CHAPTER 16

Risk Factors and Risk Assessment in Acute Kidney Injury

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OBJECTIVES

This chapter will:

1. Explain the importance of risk assessment for acute kidney injury in improving clinical outcomes.
2. Describe how to apply risk assessment principles to lower the incidence of acute kidney injury resulting from preventable causes.
3. Delineate how biomarkers may refine risk assessment strategies.

Acute kidney injury (AKI) is a well-defined deterioration in kidney function that occurs within a short period of time and ranges in severity from mild, transient elevations in serum creatinine to severe anuric kidney failure with the need for dialysis.[1] Depending upon the patient population studied, the incidence of AKI in hospitalized patients ranges from 3% to 20%.[2–6] For those patients admitted to the intensive care unit (ICU), the incidence of AKI ranges from 16% to 67%.[7–9] Furthermore, the available evidence suggests that the incidence of AKI is growing.[10] What is paramount is that the development of AKI is associated with significant increases in morbidity and mortality, even with small decreases in kidney function.[3,6,10–14] Despite this clinical importance, there are very few effective interventions either to prevent AKI in at-risk populations or to treat established AKI other than dialysis.[15]

Given this scenario, prevention of AKI and its downstream effects is critical. Preventative strategies begin with a deep understanding of the risk factors associated with AKI, especially those risk factors that are potentially amenable to intervention and/or modification. Numerous observational studies have identified a host of risk factors associated with the development of AKI (Box 16.1). Many of these risk factors are considered nonmodifiable or intrinsic susceptibilities to developing AKI. This indicates that preventative strategies cannot directly affect these risks factors to lower the event rate for AKI. However, knowledge of these risk factors is critical in allowing clinicians to identify those patients who are at highest risk and implement diagnostic and therapeutic strategies to improve outcomes. This is important because the event rate for AKI is very infrequent in low-risk populations, and implementing preventative strategies in such low-risk populations is likely to be expensive and not cost effective. This is also true for design of clinical trials, in which an enriched patient population at the highest risk for AKI is

BOX 16.1

Risk Factors for the Development of Acute Kidney Injury

Intrinsic and Nonmodifiable Susceptibilities

- Age
- Male gender
- Genetic predispositions
- Comorbid conditions:
  - Preexisting CKD
  - Diabetes mellitus (usually in combination with proteinuria and/or CKD)
  - Proteinuria or albuminuria
  - Hypertension (especially, poorly controlled)
  - Chronic liver disease with cirrhosis
  - Heart failure (systolic or diastolic)
  - Coronary artery disease and/or recent myocardial infarction
  - Chronic obstructive pulmonary disease
  - Peripheral vascular disease
  - Cancer

Extrinsic and Potentially Modifiable Exposures

- Drug toxicity, drug dosing and drug-drug interactions
- Procedure related:
  - Cardiac surgery
  - Noncardiac (especially vascular) surgery
  - Emergency surgery
  - Radiocontrast media exposure
- Treatment related:
  - Sepsis
  - Fluid resuscitation (type and amount of fluids)
  - Trauma care (such as rhabdomyolysis)
  - Anemia

CKD, Chronic kidney disease.

needed to perform an appropriately powered trial that enrolls a reasonable number of subjects. A recent study highlighted that even in low-risk populations, AKI is associated with significant mortality and thus even lower risk populations benefit from strategies focused on prevention.[16] Many of the most important and consistent susceptibilities found in observational studies associated with AKI fall into this intrinsic category and include advanced age and the presence of comorbid illnesses, especially chronic kidney disease (CKD), diabetes, and heart failure. Of increasing importance but yet to be well defined are genetic susceptibilities to kidney injury that genome-wide association studies are elucidating.[17]

The other groups of risk factors or exposures include those that may be modifiable and include events such as radiographic contrast exposure or surgery, which can be timed and predicted and protocols can be developed to lower risk. Other factors are in direct control of the clinician, such as medication choice and dosage, and also can be altered. A multinational study by Uchino et al. demonstrated the possible impact of modifying these risks.[18] Although many of the causes of AKI may not be intervened upon easily (47.5% of patients had sepsis as the primary cause and 27% had cardiogenic shock), a large percentage of cases represent those resulting from causes that may be modifiable (34% of AKI was associated with major surgery, 26% was related to hypovolemia, and 19% of AKI was potentially drug-related). Thus many of these causes have risk/exposure components that can be identified and potentially affected to lower the eventual rate of AKI in susceptible patients. For example, within causes such as cardiac surgery, the treatment of hypovolemia and avoidance of nephrotoxic medications when rapidly identified may lessen the development of AKI. Most patients will have more than one risk factor for AKI. For example, a recent study identified that the prevalence of AKI risk factors was 2.1 +/- 2.0 per patient and that 72% of patients who developed AKI had more than two risk factors (when age ≥ 65 years was included, 84% of patients with AKI had two or more risk factors).[19] An important caveat is that risk factors for AKI commonly are encountered in the hospitalized patient, and in this study, two or more AKI risk factors still were found in 43% of the cohort without AKI, suggesting that simply looking at AKI risk factors without robust prediction models may be of limited use.[19]

Kidney Disease Improving Global Outcomes (KDIGO) guidelines specifically recognize the importance of risk factor assessment in the following sections[1]:

- Guideline 2.2.1: We recommend that patients be stratified for risk of AKI according to their susceptibilities and exposures (evidence grade 1B)
- Guideline 2.2.2: Manage patients according to their susceptibilities and exposures to reduce the risk of AKI (not graded)
- Guideline 2.2.3: Test patients at increased risk for AKI with measurements of serum creatinine and urine output to detect AKI (not graded). Individualize frequency and duration of monitoring based on patient risk and clinical course (not graded)

RISK ASSESSMENT AND PREVENTATIVE STRATEGIES

Risk assessment for AKI is restricted largely to hospitalized patients or to patients undergoing outpatient procedures such as radiographic contrast administration. This is largely due to logistic issues, because the opportunity to intervene before exposures in the community setting is limited, and most patients with community-acquired AKI enter the hospital with established injury. Furthermore, risk assessment as a tool to lessen the risk of AKI is most useful when the exposure can be predicted and is timed. This allows the clinician to modify, delay, or cancel the exposure to directly lower the AKI event rate. For those exposures that cannot be predicted easily, such as sepsis, risk assessment still can be useful in that it can help stratify patients who may be exposed to subsequent nephrotoxic exposures, identify patients in need of more frequent monitoring, and guide clinicians in performing maneuvers that mitigate further injury.

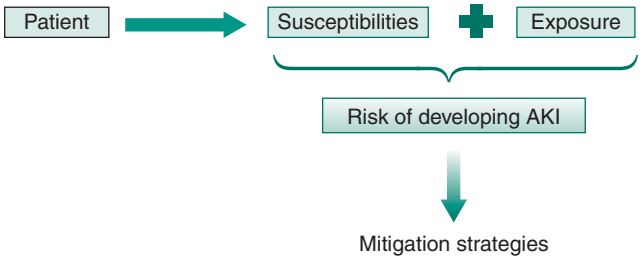

FIGURE 16.1 Risk assessment. *AKI,* Acute kidney injury.

Many clinicians intuitively perform risk assessment by integrating known clinical data to make an informed decision on how they may proceed to mitigate the eventual occurrence of AKI. In doing so, clinicians use the combination of the patient's inherent susceptibility to AKI along with details of the exposure to develop a plan to mitigate the event rate (Fig. 16.1). The utility of this approach may, in fact, be limited, because both low- and high-risk populations for AKI share many common risk factors, such as age, and thus risk assessment scoring systems have been developed to better stratify patients for informed consent purposes and initiation of mitigation strategies.

Common Risk Factors for Acute Kidney Injury

Unfortunately, many common risk factors for AKI are not modifiable. These include intrinsic patient characteristics such as age, gender, and genetic predisposition, as well as multiple comorbid medical conditions such as heart failure, diabetes, hypertension, and CKD.[1] Elderly patients, defined as somewhere between 65 and 75 years of age, depending on the study cited, are at significantly greater risk for AKI. Bagshaw et al. found that patients above the age of 65 had more than twice the rates of AKI compared with patients aged 50 to 64, and those above 75 had nearly three times the rate of AKI compared to the 50- to 64-year-old group; notably, this finding was much stronger in males than females.[20]

The relationship between gender and risk for AKI is complex. Some literature suggests that rates of hospital-acquired AKI are greater in females than in males.[21–25] However, some newer studies seem to suggest that the risk for AKI in males may be higher than previously reported; a large meta-analysis including multiple cohorts of patients from the general population and CKD groups suggests that males have a risk for AKI that is somewhere between 50% to 100% greater than that of females.[26]

Race does not seem to be a strong risk factor for AKI in most settings. Some studies reveal no observed difference

between rates of AKI in different ethnicities or races, whereas others suggest a greater risk for AKI in African-Americans.[26–28] Notably, the effects of age, gender, and race appear to be attenuated in higher stages of CKD; it is unclear whether they play less of a role biologically, or simply that patient risk for AKI with advanced CKD is great enough that the contribution of these factors is not statistically significant.[26]

Unsurprisingly, preexisting CKD carries a high risk for development of AKI. Virtually every study that addresses the risk for AKI in patients with CKD has found a substantially increased association of AKI with CKD.[1,20,22–23,29–30] In one of the largest meta-analyses to date, Grams et al. found that the hazard ratio of developing AKI at an eGFR of 45 mL/min was 3.3 compared with an eGFR of 80.[26] Unsurprisingly, rates of AKI are even higher for stage 4 CKD. However, perhaps simply because of the very high rate of AKI in patients with significant CKD compared with other populations, the presence of CKD tends to decrease the impact of other risk factors such as hypertension and diabetes.[31]

In addition to greater rates of development of AKI, patients with CKD are more likely to have nonrecovery of their GFR to baseline after episodes of AKI. Patients with eGFR < 45 mL/min had roughly a 30% increase in the likelihood of death or development of end-stage renal disease (ESRD) after AKI in a cohort of nearly 40,000 patients.[32]

Similar to advanced CKD, preexisting proteinuria confers a markedly greater chance of developing AKI. Patients with albuminuria > 300 mg/g creatinine had a risk of AKI that was more than 2.5 times that of patients with undetectable albumin in urine.[26] With reduced GFR, this risk is multiplicative, with much higher rates of AKI in patients with advanced CKD and proteinuria; patients with CKD stage 4 and nephrotic-range proteinuria have an adjusted risk of AKI more than thirty times that of patients with no proteinuria and GFR > 90 mL/min.[31]

Patients with diabetes develop AKI at varying rates compared with the general population. The association between diabetes and AKI is established most strongly in the settings of iodinated contrast administration and cardiovascular surgery.[22,23] This risk may not be equal between type 1 and type 2 diabetes mellitus; for example, a Swedish registry of more than 36,000 patients undergoing coronary artery bypass graft surgery found that patients with type 1 diabetes had an odds ratio versus nondiabetic patients of 4.89 to develop AKI, compared with a relatively modest odds ratio of 1.27 for patients with type 2 diabetes compared with nondiabetic patients.[33]

Hypertension has been shown to increase the risk for AKI in various settings, including overall risk,[31] contrast administration,[34] lung resection,[35] severe aortic dissection,[36] and abdominal surgery,[25] among others. The odds ratio for hypertension causing AKI is generally 2 or less compared with reference populations, rendering hypertension a modest risk factor for AKI compared with some others.

Clinicians know that chronic liver disease carries a very high risk for acute kidney injury. Rates of AKI in cirrhosis range from below 20% to above 50%, depending on the clinical situation[37–42] and carry a hefty risk of mortality in this patient group; the risk of mortality rises to 10 times that of patients with cirrhosis but without AKI.[43]

Heart failure has been associated with increased risk for AKI across multiple settings.[20,22,23,29] In patients admitted with decompensated heart failure, very high rates of AKI have been described, often involving more than one third to one half of the patient cohort.[44–50] AKI risk is commonly higher in patients with systolic dysfunction regardless of clinical setting.[23,24,51]

Specific Risk Settings for Acute Kidney Injury

Many procedures in cardiac surgery and vascular surgery convey a high risk of AKI to the patient. Rates of AKI requiring renal replacement therapy in cardiac surgery vary from less than 0.5% to more than 18% depending on the patient population and local practices.[52–54] In addition to the aforementioned intrinsic risk factors for development of AKI after cardiac surgery, more complex cardiac disease such as left main coronary disease, cardiogenic shock, and emergent surgery convey additional risk.[55] Longer cardiopulmonary bypass, cross-clamp time, and "off-pump" (no cardiopulmonary bypass) procedures also increase the risk for AKI in patients undergoing cardiac surgery.[55] Risk of ESRD after cardiac surgery is also substantial, with 0.4% of patients in a cohort of nearly 30,000 developing ESRD within 4 years of the procedure; the risk was much higher in patients with AKIN stage 2 or 3 AKI, with a hazard ratio of 3.8 to develop ESRD compared with all patients.[56]

Vascular surgery may carry an even higher risk of AKI compared with cardiac surgery. A cohort of more than 3600 patients undergoing vascular surgery had rates of perioperative AKI of nearly 50%; smaller studies have found rates of vascular surgery-related AKI ranging from 12% to 75%, depending on the clinical situation.[57–63] Unsurprisingly, patients with ruptured aortic aneurysms have extremely high rates of AKI.[58]

The risk of development of AKI after iodinated contrast administration has been well described. Risk for AKI after iodinated contrast varies from less than 1% to greater than 25%.[1] Patient risk for AKI with iodinated contrast is best understood as a factor derived from factors related to the contrast itself (the volume and type of contrast used) and patient factors (hemodynamic status, medications used, presence of factors such as diabetes, CKD, and age).[1,24] Multiple risk-scoring systems (discussed in more detail later) have been developed to better assess risk and counsel patients.

High-osmolality iodinated contrast has been shown in multiple trials to increase the risk of AKI, particularly in patients with preexisting CKD, and these agents have largely been phased out of routine clinical practice.[64,65] Screening for kidney function before administration of contrast is done routinely; evidence also exists for screening of proteinuria in some settings given strong associations between proteinuria and serum creatinine in patients undergoing contrast studies.[66] Volume expansion with intravenous fluids is clearly the most evidence-based intervention to decrease the risk of iodinated contrast-associated AKI.[1,24] In addition to iodinated contrast, gadolinium-containing intravenous contrast also has been associated with AKI, although not as strongly.[67,68]

Multiple medications and drugs clearly raise the risk for AKI. Perhaps no group is as extensively studied as angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs). Rim et al. found in a cohort of 5299 patients that the use of ACE inhibitors or ARBs in patients receiving iodinated contrast conveyed an increased risk of more than 40% to develop AKI. In cardiac surgery, use of ACE inhibitors and ARBs has been associated with greater rates of AKI and postoperative shock in retrospective trials.[69–71] Nonsteroidal antiinflammatory drugs (NSAIDs) clearly raise the risk for AKI in multiple clinical settings; this risk is increased with simultaneous usage of NSAIDs, ACE inhibitors/ARBs, and diuretics.[24,72] Many other drugs can cause or increase the risk of AKI, including calcineurin inhibitors, antibiotics such as vancomycin and aminoglycosides, and others; in addition to the risk conferred by each of these agents used in isolation, drug-drug interactions and dosing errors may further increase risk.[1,24,72–74]

Although AKI related to nonmedication poisoning is substantially less well studied, acute and chronic poisoning with agents such as ethylene glycol, paraquat, and others also confer risk for AKI.[24,75]

Risk Assessment Scoring Systems

To facilitate refined risk assessment and assist in decision making, informed consent, and quality improvement projects, detailed risk assessment models have been developed and validated for situations in which the timing the nephrotoxic insult is known (e.g., surgery, radiographic contrast administration, or percutaneous coronary interventions). In these models, variables associated with AKI are identified, stratified in a logistic model (given point values proportional to their risk of being associated with AKI), and combined to give a global risk assessment of AKI (percent chance of developing AKI). An important caveat for many of these models is that the definition of the defining event (AKI) is not the same across models and can range from mild AKI (stage 1) to moderate-severe AKI (stages 2, 3). As an example, using data from the National Cardiovascular Data Registry Cath-Percutaneous Catheterization Intervention (PCI) Registry, Tsai et al. identified 11 variables that were associated with AKI: older age, baseline renal impairment (categorized as mild, moderate, and severe), prior cerebrovascular disease, prior heart failure, prior PCI, presentation (nonacute cardiovascular syndrome vs. non-ST segment elevation myocardial infarction [NSTEMI] vs. STEMI), diabetes, chronic lung disease, hypertension, cardiac arrest, anemia, heart failure on presentation, balloon pump use, and cardiogenic shock.[76] STEMI presentation, cardiogenic shock, and severe baseline CKD were the strongest predictors for AKI. These variables were used to develop the risk prediction model that has been validated subsequently with good predictive ability for AKI (c-statistic of 0.76) and even better predictive ability for AKI requiring dialysis (c-statistic of 0.92).[76,77] Thus clinicians can use a table that assigns point weights to each clinical variable in the model, add these values, and determine a total risk for AKI. For example, in this model, a 78-year-old male with diabetes, prior heart failure, prior carotid endarterectomy, and presenting with a NSTEMI and an estimated GFR of 42 with a hemoglobin of 9.5 g/dL would have a calculated AKI risk of 27.5% and a risk of needing dialysis of 0.5%.[76]

Similar risk assessment scores have been developed for cardiac surgery,[78–81] percutaneous cardiac interventions,[82–85] and radiographic contrast administration.[86–89] Some risk assessment scores do not only rely on patient-specific factors but also include procedure-related risk such as the volume of iodinated contrast that is administered.[90]

There are important caveats in using these risk prediction scores.[1] It is important to use contemporary risk-scoring systems, because those systems developed more than 5 to 10 years previously may not be applicable to current care settings [2]; patients who may have low risk scores still may benefit from prevention strategies[3]; the scores tend to have better negative predictive ability over positive predictive power; and[4] the best scoring systems are developed and validated in large cohort groups with a wide span of clinical variables and associated risk.

Risk prediction scores may be particularly useful in assessing quality improvement programs, because they allow for the determination of a predicted percentage of patients that would be expected to develop AKI in a particular setting such as postcardiac surgery. If the observed rate of AKI is greater than this predicted rate, quality improvement processes are mandated and can be measured against an expected rate of AKI. As mentioned above, these risk prediction scores also can improve the informed consent process, giving patients more specific details about their risk for particular outcomes.[91]

Using Risk Factors in Clinical Decision Making When the Insult Is Not Predictable

A substantial number of AKI events occur in patients in whom the precipitating insult is not predictable, such as sepsis or hypotensive events resulting from bleeding. In these settings, preemptive risk reduction strategies are not feasible. For example, in one series of patients with sepsis presenting to the emergency department, the admission serum creatinine was on average 2.6 mg/dL (+/- 2.0), signifying that many patients already had significant levels of AKI before any opportunities for intervention.[92] However, knowing the risk factors for AKI in a particular patient can be useful in thinking about care pathways and ongoing patient monitoring with a goal to lessen the impact of AKI (such as minimizing the risk of AKI transitioning to worsening stages or the need for renal replacement therapy). For instance, higher-risk patients (those with advanced age, diabetes, heart failure, preexisting CKD) with stage 1 AKI may benefit from more frequent vital sign monitoring, targeting higher mean arterial pressures, closer medication monitoring, avoidance of radiocontrast agents, and other interventions that are targeted to prevent worsening of AKI and hasten resolution. Such a strategy has not been tested rigorously.

Biomarkers to Enhance Risk Prediction Models

Novel biomarkers of AKI, such as neutrophil gelatinase-associated lipocalin (NGAL), kidney injury molecule-1 (KIM-1), and a host of others have been found to detect evidence of AKI before traditionally used laboratory methods such as serum creatinine become clinically relevant.[93] Although multiple biomarkers have been validated clinically, none have emerged as clearly providing a new standard of care for AKI diagnosis or risk assessment; however, nephrology is closer today than it has ever been to biomarkers being ready for widespread clinical use.[94]

Of all commercially available biomarkers of AKI, none have been better studied than NGAL. Initially validated with multiple studies in the setting of AKI in cardiac surgery,[95,96] there have since been investigations revealing NGAL as an early marker of AKI in all-cause AKI in critically ill patients,[97] sepsis,[98] and poisoning,[75] among others. Examining AKI in sepsis, a meta-analysis revealed that serum NGAL had a pooled sensitivity of 83% and specificity of 57% in predicting AKI; urine NGAL was more specific with sensitivity and specificity of 80% apiece, with an area under the curve (AUC) of 0.90.[98]

Combinations of biomarkers logically may fare better than certain single biomarkers at predicting the risk for AKI. One commercially available test (NephroCheck; Astute Medical) measures urinary levels of insulin-like growth factor 7 and tissue inhibitor of metalloproteinases-2, with an AUC of 0.80 for prediction of AKI in all-cause AKI in critically ill patients compared with 0.70 for urinary NGAL in their population.[99]

Biomarkers of kidney injury occupy a space somewhere between modifying risk prediction and diagnosis of AKI; clinically, although many of them have been shown to predict AKI, they are not yet accepted as evidence that AKI has occurred.[93] However, the knowledge that biomarkers are abnormal can lead clinicians to optimize the patient's

situation to further reduce any risk for AKI (e.g., change intravenous fluid strategies, discontinue nephrotoxins, and monitor the patient's renal function and urinary output more closely).[94]

Genetic Polymorphisms and Their Association With Risk for Acute Kidney Injury

The past decade has brought with it a growing body of research examining non-Mendelian genetic factors affecting risk for AKI, specifically, studies of single nucleotide polymorphisms (SNPs) and other genetic polymorphisms of various genes that confer increased risk for AKI.[100–103] For example, du Cheyron et al. evaluated patients who were hospitalized in a critical care unit for the presence of an inserted base pair fragment in one of the introns that codes for angiotensin-converting enzyme (ACE); they found that patients who were homozygous for this ACE insertion polymorphism had a substantially elevated risk to develop AKI, with an odds ratio of 6.5 compared with heterozygotes and homozygotes.[101] In the setting of severe sepsis, SNPs in genes coding for vascular endothelial growth factor (VEGF) and pre–B-cell colony-enhancing factor were associated with AKI.[102] Other SNPs have been associated with AKI in various settings, including SNPs in the genes BCL-2, IL-6, TNFA, and many others; however, some of these associations are not robust.[103]

Genome-wide association studies allow for a broader search than testing individual genes of concern; these studies use microarrays to detect many different SNPs, allowing for discovery of novel genes that may confer risk for AKI. The only genome-wide association study of patients with AKI, performed in the setting of coronary bypass graft surgery, found two novel loci with SNPs that conferred an increased risk for AKI.[100] As increasing effort and importance is placed on "personalized medicine," preemptive identification of these genes may play a role in determining individual patients' risk for AKI.

Using the Electronic Medical Record to Assess Risk for Acute Kidney Injury

Electronic medical records (EMR) and computer-assisted order entry offer a potential method to link automated risk assessment with a series of clinical pathways designed to lessen that risk.[104] Furthermore, the large amount of data and outcomes embedded in the EMR allow for development, testing, and validation of risk prediction models.[105] For instance, a simple system alerts clinicians regarding the use of potentially nephrotoxic medications (risks) and small changes in serum creatinine.[106] In one study using such a system, the use of alerts led to a significant fall in AKI (relative risk of 0.46 [95% confidence interval]: 0.22 to 0.94).[105] Another system alerted clinicians to the risk for contrast media-associated AKI and recommended a prophylactic measure (such as hydration protocols) to those patients at risk.[107] With this intervention, the use of prophylactic measures increased from 25% to 55%, and the incidence of AKI fell from 10% to 3%. In the pediatric population, a robust nephrotoxin identification program linked to changes in serum creatinine led to 42% reduction in AKI intensity.[108] These systems focus on delivering a risk assessment to the clinician and then recommending a course of action or linking the risk with a change in kidney function.

Using a different methodology, Wilson et al. provided a simple AKI alert to clinicians via text-page and assessed this impact versus usual care.[109] In this study the composite relative maximum change in creatinine, dialysis, and death at 7 days did not differ between the alert group and the usual care group.[109] Thus simply alerting clinicians to the early development of AKI did not change outcomes in the absence of the risk assessment or recommendations for next steps. This study and other similar ones led a consensus panel to conclude that current evidence for e-alert system efficacy, although growing, remains insufficient.[110]

SUMMARY

Risk assessment for AKI is a critically important part of the care of patients and has the possibility to improve outcomes by lessening the incidence and impact of AKI. However, risk scoring systems still require refinement and greater predictive capability. Recent developments with biomarkers and genome-wide association studies may provide tools to better define prediction algorithms, and the use of EMR tools and triggers may improve implementation of these scoring systems as well as link them to improved care pathways.

Key Points

1. Given that there are few effective therapies for established acute kidney injury (AKI), prevention is a critical aspect of care that can be used to improve outcomes, and risk assessment is a key part of any preventative strategy.
2. Risk assessment scoring systems have been developed and studied in specific circumstances in which preventative strategies for AKI could be applied, such as after cardiac surgery.
3. Risk assessment strategies for causes of AKI that are not predictable (such as sepsis) are much harder and must focus on prevention of subsequent insults that may be more preventable.
4. Biomarkers and genetic polymorphisms may allow enhanced refinement of risk assessment methodologies.

Key References

1. KDIGO Clinical Practice Guideline for Acute Kidney Injury: http://www.kdigo.org/clinical_practice_guidelines/pdf/KDIGO%20AKI%20Guideline.pdf (Accessed 4 April 2016).
19. Roberts G, Phillips D, McCarthy R, et al. Acute kidney injury risk assessment at the hospital front door: what is the best measure of risk? *Clin Kidney J.* 2015;8:673-680.
76. Tsai TT, Patel UD, Chang TI, et al. Validated contemporary risk model of acute kidney injury in patients undergoing percutaneous coronary interventions: insights from the National Cardiovascular Data Registry Cath PCI Registry. *J Am Heart Assoc.* 2014;3:e001380.
80. Huen SC, Parikh CR. Predicting acute kidney injury after cardiac surgery: a systematic review. *Ann Thorac Surg.* 2012;93:337-347.
99. Kashani K, Al-Khafaji A, Ardiles T, et al. Discovery and validation of cell cycle arrest biomarkers in human acute kidney injury. *Crit Care.* 2013;17:R25.

A complete reference list can be found online at ExpertConsult.com.

References

1. KDIGO Clinical Practice Guideline for Acute Kidney Injury: http://www.kdigo.org/clinical_practice_guidelines/pdf/KDIGO%20AKI%20Guideline.pdf (Accessed 4 April 2016).
2. Ali T, Khan I, Simpson W, et al. Incidence and outcomes in acute kidney injury: a comprehensive population-based study. *J Am Soc Nephrol*. 2007;18:1292-1298.
3. Lafrance JP, Miller DR. Acute kidney injury associates with increased long-term mortality. *J Am Soc Nephrol*. 2010;21:345-352.
4. Waikar SS, Liu KD, Chertow GM. Diagnosis, epidemiology and outcomes of acute kidney injury. *Clin J Am Soc Nephrol*. 2008;3:844-861.
5. Wonnacott A, Meran S, Amphlett B, et al. Epidemiology and outcomes in community-acquired versus hospital-acquired AKI. *Clin J Am Soc Nephrol*. 2014;9:1007-1014.
6. Susantitaphong P, Cruz DN, Cerda J, et al. World incidence of AKI: a meta-analysis. *Clin J Am Soc Nephrol*. 2013;8:1482-1493.
7. Bagshaw SM, George C, Dinu I, et al. A multicenter evaluation of the RIFLE criteria for early acute kidney injury in critically ill patients. *Nephrol Dial Transplant*. 2008;23:1203-1210.
8. Ostermann M, Chang RW. Acute kidney injury in the intensive care unit according to RIFLE. *Crit Care Med*. 2007;35:1837-1843.
9. Piccini P, Cruz DN, Grammaticopolo S, et al. Prospective multicenter study on epidemiology of acute kidney injury in the ICU: a critical care nephrology Italian collaborative effort (NEFROINT). *Minerva Anestesiol*. 2011;77:1072-1083.
10. Rewa O, Bagshaw SM. Acute kidney injury- epidemiology, outcomes and economics. *Nat Rev Nephrol*. 2014;10:193-207.
11. Nisula S, et al. Incidence, risk factors and 90 day mortality of patients with acute kidney injury in Finnish intensive care units: the FINNAKI study. *Intensive Care Med*. 2013;39:420-428.
12. Thakar CV, Christianson A, Freyberg R, et al. Incidence and outcomes of acute kidney injury in intensive care units: a Veterans Administration study. *Crit Care Med*. 2009;37:2552-2558.
13. Hoste EA, et al. RIFLE criteria for acute kidney injury are associated with hospital mortality in critically ill patients: a cohort analysis. *Crit Care*. 2006;10:R73.
14. Hsu CY, et al. Nonrecovery of kidney function and death after acute on chronic renal failure. *Clin J Am Soc Nephrol*. 2009;4:891-898.
15. Okusa MD, Rosner MH, Kellum JA, et al. Therapeutic targets of human AKI: Harmonizing human and animal AKI. *J Am Soc Nephrol*. 2016;27:44-48.
16. Sileanu FE, Murugan R, Lucko N, et al. AKI in low-risk versus high-risk patients in intensive care. *Clin J Am Soc Nephrol*. 2015;10:187-196.
17. Stafford-Smith M, Li YJ, Matthew JP, et al. Genome-wide association study of acute kidney injury after coronary bypass surgery identifies susceptibility loci. *Kidney Int*. 2015;88:623-632.
18. Uchino S, Kellum JA, Bellomo R, et al. Acute renal failure in critically ill patients. A multinational, multicenter study. *JAMA*. 2005;294:813-818.
19. Roberts G, Phillips D, McCarthy R, et al. Acute kidney injury risk assessment at the hospital front door: what is the best measure of risk? *Clin Kidney J*. 2015;8:673-680.
20. Bagshaw SM, Laupland KB, Doig CJ, et al. Prognosis for long-term survival and renal recovery in critically ill patients with severe acute renal failure: a population-based study. *Crit Care*. 2005;9:R700-R709.
21. Oeyen S, Vandijck D, Benoit D, et al. Long-term outcome after acute kidney injury in critically-ill patients. *Acta Clin Belg Suppl*. 2007;337-340.
22. Mehran R, Aymong ED, Nikolsky E, et al. A simple risk score for prediction of contrast-induced nephropathy after percutaneous coronary intervention: development and initial validation. *J Am Coll Cardiol*. 2004;44:1393-1399.
23. Thakar CV, Arrigain S, Worley S, et al. A clinical score to predict acute renal failure after cardiac surgery. *J Am Soc Nephrol*. 2005;16:162-168.
24. KDIGO Clinical Practice Guideline for Acute Kidney Injury Online Appendices A-F: http://www.kdigo.org/clinical_practice_guidelines/pdf/KDIGO-AKI-Suppl-Appendices-A-F_March2012.pdf (Accessed 4 April 2016).
25. Long TE, Helgason D, Helgadottir S, et al. Acute Kidney Injury After Abdominal Surgery: Incidence, Risk Factors, and Outcome. *Anesth Analg*. 2016;122(6):1912-1920.
26. Grams ME, Sang Y, Ballew SH, et al. CKD Prognosis Consortium. A Meta-analysis of the Association of Estimated GFR, Albuminuria, Age, Race, and Sex With Acute Kidney Injury. *Am J Kidney Dis*. 2015;66(4):591-601.
27. Locatelli F, Rossi F. Incidence and pathogenesis of tumor lysis syndrome. *Contrib Nephrol*. 2005;147:61-68.
28. Thakar CV, Liangos O, Yared JP, et al. ARF after open-heart surgery: Influence of gender and race. *Am J Kidney Dis*. 2003;41:742-751.
29. Drawz PE, Miller RT, Sehgal AR. Predicting hospital-acquired acute kidney injury–a case-controlled study. *Ren Fail*. 2008;30:848-855.
30. Smith CR, Moore RD, Lietman PS. Studies of risk factors for aminoglycoside nephrotoxicity. *Am J Kidney Dis*. 1986;8:308-313.
31. James MT, Grams ME, Woodward M, et al. CKD Prognosis Consortium. A Meta-analysis of the Association of Estimated GFR, Albuminuria, Diabetes Mellitus, and Hypertension With Acute Kidney Injury. *Am J Kidney Dis*. 2015;66(4):602-612.
32. Hsu CY, Chertow GM, McCulloch CE, et al. Nonrecovery of kidney function and death after acute on chronic renal failure. *Clin J Am Soc Nephrol*. 2009;4:891-898.
33. Hertzberg D, Sartipy U, Holzmann MJ. Type 1 and type 2 diabetes mellitus and risk of acute kidney injury after coronary artery bypass grafting. *Am Heart J*. 2015;170(5):895-902.
34. Inohara T, Kohsaka S, Abe T, et al. Development and validation of a pre-percutaneous coronary intervention risk model of contrast-induced acute kidney injury with an integer scoring system. *Am J Cardiol*. 2015;115(12):1636-1642.
35. Ishikawa S, Griesdale DE, Lohser J. Acute kidney injury after lung resection surgery: incidence and perioperative risk factors. *Anesth Analg*. 2012;114(6):1256-1262.
36. Takahashi T, Hasegawa T, Hirata N, et al. Impact of acute kidney injury on in-hospital outcomes in patients with DeBakey type III acute aortic dissection. *Am J Cardiol*. 2014;113(11):1904-1910.
37. Hampel H, Bynum GD, Zamora E, et al. Risk factors for the development of renal dysfunction in hospitalized patients with cirrhosis. *Am J Gastroenterol*. 2001;96:2206-2210.
38. Peron JM, Bureau C, Gonzalez L, et al. Treatment of hepatorenal syndrome as defined by the international ascites club by albumin and furosemide infusion according to the central venous pressure: a prospective pilot study. *Am J Gastroenterol*. 2005;100:2702-2707.
39. Terra C, Guevara M, Torre A, et al. Renal failure in patients with cirrhosis and sepsis unrelated to spontaneous bacterial peritonitis: value of MELD score. *Gastroenterology*. 2005;129:1944-1953.
40. du Cheyron D, Bouchet B, Parienti JJ, et al. The attributable mortality of acute renal failure in critically ill patients with liver cirrhosis. *Intensive Care Med*. 2005;31:1693-1699.
41. Wu CC, Yeung LK, Tsai WS, et al. Incidence and factors predictive of acute renal failure in patients with advanced liver cirrhosis. *Clin Nephrol*. 2006;65:28-33.
42. Tsien CD, Rabie R, Wong F. Acute kidney injury in decompensated cirrhosis. *Gut*. 2013;62(1):131-137.
43. Wong F, O'Leary JG, Reddy KR, et al. North American Consortium for Study of End-Stage Liver Disease. New consensus definition of acute kidney injury accurately predicts 30-day mortality in patients with cirrhosis and infection. *Gastroenterology*. 2013;145(6):1280-1288.
44. Masoudi FA, Rathore SS, Wang Y, et al. National patterns of use and effectiveness of angiotensin-converting enzyme inhibitors in older patients with heart failure and left ventricular systolic dysfunction. *Circulation*. 2004;110:724-731.
45. Metra M, Nodari S, Parrinello G, et al. Worsening renal function in patients hospitalised for acute heart failure: clinical

implications and prognostic significance. *Eur J Heart Fail*. 2008;10:188-195.
46. Metra M, Davison B, Bettari L, et al. Is worsening renal function an ominous prognostic sign in patients with acute heart failure? The role of congestion and its interaction with renal function. *Circ Heart Fail*. 2012;5:54-62.
47. Logeart D, Tabet J-Y, Hittinger L, et al. Transient worsening of renal function during hospitalization for acute heart failure alters outcome. *Int J Cardiol*. 2008;127:228-232.
48. Patel UD, Greiner MA, Fonarow GC, et al. Associations between worsening renal function and 30-day outcomes among Medicare beneficiaries hospitalized with heart failure. *Am Heart J*. 2010;160:132-138.
49. Smith GL, Vaccarino V, Kosiborod M, et al. Worsening renal function: what is a clinically meaningful change in creatinine during hospitalization with heart failure? *J Card Fail*. 2003;9:13-25.
50. Forman DE, Butler J, Wang Y, et al. Incidence, predictors at admission, and impact of worsening renal function among patients hospitalized with heart failure. *J Am Coll Cardiol*. 2004;43:61-67.
51. Solomon RJ, Mehran R, Natarajan MK, et al. Contrast-induced nephropathy and long-term adverse events: cause and effect? *Clin J Am Soc Nephrol*. 2009;4:1162-1169.
52. Mangos GJ, Brown MA, Chan WY, et al. Acute renal failure following cardiac surgery: incidence, outcomes and risk factors. *Aust N Z J Med*. 1995;25:284-289.
53. Hein OV, Birnbaum J, Wernecke KD, et al. Three-year survival after four major post-cardiac operative complications. *Crit Care Med*. 2006;34:2729-2737.
54. Pickering JW, James MT, Palmer SC. Acute kidney injury and prognosis after cardiopulmonary bypass: a meta-analysis of cohort studies. *Am J Kidney Dis*. 2015;65(2):283-293.
55. Rosner MH, Okusa MD. Acute kidney injury associated with cardiac surgery. *Clin J Am Soc Nephrol*. 2006;1:19-32.
56. Rydén L, Sartipy U, Evans M, et al. Acute kidney injury after coronary artery bypass grafting and long-term risk of end-stage renal disease. *Circulation*. 2014;130(23):2005-2011.
57. Huber M, Ozrazgat-Baslanti T, Thottakkara P, et al. Cardiovascular-Specific Mortality and Kidney Disease in Patients Undergoing Vascular Surgery. *JAMA Surg*. 2016;151(5):441-450.
58. Kopolovic I, Simmonds K, Duggan S, et al. Risk factors and outcomes associated with acute kidney injury following ruptured abdominal aortic aneurysm. *BMC Nephrol*. 2013; 14(1):99.
59. Arora P, Davari-Farid S, Pourafkari L, et al. The effect of acute kidney injury after revascularization on the development of chronic kidney disease and mortality in patients with chronic limb ischemia. *J Vasc Surg*. 2015;61(3):720-727.
60. Kabbani LS, West CA, Viau D, et al. Survival after repair of pararenal and paravisceral abdominal aortic aneurysms. *J Vasc Surg*. 2014;59(6):1488-1494.
61. Drews JD, Patel HJ, Williams DM, et al. The impact of acute renal failure on early and late outcomes after thoracic aortic endovascular repair. *Ann Thorac Surg*. 2014;97(6):2027-2033.
62. Adalbert S, Adelina M, Romulus T, et al. Acute kidney injury in peripheral arterial surgery patients: a cohort study. *Ren Fail*. 2013;35(9):1236-1239.
63. Piffaretti G, Mariscalco G, Bonardelli S, et al. Predictors and outcomes of acute kidney injury after thoracic aortic endograft repair. *J Vasc Surg*. 2012;56(6):1527-1534.
64. Goldfarb S, Spinler S, Berns JS, et al. Low-osmolality contrast media and the risk of contrast-associated nephrotoxicity. *Invest Radiol*. 1993;28(suppl 5):S7-S10.
65. Barrett BJ, Carlisle EJ. Metaanalysis of the relative nephrotoxicity of high- and low-osmolality iodinated contrast media. *Radiology*. 1993;188:171-178.
66. Lameire N, Adam A, Becker CR, et al. Baseline renal function screening. *Am J Cardiol*. 2006;98:21K-26K.
67. Perazella MA. Current status of gadolinium toxicity in patients with kidney disease. *Clin J Am Soc Nephrol*. 2009;4:461-469.
68. Briguori C, Colombo A, Airoldi F, et al. Gadolinium-based contrast agents and nephrotoxicity in patients undergoing coronary artery procedures. *Catheter Cardiovasc Interv*. 2006;67:175-180.
69. Arora P, Rajagopalam S, Ranjan R, et al. Preoperative use of angiotensin-converting enzyme inhibitors/angiotensin receptor blockers is associated with increased risk for acute kidney injury after cardiovascular surgery. *Clin J Am Soc Nephrol*. 2008;3:1266-1273.
70. Miceli A, et al. *J Am Coll Cardiol*. 2009;54:1778-1784.
71. Bertrand M, et al. *Anesth Analg*. 2001;92:26-30.
72. Lapi F, Azoulay L, Yin H, et al. Concurrent use of diuretics, angiotensin converting enzyme inhibitors, and angiotensin receptor blockers with non-steroidal anti-inflammatory drugs and risk of acute kidney injury: nested case-control study. *BMJ*. 2013;346:e8525.
73. Loboz KK, Shienfield GM. Drug combinations and impaired renal function- the 'triple whammy. *Br J Clin Pharmacol*. 2004;59:239-243.
74. Fournier JP, Sommet A, Durrieu G, et al. Drug interactions between antihypertensive drugs and non-steroidal anti-inflammatory agents: a descriptive study using the French pharmacovigilance database. *Fundam Clin Pharmacol*. 2014;28: 230-235.
75. Ahn JY, Lee MJ, Seo JS, et al. Plasma neutrophil gelatinase-associated lipocalin as a predictive biomarker for the detection of acute kidney injury in adult poisoning. *Clin Toxicol (Phila)*. 2016;54:2, 127-133.
76. Tsai TT, Patel UD, Chang TI, et al. Validated contemporary risk model of acute kidney injury in patients undergoing percutaneous coronary interventions: insights from the National Cardiovascular Data Registry Cath PCI Registry. *J Am Heart Assoc*. 2014;3:e001380.
77. Inohara T, Kohsaka S, Miyata H, et al. Performance and validation of the US NCDR Acute Kidney Injury Prediction Model in Japan. *J Am Coll Cardiol*. 2016;67:1715-1722.
78. Jorge-Monjas P, Bustamante-Munguira J, Lorenzo M, et al. Predicting cardiac surgery-associated acute kidney injury: the CRATE score. *J Crit Care*. 2016;31:130-138.
79. Wong B, St. Onge J, Korkola S, et al. Validating a scoring tool to predict acute kidney injury (AKI) following cardiac surgery. *Can J Kidney Health Dis*. 2015;2:3.
80. Huen SC, Parikh CR. Predicting acute kidney injury after cardiac surgery: a systematic review. *Ann Thorac Surg*. 2012; 93:337-347.
81. Engleberger L, Suri RM, Li Z, et al. Validation of clinical scores predicting severe acute kidney injury after cardiac surgery. *Am J Kidney Dis*. 2010;56:623-631.
82. Chen YL, Fu NK, Xu J, et al. A simple preprocedural score for risk of contrast-induced acute kidney injury after percutaneous coronary intervention. *Catheter Cardiovasc Interv*. 2014;63:E8-E16.
83. Inohara T, Kohsaka S, Abe T, et al. Development and validation of pre-percutaneous coronary intervention risk model of contrast-induced acute kidney injury with an integer scoring system. *Am J Cardiol*. 2015;115:1636-1642.
84. Skelding KA, Best PJ, Bartholomew BA, et al. Validation of a predictive risk score for radiocontrast-induced nephropathy following percutaneous coronary intervention. *J Invasive Cardiol*. 2007;19:229-233.
85. Mehran R, Aymong ED, Nikolsky E, et al. A simple risk score for prediction of contrast-induced nephropathy after percutaneous coronary intervention: development and initial validation. *J Am Coll Cardiol*. 2004;44:1393-1399.
86. Abellas-Sequeiros RA, Raposeiras-Roubin S, Abu-Assi E, et al. Mehran contrast nephropathy risk score: is it still useful 10 years later? *J Cardiol*. 2016;67:262-267.
87. Li J, Li Y, Wang W, et al. Age, estimated glomerular filtration rate and ejection fraction score predicts contrast-induced acute kidney injury in patients with diabetes and chronic kidney disease: insight from the TRACK-D study. *Chin Med J*. 2014;127:2332-2336.
88. Liu EH, Lau KK, Polkinghome K, et al. Efficacy of patient questionnaire in predicting renal dysfunction in outpatients older than 60 years of age prior to contrast-enhanced computed tomography. *J Med Imaging Radiat Oncol*. 2012;56: 168-172.
89. Herts BR, Schneider E, Obuchowski N, et al. Probability of reduced renal function after contrast-enhanced CT: a model

based on serum creatinine level patient age and estimated glomerular filtration rate. *AJR Am J Roentgenol*. 2009;193:494-500.
90. Liu Y, Chen SQ, Dian CY, et al. Contrast volume-to-creatinine clearance ratio predicts the risk of contrast-induced nephropathy after percutaneous coronary intervention in patients with reduced ejection fraction. *Angiology*. 2015;66:625-630.
91. Arnold SV, Decker C, Ahmad H, et al. Converting the informed consent from a perfunctory process to an evidence-based foundation for patient decision making. *Circ Cardiovasc Qual Outcomes*. 2008;1:21-28.
92. Rivers E, Nguyen B, Havstad S, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med*. 2001;345:1368-1377.
93. Pickering JW, Endre ZH. Secondary prevention of acute kidney injury. *Curr Opin Crit Care*. 2009;15(6):488-497.
94. Ronco C, Ricci Z. The concept of risk and the value of novel markers of acute kidney injury. *Crit Care*. 2013;17:117.
95. Haase-Fielitz A, Bellomo R, Devarajan P, et al. Novel and conventional serum biomarkers predicting acute kidney injury in adult cardiac surgery–a prospective cohort study. *Crit Care Med*. 2009;37(2):553-560.
96. Perry TE, Muehlschlegel JD, Liu KY, et al. CABG Genomics Investigators. Plasma neutrophil gelatinase-associated lipocalin and acute postoperative kidney injury in adult cardiac surgical patients. *Anesth Analg*. 2010;110(6):1541-1547.
97. de Geus HR, Bakker J, Lesaffre EM, et al. Neutrophil gelatinase-associated lipocalin at ICU admission predicts for acute kidney injury in adult patients. *Am J Respir Crit Care Med*. 2011;183(7):907-914.
98. Zhang A, Cai Y, Wang P-F, et al. Diagnosis and prognosis of neutrophil gelatinase-associated lipocalin for acute kidney injury with sepsis: a systematic review and meta-analysis. *Crit Care*. 2016;20:41.
99. Kashani K, Al-Khafaji A, Ardiles T, et al. Discovery and validation of cell cycle arrest biomarkers in human acute kidney injury. *Crit Care*. 2013;17:R25.
100. Stafford-Smith M, Li Y-J, Mathew JP, et al. Genome-wide association study of acute kidney injury after coronary bypass graft surgery identifies susceptibility loci. *Kidney Int*. 2015;88:823-832.
101. du Cheyron D, Fradin S, Ramakers M, et al. Angiotensin converting enzyme insertion/deletion genetic polymorphism: its impact on renal function in critically ill patients. *Crit Care Med*. 2008;36(12):3178-3183.
102. Cardinal-Fernández P, Ferruelo A, El-Assar M, et al. Genetic predisposition to acute kidney injury induced by severe sepsis. *J Crit Care*. 2013;28(4):365-370.
103. Vilander LM, Kaunisto MA, Pettilä V. Genetic predisposition to acute kidney injury–a systematic review. *BMC Nephrol*. 2015;16:197.
104. Chang J, Ronco C, Rosner MH. Computerized decision support systems: improving patient safety in nephrology. *Nat Rev Nephrol*. 2011;7:348-355.
105. Sutherland SM, Chawla LS, Kane-Gill SL, et al. Utilizing electronic health records to predict acute kidney injury risk and outcomes: workgroup statements from the 15th ADQI Consensus Conference. *Can J Kidney Health Dis*. 2016;doi:10.1186/s40697-016-0099-4.
106. Rind DM, Safran C, Phillips RS, et al. Effect of computer-based alerts on the treatment of and outcomes of hospitalized patients. *Arch Intern Med*. 1994;154:1511-1517.
107. Cho A, Lee JE, Yoon JY, et al. Effect of an electronic alert on risk of contrast-induced acute kidney injury in hospitalized patients undergoing computed tomography. *Am J Kidney Dis*. 2012;60:74-81.
108. Goldstein SL, Kirkendall E, Nguyen H, et al. Electronic health record identification of nephrotoxin exposure and associated acute kidney injury. *Pediatrics*. 2013;132:756-767.
109. Wilson FR, Shashaty M, Testani J, et al. Automated, electronic alerts for acute kidney injury: a single-blind, parallel-group, randomized controlled trial. *Lancet*. 2015;385:1966-1974.
110. Hoste EA, Kashani K, Gibney N, et al. Impact of electronic-alerting of acute kidney injury: workgroup statements from the 15th ADQI Consensus Conference. *Can J Kidney Health Dis*. 2016;3:10. doi:10.1186/s40697-016-0101-1.