and, in addition, increases right ventricular afterload (Qvist et al., 1975; Jardin et al., 1981; Luecke et al., 2004). Decreased cardiac output may lead to decreased renal perfusion and is associated with reduced renal function. Kuiper et al. showed an immediate decline

Table 249.2 Experimental studies that examine kidney injury after lung injury

Model	Manoeuvre	Haemodynamic changes	Renal inflammation (biotrauma)	Others	Study
Sheep	PEEP	↓ LV *function at the highest* level of PEEP			(Luecke et al., 2004)
Rat	PEEP	↓ 40% RBP in lung-injurious ventilation		↑ renal ET in lung-injurious ventilation	(Kuiper et al., 2008)
Monkey, dog	PEEP	Reversal of outer and inner cortical blood flow			(Hall et al., 1974; Moore et al., 1974)
Dog	PEEP	↑ EEP, renin, aldosterone			(Kaczmarczyk et al., 1996)
Dog	PEEP	↓ RBP		↑ sympathetic tone	(Fewell and Bond, 1979)
Rat (SS)	10% CO_2, 10 min			↑ iNE in heart and kidneys	(Sobajima et al., 2011)
Human	Infusion of ANP during PEEP			returned renal haemodynamics and excretory function	(Andrivet et al., 1991)
Human	Hypo/normo-capnic hypoxaemia, hyperventilation w/wo face mask	↑ RBP during hypocapnic hypoxaemia, hyperventilation, and normocapnic hypoxaemia		↓ proximal tubular reabsorption and natriuresis during hyperventilation	(Vidiendal Olsen et al., 1998)
Rat, proximal tubular cell	Hypoxia, hypoxic + hypercapnic, hypercapnic			Apoptosis in hypoxia + hypercapnia	(Hotter et al., 2004)
Rat	VT; 6 mL/kg; VT (6 mL/kg) and PEEP; 5 cm H_2O; VT (12 mL/kg); VT (12 mL/kg) and PEEP (5 cm H_2O).		↓ adenyl nucleotide 2b mRNA		(Douillet et al., 2005)
Rabbit	Low VT (5–7 mL/kg) and high PEEP (9–12 cm H_2O); high VT (15–17 mL/kg) and low PEEP (0–3 cm H_2O)		↑ MCP-1, IL-8, and GRO in injurious group	Apoptosis in injurious group	(Imai et al., 2003)
Rat	Low VT (7 mL/kg); high VT (20 mL/kg)		↑ VEGF, eNOS in high VT	Microvascular leak in high VT	(Choi et al., 2003)

ADH = antidiuretic hormone; ANP = atrial natriuretic peptide; CO_2 = carbon dioxide; eNOS = endothelial nitric oxide synthase; ET = endothelin; GRO = growth-regulated oncogene; IL-8 = interleukin-8; LV = left ventricle; MCP-1 = monocyte chemotactic protein-1; mRNA = messenger ribonucleic acid; PEEP = positive end expiratory pressure; RBP = renal blood flow; iNE = interstitial norepinephrine; VEGF = vascular endothelial growth factor; VT = tidal volume.

in urinary output after the start of mechanical ventilation (Kuiper et al., 2005). Several studies have shown redistribution of blood flow from the cortical to the juxtamedullary nephrons during ventilation with positive end-expiratory pressure (PEEP), whereas total RBF remained unchanged (Hall et al., 1974; Moore et al., 1974) and this phenomenon resulted in greater fluid retention at any level of renal perfusion. PPV may lead to a decrease in atrial natriuretic peptide (ANP), and increase in antidiuretic hormone (ADH), renin, and aldosterone (Andrivet et al., 1991; Kaczmarczyk et al., 1996). Mechanical ventilation with PEEP increases sympathetic tone resulting in increased plasma renin activity, hence decreasing glomerular filtration rate by reducing blood flow (Fewell and Bond, 1979).

Systemic release of inflammatory mediators (biotrauma)

There are two independent pathways of the biotrauma hypothesis: first, ventilation may cause release of mediators, and second, these mediators have biological activity. Douillet et al. showed that mechanical ventilation can alter nucleotide and purinoceptor expression in the kidney (Douillet et al., 2005). Imai et al. demonstrated that injurious mechanical ventilation strategies induced production of a variety of inflammatory cytokines (interleukin (IL)-8 and monocyte chemotactic protein-1, amongst others). They further demonstrated that this injurious strategy induced epithelial cell apoptosis in kidney and proved the mechanistic hypothesis underlying ventilator-induced kidney injury by showing that plasma from injuriously ventilated rabbits induced apoptosis in fresh, healthy rabbit proximal tubular cells, to a significantly greater extent than plasma from controls that received lung-protective ventilation (Imai et al., 2003). Kuiper et al. demonstrated that lung-injurious ventilation led to a significant increase in renal endothelin-1 production, presumably leading to increased renal vasoconstriction (Kuiper et al., 2008). Choi et al. showed that PPV with injurious high tidal volumes (20 mL/kg) induced nitric oxide synthase (NOS) expression in both the lung and the kidney. At the same time, an increase in systemic microvascular leak was also seen in both organs (Choi et al., 2003).

Kidney to lung

The pathophysiologic mechanism underlying new-onset lung dysfunction in the setting of AKI has been explored in several studies and is summarized below and in Table 249.3.

Leucocytes and inflammation

Deng et al. demonstrated that inflammatory cells infiltrate into the lung rapidly after renal ischaemia, as measured by counting leucocytes and myeloperoxidase (MPO) activity (Deng et al., 2004). They also found that alpha melanocyte stimulating hormone (α-MSH) given just before reperfusion inhibits acute renal and pulmonary injury after renal ischaemia through inhibiting leucocyte infiltration and preventing activation of transcription factors and stress genes. Ishii et al. showed neutrophil infiltration and increased neutrophil elastase (NE) activity in ALI induced by bilateral nephrectomy (Ishii et al., 2010). They also revealed that treatment

Table 249.3 Experimental studies that examine lung injury after kidney injury in animals

Model	Histology	Vascular permeability	Inflammation	Lung genes/RNA/protein	Study
Bilateral nephrectomy					
Rats				↓ aquaporin 5 mRNA (48 h)	(Rabb et al., 2003)
Rats	Abnormal (48 h)	↑ EBD (48 h)	↑ neutrophil infiltration ↑ BALF cells	↑ CINC2, ↑ CXCR2 mRNA (48 h) ↑ DNAJ-B1, ↑ HSP70, ↑ HSP70-4, ↑ HSP70-5, ↓ HSP47 protein (48 h)	(Kim et al., 2006)
Rats	Abnormal (48 h)	↑ BALFP (48 h); ↑ BALF albumin (48 h)	↑ BALF cells (48 h)	↑ plasminogen in BALf (48 h) ↑ serine protease activity in BALf (48 h)	(Heidland et al., 1984)
Mice		Wet/dry unchanged (10 h) PaO_2 unchanged (10 h)			(Zarbock et al., 2006)
Sheep		Wet/dry unchanged (3 d) Lymph protein flow unchanged (3 d) ↑ lymph protein flow with stress (3 d)			(Peterson et al., 1986)
Mice	Unchanged (6, 36 h)	BALFP unchanged (6, 36 h)		Gene expression unchanged (6 h) ↑ 226 genes; ↓ 293 genes (36 h)	(Hassoun et al., 2007)
Mice	Abnormal (24 h)	↑BALFP (24 h)	↑ MPO activity (24 h)	↑ MIP-2 (4 h)	(Hoke et al., 2007)
Mice	Abnormal (4 h)	↑EBD (4 h)	↑ MPO activity (2, 4, 24 h)	↑ KC (2, 4) ↑ MIP-2 (2, 4, 24) No change VCAM-1; ICAM-1 (2, 4, 24)	(Klein et al., 2008)
Mice		↑ BALFP (24 h)	↑Neutrophil infiltration (6 h) ↑NE activity (6 h)	↑ IL-6, KC, TNF-α (6, 24 h)	(Ishii et al., 2010)
Ischaemic AKI					
Rats: 30-min ischaemia	Abnormal (24 h)	↑ EBD (24, 48 h)			(Kramer et al., 1999)
Rats: 30-min ischaemia				↓ eNac, ↓ aquaporin 5 mRNA (48 h) ↓ Aquaporin -5, ↓ NaKATPase protein (48 h)	(Rabb et al., 2003)
Rats: 60-min ischaemia	Abnormal (48 h)	↑ EBD (48 h)	↑ neutrophil infiltration		(Kim et al., 2006)
Mice: 22.5-min ischaemia	Abnormal (6 h)				(Nath et al., 2005)
Mice: 40-min ischaemia	Abnormal (4, 8 h)	↑ wet/dry (4, 8 h)	↑ neutrophil infiltration (4, 8 h) ↑ MPO activity (4, 8 h)	↑ TNF-α; ↑ ICAM-1 mRNA (4, 8 h) ↑ NF-κB (4, 8 h)	(Deng et al., 2004)

(*Continued*)

Table 249.3 Continued

Model	Histology	Vascular permeability	Inflammation	Lung genes/RNA/protein	Study
Mice: 32-min ischaemia		Wet/dry unchanged (22 h) PaO2 unchanged (22 h)			(Zarbock et al., 2006)
Mice: 60-min ischaemia	Abnormal (6, 36 h)	BALf protein unchanged (6 h) ↑ BALf protein (36 h)		↑ 266 genes; ↓615 genes (6 h) ↑ 600 genes; ↓327 genes (36 h)	(Hassoun et al., 2007)
Mice: 22-min ischaemia	Abnormal (24 h)				(Hoke et al., 2007)
Mice: 30-min or 60-min ischaemia	30 min: abnormal (6 h); Resolved (36 h) 60 min: abnormal (6, 36 h)			109 inflammatory genes analysed 31 genes affected (6 h) 28 genes affected (36 h) 55 genes affected (6 h) 54 genes affected (36 h)	(Grigoryev et al., 2008)
Mice: 22-min ischaemia	Abnormal (4 h)	↑ EBD (4 h)	↑ MPO activity (2, 4, 24 h)	↑ KC (2, 4 h) ↑ MIP-2 (2, 4, 24 h) VCAM-1; ICAM-1 unchanged (2, 4, 24 h)	(Klein et al., 2008)
Mice: 32-min ischaemia	Abnormal (24 h)		↑neutrophil infiltration		(Awad et al., 2009)
Mice: 30-min ischaemia		↑ EBD in LTV (7 mL/kg) vs. SB ↑ EBD in HTV (30mL/kg) vs LTV (sham >> AKI) ↑ BALf protein in LTV << HTV	↑ BALf neutrophil in LTV << HTV in sham ↑ BALf neutrophil in LTV but not in HTV in AKI		(Dodd et al., 2009)
HO-1−/− mice: 15-min ischaemia				↑HO-1 mRNA in HO-1+/+ mice ↑ IL-6 mRNA (HO-1−/− >> HO-1 +/+)	(Tracz et al., 2007)
Mice: 60-min ischaemia	Abnormal: apoptosis (24 h)			activated a total of 66 unique apoptosis-related lung genes	(Hassoun et al., 2009)
Rat: rhabdomyolysis	Abnormal	↑ BALf protein	↑ BALf cell count (4, 6 h)	↓ GSH and the GSH:GSSG Ratio ↓ activity of GSH-Px	(Rodrigo et al., 2006)

Note: abnormal lung histology is characterized by neutrophil infiltration and increased septal oedema.

AKI = acute kidney injury; BAL = bronchoalveolar; BALf = bronchoalveolar lavage fluid; CINC = cytokine-induced neutrophil chemoattractant 2 (CINC2); CXCR2 = CXC chemokine receptor 2; d = days; DNAJ-B1 = HSP40; EBD = Evans blue dye; eNaC = epithelial sodium channels; GSH = reduced glutathione; GSH-Px = GSH peroxidase; GSSG = GSH disulfide; h = hours; HO-1 = haem oxygenase-1; HSP = heat shock protein; HTV = high tidal volume; ICAM-1 = intercellular adhesion molecule-1; IL-6 = interleukin-6; KC = keratinocyte-derived chemokine (KC/CXCL1); LTV = low tidal volume; MIP-2 = macrophage-inflammatory protein-2 (MIP-2/CXCL2); MPO = myeloperoxidase; mRNA = messenger ribonucleic acid; NaKATPase = sodium-potassium ATPase channel; NE = neutrophil elastase; NF-κB = nuclear factor; TNF-α = tumour necrosis factor- α; VCAM-1 = vascular cell adhesion molecule-1.

From Faubel (2008) with modification.

with a specific NE inhibitor, ONO-5046, attenuated systemic and pulmonary NE activity and decreased neutrophil infiltration and inflammatory cytokine expression in the lung. On the other hand, uraemic neutrophils may have a role as primarily protective mediators under inflammatory circumstances. In a neutrophil-dependent murine model of aspiration pneumonitis, pre-existing acute uraemia impaired pulmonary neutrophil recruitment regardless of underlying renal inflammation (Zarbock et al., 2006).

Dodd et al. found that animals with AKI and low tidal volume ventilation had increased pulmonary capillary leak (Evans blue dye) compared to controls without AKI. This increased leak was associated with decreased oxygenation but not with an increase in bronchoalveolar lavage (BAL) fluid total protein or BAL neutrophils. In those mice exposed to high tidal volume (30 mL/kg) ventilatory strategy, AKI did not worsen the ALI as measured by Evans blue dye, oxygenation, and BAL (protein and neutrophils). However, animals with AKI had fewer neutrophils in the BAL fluid compared to controls, which suggests that AKI may lead to reduced airspace inflammation (Dodd et al., 2009).

Cytokines and chemokines

Klein at al. showed that IL-6 contributed to lung injury following AKI (Klein et al., 2008). They used anti-IL-6 antibody to test the hypothesis that lung injury after AKI is IL-6 dependent and they

demonstrated that administration of anti-IL-6 antibody was associated with reduced lung keratinocyte-derived chemokine (KC) and improved lung injury after AKI. Acute absence of kidney function results in pulmonary injury independent of renal ischaemia and demonstrates the critical role of the kidney in the maintenance of serum cytokine balance and pulmonary homeostasis (Hoke et al., 2007).

Effect of oxidative stress

Induction of oxidative stress also plays a major role in ALI in AKI. In a rat model, rhabdomyolysis induced by glycerol may cause biochemical, functional, and ultrastructural lung damage associated with and likely mediated by increased oxidative stress, as occurs in other organs, thereby providing some insights for the pathogenic mechanism of ALI in patients with AKI (Rodrigo et al., 2006).

Mice lacking haem-oxygenase 1 (HO-1), critical for reducing oxidative stress and generation of antioxidant metabolites, had a marked induction of IL-6 mRNA and its downstream signalling effector, phosphorylated signal transducer and activator of transcription 3 (pSTAT3), in the kidney and lung (Tracz et al., 2007). In addition, unilateral kidney ischaemic reperfusion injury in both mice and rabbits has been shown to decrease distant organ hepatic levels of superoxide dismutase, catalase, and glutathione, suggesting that ischaemic AKI might compromise the host response to systemic oxidative stress (Serteser et al., 2002; Yildirim et al., 2003)

Lung apoptosis

In a mouse model of ischaemic AKI-induced distant lung dysfunction, Hassoun et al. found that AKI induced a marked upregulation of apoptosis genes and they demonstrated AKI induced pulmonary endothelial apoptosis by caspase-3 upregulation and terminal deoxynucleotidyl transferase-mediated dUTP nick end-labelling (TUNEL) staining (Hassoun et al., 2009). Rabb et al. reported that ischaemic AKI leads to downregulation of pulmonary epithelial sodium channel (ENaC), Na,K-ATPase, and aquaporin-5 (Rabb et al., 2003). Since bilateral nephrectomy but not single-kidney I/R injury also leads to lung changes, they suggested that these changes are likely mediated by systemic effects of AKI rather than reperfusion products. Along with this investigation, many researchers have shown that pulmonary expression of these proteins play important roles in the salt and water/fluid handling and permeability of alveolar epithelium (Hummler et al., 1996, 1997; Ma et al., 2000).

Genomics

In functional genomic analysis, AKI may trigger gene expression changes which may alter lung vascular stability. In an experimental murine kidney ischaemia model, Grigoryev et al. identified pro-inflammatory and pro-apoptotic gene upregulation in the lung transcriptome (Grigoryev et al., 2008). Pro-inflammatory genes such as *Cd14*, lipocalin-2, chemokine ligand-2 (*CXCL2*), and *IL-6* are all upregulated after ischaemia. This group also showed that reduction of the IL-6 effect using chemical inhibition of IL-6 or use of IL-6-deficient mice reduced lung inflammation after ischaemic AKI (Grigoryev et al., 2004). Caspase-3, a marker of cellular apoptotic activity, is upregulated in type II pneumocytes after experimental AKI (Subramanian et al., 2005).

In summary, experimental evidences suggest that the kidney and lung communicate with each other and various pathways are involved. Mechanical ventilation has significant effects on secondary renal dysfunction and inflammation plays a major role in both AKI and lung injury. As our understanding of these mechanisms evolves, specific targets will be identified and offer opportunities for prevention and treatment of AKI and lung injury (Table 249.4).

Application to clinical care

The clinical management of patients with AKI and lung injury includes several different domains. Given our current knowledge base we propose considering several distinct yet related issues including risk assessment and primary prevention, early recognition and targeted interventions to attenuate the effects of injury, and management of the consequences of organ dysfunction. We offer a framework for the clinician in each of these areas to help optimize the management of these patients.

Risk assessment and primary prevention

Identifying patients who are at risk for AKI in lung injury or lung injury in AKI permits the application of primary preventive strategies. Several factors have been identified as independent risk factors for AKI (Table 249.5). Since mechanical ventilation is well

Table 249.4 Experimentally proposed treatment strategies

Agent	Effect	Study
ALI following AKI		
Specific NE inhibitor, ONO-6046	Reduced NE activity and improved pulmonary inflammatory responses	(Ishii et al., 2010)
Adenosine 2A-agonist (ATL)	reduced kidney interstitial neutrophils (56% reduction from IRI; $P < 0.05$)	(Awad et al., 2009)
Anti-IL-6 antibody	Reduced lung KC, improved lung injury after AKI and finally reduced mortality	(Tracz et al., 2007; Klein et al., 2008)
Caspase inhibitor, Z-VAD-FMK	Reduced lung microvascular changes after kidney IRI	(Hassoun et al., 2009)
AKI in mechanical ventilation		
NOS inhibitor, N-nitro-L-arginine methyl ester	Attenuated the microvascular leak of lung and kidney and the proteinuria with large TV ventilation	(Choi et al., 2003)
Peroxynitrite decomposition catalyst, PJ-34 and WW85	Attenuated renal endothelial dysfunction and maintained renal blood flow in high tidal volume mechanical ventilation	(Vaschetto et al., 2010)

NE = neutrophil elastase; NOS = nitric oxide synthase; TV = tidal volume.

Table 249.5 Risk factors for AKI in lung injury patients

Population	Risk factors for AKI	Study
Patients with septic shock	Large BMI, abdominal or urinary tract infection, old age, high APACHE III variant allele of rs8094315 in the Bcl2 gene (decreased AKI)	(Frank et al., 2010)
Patients in ICU	Sepsis	(Fonseca Ruiz et al., 2011)
Patients in ICU	Elevations in PAI-1, interleukin-6, and the sTNFRs	(Liu et al., 2007)
Patients with septic shock	Delay to initiation of adequate antibiotics, intra-abdominal sepsis, blood product transfusion, use of ACEI/ATRA, and BMI ACS	(Plataki et al., 2011)

ACEI/ATRA = angiotensin converting enzyme inhibitor/angiotensin II receptor antagonist; AKI = acute kidney injury; APACHE = Acute Physiology And Chronic Health Evaluation; BMI = body mass index; PAI-1 = plasminogen activator inhibitor-1; sTNFRs = soluble tumour necrosis factor receptors;

recognized as a contributor to AKI, preventive strategies have been proposed; however, these have not been tested directly in high-risk patients. As mentioned earlier, lung injurious high tidal volume mechanical ventilation leads to a renal injury (Imai et al., 2003; Kuiper et al., 2008). In a short-term study, maintaining spontaneous breathing during ventilator support in patients with ALI resulted in a decreased level of airway pressure, increased cardiac index, and improved renal function, assessed by an increase of the effective RBF and glomerular filtration rate (Hering et al., 2002). Thus, in patients with ALI/ARDS, ventilation using lung protective ventilatory strategies avoided high VT and airway plateau pressure > 30 cm H_2O. Several strategies used for prevention of AKI in mechanical ventilation are listed in Table 249.6.

Table 249.6 Prevention methods of AKI in mechanical ventilation

Population	Treatment	Effect	Study
Mechanical ventilation without ALI			
Cardiac surgery	Pentoxifylline	Yes	(Barkhordari et al., 2011)
Mechanical ventilation	Low tidal volume (6 mL/kg vs 10 mL/kg)	No	(Cortjens et al., 2012)
ALI			
ALI and mechanical ventilation	Fluid restriction	No	(Wiedemann et al., 2006)
ALI and mechanical ventilation	Airway pressure release ventilation with spontaneous breathing	Yes	(Hering et al., 2002)
ALI and ARDS	Low tidal volume (6 mL/kg vs 12 mL/kg)	Yes	(The Acute Respiratory Distress Syndrome Network, 2000)
ARDS	Lung protective ventilation (Pplat < pressure at the UIP, peep 2–3 cmH_2O higher than the pressure at Pflex)	Yes	(Ranieri et al., 2000)

ALI = acute lung injury; ARDS = acute respiratory distress syndrome.

Primary prevention of ALI in AKI has been somewhat limited as there are no established risk factors in these patients. Interdisciplinary intervention effectively decreased large tidal volumes and unnecessary transfusion in mechanically ventilated patients and was associated with a decreased frequency of new ALI (Yilmaz et al., 2007). Strategies to limit fluid accumulation particularly from aggressive fluid resuscitation need to be tested further (Schrier, 2010).

Recognition of AKI in lung injury and interventions to attenuate injury

The diagnosis of AKI is now well established with the utilization of the AKIN serum creatinine and urine output criteria (Mehta et al., 2007) and are applicable to patients with lung injury. However, Macedo et al. reported that in critically ill patients, the dilution of serum creatinine by fluid accumulation may lead to underestimation of the severity of AKI, thus, efforts to correct creatinine for fluid balance can improve diagnosis and staging of AKI (Wiedemann et al., 2006; Macedo et al., 2010; Liu et al., 2011). In ICU patients, urine output is a sensitive and early marker for AKI and is associated with adverse outcomes (Macedo et al., 2011; Prowle et al., 2011). However, other reports have revealed that the occurrence of short periods (1–6 hours) of oliguria lacked utility in discriminating patients with incipient AKI (Prowle et al., 2011). The emergence of specific kidney injury biomarkers offers an additional tool to evaluate renal dysfunction; however, these have not been specifically evaluated in patients with ALI alone. Various parameters have been established to diagnose ALI in AKI but there is limited data demonstrating their application in patients with AKI. A key issue in the interpretation of biomarker data is the effect of individual organ dysfunction on the levels and thresholds, for example, neutrophil gelatinase-associated lipocalin levels are higher in patients with cardiac failure (Damman et al., 2008). A few studies have identified common biomarkers that are altered in both kidney and lung function. Tables 249.7 and 249.8 explore various serum and urinary biomarkers that can be clinically used for diagnosis and prognosis of AKI and ALI. Once AKI is recognized, specific interventions to limit the injury have focused on limiting deleterious ventilator strategies but these may not be always be possible depending on the severity of underlying lung injury (Table 249.9). The utilization of diuretics to improve AKI in ALI has not met with much success. Although urine output may increase particularly when the diuretics are given along with

Table 249.7 Biomarkers currently used to diagnose AKI and ALI

Biomarker	Kidney	Lung
Serum		
Cystatin C	+++ (Dharnidharka et al., 2002)	
NGAL	+++ (Dent et al., 2007; de Geus et al., 2011)	
PAI-1	+ (Liu et al., 2007)	+ (Ware et al., 2007)
Protein C		+ (Ware et al., 2007)
IL-6	+ (Liu et al., 2007)	+ (Cepkova et al., 2006)
IL-8		+ (Cepkova et al., 2006)
ICAM-1		+ (Cepkova et al., 2006)
vWF		+ (Cepkova et al., 2006, van der Heijden et al., 2008)
sTNFRs	+ (Liu et al., 2007)	
Angiopoietin-2		+ (van der Heijden et al., 2008)
BNP	++ (de Cal et al., 2011)	+ (Reel et al., 2009)
Urine		
Creatinine	+ (Vaidya et al., 2008)	
Cystatin C	+++ (Koyner et al., 2008)	
NAG	+ (Han et al., 2009)	
NGAL	+++ (Bennett et al., 2008, Nickolas et al., 2008)	
IL-6	+ (Dennen et al., 2010)	
IL-18	+ (Parikh et al., 2005)	
KIM-1	+ (Liangos et al., 2009)	
HGF	++ (Vaidya et al., 2008)	
VEGF	+ (Vaidya et al., 2008)	
πGST and αGST	+++ (Westhuyzen et al., 2003)	
L-FABP	++ (Portilla et al., 2008)	

BNP = brain natriuretic peptide; GST = glutathione S-transferase; HGF = hepatocyte growth factor; ICAM-1 = intercellular adhesion molecule-1; IL = interleukin; KIM-1 = kidney injury molecule-1; L-FABP = liver-type fatty acid binding protein; NAG = N-acetyl-ß-d-glucosaminidase; NGAL = neutrophil gelatinase-associated lipocalin; PAI-1 = plasminogen activator inhibitor-1; sTNFRs = soluble tumour necrosis factor receptors; VEGF = vascular endothelial growth factor; vWF = von Willebrand factor.

Table 249.8 Biomarkers for prediction of prognosis for recovery of kidney and lung function

Biomarker	Kidney	Lung	Comments
Serum			
Cystatin C	++ (Perianayagam et al., 2009)		
NGAL	++ (Haase et al., 2009, Kumpers et al., 2010b)		
PAI-1		+ (Prabhakaran et al., 2003)	
Protein C		+ (Matthay and Ware, 2004)	
IL-6		+ (Parsons et al., 2005)	
ICAM-1		+ (Calfee et al., 2009)	
vWF		+ (Ware et al., 2004)	
sTNFRs		+ (Parsons et al., 2005)	
Angiopoietin-2	+ (Kumpers et al., 2010a)	+ (Ong et al., 2010)	
Osteopontin	++ (Lorenzen et al., 2011)		
BNP		+ (Reel et al., 2009; Lin et al., 2010)	
Urine			
Cystatin C	+++ (Herget-Rosenthal et al., 2004)		
NAG	+ (Liangos et al., 2007)		
NGAL	++ (Haase et al., 2009)		
IL-6			
IL-18	+ (Parikh et al., 2005)		
KIM-1	+ (Liangos et al., 2007)		
L-FABP	+++ (Ferguson et al., 2010)		

HGF = hepatocyte growth factor; ICAM-1 = intercellular adhesion molecule-1; IL = interleukin; KIM-1 = kidney injury molecule-1; L-FABP = liver-type fatty acid binding protein; NAG = N-acetyl-ß-d-glucosaminidase; NGAL = neutrophil gelatinase-associated lipocalin; PAI-1 = plasminogen activator inhibitor-1; sTNFRs = soluble tumour necrosis factor receptors; VEGF = vascular endothelial growth factor; vWF = von Willebrand factor.

colloid solutions (Martin et al., 2002), these data have not been confirmed in larger studies.

It is currently unclear whether specific measures to treat ALI have any benefit in improving AKI (Table 249.10). Sedation with benzodiazepines and analgesia with opioids are useful in patients with ALI because they improve tolerance of mechanical ventilation and decrease oxygen consumption (Cernaianu et al., 1996; Elsasser et al., 1999). However, because they are seldom removed by continuous renal replacement therapy (CRRT) (Jamal et al., 1998; Swart et al., 2005), they have to be used very carefully. Occasionally, haloperidol or propofol may be useful alternatives in prolonged use but since these agents may cause rhabdomyolysis and AKI (Marsh and Dolson, 1995; Casserly et al., 2004), physicians should pay attention in their use. Recently, Hsing et al. reported that propofol treatment could protect kidney by increasing BMP-7 expression, decreasing inflammatory cytokines, and inhibiting oxidative stress in sepsis-induced AKI model (Hsing et al., 2011).

Management of consequences of AKI and ALI

Extracorporeal lung support and the kidney

Extracorporeal membrane oxygenation (ECMO) has been increasingly used to support patients with cardiac or respiratory failure who do not respond to conventional intensive care. Chen

Table 249.9 Treatment of AKI (secondary prevention)

Population	Treatment	Effect	Study
ARDS	Limited ventilation PIP ≤ 30 cmH_2O, TV ≤ 8 mL/kg	No	(Stewart et al., 1998)
ARDS	Protective ventilation TV < 6 mL/kg, RR < 30/min	No	(Amato et al., 1998)
ICU patient with AKI	Intensive RRT (CRRT: 35 mL/kg/h vs 20 mL/kg/h or HD: 6/wk vs 3/wk)	No	(Palevsky et al., 2008)
ALI	25 g of albumin every 8 h with furosemide	Improved fluid balance	(Martin et al., 2002)

AKI, acute kidney injury; ALI, acute lung injury; ARDS, acute respiratory distress syndrome; CRRT, continuous renal replacement therapy; HD, haemodialysis; ICU, intensive care unit; PIP, peak inspiratory pressure; RR, respiratory rate; RRT, renal replacement therapy; TV, tidal volume.

et al. identified a hospital mortality rate of 57.8% in the critically ill patients on ECMO. They demonstrated the excellent discriminative power of AKIN creatinine criteria at 48 hours in predicting hospital mortality of critically ill patients already on ECMO support so they recommended physicians use 48-hour AKIN to assess short-term prognosis in this patient group (Chen et al., 2011). Paden et al. evaluated the outcomes of 154 ECMO/CRRT paediatric patients and they found that among 68 (44%) ECMO/CRRT survivors, renal recovery occurred in 65 (96%) before discharge (Paden et al., 2011). However, the mortality was higher in patients receiving concomitant CRRT and ECMO compared with those receiving ECMO alone. Askenazi et al. also reported that AKI and RRT independently predict mortality in neonates and children who receive ECMO (Askenazi et al., 2011). Hoover et al. reported that the use of continuous veno-venous haemofiltration (CVVH) in ECMO was associated with improved fluid balance, increased caloric intake, and less diuretics administration compared with case-matched ECMO controls (Hoover et al., 2008). Shaheen et al., however, showed that patients who required ECMO and CVVH suffered from 1.5-fold increased mortality with respect to the group of patients who required CVVH alone (Shaheen et al., 2007).

Dialysis support and its effects on ALI

Recently, Kielstein et al. reported that AKI requiring dialysis therapy for > 1 month (extended dialysis, ED) in patients undergoing iLA (interventional lung assist treatment) increases mortality in ICU patients. While patients without ED showed a 28-day survival of 40%, the survival of patients with ED was only 19%. Furthermore, patients undergoing ED had a 5% 1-year survival but patients without the need for RRT had a 25% 1-year survival (Kielstein et al., 2011).

Summary and recommendations

AKI is encountered commonly in patients with lung injury and lung dysfunction can complicate the course of AKI. It is evident from experimental models and clinical studies that the kidney and lung influence each other and multiple pathways are involved in

Table 249.10 Treatment strategies for ALI and consideration in AKI patients

Strategy	Treatment	Study	In AKI
Supportive care			
Sedation	Benzodiazepine + opioids	Cernaianu et al., 1996; Elsasser et al., 1999	With close drug monitoring (Jamal et al., 1998; Swart et al., 2005)
	Haloperidol	Riker et al., 1994	With caution
	Propofol	Sherman, 1996	With caution, beneficial
Nutritional support	Enteral plus supplemental parenteral nutrition Head elevation	Turner et al., 2011 Cook et al., 2002	Beneficial (Sezer et al., 2008)
Glucose control	Fasting glucose 80–110 mg/dL	Van den Berghe et al., 2006	Beneficial (Mehta, 2007)
Management of hypoxaemia			
Mechanical ventilation	Low tidal volume Plateau pressure </ 30 cm H_2O	Putensen et al., 2009	No benefit (Cortjens et al., 2012)
Fluid management steroids/antibiotics	Conservative (CVP < 4 mmHg, PCWP < 8 mmHg)	Wiedemann et al., 2006	Beneficial (Grams et al., 2011)

these interactions. Early recognition of organ dysfunction is now enhanced with the availability of various functional and injury biomarkers. Management strategies should include risk assessment, ongoing monitoring in high-risk patients for avoidance of aggravating factors, and early institution of supportive interventions to manage consequences. Further research is needed to identify additional targets and specific interventions to improve patient outcomes.

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CHAPTER 250

Acute kidney injury in pregnancy

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Introduction

Pregnancy-related acute kidney injury (PR-AKI) is, besides typical pregnancy-related disorders, due to any kind of acute renal deterioration that may occur in young women and may develop coincidentally for the first time during pregnancy. However, pregnancy-related complications characteristic of each trimester can result in AKI (Krane, 1988; Fakhouri et al., 2012).

In early pregnancy (12–18 weeks), PR-AKI is frequently a consequence of volume depletion due to hyperemesis gravidarum (Fig. 250.1). An additional less frequent cause is septic abortion which may induce septic shock and renal cortical necrosis (Prakash, 2012). Pregnancy-related susceptibility to vascular effects of Gram-negative endotoxin (Schwartzmann phenomenon) could be a precipitating factor (Zavan et al., 2012). The majority of PR-AKI cases occur between late pregnancy (after week 35) and puerperium due to pre-eclampsia and bleeding complications associated with placental abruption or other causes of obstetric haemorrhage (Fig. 250.1). Thrombotic microangiopathies (TMAa), which feature haemolytic uraemic syndrome (HUS) and thrombotic thrombocytopenic purpura (TTP), are important clinical entities which share some clinical and laboratory features with the HELLP (Haemolysis, Elevated Liver enzymes, Low Platelet count) variant of pre-eclampsia (Fakhouri et al., 2012).

PR-AKI is a significant cause of feto-maternal morbidity and mortality, in particular in developing countries (Prakash et al., 2010). The incidence of PR-AKI varies greatly between high- and low-income countries. The current incidence of PR-AKI in high-income countries, for example, Italy, is estimated to be around 1 in 20,000 pregnancies (Stratta et al., 1996) and is steadily decreasing. In contrast, for example, in India, PR-AKI occurs in roughly 1 in 50 pregnancies and accounts for up to 20% of all AKI cases (Prakash et al., 2010). Septic abortions, overall poor follow-up of pregnancy with limited screening of hypertensive complications during pregnancy, and late referral of patients are specific factors which may explain this huge discrepancy in the incidence of PR-AKI. Fortunately, the incidence of PR-AKI is also decreasing in low-income countries, as exemplified in the more recent studies from India (Prakash et al., 1995, 2006, 2010).

Diagnostic modalities

Markers of renal function

During pregnancy, rising glomerular filtration rate (GFR) and renal plasma flow contribute to increased creatinine clearance with re-establishment of a steady state in serum creatinine concentration with lower values ranging from 45 to 55 μmol/L (Table 250.1). Thus, diagnosis of PR-AKI may be delayed due to false interpretation of serum creatinine concentrations re-established at lower levels caused by increased GFR and haemodilution. Novel biomarkers such as neutrophil gelatinase-associated lipocalin (NGAL), kidney injury molecule 1 (KIM-1), and calprotectin may have potential, however, these have not yet been thoroughly investigated in pregnancy.

Urinalysis: haematuria, proteinuria, leucocyturia, and bacteriuria

Haematuria, proteinuria, leucocyturia, and asymptomatic bacteriuria may be detected, and are either related to pregnancy or coincidental. Persistent microhaematuria may reveal glomerular disease or manifest with polycystic kidneys or with renal calculi. The most common cause of macrohaematuria in pregnancy is haemorrhagic bacterial cystitis. A massive postpartum haematuria may occur due to decompression of the obstructed right collecting system and may cease spontaneously. The development of new and significant proteinuria during pregnancy is almost always associated with the development of pre-eclampsia and should therefore lead to initiation of thorough investigations, including the measurement of blood pressure, liver function tests, and determination of serum uric acid levels. In the absence of urinary tract infection or pre-eclampsia, isolated proteinuria usually reflects new-onset glomerular disease. When dipstick proteinuria (> 100 mg/dL) is persistently detected, the urine protein:creatinine ratio should be measured in a random urine sample.

Kidney biopsy

Percutaneous renal biopsy is usually avoided during pregnancy because of the fear of bleeding complications. Renal biopsy is not usually required for the diagnosis of pre-eclampsia, however it is indicated when a renal disease that may be successfully treated during pregnancy is suspected. Diseases in this category include lupus nephritis, minimal change nephropathy, immune-mediated interstitial nephritis, and crescentic glomerulonephritis due to various causes. The biopsy procedure may be performed with ultrasound location in the usual prone position or with the woman lying on her right side.

Thrombotic microangiopathy: haemolytic uraemic syndrome and thrombotic thrombocytopenic purpura

Thrombotic microangiopathy due to HUS or TTP is rare, yet an important cause of PR-AKI with considerable morbidity. HUS/

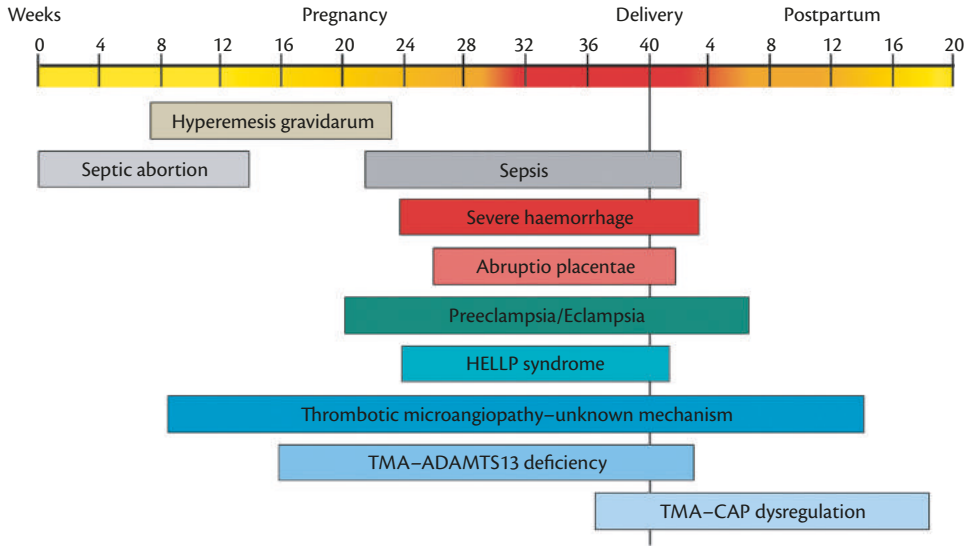

Fig. 250.1 Main causes of pregnancy-related acute kidney injury according to pregnancy and postpartum weeks. ADAMTS13 = a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; CAP = complement alternative pathway; HELLP = haemolysis, elevated liver enzymes, low platelet count; TMA = thrombotic microangiopathy;
Adapted from Fakhouri et al. (2012).

TTP disorders share some clinical and laboratory features with the HELLP variant of pre-eclampsia. Timing of onset and the pattern of laboratory abnormalities may be helpful in differentiation of HUS, TTP, and HELLP (Fig. 250.1 and Table 250.1). HELLP syndrome typically develops in the third trimester, and rarely in the postpartum period within a few days of delivery. Pre-eclampsia-HELLP is much more common than HUS/TTP and is usually preceded by hypertension and proteinuria. Unlike in HUS/TTP, renal failure in pre-eclampsia-HELLP patients is rare even in severe cases, unless significant bleeding or haemodynamic instability or marked disseminated intravascular coagulation (DIC) occurs. In contrast, HUS/TTP may begin antepartum or more frequently postpartum, and may often lead to persistent renal impairment with many patients requiring long-term renal replacement therapy. Based on improved pathogenetic understanding, TMAs, usually diagnosed as HUS/TTP, can be reclassified according to their pathophysiological mechanisms. Reduced activity of ADAMTS13 either due to inhibitory antibodies or because of inherited deficiency has been linked to some forms of TTP. On the other hand, dysregulation of the complement alternative pathway (CAP) secondary to diverse mutations of complement system components (Le Quintrec et al., 2010), acquired inhibitory autoantibodies (Dragon-Durey et al., 2010), or other causes have been found in many cases of atypical HUS, secondary HUS (Le Quintrec et al., 2008), and typical verotoxin-induced HUS (Lapeyraque et al., 2011; Morigi et al., 2011). Pregnancy-associated TMA (PR-TMA) is considered a secondary TMA (Fakhouri et al., 2012). Aetiologically, ADAMTS13 deficiency, complement dysregulation, and unknown mechanisms can be operative. While PR-TMA due to ADAMTS13 deficiency occurs mainly in the second and third trimesters, CAP dysregulation-associated PR-TMA is an event predominantly of the postpartum period (Fakhouri et al., 2012) (Fig. 250.1).

Pre-eclampsia

Pre-eclampsia is the most frequently encountered renal complication in pregnancy and occurs in approximately 5% of all pregnancies. It is characterized by the new onset of hypertension

Table 250.1 Time courses of renal function markers during pregnancy

	Controls (N = 58)	6–13 weeks (N = 94)	22–27 weeks (N = 107)	34–36 weeks (N = 88)	37–42 weeks (N = 109)
Creatinine (μmol/L)	65.2	52.9[a]	50.8[a]	52.7[a]	54.9[a]
	48–82 (100%)	36–70 (−19%)	37–64 (−22%)	39–66 (−20%)	37–73 (−16%)
Urate (μmol/L)	236	173[a]	204[a]	241	295[a]
	121–351 (100%)	207–239 (−27%)	127–281 (−13%)	146–336 (+2%)	162–428 (+25%)
Cystatin C (mg/L)	0.84	0.82	0.84	1.08[a]	1.16[a]
	0.66–1.02 (100%)	0.66–1.00 (−2%)	0.64–1.04 (±0%)	0.79–1.37 (+29%)	0.79–1.53 (+39%)

Mean plasma concentrations, reference interval (± 1.96 SD), and percentage relation (%) to the control (= non-pregnant) group for each trimester.

[a]Significant difference to controls

Adapted from Greenhill and Gruskin (1976).

and proteinuria usually after 20 weeks of pregnancy and is commonly associated with oedema and hyperuricaemia. A blood pressure > 140/90 mmHg in the second half of the pregnancy is required for the diagnosis. Nevertheless, women with blood pressure < 140/90 mmHg who have experienced an increase of 30 or 15 mmHg in systolic or diastolic levels, respectively, should be managed as high-risk patients. A urinary protein:creatinine ratio > 30 mg/mmol serves for a sufficiently reliable definition of proteinuria and avoids the need for 24-hour urine collection. Although serum uric acid is not included in the formal definition of pre-eclampsia, levels > 5.5 mg/dL (325 μmol/L) may help in diagnosis of pre-eclampsia in patients with pre-existing renal disease or hypertension, keeping in mind other causes of hyperuricaemia. Pre-eclampsia is considered severe with urine protein:creatinine ratio > 50 mg/mmol, a blood pressure of 160/100 mmHg or higher, with evidence of the HELLP syndrome or central nervous system dysfunction, or in presence of intrauterine fetal growth retardation.

Predisposing factors include pre-existing hypertension, chronic renal disease, obesity, diabetes mellitus, thrombophilias (factor V Leiden mutation, antiphospholipid antibodies, and antithrombin III deficiency), and multiple gestation. Hereditary, immune, and high-altitude-associated hypoxia-related factors may explain higher frequency of pre-eclampsia in some women. Pre-eclampsia occurs only in the presence of a placenta, even in the absence of fetus (hydatiform mole) and usually remits when the placenta is delivered. Widespread systemic endothelial dysfunction and microangiopathy in the mother and fetal growth restriction due to abnormal placenta are major features of pre-eclampsia. The leading abnormality of pre-eclamptic placenta shows impaired endovascular invasion of cytotrophoblasts and a decreased adaptive remodelling of the uterine spiral arterioles. Placentas from advanced pre-eclamptic pregnancies often show numerous placental infarcts and obliterative arteriolopathy. Uteroplacental blood flow is usually diminished and uterine vascular resistance increased in pre-eclamptic women.

A unique and specific renal lesion of pre-eclampsia is glomerular endotheliosis (for exemplary histology, see Ludmir and Smith, 1998). As detected by light microscopy, glomeruli are enlarged, glomerular capillaries are narrowed and appear bloodless and unlike other TMAs there are no prominent capillary thrombi. There are no immune deposits in the glomeruli and serum complement levels are normal. Immunofluorescence may, however, reveal deposition of fibrinogen derivatives. Electron microscopy shows loss of endothelial fenestrae and swollen endothelial cells which are separated from the basement membrane. Podocyte foot processes are relatively preserved.

Current pathophysiologic concepts emphasize the importance of circulating antiangiogenic factors which antagonize vascular endothelial growth factor (VEGF) and placental growth factor pivotal to physiological placental vascular adaptation, induction of vasodilatory factors, and surveillance of fenestrated endothelia. Production of soluble fms-like tyrosine kinase 1 protein, a splice variant of the VEGF receptor-1 lacking the transmembrane cytoplasmic domain of the membrane bound receptor, is increased in the pre-eclamptic placenta.

Infusions of magnesium sulphate ($MgSO_4$) are effective in preventing eclamptic seizures and lowering blood pressure. $MgSO_4$ should not be continued in the absence of deep tendon reflexes and caution is warranted at higher concentrations which may depress the respiratory centre. Platelet transfusions are indicated if there is significant maternal bleeding or if platelet counts are < 20×10^9/L.

Systemic lupus erythematosus and antiphospholipid syndrome

Antiphospholipid antibodies occurring in patients with systemic lupus erythematosus (SLE) pose a substantial risk for tissue ischaemia secondary to microthromboembolic events resembling HUS/TTP and HELLP (Lockshin and Erkan, 2003). Although the clinical presentation can include hypertension and renal involvement with proteinuria—identical to patients with pre-eclampsia—therapeutic management of an SLE flare differs considerably: lupus nephritis is treated with prednisone. Patients with antiphospholipid antibodies should receive prednisone in combination with an antiplatelet agent (low-dose acetylsalicylic acid). The most severe form, the catastrophic antiphospholipid antibody syndrome, occurs in < 1% of patients with SLE-related antiphospholipid antibodies. It is characterized by thrombotic microangiopathy affecting three or more organs, most commonly the kidneys, the cardiorespiratory system, and the central nervous system. Treatment options include full anticoagulation with heparin, glucocorticoids, and plasma exchange.

Sepsis

Most cases of sepsis occur during late pregnancy and in the postpartum period. Although sepsis is infrequent, it is an important pregnancy-related complication since it accounts for the majority of maternal deaths in developing countries (Goplani et al., 2008). Clinical features include inflammation, severe hypotension, DIC, and AKI that also imperil the child. Early recognition of sepsis-related PR-AKI and initiation of treatment are key to prevent complications. Common underlying infections are chorioamnionitis, endomyometritis, septic abortion, and postpartum fever, but also non-obstetric infections such as pneumonia or pyelonephritis can be the initial focus. Young age and few comorbidities are negatively correlated with severe sepsis, septic shock, and death in pregnant women. Gram-negative bacteria are found more frequently than Gram-positive bacteria, and commonly used broad-spectrum antimicrobial agents are usually effective.

Management of acute kidney injury in pregnancy

Dependent on the cause of AKI, either restoration of fluid volume deficits, or later in pregnancy, delivery of the baby and placenta as quickly as possible are the only interventional options. There is no therapy for acute cortical necrosis and most patients require dialysis, however 20–40% experience partial recovery of renal function. Regarding the choice of dialysis modality, haemodialysis is a preferred option, as peritoneal dialysis may impair uteroplacental blood flow. Treatment of pregnancy related-TMAs should be guided by the underlying pathomechanism. The goal in cases with reduced ADAMTS13 activity is to restore enzymatic activity to a sufficient level by removing autoantibodies using plasma exchange (Table 250.2). Fresh frozen plasma infusions alone can be applied when constitutive ADAMTS13 deficiency is present. Corticosteroids are frequently used as an adjunctive treatment in all forms of TTP. If these measures fail, the B-cell-depleting

Table 250.2 Differentiating features of HELLP syndrome and thrombotic microangiopathies

	Cause	Renal failure	Histology	Treatment
HELLP	Unknown	Rare	Glomerular endotheliosis	PE, GC
TMA-ADAMTS13 (e.g. TTP)	Decreased ADAMTS13 activity: ◆ inhibiting autoantibodies ◆ constitutional	Frequent	Fibrin/platelet thrombi in glomerular capillaries	PE, FFP, rituximab
TMA-CAP (e.g. HUS)	Dysregulated complement alternative pathway: ◆ mutations (factor H, factor I, membrane cofactor protein) ◆ inhibiting autoantibodies	Frequent	Fibrin/platelet thrombi in glomerular capillaries	PE, FFP, eculizumab

ADAMTS13 = a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; CAP = complement alternative pathway; FFP = fresh frozen plasma; GC = glucocorticoid; HELLP = haemolysis, elevated liver enzymes, low platelet count; HUS = haemolytic uraemic syndrome; PE = plasma exchange; TMA = thrombotic microangiopathy; TTP = thrombotic thrombocytopenic purpura.

antibody rituximab can be chosen as a second-line therapy, but caution has to be exercised since rituximab might harm the fetus (Chakravarty et al., 2011; Ton et al., 2011). In case of pregnancy related-TMA with complement dysregulation, complement activation should be inhibited. This can be achieved by plasma exchange or infusion of fresh frozen plasma. A novel, alternative, targeted therapeutic approach is to inhibit the cleavage of C5 with the monoclonal humanized antibody eculizumab (Table 250.2). It prevents the formation of C5b, the initiator of the formation of the membrane attack complex (Kaplan, 2002; Woodruff et al., 2011), thus blocking the common terminal activation step of all three complement pathways. Fetal toxicity is usually not an issue because this entity most frequently occurs after delivery (Fakhouri et al., 2012).

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CHAPTER 251

Acute kidney injury in the cancer patient

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Introduction

Over the past two decades, the prognosis of patients with a cancer diagnosis has improved significantly due to more effective and safer therapies, improved risk stratification of patients, and advances in supportive care (Benoit and Hoste, 2010; Denker et al., 2011). Moreover, the landscape of oncology therapeutics has evolved so that patients are now benefitting from increased survival rates, decreased tumour progression, and in some cases from less severe adverse drug effects (Benoit and Hoste, 2010; Denker et al., 2011).

Despite these important advances, a number of complications develop in patients with underlying malignancy (Perazella and Moeckel, 2010). One of the more common and dreaded complications that occur in this population of patients is acute kidney injury (AKI), which is associated with increased risk for adverse short- and long-term outcomes (Perazella and Moeckel, 2010). Cancer-related renal injury is a relatively common cause of AKI in hospitalized patients, in particular in patients admitted to the intensive care unit (ICU) (Benoit and Hoste, 2010). Patients with haematologic malignancies, such as multiple myeloma, leukaemia, and lymphoma, and those status post therapy with bone marrow or haematopoietic stem cell transplantation (BMT/HSCT) are at even higher risk to develop AKI than solid tumours (Givens and Wethern, 2009; Benoit and Hoste, 2010). Approximately 20–40% of patients with newly diagnosed multiple myeloma have evidence of renal impairment, much of which is AKI (Givens and Wethern, 2009). More than 30% of patients with either leukaemia or lymphoma, especially while undergoing chemotherapy, develop various forms of kidney injury and patients who undergo BMT/HSCT have a 50% risk of developing AKI and other renal complications (Givens and Wethern, 2009).

Cancer patients admitted to the ICU are at even higher risk to develop AKI and > 80% of AKI cases in these patients are due to a multifactorial aetiology, such as sepsis, hypotension, and nephrotoxic drug exposure (Maccariello et al., 2011). Depending on the AKI definition utilized and the type of malignancy present, the incidence of AKI in cancer patients ranges from 13% to 60% (Benoit and Hoste, 2010), but these numbers will likely increase in the future with the use of the Acute Kidney Injury Network (AKIN) definition of AKI (stage 1 defined by serum creatinine increase of 0.3 mg/dL). Importantly, AKI develops at a higher rate in ICU patients with haematologic malignancies, than in patients with solid tumours (Benoit and Hoste, 2010). As a frame of reference, cancer-related AKI in the ICU is more common than in general ICU patients, although the incidence was lower than in those with underlying liver disease and, in one study, lower than in critically ill cardiac or pulmonary disease patients (Bagshaw et al., 2005; Benoit and Hoste, 2010). The incidence ranges from 10% (patients with solid tumours) to as high as 60% of AKI cases (especially in patients with multiple myeloma and other haematologic malignancies). Cancer patients in the ICU who develop AKI often require initiation of renal replacement therapy (RRT) to treat uraemia, control the volume status, and correct various metabolic disturbances (Benoit and Hoste, 2010). Often times, RRT-requiring AKI occurs in cancer patients with evidence of multiorgan failure, especially acute respiratory failure and shock, which require mechanical ventilation and vasopressors, respectively (Benoit and Hoste, 2010).

Short-term consequences of AKI in hospitalized cancer patients include prolonged ICU stay and increased in-hospital morbidity and mortality (Perazella and Moeckel, 2010). In-hospital complications such as increased infection rates, bleeding risk, bone marrow suppression, and other end-organ complications occur more frequently and typically result directly from AKI and from the accumulation of certain toxic chemotherapy agents when renal drug clearance declines (Perazella and Moeckel, 2010). The presence of AKI also limits the full employment of aggressive chemotherapeutic regimens, in particular with those agents that either require kidney excretion (avoidance or under-dosing) or have nephrotoxic side effects, resulting in potential tumour under-treatment and risk of cancer progression. Removal of chemotherapeutic agents by RRT (without appropriate drug dosing) may also lead to under-therapy and adverse outcomes. Mortality is increased in these patients, in part due the direct consequences of AKI, the untoward effects of the underlying malignancy, and the complications due to prolonged hospital length of stay.

Critically ill patients with cancer who develop AKI with a 10% increase in their serum creatinine concentration have a twofold increase in mortality (Tumlin et al., 2005). Moreover, hospital mortality is higher in ICU cancer patients with RRT-requiring AKI (78%) versus non-cancer patients requiring RRT (68%) (Maccariello et al., 2011). Hospital and 6-month mortality rates in patients with and without cancer who had AKI-requiring RRT were similar—51.1% versus 42.9% and 65% versus 63.1%, respectively

(Darmon et al., 2007). Cancer patients with severe AKI have a 1-year survival of 15.8% versus 40.1% in non-cancer patients with severe AKI (Bagshaw et al., 2005). Patients with haematologic malignancies complicated by AKI that requires RRT have worse outcomes and higher crude ICU mortality rates (79.5% vs 55.7%) and higher in-hospital mortality rates (83.7% vs 66.1%) as well as lower 6-month survival rates (14% vs 28%) compared to those without haematologic malignancy (Benoit and Hoste, 2010).

While it is tempting to conclude that the presence of cancer in patients with AKI, particularly those requiring RRT, increases the mortality risk, several recent studies support that other factors are more important and drive the mortality when multivariate adjustment is undertaken. In the majority of these studies, the number and severity of associated organ failure (multiorgan failure) is associated with mortality. Higher APACHE (Acute Physiologic and Chronic Health Evaluation) and SOFA (Sequential Organ Failure Assessment) scores as measures of illness severity and end-organ failure are associated with increased mortality in several studies (Liborio et al., 2011). Factors independently associated with increased 6-month mortality are worsening kidney function, age > 60 years, poor performance status, and uncontrolled cancer progression (Soares et al., 2006).

Following AKI, cancer survivors may develop chronic kidney disease (CKD) or even end-stage renal disease (ESRD) that requires chronic maintenance dialysis therapy or renal transplantation (Perazella and Moeckel, 2010). This most often is the result of the episode of AKI itself, malignancy- or therapy-related kidney injury that promoted tubulointerstitial fibrosis, and/or glomerulosclerosis. Both of these forms of CKD are associated with increased morbidity such as cardiovascular disease, anaemia, metabolic bone disease, malnutrition, and infectious complications as well as enhanced mortality. Hypertension frequently complicates CKD, further increasing the risk for various cardiovascular complications, including death. Metabolic complications from chemotherapeutic agents or tumour-related renal injury may also develop leading to various chronic clinical conditions such as osteomalacia, osteoporosis, and risk for cardiac arrhythmias (Perazella and Moeckel, 2010).

Table 251.1 Risk factors for cancer-associated acute kidney injury

Older age	◆ Structural kidney changes: • Increased glomerulosclerosis • Age-related vasculopathy • Tubulointerstitial disease • Peritubular capillary dropout • Interstitial fibrosis ◆ Functional renal disturbances: • Reduced renal plasma flow and GFR • Exaggerated vasoconstrictor response • Blunted vasodilatory response ◆ Host co-morbidities ◆ Hypertension, diabetes mellitus, chronic kidney disease ◆ Cardiovascular disease (in particular acute and/or chronic cardiorenal syndrome) ◆ Nephrotic syndrome, cirrhosis, obstructive jaundice ◆ Nephro-injurious procedures ◆ Nephrotoxic medications ◆ Chemotherapeutics ◆ NSAIDs, angiotensin-converting enzyme inhibitors, aminoglycosides ◆ Aciclovir, amphotericin, colistin ◆ Radiocontrast
True or effective circulating blood volume depletion	◆ Diminished GFR ◆ Increased proximal tubular toxin reabsorption ◆ Sluggish distal tubular urine flow rates
Metabolic disturbances	◆ Hypokalaemia, hypomagnesaemia, hypocalcaemia ◆ Hypercalcaemia ◆ Alkaline or acid urine pH

Risk factors for cancer-induced acute kidney injury

In the setting of malignancy, AKI develops via two major pathologic mechanisms that affect the kidneys and their function: direct renal infiltration with tumour and/or indirect cancer-related kidney injury (Lameire et al., 2008) (Table 251.1). Regardless of the pathways of renal injury promoted by the malignant process, several risk factors increase the possibility of AKI in certain patient populations. Patients at an age > 65 years are at increased risk for AKI from malignancy or its therapy due to age-related renal changes, underlying chronic kidney disease, and other co-morbidities (Anderson et al., 2011). Age-related structural changes of the kidney include increased percentage of sclerosed glomeruli, vascular intimal sclerosis, and tubulointerstitial fibrosis (Kang et al., 2001; Martin and Sheaff, 2007). Functional renal disturbances with decreased renal glomerular filtration rate (GFR) and co-morbidities such as hypertension, diabetes mellitus, cardiovascular disease (in particular acute and/or chronic cardiorenal syndrome), and nephrotoxic medications are prevalent in the elderly and contribute to an increased AKI risk in this group of patients (Castellani et al., 1998; Fuiano et al., 2001).

Moreover, states of true and effective intravascular volume depletion are potent risk factors for AKI, especially with certain types of cancer. For example, reduced GFR along with sluggish urinary flow through the tubules will enhance precipitation of abnormal urinary light chains and cause kidney injury in the setting of multiple myeloma or tumour lysis syndrome. Intravenous radiocontrast exposure, non-steroidal anti-inflammatory drugs (NSAIDs), and loop diuretics will increase risk for light chain cast formation in myeloma patients (Dimopoulos et al., 2010). Severe hypercalcaemia associated with different tumour types and acting through various mechanisms (parathyroid hormone-related protein, 1,25 (OH) vitamin D, osteoclast activation, cytokines) increase risk for AKI through haemodynamic effects (afferent arteriolar vasoconstriction, sodium and water wasting) and via acute nephrocalcinosis (Lameire et al., 2010).

The various causes of acute kidney injury in patients with cancers may be approached in a similar fashion as AKI in the traditional setting (Tables 251.2 and 251.3).

Table 251.2 Types of chemotherapy-induced acute kidney injury

Haemodynamic kidney injury (capillary leak syndrome)	Interleukin-2, denileukin diftitox
Thrombotic microangiopathy	Mitomycin C, gemcitabine, anti-angiogenesis drugs, cisplatin
Collapsing focal segmental glomerulosclerosis	Pamidronate, interferon
Acute tubular necrosis	Platinums, zoledronate, ifosfamide, mithramycin Pentostatin, imatinib, diaziquone
Crystal nephropathy	Methotrexate

Table 251.3 Causes of acute kidney injury in cancer

Prerenal causes	Nausea Vomiting Diarrhoea NSAIDs Contrast Hypercalcaemia Capillary leak syndrome Hepatic veno-occlusive disease Calcineurin inhibitors
Intrinsic renal causes: *Tubular* *Interstitial/parenchyma* *Glomerular and vascular*	Ischaemia Tubulotoxins: platinums, zoledronate, ifosfamide, mithramycin, pentostatin, imatinib, diaziquone Tumour lysis syndrome—acute urate nephropathy, calcium phosphate deposition Cast nephropathy Crystals—methotrexate, urate, calcium phosphate Hypercalcaemia Tumour infiltration TMA (gemcitabine, mitomycin C, bleomycin, cisplatin, 5-fluorouracil, CNIs, VEGF inhibitors) Focal segmental glomerulosclerosis (bisphosphonates, interferon)
Postrenal causes: *Intrinsic* *Extrinsic*	Haematuria and blood clots Invasion of tumour Fibrosis Compression from lymphadenopathy Prostate cancer
Miscellaneous	Renal vein obstruction Renal arterial occlusion Radiation nephritis

Prerenal causes

Prerenal failure is resultant from decreased effective circulating volume, which in turn reduces perfusion to the kidneys. Patients being treated with chemotherapeutic agents often suffer from side effects such as nausea, vomiting, poor fluid intake, and diarrhoea. Patients with gastrointestinal malignancies may have ostomies and significant volume loss from these. These factors may lead to volume depletion if they are not appropriately compensated for. Metastatic malignancies to the liver may lead to hepatorenal syndrome, causing a prerenal-like state. Older patients have increased responsiveness to angiotensin II and endothelin, which predisposes these patients to prerenal failure (Perazella and Moeckel, 2010).

Several chemotherapeutic agents, such as doxorubicin, have an effect on cardiac function (Patel et al., 2009) and recombinant interleukin (IL)-2 therapy is associated with capillary leak syndrome, which has been shown to decrease plasma volume. Both of these drugs may cause prerenal failure (Mercatello et al., 1991; Guleria et al., 1994). Another important cause of AKI is hepatic veno-occlusive disease. This is caused by acute radiochemotherapy-induced endothelial cell injury of hepatic venules. This leads to venous thrombosis and subsequently sinusoidal and hepatic portal hypertension. The physiology is similar to the hepatorenal syndrome (McDonald et al., 1993; Parikh and Coca, 2006).

Cancer patients have increased incidence of electrolyte and metabolic abnormalities, which renders their kidneys more susceptible to prerenal injury. Hypercalcaemia, which is seen in patients with multiple myeloma, causes afferent arteriolar constriction and a subsequent decrease in GFR. Hypercalcaemia also activates signalling through the calcium-sensing receptor. These effects lead to impaired sodium and chloride uptake in the loop of Henle and a blunting effect of antidiuretic hormone leading to polyuria and salt-wasting. A clinical consequence is the increased tendency to volume depletion. Several cancer patients are administered analgesics in the form of NSAIDs, and are exposed to a great deal of radiological imaging with contrast administration, making these patients vulnerable to prerenal injury.

Postrenal causes

Postrenal causes of AKI in the setting of cancer may be separated into extrinsic and intrinsic (see Fig. 251.1). Extrinsic causes are secondary to tumour compression, retroperitoneal lymphadenopathy, or fibrosis. Intrinsic causes are tumour infiltration of the renal pelvis or ureter and haematuria leading to clots that cause obstruction of the urinary outflow tract. Malignant ureteral obstruction is a common complication of advanced cancers. A wide spectrum of malignancies may contribute to this lesion, ranging from urological to gastrointestinal to gynaecological cancers. Obstruction must be considered even in the absence of obvious hydronephrosis and urological intervention, in the form of ureteral stents or nephrostomy placement, to relieve the obstruction should be pursued (Wong et al., 2007).

Renal causes

Intrarenal causes may be divided into tubular, interstitial/parenchymal, glomerular, and vascular causes (Table 251.3).

Tubular injury

Tubular injury may be resultant from direct tubulotoxic effects of drugs, from ischaemic insults, light chain casts, or crystal deposition (see Fig. 251.2). The proximal tubules are particularly vulnerable to high doses of chemotherapeutic agents. This is a result of excessive uptake via basolateral membrane transport (Enomoto

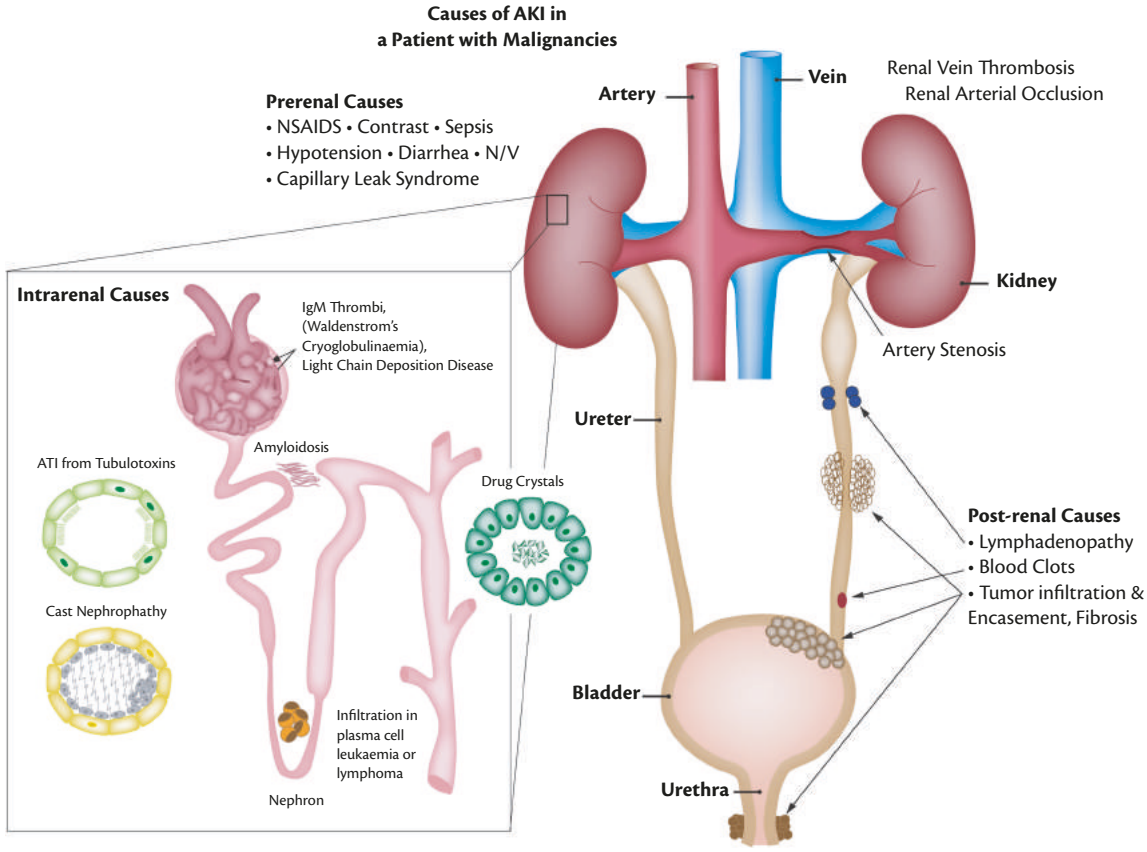

Fig. 251.1 Summary of kidney lesions seen in cancer patients.
N/V: nausea/vomiting

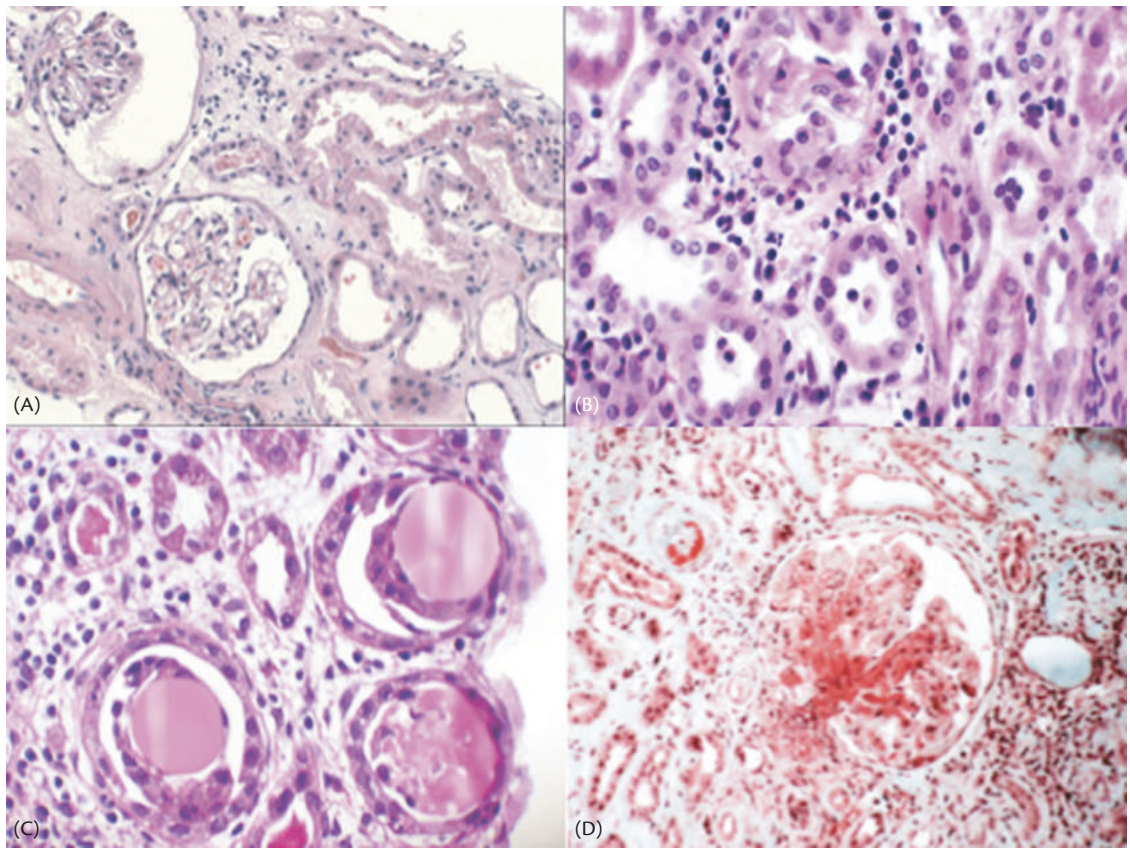

Fig. 251.2 (A) Acute tubular injury (H&E, x200); (B) Acute interstitial nephritis (H&E, x200); (C) Light chain cast nephropathy (Trichome, x200); (D) Thrombotic microangiopathy (PAS, x100)

and Endou, 2005). Given that the kidney receives 25% of the cardiac output, the amount of drug exposure can be significant. The most classic tubulotoxins belong to the 'platin' class of chemotherapeutic agents. Cisplatin-mediated acute tubular injury (ATI) occurs in a dose-related fashion due to its metabolism to toxic molecules, including thiol compounds and monohydroxyl compounds which accumulate within the cell. These metabolites have multiple intracellular effects, which affect gene regulation, reactive oxygen species generation, activation of mitogen-activated protein kinases, induction of apoptosis, and stimulation of fibrosis and inflammation. In addition to renal failure, there are disturbances in handling of sodium, potassium, and magnesium (Yao et al., 2007; Perazella and Moeckel, 2010). Other drugs associated with tubular injury are zoledronate, ifosfamide, mithramycin, pentostatin, imatinib and diaziquone.

Moreover, certain malignant processes directly injure the tubules. Light chain cast nephropathy is the main cause of impaired renal function in patients with multiple myeloma. A subset of patients present with acute oliguric renal failure, which is seen in conjunction with dehydration with extensive cast deposition in the distal tubule (Herrera and Sanders, 2007). The classic light microscopic findings are fractured casts in tubular lumen with monocytic, epithelioid reaction surrounding the casts, sometime forming giant cells (see Fig. 251.2). The casts consist of light chains, which show monoclonal predominance by immune fluorescence staining.

Intrarenal obstruction at the tubular level may also be seen in cancer patients. This occurs due to intratubular crystal deposition, myoglobin casts, or direct infiltration by lymphoma. Tumour lysis syndrome (TLS) refers to a set of metabolic complications that ensue with the treatment of a rapidly proliferating neoplasm (see Fig. 251.3). TLS has been associated with cancers with high tumour burden and with high-grade lymphomas, such as Burkitt lymphoma and acute lympoblastic leukaemia but also with chronic leukaemias and low-grade lymphomas (Cohen et al., 1980; Tsokos et al., 1981; Trendle and Tefferi, 1994). Cell lysis in response to chemotherapy results in hyperkalaemia, hyperuricaemia, hyperphosphataemia, and AKI in TLS. Uric acid precipitates in the acidic environment of the distal tubules and collecting ducts. This promotes the development of intratubular obstruction and tubular damage. The mechanism of toxicity from hyperphosphataemia is thought to be related to intrarenal calcium phosphate precipitation and direct tubular toxicity of the phosphorous (Humphreys et al., 2005). Rising serum creatinine levels and decline in urine output are the main clinical features of TLS. Metabolic abnormalities that lead to acidic urine may promote deposition of uric acid crystals.

Rhabdomyolysis and AKI shortly after completion of a chemotherapeutic regimen for acute myelogenous leukaemia (AML) that included high-dose cytarabine has been reported (Truica and Frankel, 2002). The underlying mechanism of cytarabine-induced muscle cell injury is increased apoptosis (Kim et al., 1997). Kidney biopsies may show extensive myoglobin casts within the distal nephron. Direct tubulotoxicity by myoglobin casts is the underling mechanism of the acute renal failure.

Interstitial and parenchymal injury

In addition to the potential for the multitude of chemotherapeutic agents to cause acute interstitial nephritis, there are several other causes of tubulointerstitial injury. Hypercalcaemia may lead to calcium deposition in the interstitium leading to parenchymal injury. Haematologic malignancies like lymphoma and leukaemia can infiltrate the renal parenchyma and cause AKI, although the incidence of AKI from infiltration is very low. This is usually accompanied by enlarged kidney size. As the cancer is treated, the

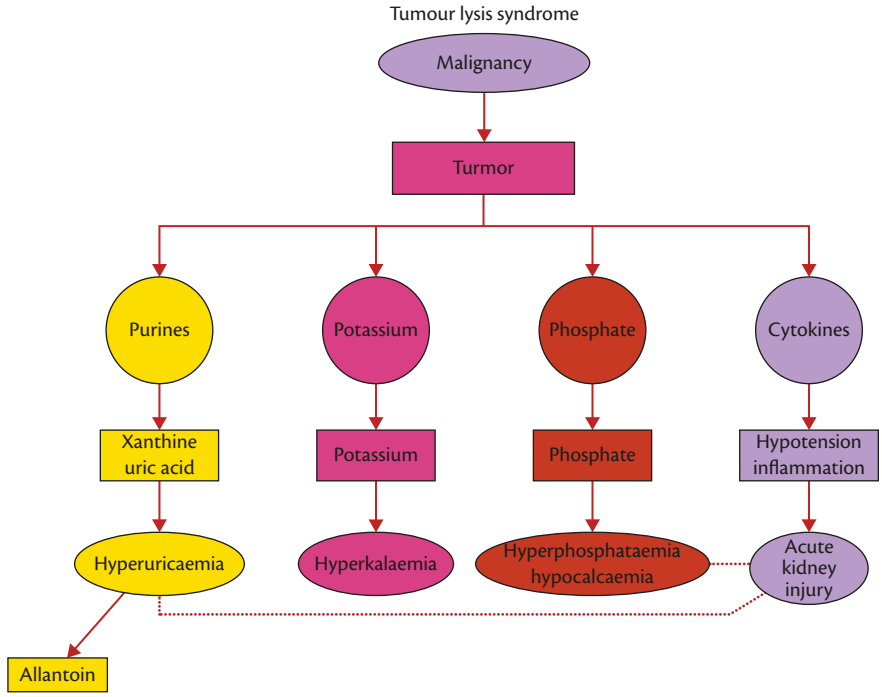

Fig. 251.3 Summary of injury pathways that lead to AKI in tumour lysis syndrome.

renal function typically improves (Sellin et al., 2004). Plasma cell leukaemia is a rare and aggressive variant of multiple myeloma with a mean survival of only 6 months (International Myeloma Working Group, 2003). Direct renal involvement by infiltrating abnormal plasma cells is considered to be rare, although it has been documented in the majority of autopsy cases in one series (Pruzanski et al., 1969). The abnormal plasma cells may form discrete nodules or show a diffuse infiltrate.

The kidney is a common site of involvement by non-Hodgkin lymphoma. The incidence of renal involvement by disseminated lymphoma may be as high as 60% and lymphomas of B-cell lineage are more prevalent than T-cell lymphomas (Pickhardt et al., 2000). Most renal involvement by lymphoma is asymptomatic and is discovered during staging procedures or on autopsy. Renal failure in patients with lymphoma is more commonly attributed to dehydration, hypercalcaemia, obstruction, glomerulonephritis, or therapy-related effects. When non-Hodgkin lymphoma involves the kidney it is often secondary, although primary renal lymphomas have been described (Brouland et al., 1994; Malbrain et al., 1994). The light microscopic findings are those of a packed infiltrate of abnormal lymphocytes with expansive features pushing the adjacent tubular structures aside (see Fig. 251.4). The aetiology of AKI by direct renal involvement in non-Hodgkin lymphoma is enigmatic, but likely the abnormal lymphocytic infiltrate compresses vessels and tubules leading to subsequent renal failure. This hypothesis is supported by the fact that in most cases of infiltrative lymphoma the renal function returns to normal with decreasing tumour burden following induction of chemotherapy (Seo-Mayer et al., 2010). Alternatively cytokines secreted by lymphoma cells, such as IL-6, IL-1, tumour necrosis factor alpha, and transforming growth factor beta, may cause tubular injury and interstitial fibrosis (Hsu et al., 1993).

AKI is a common complication in haematopoietic cell transplantation (HCT). HCT is now used to treat several malignant haematologic disorders, such as multiple myeloma, leukaemia, and lymphomas. AKI usually occurs within the first 100 days after HCT with an incidence ranging between 19% and 51% for autologous versus allogeneic HCT respectively (Patzer et al., 2003; Hingorani et al., 2005). Graft-versus-host disease (GVHD) is the major factor contributing to the higher incidence in allogeneic HCT (Pinana et al., 2009). GVHD can contribute to renal lesions directly through cytokine- and immuno-related injury or indirectly through nephrotoxic injury by ciclosporin given as prophylaxis for GVHD (Burns, 2009; Pinana et al., 2009).

About 15% of cases of lymphoproliferative disorders with renal involvement are associated with reactive lymphocytic infiltration (Xiao et al., 1997). Metastatic solid tumours rarely lead to AKI. It is predominantly associated with lung cancer, followed by gastric and breast carcinomas (Manning et al., 1996).

Glomerular and vascular lesions

Glomerular and vascular lesions resulting in haematuria, proteinuria, and AKI are not infrequent. Although there are several nephritic and nephrotic lesions caused by different chemotherapeutic agents, only occasionally do they cause AKI.

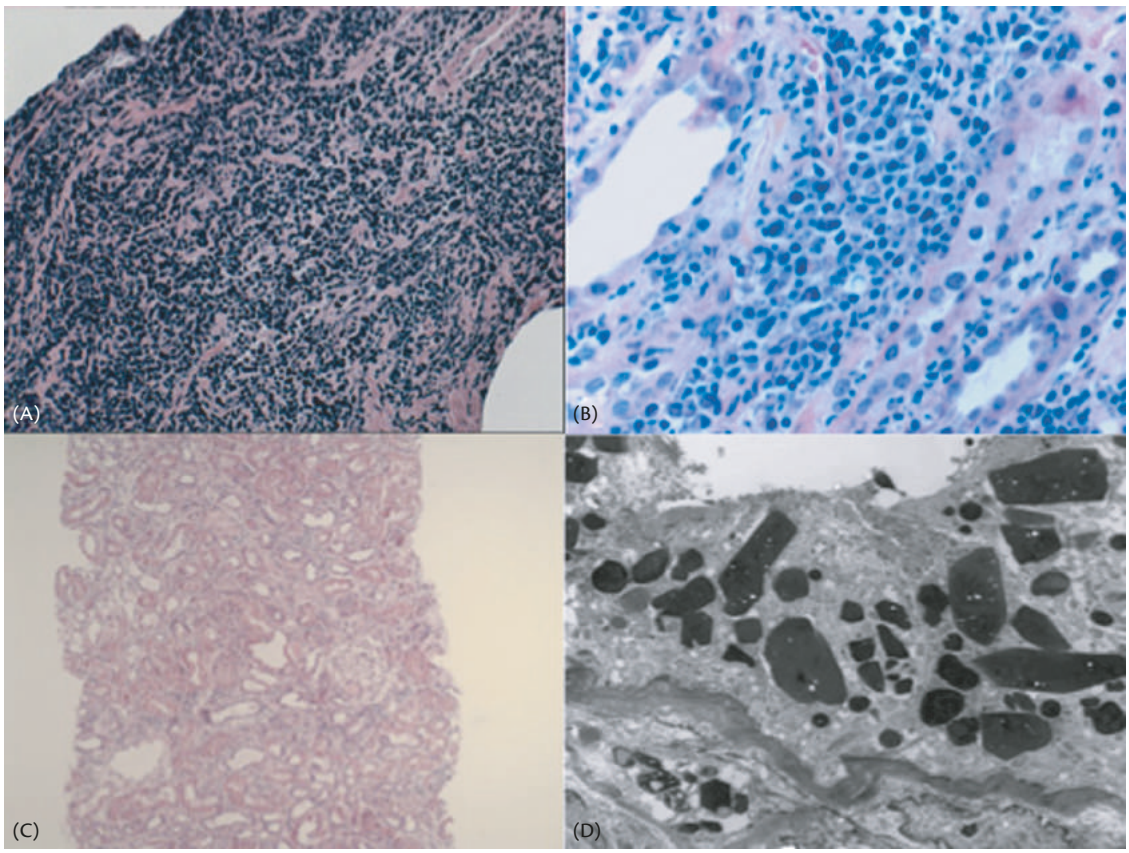

Fig. 251.4 (A) Lymphoma involving the kidney (H&E, ×200). (B) Lymphoplasmacytic leukaemia (H&E, ×400). (C) Cytoplasmic tubular light chain inclusions (H&E, ×100). (D) Light chain crystals in proximal tubule by electron microscopy (×10 500).

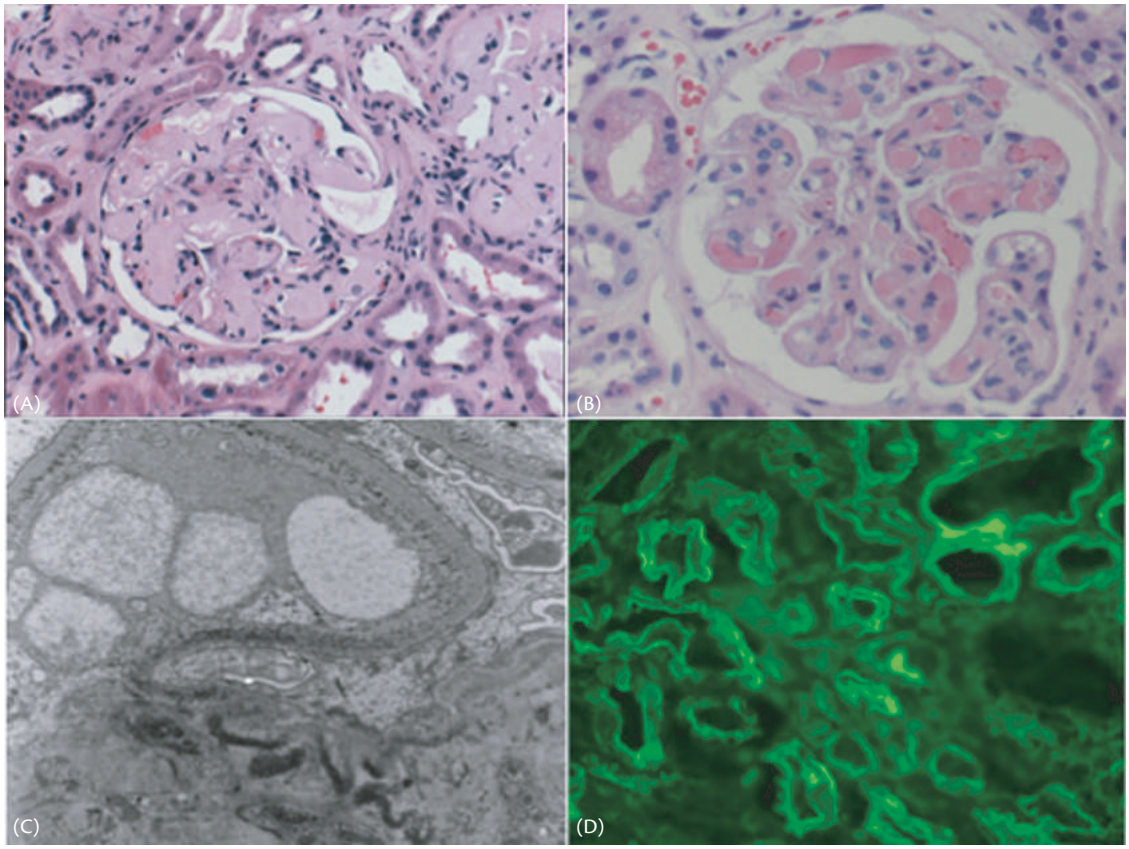

Fig. 251.5 (A) Amyloidosis (H&E, x400); (B) Cryoglobulinemic GN (H&E, x200); (C) Light chain deposition disease by EM (x8000); (D) Lambda light chain fluorescence in tubular basement membranes (x400).

Amyloidosis occurs in up to 10% of patients with multiple myeloma and presents often with nephrotic-range proteinuria (Herrera and Sanders, 2007). It refers to the deposition of fibrils that are derived from specific precursor proteins that undergo conformational changes to form beta pleated sheets (Herrera and Sanders, 2007). By light microscopy the mesangial regions of the glomeruli show expansion with eosinophilic, amorphous material, which is usually Congo red positive and shows apple green birefringence upon polarization (see Fig. 251.5). Similar material may be seen in vessels or in the interstitium. When amyloid protein is deposited in the subepithelial region of the glomerulus, prominent spikes may be seen on the silver-stained sections. In the case of AL-amyloidosis, the immunofluorescence-stained sections show lambda or kappa light chain predominance. The amyloid deposits often stain positive for thioflavin T. Electron microscopy studies reveal fibrillary substructures within these deposits that measure 8–10 nm in diameter.

Light chains may also be directly deposited along glomerular capillary loops or tubular basement membranes and cause light chain deposition disease. Light microscopy shows nodular mesangial expansion mimicking those of diabetic nephropathy. Electron microscopy examination shows characteristic finely granulated, band-like deposits, which are seen in the subendothelial region of glomerular capillary loops and on the outer side of tubular basement membranes. These deposits show monoclonal predominance (either kappa or lambda light chain) by immune fluorescence.

A pathologic lesion seen in cancer patients that induces AKI is thrombotic microangiopathy (TMA). The characteristic lesion is microvascular thrombosis composed of platelets and fibrin, resulting from endothelial damage (see Fig. 251.2). This may occur in association with a malignancy itself, with chemotherapeutic agents, or BMT. Solid organ carcinomas related to TMA are gastric, breast, and lung. Renal failure as a manifestation is rare. Antitumour agents are more commonly associated with TMA syndromes and the incidence appears to be dose related. Of significance are gemcitabine, mitomycin C, bleomycin, cisplatin, and 5-fluorouracil. Patients receiving allogenic bone marrow transplants seem to be at a high risk for development of TMA. This is potentiated by therapy with calcineurin inhibitors which by themselves have potential to cause thrombotic thrombocytopenic purpura-like syndromes. In the presence of GVHD, there is endothelial damage which promotes TMA development (Kwaan and Gordon 2001; Humphreys et al., 2005).

High-potency, intravenous (IV) bisphosphonates used in malignancy-related bone disorders have been known to cause nephrotoxicity. The lesions described are acute tubular necrosis and the collapsing variant of focal segmental glomerulosclerosis. The IV forms of bisphosphonate are zoledronate and pamidronate. High-grade proteinuria and AKI are associated with high doses of these drugs given at frequent intervals. The mechanism of injury appears to be podocyte apoptosis and tubular epithelial damage (Perazella and Markowitz, 2008; Perazella and Moeckel, 2010).

The more recent introduction of vascular endothelial growth factor inhibitors has created a new spectrum in disease pathology, which includes AKI, hypertension, glomerular endotheliosis, TMA, and other lesions. The mechanism of injury includes

Table 251.4 Prevention and treatment of acute kidney injury in patients with cancer

General preventative measures	Specific preventive measures	Specific therapeutic measures
Intravenous isotonic fluids to increase and maintain high urinary flow rates Discontinue NSAIDs, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers Avoid iodinated contrast and gadolinium-based contrast exposure Appropriately adjust drug doses for level of kidney and liver function	Metabolic aetiologies *Tumour lysis syndrome* Intravenous isotonic fluids Urinary alkalinization Allopurinol *Hypercalcaemia* Intravenous isotonic fluids	Metabolic aetiologies *Tumour lysis syndrome* Intravenous isotonic fluids Allopurinol Rasburicase Haemodialysis/CRRT *Hypercalcaemia* Intravenous isotonic fluids Bisphosphonates or steroids Haemodialysis/CRRT
	Drugs *Methotrexate* Intravenous isotonic fluids Urinary alkalinization *Cisplatin* Dose-adjusted cisplatin Intravenous isotonic fluids Carboplatin or oxaloplatin in high-risk patients *Ifosfamide* Limit total doses in high-risk patients *Interleukin-2* Limit intravenous fluids (avoid hypervolaemia)	Drugs *Methotrexate* Intravenous isotonic fluids Leucovorin rescue Carboxypeptidase G2 High-flux haemodialysis (controversial) *Cisplatin* Intravenous isotonic fluids Amifostine Replete magnesium *Ifosfamide* Mesna, *N*-acetylcysteine *Interleukin 2* Monitor volume status carefully
	Specific cancers *Myeloma cast nephropathy* Intravenous isotonic fluids Urinary alkalinization *Lymphoma/leukaemia* Same preventive measures for both tumour lysis syndrome and hypercalcaemia (if present)	Specific cancers *Myeloma cast nephropathy* Intravenous isotonic fluids Urinary alkalinization Correct hypercalcaemia and hyperuricaemia if present High cut-off haemodialysis Plasmapheresis (IgM myeloma) *Lymphoma/leukaemia* Same therapeutic measures for both tumour lysis syndrome and hypercalcaemia (if present) Relieve urinary obstruction if present (percutaneous nephrostomy tube placement) Radiation of kidneys if tumour infiltration present

nitric oxide pathway inhibition, rarefaction, and oxidative stress. Glomerular injury results from the inhibition of the effect of vascular endothelial growth factor in maintaining the filtration barrier (Perazella and Moeckel, 2010). There has been an association between antineutrophil cytoplasmic antibody vasculitis and the presence of malignancy (Pankhurst et al., 2004).

Miscellaneous

Radiation nephritis: exposure to ionizing radiation can lead to radiation nephropathy. There is a severe acute form that results in azotaemia, hypertension, and anaemia within a few months of radiation. Although the incidence of this entity has reduced due to alternative forms of chemotherapy, it is still prevalent in the presence of total body irradiation that is performed in preparation for BMT. The damage that is caused is usually dose dependant and can cause glomerular, tubular, and interstitial diseases. Radioisotope studies are yet another source of radiation nephritis. The isotope proteins are filtered at the glomerulus and reabsorbed by the tubular epithelium. The concentrated isotope at the level of the epithelium causes damage. This is dependent on the decay time of the isotope (Cohen and Robbins, 2003).

Renovascular causes: include renal vein thrombosis and renal arterial obstruction. Malignancies are often associated with hypercoagulable states due to factors with increased procoagulant activity. Acute renal vein thrombosis may be a cause of AKI in patients with cancers like pancreatic cancers and renal cell carcinoma. The

typical presentation would include dramatic flank pain, haematuria, and an increase in renal size on imaging. The highest incidence of thromboembolism is associated with cancers of the pancreas, brain, liver, and multiple myeloma (Cronin-Fenton et al., 2010).

Prevention and treatment

A summary of strategies for prevention and treatment of acute kidney injury in patients with cancer is given in Table 251.4.

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CHAPTER 252

Acute kidney injury in polytrauma and rhabdomyolysis

Mehmet Şükrü Sever and Raymond Vanholder

Introduction

The term 'polytrauma' refers to blunt trauma (or *crush trauma*) that involves multiple body regions or cavities, which compromises the patient's physiology, and potentially causes dysfunction of uninjured organs (Butcher and Balogh, 2009). These patients are at risk of higher morbidity, and mortality than what can be expected from the sum of expected morbidity, and mortality of their individual components. Trauma to muscles resulting in rhabdomyolysis deserves special mention, because it may result in crush syndrome that negatively affects the ultimate outcome.

In daily life, polytrauma is quite frequent, mostly resulting from motor vehicle accidents, and affects a limited number of patients. In unusual situations, however, such as man-made or natural disasters (wars, terrorist attacks, earthquakes), thousands of polytrauma victims may be observed at once.

Polytrauma may differ in type and intensity; it may:

- involve only the extremities, and/or head, thorax, and abdomen
- affect only soft tissues, and/or bony structures
- cause mild or very serious injuries, or even result in instant death
- present with solely surgical features or with additional medical complications either directly related or unrelated to the trauma.

Sometimes polytrauma or crushing may result in trapping of the victims, and subsequent compression of the muscles and other organs.

Crush injury to the muscles is characterized by muscle swelling and/or neurological disturbances in the affected parts of the body; medical problems may be associated with crushing as well. Among the latter, rhabdomyolysis-induced acute kidney injury (AKI) deserves special mention, because it may result in high risk of morbidity and mortality while it is not well-known by many physicians.

By definition, *rhabdomyolysis* is damage to striated muscle cells of traumatic or non-traumatic aetiology, which results in the release of intracellular components of muscle (myoglobin, potassium, lactic acid, thromboplastin, creatine kinase, nucleic acids, phosphate, and creatine) into the systemic circulation (Vanholder et al., 2000b). The features of rhabdomyolysis range from asymptomatic elevations of muscle enzymes to life-threatening systemic manifestations, which are referred to as '*crush syndrome*' and may include AKI, sepsis, acute respiratory distress syndrome, disseminated intravascular coagulation, bleeding, hypovolaemic shock, electrolyte disturbances, arrhythmias, cardiac failure, and psychological trauma (Sever, 2005). The incidence of AKI varies between 30% and 50% in most series of cases with rhabdomyolysis (Gabow et al., 1982; Ward, 1988; Slater and Mullins, 1998).

In what follows, 'crush syndrome', 'AKI in polytrauma victims' or 'myoglobinuric AKI' will be used interchangeably.

Structure and function of the muscles

Muscles are the largest organ in the body accounting for approximately 40% of total body mass (Guyton and Hall, 2006); they are distributed over a large number of compartments, which are spaces restricted by rigid, non-compliant fascias surrounding the muscles. Normally, the pressure in these compartments is very low (i.e. 0–20 mmHg). An increased pressure in the compartment that disrupts the perfusion, and hinders the function of the tissues, is referred to as 'compartment syndrome'.

Anatomically, muscles consist of innumerable, elongated, multinucleated cells (*muscle fibres* or *myocytes*). Each myocyte contains thousands of thin, longitudinal fibres, that is, *myofibrils*. Each myofibril contains thousands of thick (*myosin*), and thin (*actin*) filaments, lying side by side.

The cell membrane of myocytes (*sarcolemma*) is impermeable to extracellular fluid, and electrolytes. The cytoplasm of myocytes containing intracellular organelles is called *sarcoplasm*. It holds large amounts of potassium, magnesium, phosphate, proteolytic enzymes, and mitochondria; the latter form ATP, which supplies energy to the muscle during contraction. As compared with the extracellular fluid, the sarcoplasm is hyperoncotic, and electronegative; it contains significantly lower calcium, and sodium, but markedly higher potassium concentrations than the plasma (Zager, 1996; Guyton and Hall, 2006). *Sarcoplasmic reticulum* is the endoplasmic reticulum of the muscle fibre, and contains a substantial number of calcium ions.

The main function of the muscles is to convert biochemical energy into mechanical energy, thus performing movements. In brief, muscle physiology is the physiology of muscle contraction and relaxation.

Table 252.1 Aetiology of rhabdomyolysis

Non-physical causes	Physical causes
Electrolyte abnormalities	*Trauma, and/or compression of the muscles*
Hypokalaemia, hypocalcaemia, hypophosphataemia,	Natural, and man-made disasters, traffic or working accidents, torture, beating, long-term confinement to the same position
Hyponatraemia, hypernatraemia	*Occlusion or hypoperfusion of the muscular vessels*
Alcohol, drugs, and toxins	Thrombosis, embolism, vessel clamping, shock
Regular, and illegal drugs (i.e. statins, colchicine, corticosteroids, diuretics, cocaine, ecstasy, heroin)	*Electrical current*
Toxins (i.e. snake, and insect venoms, fish toxins)	High-voltage electrical injury, cardioversion
Infections	*Hyperthermia*
Infections localized in muscles (e.g. pyomyositis) or	High ambient temperatures, neuroleptic malignant syndrome, malignant hyperthermia, sepsis
metastatic infections (e.g. sepsis)	*Strainful exercise*
Other bacterial, and viral infections	Exercise, delirium tremens, epilepsy, tetanus, status asthmaticus
Metabolic myopathies	
Myophosphorylase deficiency (McArdle disease) and other enzymatic defects	
Endocrine disorders	
Hypothyroidism, diabetic coma	
Polymyositis, dermatomyositis	

Adapted from Vanholder et al. (2000b).

Aetiopathogenesis of rhabdomyolysis-induced acute kidney injury (crush syndrome)

Aetiology

Rhabdomyolysis may result from both non-traumatic, and traumatic aetiologies (Table 252.1).

The incidence of the listed causes in Table 252.1 varies according to the geographical region, and the moment or occasion in relation to which the epidemiological analysis took place. For example, drug abuse is a major cause in Western countries, while traumatic events are more common in developing countries; non-traumatic aetiologies are frequent in daily life, whereas traumatic causes become more prominent following disasters.

In general, most cases are related to alcohol consumption, drug use, and compression of muscles resulting from prolonged immobility.

Pathogenesis

Development of crush-related AKI is the result of two consecutive mechanisms: (1) traumatic rhabdomyolysis and (2) rhabdomyolysis-induced AKI.

Pathogenesis of traumatic rhabdomyolysis

When muscles are compressed, permeability of the sarcolemma increases, and substances which are abundant in the extracellular environment such as calcium, sodium, and water move to the intracellular milieu, whereas solutes which are essentially present in the muscle cells (such as potassium and myoglobin) are released into the extracellular compartment (Better and Stein, 1990; Sever, 2007) (Fig. 252.1). Once a critical intracellular free calcium concentration is reached in muscular cells, sustained contraction ensues, which depletes ATP stores. Increased cytosolic calcium also activates proteases, phospholipases, and other enzymes resulting in myofibril and membrane phospholipid damage. Furthermore, calcium induces mitochondrial dysfunction resulting in excessive superoxide production, and subsequently cellular injury. The net result is myocyte lysis and release of toxic intracellular constituents into the extracellular micro-environment.

Local accumulation of these products results in microvascular damage, producing capillary leak, subsequently contributing to compartmental syndrome. The latter then increases pressure on the capillaries triggering occlusion of the microcirculation, and rapidly depleting myoglobin oxygen content. Similarly, creatine phosphate

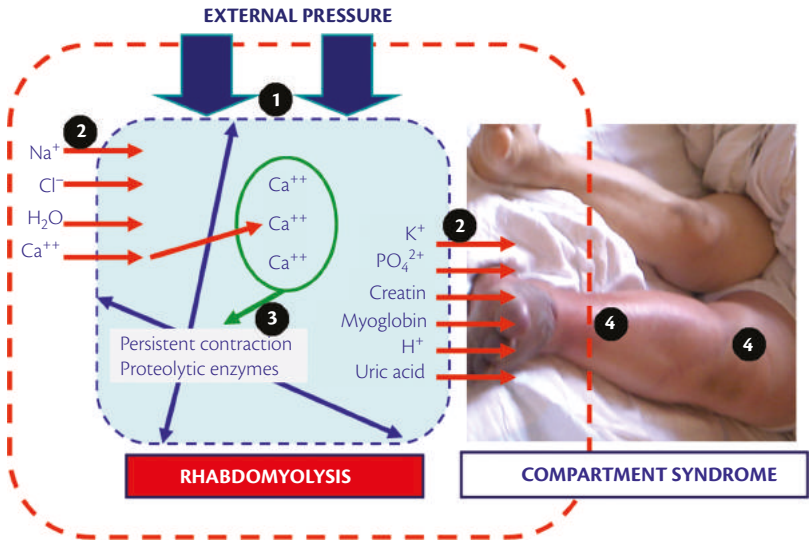

Fig. 252.1 When muscles are compressed: (1) sarcolemmal permeability increases; (2) substances move to the extracellular, and intracellular milieu according to their concentration gradients; (3) high cytosolic calcium induces myofibril and cell membrane damage; (4) local accumulation of intracellular elements in the extracellular milieu results in microvascular damage producing capillary leak, and subsequently compartmental syndrome (see text for details) (Zager, 1996; Vanholder et al., 2000b).

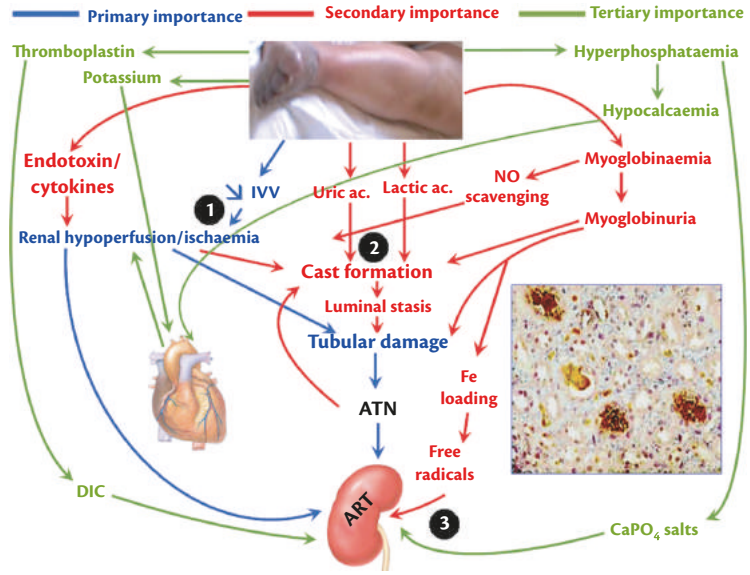

Fig. 252.2 Several mechanisms play a role in pathogenesis of crush-related AKI: (1) renal hypoperfusion and ischaemia-induced damage; (2) myoglobinuria-associated secondary mechanisms; (3) many other tertiary factors further increasing the extent of renal damage (see text for details) (Zager 1996; Vanholder et al., 2000b).
IVV = intravascular volume, ATN = acute tubular necrosis; DIC = disseminated intravascular coagulation; Lactic ac. = lactic acid; NO = nitric oxide; Uric ac. = uric acid.

and glycogen stores are exhausted as well, and severe ATP depletion ensues (Zager, 1996). This lack of metabolic energy then results in further muscular damage and necrosis.

On the other hand, in ischaemic tissue injury, most of the damage occurs after blood flow into the damaged tissue is restored, that is, after extrication and release of muscular compression. Only then do leucocytes start migrating into the traumatized muscular tissues, and production of free radicals is activated because oxygen becomes available again (*reperfusion injury*) (Zager et al., 1995; Vanholder et al., 2000b; Bosch et al., 2009).

This theoretical chain of events is reflected by clinical reality as reported in several anecdotic observations. Some entrapped victims who suffer from crush injury and initially appear well, suddenly deteriorate and die immediately after extrication (*rescue death*) (Noji, 1992; Ashkenazi et al., 2005). This likely occurs as a consequence of reperfusion injury, which can stimulate life-threatening hyperkalaemia, acidosis, and hypovolaemia.

Pathogenesis of rhabdomyolysis-induced AKI

AKI due to crush injury is prerenal; and thus, in principle, transient in the initial phase; if not treated early, and properly, however, persistent AKI with parenchymal damage, which is almost always due to acute tubular necrosis (ATN), develops. Major mechanisms in this pathology include:

1. Renal hypoperfusion, and ischaemia, due to (a) intravascular volume depletion as a result of fluid third spacing in muscle compartments, (b) renal vasoconstriction caused by cytokines released from damaged muscles, (c) nitric oxide (NO) scavenging by plasmatic myoglobin, and (d) cardiac output depression due to hypocalcaemia, and hyperkalaemia.
2. Intratubular obstruction caused by myoglobin and uric acid plugs.
3. Direct tissue damage, and inflammation, due to (a) myoglobinuria, (b) free radicals catalysed by iron released from intratubular myoglobin, (c) $CaPO_4$ precipitation due to hyperphosphataemia, and (d) disseminated intravascular coagulation resulting in thrombi in the glomerular capillary tufts (Zager, 1996; Vanholder et al., 2000b; Bosch et al., 2009) (Fig. 252.2).

Clinical findings in crush-related acute kidney injury

Clinical features of myoglobinuric AKI include (1) local findings of traumatic rhabdomyolysis, and (2) systemic manifestations (or signs and symptoms of crush syndrome) (Vanholder et al., 2000a; Sever et al., 2002b):

1. The most typical local finding is *compartment syndrome* due to swollen muscles. Patients suffer from severe pain, and weakness, paraesthesia, paresis or paralysis, and pallor in the affected extremities. Distal pulses may be absent when intracompartmental pressure is very high.
2. Findings of crush syndrome include hypovolaemic shock, sepsis, electrolyte disturbances (most importantly hyperkalaemia), heart failure, arrhythmias, acute respiratory distress syndrome, disseminated intravascular coagulation, bleeding, psychological trauma, and most importantly AKI (Sever et al., 2002b).

Myoglobinuric AKI is usually characterized by an initial oliguric period that is followed by polyuria, which starts within 1–3 weeks after the primary event, while some cases may present with a non-oliguric course from the beginning (Sever, 2005).

Laboratory findings in crush-related acute kidney injury

Urinary findings

Dirty-brownish discoloration of the urine as a result of myoglobinuria is typical (Fig. 252.3). However, normal colour can be noted

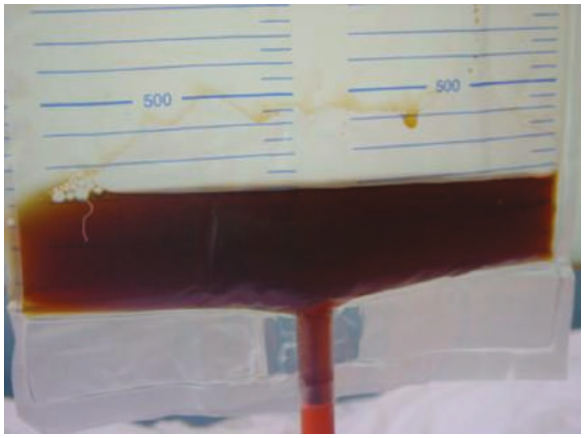

Fig. 252.3 Myoglobinuric discoloration of the urine in a crush victim.

as well when (a) filtered myoglobin load is low, (b) myoglobinuria resolves before admission, or (c) pigment excretion is limited because of kidney dysfunction. In practice, myoglobinuria is most often detected by dipstick testing; a positive test can indicate haematuria, myoglobinuria, or haemoglobinuria, but is not typical for final diagnosis (Vanholder et al., 2000b). At microscopic investigation, the presence of only few erythrocytes despite a strong blood reaction at dipstick testing rule out haematuria and suggest pigment in the urine. The suggestion that this is due to myoglobinuria is sustained by detection of dark-pigmented urine casts.

In the early course, when the patients are usually hypovolaemic, urinary indices are consistent with prerenal AKI (high specific gravity, and osmolality, low urinary sodium concentration, and lower than 1% fractional sodium excretion (FE_{Na})). Proteinuria, isosthenuria, and necrotic tubular epithelial cells in the urinary sediment are detected in the later course, all of which suggest development of ATN. Interestingly, FE_{Na} may continue to be low at this stage as well, a finding that may reflect the primacy of tubular obstruction rather than tubular necrosis.

Biochemical features

Increased serum levels of substances (myoglobin, urea, creatinine, uric acid, potassium, phosphate, protons) and muscle enzymes (creatine kinase (CK), aspartate aminotransferase (AST), alanine aminotransferase (ALT), and lactic dehydrogenase (LDH)) released from the injured muscles, together with a decrease of serum calcium due to shift into the muscles are frequent (Sever et al., 2002a). Among these, serum levels of myoglobin, CK, potassium, calcium, and creatinine deserve special mention, because of their value as prognostic or diagnostic markers and/or as alarm signs that should incite life-saving therapeutic interventions.

1. *Serum myoglobin*: the most reliable finding of rhabdomyolysis is increased myoglobin in serum. However, it has no practical diagnostic value, because the half-life of myoglobin is very short (about 1–3 hours), so that it is completely removed from the plasma within 6 hours (Honda, 1983). Except for early admitted patients, myoglobin level is usually normal at admission to hospitals.
2. *Serum CK*: this enzyme is abundant in the muscles; normal plasma levels vary between 45 to 260 U/L (Slater and Mullins, 1998). An increased level is a useful indicator of muscle damage; a serum CK level five times above the upper normal limit suggests rhabdomyolysis (Ward, 1988). CK reaches peak levels within the first 12–24 hours after injury, and has a half-life of 48 hours (Knochel, 1998). Controversy exists regarding the prognostic value; increased levels may (Oda et al., 1997; Sever et al., 2002a) or may not (Gabow et al., 1982) point to an increased risk of subsequent AKI, and/or need for dialysis.
3. *Serum potassium*: hyperkalaemia is very frequent after rhabdomyolysis, because of (a) efflux of intracellular potassium (which is present in muscle cells at a concentration of approximately100 mmol/kg) into the extracellular environment; (b) inadequate excretion of potassium by the failing kidneys; (c) increased general catabolism due to trauma, surgery, and complications such as inflammation and acidosis; and (d) medical interventions (i.e. blood transfusions). Hyperkalaemia may result in a high mortality before the victims reach the hospital.
4. *Serum calcium*: asymptomatic or symptomatic hypocalcaemia is common in rhabdomyolysis (Knochel, 1998; Vanholder et al., 2000b). Factors, involved in the pathogenesis are (Honda, 1983; Knochel, 1998; Vanholder et al., 2000b): (a) direct or indirect consequences of hyperphosphataemia by suppression of calcitriol synthesis, (b) influx of plasma calcium into the injured muscles, (c) precipitation of $CaPO_4$ salts into the damaged muscles, and (d) resistance of bones to the calcium releasing effects of PTH. However, hypercalcaemia may also develop both early, and late after rhabdomyolysis; if the patients have been treated with calcium salts during the hypocalcaemic stage. This can be a source of hypercalcaemia later on when intracellular calcium is released back into circulation. Therefore, calcium supplementation is suggested only for symptomatic hypocalcaemia or severe hyperkalaemia.
5. *Serum creatinine*: intracellular energy production largely depends upon presence of creatine; it is released in large quantities from damaged myocytes, and converted into creatinine in the circulation. Therefore, a higher ratio of serum creatinine/BUN (blood urea nitrogen) has been suggested in myoglobinuric AKI (Grossman et al., 1974; Better and Stein, 1990). However, not all authors confirm this hypothesis (Gabow et al., 1982; Oh, 1993; Vanholder et al., 2000b; Sever et al., 2002a), because creatinine generation is not always increased in rhabdomyolysis. Alternatively, increased urea synthesis by the liver in highly catabolic patients (Rose and Post, 2001) may contribute to the maintenance of this physiologic ratio.

Prognosis in crush-related acute kidney injury

Myoglobinuric AKI is most often linked to multiple surgical and medical complications (Sever et al., 2002b); therefore, a worse prognosis can be expected than for AKI in general. Indeed, mortality rates up to 40% are reported in the literature (Ward, 1988; Atef et al., 1994; Oda et al., 1997). However, in recent reports on disaster crush victims, mortality rates were as low as 15–20% (Sever et al., 2004; Hatamizadeh et al., 2006; Vanholder et al., 2011). This improvement may be related to increased awareness, better treatment, and overall more accurate and faster disaster response.

Prophylaxis in crush-related acute kidney injury

Fluid resuscitation

The most important strategy for preventing rhabdomyolysis-induced AKI is energetic fluid resuscitation. The goals of volume repletion are reversing hypovolaemic shock, enhancing renal perfusion to minimize ischaemic injury, and increasing the urine flow rate to wash out obstructive casts. A urine output of 200–300 mL/hour is desirable as long as myoglobinuria persists (Sever et al., 2012). Systemic alkalinization for reducing acidosis and hyperkalaemia is important, but has lower priority than rehydration per se. Reducing intracompartmental pressures is also important.

The following issues should be considered for fluid resuscitation:

Timing

Fluids (preferably isotonic saline) should be given intravenously at the earliest occasion (Better and Stein, 1990). For crush casualties, if possible, volume resuscitation should be started even when the victim is still entrapped under the rubble, and continued during and after extrication.

Volume

Initially, isotonic saline should be given at a rate of 1000 mL/hour in adults (15–20 mL/kg/hour for children). The victim should be monitored for a 6-hour period while receiving overall 3–6 L of fluid. Demographic features, medical signs, and symptoms, as well as fluid losses should be considered for defining this volume (Sever et al., 2012). Large amounts of fluid may accumulate in the damaged muscles, hence it is useful to administer 4–5 L more fluids than all visible losses.

For further fluid policy, urinary response, and also environmental, and logistic factors should be considered. In oligo-anuric patients, after hypovolaemia has been excluded, all fluids should be restricted to 500–1000 mL/day in addition to a volume equivalent to all measured or estimated fluid losses of the previous day. In the case of urinary response to intravenous fluid administration (urine volume > 50 mL/hour), fluids should be given 3–6 L/day if victims cannot be monitored closely. In case of close follow-up, however, more fluids even up to 12 L/day may be administered (Sever et al., 2012).

Extensive volumes carry the risk of hypervolaemia, hypertension, and heart failure, especially in the elderly patients.

Type

Isotonic saline is effective in volume replacement, is readily available, and carries the lowest risk of side effects. Isotonic saline + 5% dextrose solution provides the additional advantage of supplying calories, and attenuating hyperkalaemia.

Sodium bicarbonate, added to half-isotonic solutions is effective for alkalinizing the urine to prevent the tubular deposition of myoglobin, and uric acid, correcting metabolic acidosis, and also reducing hyperkalaemia (Zager, 1989; Better and Stein, 1990). If available, alkaline solutions could therefore be administered as well (and even preferred), unless symptoms of alkalosis are present. If the urine pH does not rise above 6.5 or if symptomatic hypocalcaemia develops after 3–4 hours of administration of alkaline solution, it should be discontinued. The usual requirement for bicarbonate is 200–300 mEq for the first day (Sever et al., 2012). However, preparing such combined solutions is time-consuming, and carries the risk of contamination, and errors in chaotic circumstances. In addition, such solutions may not be readily available. Therefore, priority is given to saline solutions, essentially because of practical reasons.

Mannitol expands extracellular volume, increases urine output, prevents renal tubular cast deposition, and decreases muscle intracompartmental pressure (Better et al., 1991, 1997). However, its questioned efficacy (Brown et al., 2004) and the risk of side effects (congestive heart failure and potential nephrotoxicity) (Gadallah et al., 1995) makes its use controversial. Mannitol is contraindicated in anuric patients.

By no means should potassium-containing solutions be used empirically, as they are a cause of hyperkalaemia and subsequently of death.

Colloids should not be used for fluid resuscitation in crush cases considering no major benefit on morbidity, and mortality, and a high risk of side effects (Choi et al., 1999; Perel and Roberts, 2007; Brunkhorst et al., 2008).

An energetic fluid protocol should be continued until myoglobinuria disappears (practically until normalization of the urinary colour), which usually occurs within 2–3 days following the initial insult.

Controversial interventions

Elimination of myoglobin by plasma exchange or special haemofilters has not been proven to prevent crush-related AKI (Berns et al., 1991; Knochel, 1998).

Loop diuretics may be beneficial by increasing urine volume; however, they may worsen hypocalcaemia by inducing calciuria and increase the risk of cast formation by acidifying the urine (Better and Stein, 1990; Slater and Mullins, 1998). Despite these concerns, however, in older patients, especially if they are hypervolaemic, use of loop diuretics is justified.

Other interventions with unproven efficacy in preventing rhabdomyolysis-induced AKI include NO synthase inhibitors or NO scavengers (Rubinstein et al., 1998), pentoxifylline (Savic et al., 2002), glutathione (Abul-Ezz et al., 1991), aminosteroids (Nath et al., 1995; Salahudeen et al., 1996), deferoxamine (Paller, 1988; Zager, 1992) superoxide dismutase, vitamin C and E (Walker et al., 1987), and acetaminophen (Boutaud et al., 2010).

Fasciotomies

Fasciotomy effectively lowers intracompartmental pressure, and decreases the extent of rhabdomyolysis, risk of AKI development, and irreversible neurological damage (Sheridan and Matsen, 1976; Sheng, 1987; Shaw et al., 1994); however, it may also result in infection, leakage of plasma out of the body, bleeding, and severe disability in the long term (Reis and Michaelson, 1986; Matsuoka et al., 2002; Better et al., 2003). On the other hand, even authors who disfavour fasciotomy for a more conservative approach, support urgent fasciotomy in the case of open crush injury, absence of distal pulses, and overall failure of the perfusion of the extremity (Michaelson et al., 1984; Reis and Michaelson, 1986; Better et al., 1997). Intracompartmental pressure measurement is the best method as an objective criterion for decision-making with regard to the performing of fasciotomies (Mubarak et al., 1978).

Treatment modalities in crush-related acute kidney injury

There is no specific therapy of myoglobinuric AKI once overt kidney failure develops; maintenance of nutritional status, appropriate

treatment of complications (if any), and dialysis support should be considered.

Nutrition

Proper nutrition is critical for the maintenance of body mass, wound healing, and prevention of hypercatabolism (Burzstein et al., 1991; Ikizler and Himmelfarb, 1997; Druml, 2001). Severe catabolism is a bad prognostic indicator in AKI in general (Bullock et al., 1985) and is frequent in crush victims, because of the inflammation caused by (a) trauma, (b) major surgical interventions, and (c) medical and surgical complications (Sever et al., 2002b; Li et al., 2010).

Proper nutrition as described for overall AKI patients (see Chapter 228) is valid for polytrauma-related AKI victims as well, and is vital to improve ultimate outcome (Lameire et al., 2005; Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group, 2012).

Treatment of complications

Irrespective of the cause of AKI, extrarenal complications aggravate the course of the disease, and increase morbidity and mortality (Chertow et al., 1995; Sever et al., 2004). This is even more the case in crush injury. Infections deserve special mention due to difficulties in diagnosis and contribution to mortality in 30–88% of cases (Rabinowitz et al., 2000; Keven et al., 2003). Fever and leucocytosis, key indicators of infection, may however also be the consequence of other causes like rhabdomyolysis per se, haematoma, or pulmonary emboli (Rabinowitz and Caplan, 1999). Nevertheless, even if physical findings and laboratory results do not confirm an infection, a high index of suspicion should be maintained.

Dialysis

In polytrauma-related AKI victims, dialysis is initiated based on the usual indications. However, more liberal indications for dialysis should be considered than usual if potential complications are foreseen, especially hyperkalaemia. Twice- or even thrice-daily haemodialysis may be needed for treating life-threatening complications (Sever, 2005).

All dialytic modalities have both advantages and disadvantages in the treatment of crush victims (Table 252.2) (Solez et al., 1993; Vanholder et al., 2000b; Sever et al., 2002c).

No dialysis strategy is ideal for all patients with AKI due to polytrauma. Dialysis should be prescribed on the basis of the individual and potentially changing needs of the victims. Intermittent haemodialysis, however, has the advantage of being applicable to several patients per day at the same position, of minimization of anticoagulation, and of effective removal of life-threatening small molecules such as potassium.

Treatment of crush victims after mass disasters

Crush syndrome is the second most frequent cause of death in immediate survivors of catastrophic earthquakes, the first cause being direct traumatic impact (Ukai, 1997). Calculated/registered number of crush syndrome victims after earthquakes has been reported to be as high as 3000, 600, and 639 after the Tangshan-China, Armenian, and Marmara-Turkey earthquakes, respectively (Sheng, 1987; Collins, 1989; Sever et al., 2001); hence, in addition to the primary catastrophe, a subsequent one may be added, which has been named 'renal disaster' (Solez et al., 1993). Many of these patients survive the first hours of rescue, but may die at a later stage, especially if local dialysis facilities are damaged or overwhelmed.

Most of the time medical and logistic problems cannot be coped with locally, and well-organized material and personnel support may be needed (Solez et al., 1993). The International Society of Nephrology installed the 'Renal Disaster Relief Task Force' as an organization to decrease the extent of problems in chaotic disaster circumstances (Lameire et al., 2003), which was instrumental in saving several hundreds of crush-related AKI patients in recent catastrophes (Vanholder et al., 2001, 2007).

Table 252.2 Potential advantages and drawbacks of various renal replacement therapies in disaster trauma victims

Dialysis modality	Advantages	Drawbacks
IHD	High clearance rate of low molecular weight solutes (like potassium) Possibility to dialyse without anticoagulation	Problematic in hypotension-prone victims Increased risk of disequilibrium syndrome
CRRT	Better control of fluid status Lower risk of disequilibrium syndrome Giving opportunity to freely feed the patient	Need for continuous heparinization in patients often suffering from or susceptible to bleeding Low removal capacity for small solutes
PD	No need for vascular access Simpler technique, and less haemodynamic instability	Low clearance of small molecules Difficulty in maintaining sterile technique Difficult application if the patient cannot lie down due to medical and/or surgical problems

CRRT = continuous renal replacement therapy; IHD = intermittent haemodialysis; PD = peritoneal dialysis.

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CHAPTER 253

Acute kidney injury in patients with severe burn injury

Nele Brusselaers and Eric A. J. Hoste

Introduction

Severe burn injuries are among the most serious acute diseases, requiring hospitalization often up to several months in highly specialized burn and intensive care units (ICUs). The annual incidence of burns ranges between 11 and 52/10,000 population (Othman and Kendrick, 2010) and 4–22% of these require hospitalization (0.2–2.9/10,000 population/year) (Wasiak et al., 2009; Brusselaers et al., 2010b). The prognosis of these patients depends on three factors: increasing age, total burned surface area (TBSA), and presence of an inhalation injury (Ryan et al., 1999; Belgian Outcome in Burn Injury Study Group, 2009). Also, other factors influence the outcome of the individual burn patient, but in contrast to the general ICU population, burn patients are generally in good health prior to the accident, so underlying co-morbidities are believed to have less impact. Nevertheless, severe burns are associated with a high risk for morbidity and mortality, due to often extensive wounds, the associated trauma (e.g. inhalation injury), the need for multiple surgical interventions, and increased risk of bleeding and infections—all contributing to a potentially major deregulation of most organ systems. Acute kidney injury (AKI) is thus a frequent and serious complication, and one of the major causes of death (often combined with other organ dysfunctions), although its importance is frequently underestimated.

Prevalence and outcome of acute kidney injury

A recent systematic review and meta-analysis included 57 cohort studies on kidney injury in severely burned patients published between 1960 and 2009; the review covers almost 2000 patients with burn injury and AKI (Brusselaers et al., 2010a). Eight of these studies only considered paediatric burn patients. This meta-analysis revealed that AKI occurs in approximately one-quarter of all patients with severe burn injury (as defined by the RIFLE (Risk, Injury, Failure, Loss, and End-stage renal disease) consensus classification), and approximately 3% of the paediatric burn patients. Yet, the prevalence varied considerably among these studies (range 0.2–64.1%), with lower prevalence for more specific and less sensitive definitions (> 20 different definitions used) (Table 253.1). The prevalence of AKI was lower in the population with burn injury compared with a general ICU population (27% vs 30–66%) but mortality was comparable or increased (35% vs 17–36%), in particular for the RIFLE-failure group (75% vs 26–57%) (Hoste et al., 2006; Ostermann and Chang, 2007; Hoste and Schurgers, 2008; Mandelbaum et al., 2011). The lower prevalence may be explained by an age difference between populations with burn injury and general ICU populations, because populations with burn injury were younger, with consequently a lower prevalence of co-morbidities (Brusselaers et al., 2010a).

Overall, the meta-analysis showed a three- to sixfold higher mortality for burn patients with AKI, depending on the applied definition. When AKI is defined by the sensitive RIFLE classification, median mortality of AKI was approximately 35%.

Since this meta-analysis, several recent, large studies have confirmed these findings (Mosier et al., 2010; Stewart et al., 2012; Chung et al., 2012).

The first reports of patients with burn injury who developed AKI and did survive hospital stay dated from the early 1960s (Goldsmith et al., 1960; Creyssel et al., 1962; Hockmuth and Ziffren, 1963; Proyard and Cuypers, 1963). Severe AKI, with need for treatment with renal replacement therapy (RRT), occurred in 3% of all burn patients and was associated with a particular unfavourable prognosis (median mortality of 80%) (Brusselaers et al., 2010a). Since these early reports, the prevalence of AKI slightly increased (possibly linked to a more sensitive AKI diagnosis), but the prevalence of AKI-RRT decreased. This was paralleled by an improvement in outcome of all AKI patients as well as of AKI patients requiring RRT (Brusselaers et al., 2010a).

Pathophysiology and contributing factors

The pathophysiology of AKI in burn injury is not completely understood, probably due to its heterogeneous and multifactorial character with several hits. Decreased kidney perfusion, secondary to burn shock and inflammation, are two important contributing factors (Colpaert and Hoste, 2008). The exact role of renal ischaemia and hypoperfusion is uncertain, but may be less prominent than presumed (Arturson, 1985; Langenberg et al., 2006; Colpaert and Hoste, 2008). Instead, inflammation and apoptosis may be important causal factors (Jeschke et al., 2007; Colpaert and Hoste, 2008; Mariano et al., 2008; Wan et al., 2008) although also rhabdomyolysis, and volume overload resulting in increased central venous pressure, intra-abdominal hypertension, and abdominal compartment syndrome, may play a role.

Inflammatory response and infection

Local inflammation following injury is essential for wound healing and host defence against infection. The immunologic response to severe burn injury is initially pro-inflammatory but later becomes

Table 253.1 Epidemiology of AKI in patients with severe burn injury

AKI defined by:	Prevalence (%) Median (interquartile range)	Mortality (%) Median (interquartile range)
Fixed SCr cut-off (SOFA)	20.7 (9.5–30.9)	73.3 (48.8–88.2)
Relative increase SCr (RIFLE)	26.6 (18.5–47.4)	34.9 (28.4–52.6)
Renal replacement therapy	3.2 (1.6–11.6)	80.0 (67.9–100)
	Risk ratio (interquartile range)	
RIFLE-Risk	2.59 (0.68–9.82)	
RIFLE-Injury	5.31 (2.47–11.46)	
RIFLE-Failure	9.88 (6.83–14.27)	
All RIFLE categories	6.17 (3.98–9.55)	
Renal replacement therapy	6.37 (3.99–10.17)	

Data adapted from a systematic review and meta-analysis including studies published in the period 1960–2009 (Brusselaers et al., 2010a).

SCr = serum creatinine.

predominantly anti-inflammatory, in an attempt to maintain homeostasis and restore normal physiology. Both of these phases are characterized by fever, the generation of acute phase proteins, and an overall state of catabolism, mediated by several local and systemic inflammatory mediators and stress hormones (Church et al., 2006; Jeschke et al., 2007; Colpaert and Hoste, 2008; Mariano et al., 2008; Wan et al., 2008). There is an increase in the levels of vasopressin, aldosterone, growth hormone, cortisol, glucagon, and catecholamines. The anti-inflammatory response and the subsequent immunosuppression following burn injury are characterized by a set of opposing cell types and cytokines.

In patients with severe burn injuries, the most common cause of systemic inflammatory response syndrome (SIRS) is the burn itself, although later in the disease course, infected burn wounds—from catheter tips or other sources of infection—may lead to sepsis, potentiating the already activated immune system (Bang et al., 2002; Church et al., 2006). Compared to other ICU patients, including other trauma patients, burn patients have a longer and more severe inflammatory response (Jeschke et al., 2007).

Burn shock

Without adequate therapy, deep burn injuries covering > 10–15% of the body result in 'burn shock'. Burn shock is caused by fluid losses through burned skin, and massive fluid shift from the blood into the interstitial compartment, especially in burned tissue, but to a lesser extent also in non-injured organs and tissues (Lund et al., 1992). Oedema development in burned skin is characterized by the extremely rapid onset of tissue water content, which can double within the first hour (Arturson, 1985). The amount of oedema formation depends on the type and extent of the injury, as well as the type and volume of fluid administration (Arturson, 1985; Lund et al., 1992). Burn shock is thus characterized by haemodynamic changes similar to those that occur after haemorrhage, including decreased plasma volume, cardiac output, and urine output, and increased system vascular resistance resulting in a reduction of peripheral blood flow. However, an increase in haematocrit and haemoglobin concentration will often appear even with adequate fluid resuscitation. The primary therapeutic goal in treating hypovolaemic shock is to promptly restore vascular volume and to preserve tissue perfusion in order to minimize tissue ischaemia (Baker et al., 2007; Pham et al., 2008).

Abdominal compartment syndrome

Excessive volume resuscitation to prevent and treat burn shock may lead to intra-abdominal hypertension and abdominal compartment syndrome (ACS). ACS is characterized by a combination of increased intra-abdominal pressure, and organ dysfunction, such as oliguria, respiratory insufficiency, or haemodynamic instability, and is life-threatening when left untreated (Ivy et al., 1999; Ivy et al., 2000; Oda et al., 2006; De Waele et al., 2011). Intra-abdominal hypertension is probably an underestimated contributor to the development of late AKI after burn shock (Tuggle et al., 2007; Colpaert and Hoste, 2008; De Waele et al., 2011). Main risk factors are high TBSA, presence of circumferential burns on the abdomen, and massive resuscitation fluid volumes (Ivy et al., 1999; Ivy et al., 2000; Oda et al., 2006; Tuggle et al., 2007; De Waele et al., 2011). The extent of gut oedema and amount of ascites, by increasing the volume of the abdominal cavity, might also be important contributing factors (Oda et al., 2006). In burn patients, intra-abdominal hypertension and ACS may occur during the resuscitation period or later in the hospital course due to sepsis (Latenser et al., 2002; Oda et al., 2006).

The exact pathophysiology by which intra-abdominal hypertension leads to AKI is complex. Haemodynamic factors play an important role. Intra-abdominal hypertension leads to decreased renal arteriolar and microcirculatory blood flow and also increased renal venous pressure (Bradley and Bradley, 1947; Harman et al., 1982; Doty et al., 1999; Wauters et al., 2009). In addition, increased renal parenchymal pressure (Doty et al., 2000; Herrler et al., 2010) and inflammation secondary to intra-abdominal hypertension (Oda et al., 2002; Rezende-Neto et al., 2002; Kowal-Vern et al., 2006) also play a role in the pathogenesis of intra-abdominal hypertension-related AKI.

Intra-abdominal hypertension is probably a frequent and underestimated complication in burn patients and has been reported in

up to 70% of patients with severe burn injury. ACS is present in 17–30% of patients (Ivy et al., 2000; Latenser et al., 2002; Oda et al., 2006). Several reports mention that intra-abdominal hypertension can be prevented by decreasing the amount of resuscitation fluid, and the use of plasma or hypertonic saline (O'Mara et al., 2005; Oda et al., 2006; Arlati et al., 2007). Intra-abdominal hypertension can usually be treated conservatively, by drainage of excess fluids; although in case of ACS, tangential excision of the burn eschar (escharotomy) on the abdomen or even abdominal decompressive laparotomy may be necessary to decompress the abdominal cavity.

Intra-abdominal pressure can easily be measured by means of a urinary bladder catheter, and intra-abdominal hypertension can thus be detected in an early phase. Routine measurement of intra-abdominal pressure is thus recommended in patients with severe burn injury (Ivy et al., 1999; Ivy et al., 2000; Latenser et al., 2002; Oda et al., 2006; De Waele et al., 2011).

Rhabdomyolysis

Rhabdomyolysis, which occurs in one-sixth of burn patients who developed AKI, may also compromise renal function (Mustonen and Vuola, 2008; Kasaoka et al., 2010; Stollwerck et al., 2011; Stewart et al., 2013). Breakdown of damaged skeletal muscles leads to the release of breakdown products (e.g. myoglobin) into the bloodstream, which can result in AKI, presumably due to intrarenal vasoconstriction and tubular toxicity of myoglobin. Several studies found that rhabdomyolysis was frequent in burn injury patients, and increasing creatinine kinase concentrations were associated with increased risk for AKI, RRT, and even mortality (Stewart et al., 2013).

Povidone-iodine

Since complete wound closure by skin grafting following debridement often takes several days to weeks, the topical antimicrobial agent povidone-iodine for burn dressing is often used to avoid infection. Yet, in extensive burns, this may lead to elevated blood iodine concentrations, secondary to increased absorption in combination with hampered renal excretion (Lavelle et al., 1975; Pietsch and Meakins, 1976; Eloot et al., 2010). Accumulation of iodine will increase the anion gap, and leads to metabolic acidosis. In addition, iodine may directly cause AKI, and heart conduction abnormalities, eventually leading to heart block. Iodine is a halogen and may be falsely measured as chloride, leading to a false diagnosis of hyperchloraemic metabolic acidosis.

Renal insufficiency can further worsen the iodine accumulation. On the other hand, renal insufficiency of whatever cause may be aggravated by iodine.

While normal blood levels for iodine are in the range of 0.045–0.08 mg/L, blood iodine levels may be > 1000-fold higher. The actual concentration at which toxic symptoms may occur is still not exactly known. Several studies reported the presence of iodine intoxication related to wound care of open burn wounds, with lethal plasma concentrations from 10 to 30 mg/L. Measuring serum iodine levels in patients treated with large quantities of povidone-iodine is recommended.

As discontinuation of topical povidone-iodine therapy alone does not lead to immediate normalization of iodine levels, prolonged or continuous dialysis with sufficient blood flow is the best choice to reduce iodine levels relatively quickly in case of sudden important complications (Eloot et al., 2010). This is especially true since iodine is a small water-soluble compound, which can be removed by simple diffusion. It is distributed in a plasmatic and extraplasmatic volume with slow transport to the plasmatic compartment; hence the dialyser clearance during high-flux dialysis is comparable with that of small solutes such as urea. Intercompartmental clearance of iodine is low and more comparable to that of beta-2 microglobulin, which mandates long treatment times.

Definitions and diagnostic challenges

The scientific reporting on AKI is heterogeneous, with > 20 different definitions applied to describe an 'abrupt and sustained decrease in kidney function' in burn patients (and > 35 in ICU populations) (Brusselaers et al., 2010a). In the past, AKI was only considered significant when there was need for RRT (AKI-RRT), although there is still no consensus on when RRT should be initiated. Nowadays it is well known that even moderate decreases in kidney function may have a negative impact on outcome (Hoste et al., 2006).

The RIFLE consensus definition, and its later modifications by the Acute Kidney Injury Network (AKIN), and after that by the Kidney Disease: Improving Global Outcomes (KDIGO) group, has been considered the gold standard definition since 2004 (Bellomo et al., 2004; Mehta et al., 2007; Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group, 2012). It classifies AKI into three grades of increasing severity (risk, injury, failure), based on either an increase of serum creatinine (SCr) or a period of decreased urine output (these definitions are discussed in Chapter 220).

Diagnosis of AKI may be different and more challenging than in other ICU cohorts. In burn patients, SCr concentration may underestimate kidney function, due to volume resuscitation resulting in haemodilution and to less creatinine production due to inflammation and catabolism. Since large-volume resuscitation is necessary in the early phase of burn care to compensate for the massive fluid losses and decreased effective circulating volume, this may lead to haemodilution, and consequently false low SCr concentrations (Macedo et al., 2010). Loss of muscle mass, the source of creatinine, will also contribute to lower SCr concentrations for the same glomerular filtration rate (GFR) (Hoste et al., 2005). Alternatively, muscle injury, as a consequence of the burn injury, may also lead to elevations in SCr by increased release of creatinine in the circulation, while the GFR remains unaffected. Given the important impact of AKI on morbidity and mortality, early diagnosis of AKI by alternative biomarkers for early detection of functional or structural renal abnormalities seems warranted. Of these, most attention has been paid to proteinuria (Lindquist et al., 1984; Sabry et al., 2009; Hu et al., 2012), cystatin C (Cai et al., 2012), and neutrophil gelatinase-associated lipocalin (NGAL) (Hong et al., 2013). Although early studies demonstrate that these markers may allow more early diagnosis of AKI, the exact role of these emerging biomarkers in the diagnostic and treatment plan of burn patients is at present not clear.

Risk factors for acute kidney injury

Classic risk factors for AKI are chronic kidney disease, hypertension, and diabetes; as well as shock, inflammation, toxins, aminoglycosides and ACS (see Chapter 220). For patients with burn injury in particular, older age, severity of the burn injury assessed by the TBSA, sepsis, and multiorgan dysfunction are well recognized risk

factors for the development of AKI (Fig. 253.1). Inadequate fluid resuscitation during the initial burn period in particular is linked to early AKI. Sepsis and multiorgan dysfunction may lead to late AKI. As in other forms of AKI, fluid overload is also associated with worse outcomes in burn patients (Dulhunty et al., 2008).

To better predict the risk for late AKI in burn patients and to help decision-making (e.g. prophylactic measures), Schneider et al. developed a classification and regression tree with the data of 220 burn patients, based on variables which could be obtained easily within 48 hours after the trauma (Schneider et al., 2012). Of 33 possible predictors, this regression tree showed that non-renal organ failure, hypoglycaemia (< 83 mg/dL or < 4.6 mmol/L), low base deficit (<11.43 mEq/L), and early blood transfusion were the four most important predictors for late AKI (based on frequency and impact). However, these factors may not be causal but merely markers of aetiologic factors not included in the model or not considered significant.

Prevention and treatment

Similar to AKI occurring in other types of patients, there is at present no specific drug for prevention or treatment of AKI. Therefore, we can only advise a few general principles, based on data from general ICU patients, and burn patients (for more details, see Chapter 222).

Treat hypovolaemia, but prevent volume overload

Early burn shock is characterized by hypovolaemia and may lead to decreased kidney perfusion and AKI. This knowledge is currently well appreciated in the medical world, and resuscitation schedules such as the Parkland formula (amount of fluid required in the first 24 hours = 4 mL × body weight (kg) × TBSA (%)) are well known and used. Pain, and resultant opioid prescription with resultant vasodilation, may in a second stage leading to even more pronounced fluid requirements, the so-called opioid fluid creep (Sullivan et al., 2004; Saffle, 2007; Wibbenmeyer et al., 2010). However, volume overload in AKI is also associated with worse outcomes (Dulhunty et al., 2008), as also described in general ICU patients and in severe sepsis (Payen et al., 2008; Macedo et al., 2010; Vaara et al., 2012). It is at present less clear whether AKI and worse outcomes are the consequence of severe disease (leading to worse outcomes), or whether fluid overload in itself is the reason for AKI and worse outcomes. However, the repeated observations, different statistical models, and pathophysiologic mechanisms suggest that fluid overload may be the cause. The presumed mechanisms on why fluid overload may lead to AKI include intra-abdominal hypertension and ACS, increased renal venous pressure, and resultant decreased microcirculation in the kidney.

Therefore, fluid resuscitation should preferably be targeted to haemodynamic endpoints and urine output (0.5–1 mL/kg/houe), and should be reassessed on an hourly basis in the acute phase of burn injury. Also, intra-abdominal pressure should be measured, and if intra-abdominal hypertension or ACS occurs, adequate treatment measures should be applied (De Waele et al., 2011).

Optimize blood pressure

The normal autoregulation of renal blood flow is absent in patients with severe sepsis and AKI, and probably also in burn injury patients. This will result in a linear relationship between blood pressure and renal blood flow, with decreased blood flow when a patient is hypotensive. A small study in cardiac surgery patients showed that there was increased oxygen delivery to the kidney when mean blood pressure was increased from 60 to 75 mmHg (Redfors et al., 2011). Increasing the blood pressure to 85 mmHg offered no additional benefit. It is uncertain if this observation is generalizable for burn injury patients as well.

At present, the limited data available indicate that norepinephrine (noradrenaline) is the most optimal vasopressor agent for increasing blood pressure in patients with severe sepsis (Dellinger et al., 2013). Despite its peripheral vasoconstrictive effects, norepinephrine increases renal cortical and medullar blood flow.

Stop nephrotoxic medications

In patients who are at risk for AKI, as in severe burn injury, common sense dictates not to add toxicity to the kidneys (see Chapter 222). Fluids used for resuscitation may also be nephrotoxic. Synthetic colloids, such as starches and gelatins, are in a dose-dependent manner associated with AKI. This was well known for the first- and second-generation starches, but recent prospective randomized

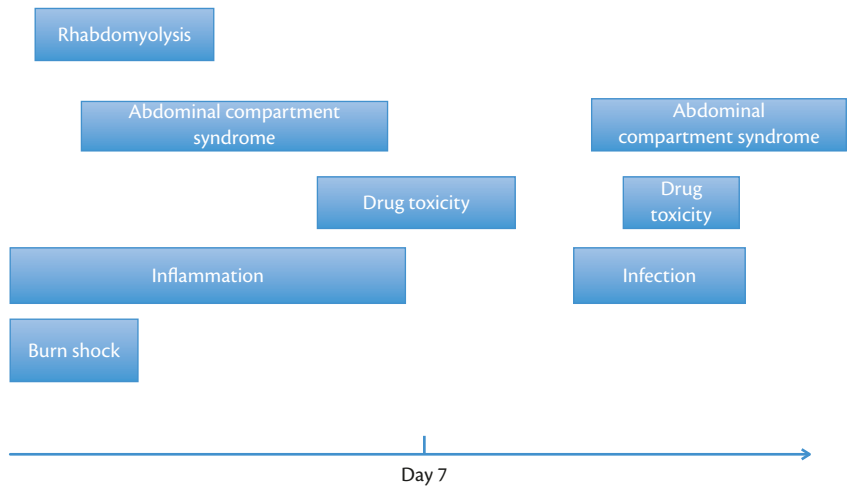

Fig. 253.1 Contributing factors for acute kidney injury in patients with severe burn injury over time.

studies in ICU patients revealed this also to be true for the more modern third-generation starches (Myburgh et al., 2012; Perner et al., 2012; Reinhart et al., 2012; Gattas et al., 2013). Observational data in ICU patients showed a similar association with AKI for gelatins (Schabinski et al., 2009). Although data in burn injury patients are lacking, the use of these synthetic colloids in burn injury patients cannot be recommended at present, especially as volume resuscitation in burn injury patients typically involves large volumes to be infused over a short time period (Reinhart et al., 2012; Gattas et al., 2013).

Large-volume crystalloid fluid resuscitation may be complicated by hyperchloraemic metabolic acidosis, especially when near isotonic saline solution (NaCl 0.9%) is used (Yunos et al., 2010, 2011). Despite its description as near isotonic, this fluid has an almost 50% higher chloride concentration compared to the normal plasma in humans (154 mmol/L compared to 105 mmol/L). Hyperchloraemic metabolic acidosis is associated with AKI, probably by decreased renal blood flow. Restricting chloride in intravenous fluids, such as by the use of Plasmalyte®, or Hartmann's or Ringer's solutions will decrease the incidence of hyperchloraemic acidosis, and its associated complications, including AKI (Yunos et al., 2010, 2012; Shaw et al., 2012).

Renal replacement therapy

At present there are no prospective randomized studies on any aspect of RRT in burn injury patients. Therefore, recommendations on, for example, timing of initiation, modality of RRT, optimal type of anticoagulation, or criteria for discontinuation of RRT can only be made either based on expert opinion, or on extrapolations of data in general ICU patients.

A protocolized programme of early initiation of continuous RRT for AKI in burned military casualties showed that this was associated with improved outcomes compared to a conservative approach with intermittent low-dose RRT (Chung et al., 2008, 2009).

Conclusions

AKI, defined by the RIFLE classification, occurs in approximately one-quarter of severe burn patients. As in other patients, AKI is associated with worse outcomes, including increased mortality. The pathophysiology of AKI in severe burn injury patients is not well understood. Several aspects may play a role in the acute phase, including decreased kidney perfusion, inflammation, volume overload, intra-abdominal hypertension, rhabdomyolysis, and the type of fluid used for resuscitation. Synthetic colloids (starches and gelatins) in particular are associated with AKI, but hyperchloraemic acidosis, a frequently occurring consequence of large volume resuscitation with near isotonic saline, may also increase the incidence of AKI.

Similar to other types of AKI, there is no specific treatment for AKI in burns; in particular only incomplete knowledge exists on the processes of care for intervention with RRT.

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