SECTION 3

Epidemiology of Acute Kidney Injury in Critical Care

CHAPTER 11

Acute Kidney Injury: From Clinical to Molecular Diagnosis

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OBJECTIVES

This chapter will:

1. Describe the evolution of definitions and criteria to make the diagnosis of acute kidney injury (AKI).
2. Discuss the different definition-classifications systems.
3. Focus on the new information and possibilities offered by the AKI biomarkers.
4. Underline the existence of subclinical forms of AKI.
5. Describe the concept of acute kidney stress.
6. Propose a new model of biomarker-driven AKI prevention and management.

The incidence of acute kidney injury (AKI) is increasing especially in hospitalized patients and particularly in intensive care units (ICUs) because of major surgery, iatrogenic interventions, and sepsis. In such conditions, age and comorbidities make the kidneys more susceptible to various exposures and insults. Thus it is important to improve the awareness of the clinical consequences associated to AKI and to expand the knowledge of the different aspects of the syndrome.

Historically, the diagnosis of AKI (defined acute renal failure, or ARF, or acute tubular necrosis, or ATN) was made by typical signs and symptoms of anuria and uremia secondary to crush syndrome in London's battlefields at World War II. *War nephritis* became another term for this concept. In the 1950s, during the Korean war, kidney damage was due to the inability to hydrate soldiers wounded in the field. Because they had received a hearty meal before the battle, they also developed hyperkalemia. At that time, the new artificial kidney, introduced by Wilhelm Kolff, was applied and allowed to significantly decrease mortality. Further decrease in incidence and mortality from AKI was achieved during the Vietnam war, where helicopters allowed a rapid medical evacuation of wounded soldiers, and rapid hydration was instituted in the field hospitals called mobile army surgical hospitals (MASH). Several years later, the case mix of community- and hospital-acquired AKI changed remarkably, moving the area of interest from nephrology wards to ICUs. The syndrome formerly called ARF or ATN was made based on signs and symptoms such as anuria or overt uremia. Studies demonstrated that ARF and ATN are not necessarily the same thing. New approaches and new terminology were used in clinical routine, and the unifying term of AKI was proposed.

Oliguria and rise in serum creatinine (SCr) still represent the main criteria for the diagnosis of AKI, but initiatives and classifications such as RIFLE, AKIN, and KDIGO have made some important advancements using the level of oliguria or biochemical derangement as a metric to define AKI presence and to classify its severity (Box 11.1).[1–3] However, all these criteria still rely solely on urine output and SCr, allowing diagnosis of a functional impairment of the kidney but precluding the possibility of a timely and accurate identification of an early damage to the kidney. In particular, these definition-classification systems cannot identify conditions of acute kidney stress (AKS), conditions of severe risk, and subclinical forms of kidney dysfunction and damage. Thus such criteria seem today inadequate to describe the wide spectrum of mechanisms and conditions of AKI patients.[4,5]

New biomarkers capable of detecting increased risk of AKI or kidney damage significantly earlier than classic methods, allowed to develop a new conceptual model for AKI with a continuum from initial kidney stress and early injury, to advanced kidney damage and/or failure. Full recovery or partial repair with progression towards chronic kidney disease (CKD) also are described in the model. The acute phase has also been called "kidney attack" (KA),[6] whereas the subsequent phases in the time window of 90

BOX 11.1

Evolution of Definitions Used to Describe Acute Kidney Injury

ATN: Acute Tubular Necrosis: Pathologic definition based on animal models often following ischemia-reperfusion. Rosen and Heyman state that this picture has little to do with the syndrome in humans where dysfunction largely exceeds morphologic changes.
ARF: Acute Renal Failure: Acute Bright's disease, war nephritis, Bywaters' crush syndrome, Homer W. Smith → ARF. Precise biochemical definition never proposed.
AKD: Acute Kidney Disease: A general term to include all acute kidney disorders (dysfunction and injury) in a time window of 3 months from the first AKI diagnosis.
AKI: Acute Kidney Injury: The most recent term using a biochemical syntax to grade severity and staging.
RIFLE: The outcome of the first ADQI conference in Vicenza resulting in creatinine and UO criteria to stage AKI.
AKIN: R, I, F substituted by stages I, II, III. Temporal window of 48 hours introduced. Stage I diagnosed by SCr increase ≥ 0.3 mg/dL. RRT automatically leads to stage III.
KDIGO: Increase in SCr by ≥0.3 mg/dL within 48 hours or increase in SCr to ≥ 1.5 times baseline (7 days), or urine volume < 0.5 mL/kg/hr for 6 hours.
ADQI: Functional criteria: Increase in SCr by ≥0.3 mg/dL within 48 hours or increase in SCr to ≥ 1.5 times baseline (7 days), or urine volume < 0.5 mL/kg/hr for 6 hours. Damage criteria: include measurement of damage biomarkers.

ARF, Acute renal failure; *RRT,* renal response time; *SCr,* serum creatinine; *UO,* urine output.

days are described as acute kidney disease (AKD) (Fig. 11.1). In each point of the continuum, biomarkers may play a role in clarifying mechanisms and evolution of AKI. Studies on biomarkers have described their positive and negative predicting value for presence and severity of the syndrome, site of damage, need of renal replacement therapy (RRT), recovery, or progression towards CKD.[7] Unfortunately, these studies present a high degree of heterogeneity, and meaningful conclusions can be obtained only by analyzing specific populations.

Zhang et al. conducted a meta-analysis[8] focusing on the value of NGAL to predict AKI and other clinical outcomes such as RRT and mortality in a specific subset of patients with sepsis. Although the renal biomarker NGAL can be a valuable clinical test to alert clinicians to AKI, its lack of specificity has limited its use as a sole indicator of AKI.

A variety of renal biomarkers have now been identified and have the potential to enhance the understanding and diagnosis of AKI, particularly as biomarker monitoring is combined with follow-up of renal function. The recent identification of cell cycle arrest biomarkers that highlights the increased risk to develop of AKI has contributed to the evolution in the molecular diagnosis and understanding of AKI.[9–11]

NORMAL KIDNEY

The definition of normal kidney generally is made on the basis of a normal morphologic analysis resulting from ultrasound techniques in which the number, dimension, shape, and location of the kidneys are reported regular. Furthermore, normal kidney function generally is defined by an estimated glomerular filtration rate (eGFR) above 90 mL/min (based on serum creatinine level) and absence of urine abnormalities. However, eGFR and effective GFR measured by creatinine clearance describe kidney function only in steady-state conditions and provide information about baseline (unstressed) GFR. Because one individual can lose up to 50% of the functioning renal mass before GFR decreases and serum creatinine increases, it may be very difficult to assess "normality" of kidney function simply by the measure of GFR in baseline conditions. To better define kidney function and the overall potential of nephron mass, the Kidney Stress Test has been used as a measure of the Renal Functional Reserve (RFR). The RFR (glomerular = RFR-G) is the difference between the maximal GFR (stressed) measured after the stimulus (acute oral or intravenous protein load), and the baseline (unstressed GFR).[12–14]

INCREASED SUSCEPTIBILITY

The concept of susceptibility is important in the evaluation of the risk to develop AKI. We may say that the balance between the intensity of the exposure to any insult and the susceptibility is the major determinant of the final outcome and the occurrence of an overt clinical AKI episode. Susceptibility can be referred to a patient and the whole organism or to the kidneys. Patient susceptibility is a term that describes the general status of health of an individual and all the present comorbidities that potentially may have an impact on kidney status. Kidney susceptibility, also defined as kidney frailty, may depend on several systemic conditions and comorbidities such as diabetes and hypertension, previous episodes of AKI, and presence of subclinical CKD (chronic kidney disease) identified by a reduction in RFR-G.

Increased susceptibility produces a higher risk to develop AKI even in presence of a limited intensity of the exposure or a minimal insult.

ACUTE KIDNEY STRESS

Early diagnosis of AKI represents a challenge. The delay in elevation of creatinine to approximately 24 to 48 hours after the insult makes this standard renal function test inappropriate for the early diagnosis of AKI.

Critical care nephrologists and intensivists have searched for an appropriate term for the clinical phase preceding AKI. The term "renal angina" (RA) has been proposed,[15] although it is recognized that AKI can result from nonischemic mechanisms, and AKI is not associated with pain. The complexity of defining AKI or a "kidney attack" using standard measures of kidney function has been recognized by nephrologists from centers around the world.[6,16]

Recently it has been proposed that the preinjury phase that leads to AKI can be described as "acute kidney stress."[5] AKS may be a condition of very early injury or increased susceptibility to exposures that may or may not lead to AKI depending on several concomitant factors. The molecules expressed by the kidney may represent reliable biomarkers to monitor initial damage and subsequent evolution of the syndrome with an attempt to proceed toward kidney repair and avoid fibrosis.

Working out criteria for AKS will be an important step to alert critical care teams to make clinical adjustments

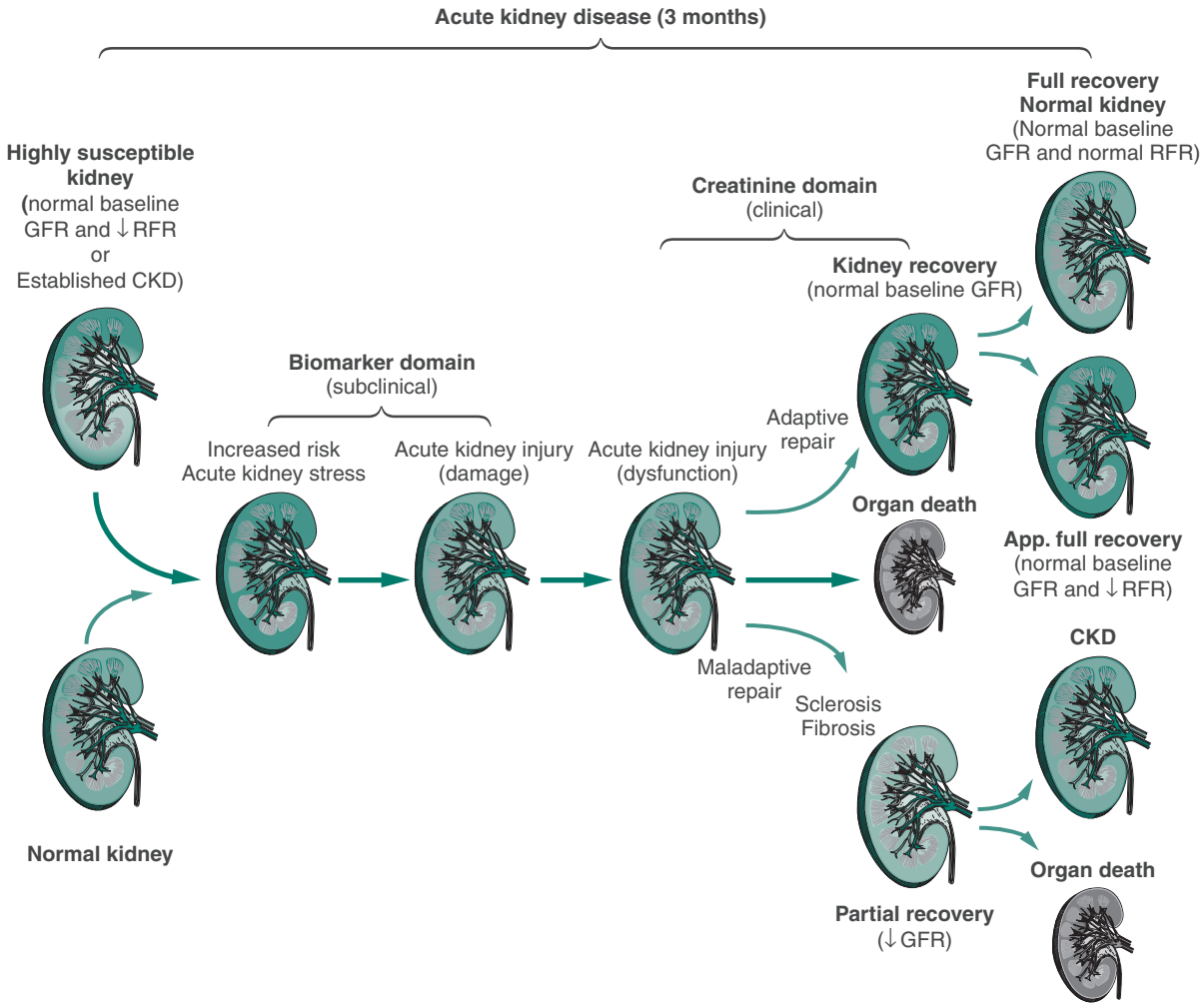

FIGURE 11.1 Clinical, biochemical, and functional evolution of acute kidney disease from the early phases to the latest outcomes. At every point, damage biomarkers or serum creatinine describe the actual situation. Apparent full recovery may occur when serum creatinine and baseline glomerular filtration rate (GFR) go back to normal, but renal functional reserve (RFR) is impaired. *CKD,* Chronic kidney disease.

before AKI occurs. Potential criteria for diagnosis of AKS include indices of renal perfusion, such as urine output per minute, changes in renal cell function, and detection of biomarkers that reflect metabolic impairment. A focus on the metabolic mechanisms of kidney stress and the associated impairments of renal cell function has the potential to lead to innovative monitoring technology and protocols resulting in earlier changes in clinical care to prevent kidney cell injury

Over the years, development of prevention and protection protocols has been impeded by lack of technology to directly measure blood flow to the kidney. AKI after major cardiac surgery remains an important source of patient morbidity and mortality[17]; an important cause of cardiac surgery associated AKI is thought to be inadequate blood flow to the kidney while the patient is on cardiopulmonary bypass (CPB) and in the ICU because of suboptimal management of hemodynamics.

The use of cerebral oximetry to detect blood pressure excursions below the cerebral autoregulation threshold represents an innovative technology to alert physicians to hemodynamics that may result in AKI.[13,18]

Renal ischemia related to infusion of vasoconstrictors, or to local impairment of flow resulting from renal artery stenosis, may go undetected until AKI occurs. Monitoring renal cell physiologic functions could alert critical care professionals to flawed goals of hemodynamic management. Hemodynamic goals based on standard ICU guidelines, rather than physiologic monitoring, may lead to undetected renal ischemia, because individual patients may have unique arterial and/or venous pressure requirements.

The term *AKS* could become increasingly useful as clinicians develop methods to diagnose and treat the early stages of AKI, which has a major impact on patient outcomes and healthcare costs, such as after cardiac surgery. The expanded use of advanced technology, such as ventricular assist devices and extracorporeal membrane oxygenation (ECMO) to support cardiorespiratory function, with the associated increased risk of AKI[19–21] highlights the need to define and identify the pre-AKI phase, which could be termed AKS.

Combining innovative monitoring of renal function with identification of new biomarkers of kidney stress and injury could lead to the early diagnosis of AKS and the implementation of corrective hemodynamic and pharmacologic management. The importance of interventions to prevent or reduce the extent of AKI is highlighted in the recognition that AKI is associated with the development of CKD and its associated mortality.[22–24]

RENAL ANGINA

AKI biomarkers can be compared with troponin as a gold standard for the diagnosis of acute coronary syndrome. Troponin is used typically in the setting of patients with chest pain, which differential diagnosis is taught to all medical students early on in their medical education. Troponin is a good biomarker because of its high sensitivity, specificity, and pretest probability; when troponin is used in a less selective scenario with patients who have a lower pretest probability, the performance of this biomarker deteriorates. In AKI, it is important to direct biomarker assessment based on a predetermined risk.[15–16]

The term *RA* was introduced in 2010 by Chawla and Goldstein,[22] considering a combination of patients' risk factors and signs of injury. The authors proposed a risk assessment score to allocate the use of biomarkers to patients' groups at greater risk for AKI. The risk factors for AKI are well documented, but AKI is not accompanied by any visceral symptom, and the typical pain of heart angina is not present in the kidney. Thus, instead of symptoms, they proposed to use modest changes in serum creatinine, urine output, and fluid overload in the grey zone where the critical increase in serum creatinine of 0.3 mg/dl was not reached (yet). Based on these data, clinicians should be able to increase alertness for the possible development of AKI.

Therefore the concept of RA is developed and proposed to better assess pretest probability of AKI combining AKI biomarkers, risk factors, signs and symptoms (when present). The purpose of RA definition is to incorporate static and dynamic factors to enable the clinician to make a risk stratification. Although the term is controversial, it describes a typical condition of subclinical AKI. First step is the identification of patients at risk for AKI: advanced age, diabetes, cirrhosis/hepatic failure, congestive heart failure, CKD, volume depletion, sepsis, CBP time, and exposure to nephrotoxins. Patients who are on mechanical ventilation and require vasoactive agents also represent a cohort at risk for AKI. Additional biochemical risk factors then are identified: increased levels of IL-6, plasminogen activator inhibitor 1, and soluble TNF-receptors. After identification of patients at high risk, the next step is to follow the RA syndrome towards AKI. Three objective criteria should prompt the concern of evolving AKI: (1) oliguria, (2) any increase in SCr, and (3) fluid overload. Once RA is recognized, the process of ruling in/out AKI should begin as soon as possible. The essential nature of this process is to look for signs and symptoms of kidney injury and to consider whether renal blood flow and other physiologic parameters are adequate. Combination of clinical risk factors and the patient's clinical context in conjunction with kidney function parameters and damage biomarkers seem to be more effective than either alone in improving the diagnosis of subclinical and early AKI.[15,25]

CONCEPT OF SUBCLINICAL ACUTE KIDNEY INJURY

Evolution of the term *ARF*, used for many years in clinical practice, has been replaced with the term *AKI*. This implies a potentially reversible injury or damage to the kidney occurring in a timeframe of hours or days and characterizing the disorder as "acute." Although the term *injury* would not necessarily encompass kidney dysfunction without damage, the diagnosis of AKI syndrome still is made on a change in serum creatinine or urine output, both likely deriving from an altered GFR. It is difficult to obtain histopathologic diagnosis in critically ill patients, because a kidney biopsy is considered to carry an inappropriate risk-benefit ratio.

The human kidney has an important functional reserve, and dysfunction of glomerular filtration becomes clinically manifest only when more than 50% of the renal mass is compromised. This explains why a rise in SCr is a sign of severe kidney damage even if the rise in creatinine is minimal. Often no information is available on tubular and other kidney functions. Standard AKI classifications such as the RIFLE criteria[1] or modified RIFLE criteria[23] demonstrate that slight changes in SCr (as low as 0.3 mg/dL) are associated with worse outcomes.[24] This approach still represents a functional criterion for AKI, and it implies an altered GFR, which indeed may have occurred long after the injury has taken place. An early diagnosis of AKI would require a single structural or functional biomarker or a combination thereof capable to detect kidney injury almost in real time.[25]

According to this modern approach, we may speculate that AKI could be diagnosed even in the absence of the classical signs that have characterized the syndrome so far.[26,27,28] We can designate this phase subclinical AKI.[4] The fact that AKI is not clinically manifest (according to RIFLE/KDIGO criteria) does not necessarily mean that the kidney is intact and the function is perfect. A subclinical AKI may be unveiled by the elevation of damage biomarkers. This new approach has several implications. The diagnosis of AKI may include a larger spectrum of conditions. The strategies of early organ protection and AKI prevention should be reconsidered. We may need to reestablish a term for renal function loss (e.g., acute renal dysfunction) to distinguish this condition from acute kidney damage with no dysfunction (Fig. 11.2). Sequential measurements and monitoring of biomarkers curves could be capable of identifying trends characteristic of an isolated or an ongoing renal insult.

In conclusion we are entering a postcreatinine world, where creatinine should not be abandoned, but we should move beyond. What today is considered subclinical AKI (tubular damage biomarker positive without dysfunction), thanks to the new biomarkers can be defined as AKI. We cannot afford to neglect such conditions when associated with negative outcomes. In light of this concept, end points for clinical trials on renal toxicity or renal safety of drugs and procedures may have to be reconsidered. The accuracy of new biomarkers is crucial in this process, and we should start considering not only cutoff values but also trends and biomarker curves, especially now that high sensitivity assays are becoming available.

MOLECULAR DIAGNOSIS OF ACUTE KIDNEY INJURY

From clinical signs and symptoms we moved to a series of new parameters to make the diagnosis of AKI. In the last 70 years, we evolved from a clinical observation (oliguria and uremia) to numerous definitions based on quantitative and discrete values of serum creatinine and urine output. A biochemical and physiologic syntax was proposed when the RIFLE, AKIN, and KDIGO criteria were introduced. In

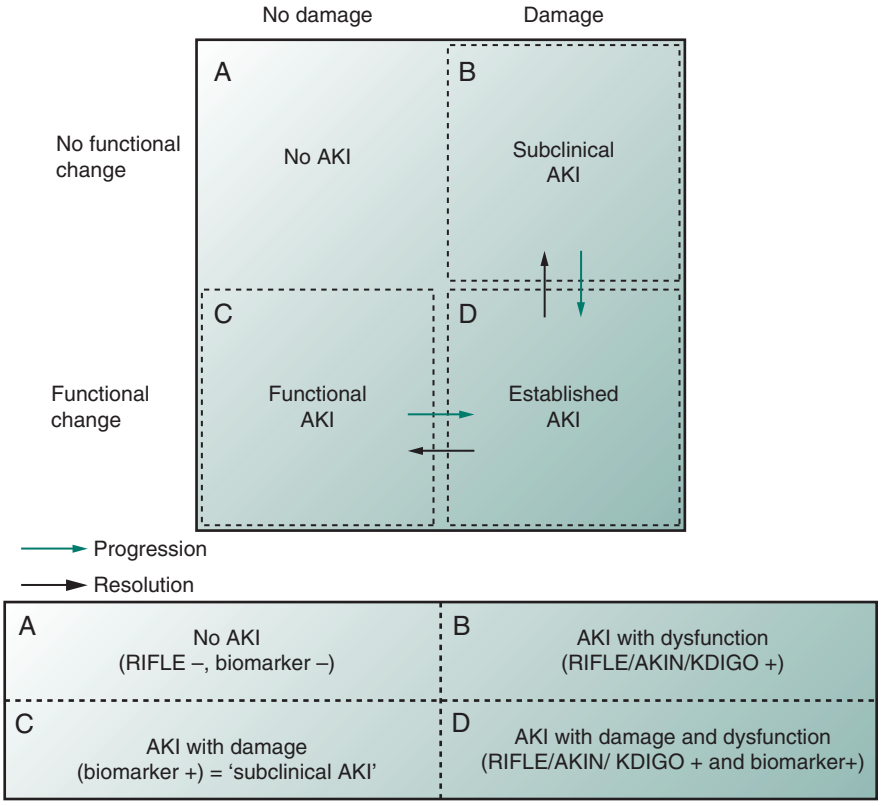

FIGURE 11.2 Entities of acute kidney injury (AKI) syndrome by damage and dysfunction (or both). A, No AKI. B, AKI with tubular damage (biomarker-positivity) (subclinical AKI). C, AKI with dysfunction (RIFLE/AKIN/KDIGO). D, AKI with tubular damage (biomarker-positivity) and dysfunction (RIFLE/AKIN/KDIGO). *Arrows* indicate progression *(green)* or resolution *(black)* of the process. The lower table describes the parameters used to identify the specific entity. *AKIN,* Acute Kidney Injury Network; *KDIGO,* Kidney Disease: Improving Global Outcome. (Modified from www.ADQI.org.)

recent years, the discovery and validation of cell cycle arrest biomarkers, NGAL, and other damage markers have permitted to introduce the concepts of AKI risk, AKS, and subclinical AKI. The quantitative evaluation of these markers have moved the diagnosis of AKI from clinical/biochemical to cellular/molecular level (Fig. 11.3). The further step will be to better understand if there is a typical molecular signature for different types of AKI and for different stages of the disorder within the 90 days of the evolution of the AKD episode.

The introduction in the clinical routine of novel independent biomarkers of AKI appears today crucial for identification of subclinical forms, early diagnosis, and improved risk assessment. A continuous improvement in the understanding of pathophysiology of AKI would help comprehensive characterization of the molecular pathways involved in the propagation of kidney injury.

A new potential modification of the diagnostic framework for AKI has been proposed by the consensus group of Acute Disease Quality Initiative (ADQI) (Fig. 11.4). The limitation identified by the group was in the lack of quantitative and discrete values for biomarkers such as NGAL to characterize severity and to correlate with outcomes.[29]

A clinical routine biomarker test should be easy and simple to measure, should be consistent in repetitive measurement, should have a rationale for its use being meaningful, should present threshold values that are well documented and validated, should correlate with the presence of illness and with its severity, must have a reasonable cost, and finally should be measurable in biologic fluids that are easily achievable.[30] Among others, neutrophil gelatinase-associated lipocalin (NGAL) appears to be an interesting option in urine and plasma. AKI can be diagnosed early with NGAL before creatinine rises. Bagshaw et al. demonstrated that critically patients who developed worsening AKI had a higher serum level of Plasma neutrophil gelatinase-associated lipocalin (pNGAL) compared with those whose AKI did not deteriorate.[31] A systematic review by Haase et al. demonstrated the predictive value of NGAL for RRT.[32] In extended criteria kidney donors, NGAL has been shown to be an early indicator of kidney graft function and calcineurin inhibitors nephrotoxicity. In cases of suspected sepsis, Kim et al.[33] demonstrated the utility of NGAL with SCr in the diagnosis and staging of sepsis-related AKI. Plasma NGAL was significantly better associated than SCr with the renal sequential organ failure assessment (SOFA) subscore.

There is a limited applicability of the RIFLE criteria in the emergency setting because of a lack of baseline SCr measures; therefore the additive value of NGAL testing in AKI becomes remarkable in clinical judgment accuracy as well as in patient risk stratification.[34] Fast, accurate biomarker assays may improve significantly morbidity and mortality by providing diagnosis in hours, rather than days, and by allowing a faster and effective decision-making process in AKI. Recently, a new score has been proposed to implement NGAL values in the routine of AKI diagnosis and stratification in patients with recent cardiac surgery (Fig. 11.5).[35–38] The same quantitative approach has been made available in the case of cell cycle arrest biomarkers (Fig. 11.6).[39–41]

Cell Cycle Arrest Biomarkers

Today we are facing a new era in which the possibility of molecular diagnosis of disease implies a careful evaluation of all aspects of a clinical disorder, including organ dysfunction and tissue damage. This approach represents a paradigm shift because it may allow an early identification of patients at risk, undergoing kidney stress, subject to damage progression or complete organ dysfunction. This ultimately predicts

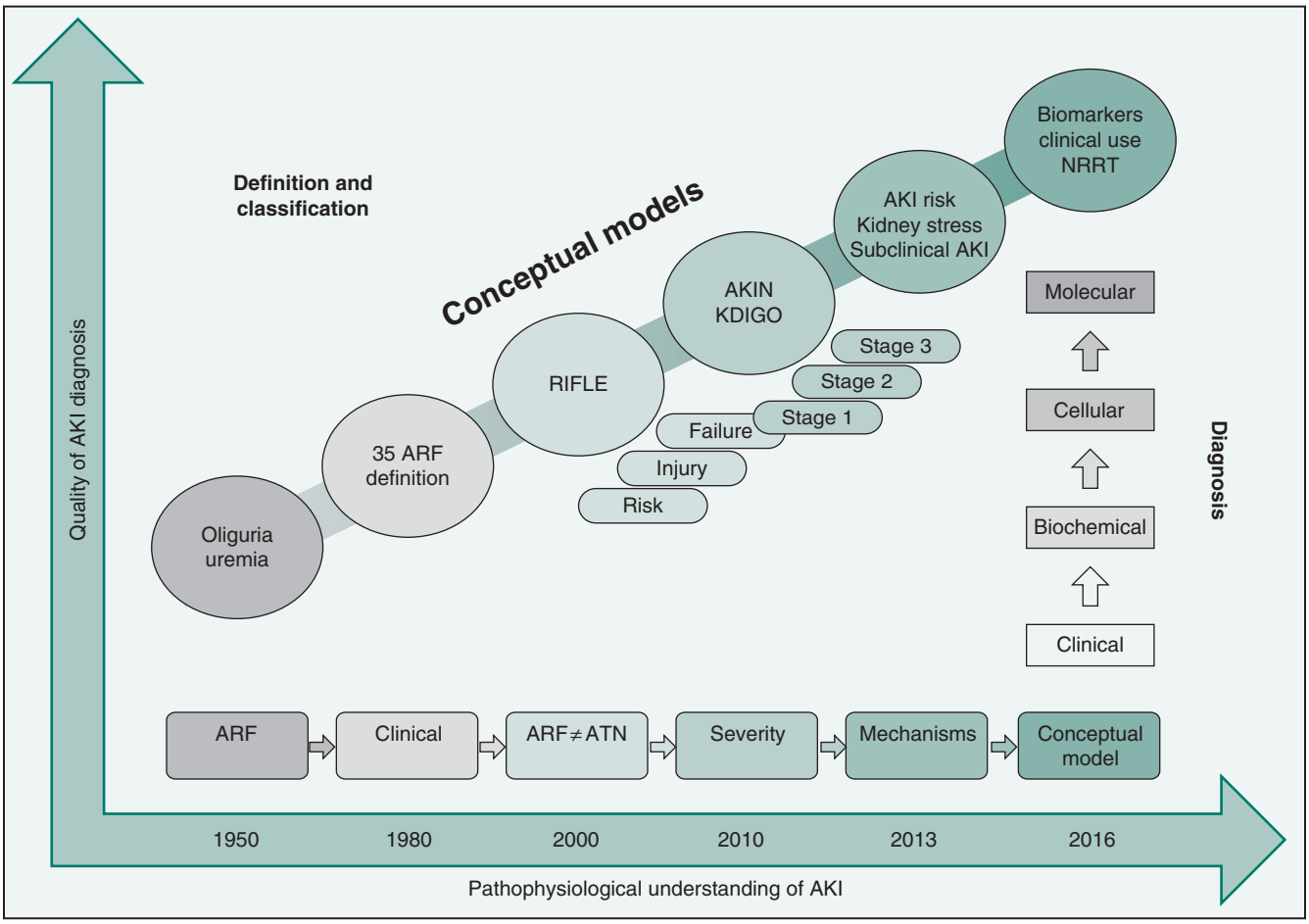

FIGURE 11.3 The diagram describes the evolution of acute kidney injury (AKI) in terms of accuracy of diagnosis and understanding of pathophysiology. In the last 70 years, from clinical observation (oliguria and uremia), we moved to numerous definitions based on serum creatinine. Subsequently a biochemical syntaxes was proposed when the RIFLE, Acute Kidney Injury Network (AKIN), and Kidney Disease: Improving Global Outcomes (KDIGO) criteria were introduced. In recent years, the discovery and validation of cell cycle arrest biomarkers, neutrophil gelatinase-associated lipocalin (NGAL), and other markers have permitted to introduce the concepts of AKI risk, kidney stress, and subclinical AKI. The quantitative evaluation of these markers have moved the diagnosis of AKI from clinical/biochemical to cellular/molecular level. A clinically manifest episode of AKI can be diagnosed by serum creatinine or urine output, allowing classification of patients into stages 1–3. Before that, however, a condition of initial or subclinical damage can be uncovered by injury biomarkers. This may occur in patients with intact nephron mass or with reduced nephron mass but still normal GFR. The phase of recovery from AKI is somehow specular. Patients may go back to normal serum creatinine and the AKI episode is resolved, but this does not mean that full recovery has occurred. Patients in fact may go back to a completely intact nephron mass, or they may present a population of nephrons that are damaged. However, because the remnant nephron mass is sufficient to maintain baseline GFR normal, patients are not identified as "highly susceptible" or with initial CKD, unless they are studied with glomerular and tubular renal stress test. In this case they may display inability to increase GFR in response to a specific stimulus. The portion of the diagram below the line of normal serum creatinine is characterized potentially by new biomarkers that allow a molecular diagnosis of AKI. *NRRT,* Nephrology rapid response team.

clinical outcomes such as morbidity, mortality, and dialysis requirement.

The identification of patients at risk and the evaluation of the susceptibility of the kidney to exposures is a challenging task. The need of an early recognition of the injury/dysfunction of the target organ and the monitoring of progression toward severe dysfunction, chronic disease, or possible recovery are difficult objectives in the management of critically ill patients. These challenges are even more pronounced when other conditions such as sepsis and multiple organ dysfunction are involved or the patient is admitted to the emergency room.[36] In this evolving area of research and care, the process of implementation of new biomarkers is becoming crucial. Even minimal kidney damage resulting from an insult (exposure) in the tubular or glomerular structure may evolve into progressive apoptosis and fibrosis and possibly into devastating glomerular destruction with inevitable hyperfiltration of the reaming parenchyma.

The process of discovery has been conducted by evaluation several molecules that are expressed in the blood or urine of patients with AKI, such as interleukin-18 (IL-18), liver-type fatty acid binding protein (L-FABP), and kidney injury molecule-1 (KIM-1), among others.[37-38] In this case, candidate biomarkers have been studied, selecting the most suitable molecules. The subsequent step was the validation in which specific molecules have been evaluated prospectively in a cohort of patients to establish their capacity to predict the occurrence of a certain event or even to identify the individuals at risk to develop the syndrome. New biomarkers should be capable to offer predictive capabilities above 80% or even 90%.

In spite of a growing body of publications, many new biomarkers have not satisfied these requirements and most of them have not been yet used in clinical routine because of a series of unresolved issues. In addition, a major concern has been that once significant damage has occurred, the possibility to modify the clinical course and especially the recovery phase was considered minimal or absent. Although a number of patients with AKI recover kidney function, others inevitably may progress toward chronic kidney disease. The final outcome is probably susceptible to be influenced especially at the earliest stages of stress and injury, when it may be possible to prevent further damage and preserve remaining kidney function. Removing potentially injurious exposures such as nephrotoxic drugs or providing protective measures such as heightened attention to fluid and hemodynamic management.[39]

Recently, the US Food and Drug Administration made an important step forward in the battle against AKI and its consequences. FDA cleared the marketing of the Nephro-Check Test (Astute Medical Inc. San Diego, USA), a rapid test for the quantitative measurement of the cell cycle arrest biomarkers: Tissue Inhibitor of Metalloproteinase-2 (TIMP2) and Insulin-Like Growth Factor Binding Protein -7 (IGFBP7).[40] The combination of the two biomarkers ([TIMP2]·[IGFBP7]) measured by the test seems to be highly predictive of which patients will develop moderate to severe AKI in the next 12 to 24 hours.

Early work in the international multicenter Sapphire study of 728 critically ill patients showed that elevation of the combination of biomarkers measured by the NephroCheck.[41] This test is specific to AKI (i.e., is not caused by other comorbidities such as sepsis or CKD) and provides a strong signal or "renal alarm" to identify when a patient is at imminent risk of developing AKI.[42] These urinary biomarkers are believed to be elevated in response to renal tubule cell stress or early injury associated with the types of exposures known to cause AKI. A primary clinical cutoff value (0.3) for the combination of the two biomarkers was derived from the Sapphire study data and verified in a new cohort of 153 critically ill patients (Opal study).[43] This cutoff was selected to have high sensitivity for the primary endpoint of moderate to severe AKI in the next 12 hours, with the intent to be used in routine clinical practice to identify patients at high risk for AKI who therefore are candidates for kidney-sparing management strategies such as those outlined in the KDIGO guideline for high-risk patients.[44–49] A second, high-specificity cutoff (2.0) was selected and verified to identify the subgroup of patients who are at the highest risk of AKI and who therefore may be appropriate for more active interventions. Both cutoffs (0.3 and 2.0) were validated subsequently in a 23-site study of 408 critically ill patients in the United States (Topaz study) using clinical adjudication to determine the primary endpoint of moderate-severe AKI.[50–52]

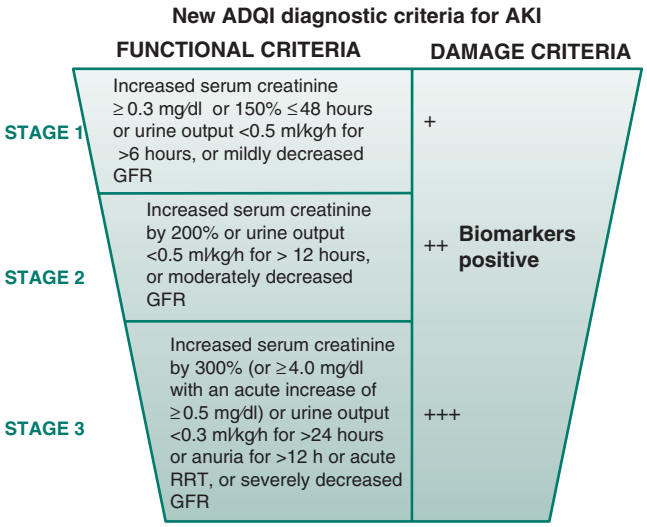

FIGURE 11.4 The new ADQI diagnostic criteria for acute kidney injury. The proposed diagram requires discrete values for biomarkers.[26,27,28] *AKI,* Acute kidney injury; *GFR,* glomerular filtration rate; *RRT,* renal replacement therapy.

NGAL Score in CSa-AKI
Cardiac surgery associated (CSA) acute kidney tubular damage-$NGAL_{CSA}$ Score

Concentration Sample	(ng/mL)	Delta (Δ) NGAL at following measurement	$NGAL_{CSA}$ Score	
uNgal	50		0	Tubular damage unlikely
pNGAL	<100			
uNgal	50 – <150		1	Tubular damage possible
pNGAL	100 – <200			
uNgal	150 – <1000 or	Δ >100+ second value ≥125	2	Tubular damage
pNGAL	200 – <1000 or	Δ >100+ second value ≥150		
uNgal	>1000		3	Severe tubular damage
pNGAL				

FIGURE 11.5 Neutrophil gelatinase-associated lipocalin (NGAL) score proposed for cardiac surgery patients. (From de Geus HR, Ronco C, Haase M, Jacob L, Lewington A, Vincent JL. The cardiac surgery-associated neutrophil gelatinase-associated lipocalin [CSA-NGAL] score: a potential tool to monitor acute tubular damage. *J Thorac Cardiovasc Surg* 2016;151[6]:1476–1481.) *uNgal,* urine neutrophil gelatinase-associated lipocalin; *pNGAL,* plasma neutrophil gelatinase-associated lipocalin.

The NephroCheck quantitatively measures the combination of the two cell cycle arrest biomarkers ([TIMP2]·[IGFBP7]) by point-of-care techniques and other laboratory platforms, thus expanding the availability of the test worldwide. NephroCheck may be used alone or in combination with other biomarkers of AKI as a discriminating test to alert physicians. All these considerations assume that putting the diagnostic clock ahead by 12 to 24 hours compared with the clinical clock can make a difference. Even a subclinical (creatinine negative) injury, which may appear to be negligible, can produce significant parenchymal damage.[4] This may be underestimated because of the presence of a significant renal functional reserve in the kidney and the absence of clinical signs and symptoms.[45]

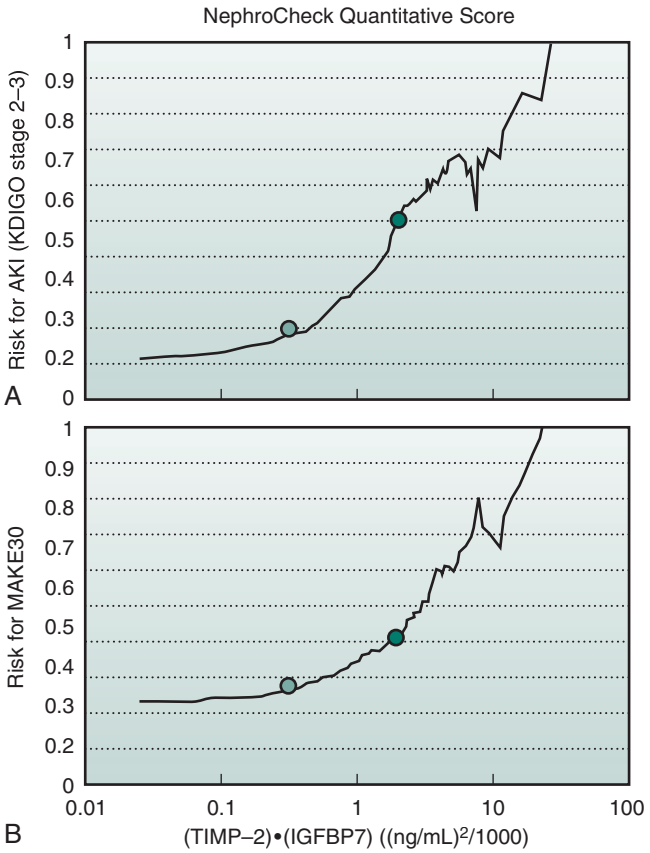

FIGURE 11.6 Correlation of NephroCheck quantitative thresholds and risk for acute kidney injury (AKI) at 12 hours (Kidney Disease: Improving Global Outcome [KDIGO] stage 2–3) and major adverse kidney events within 30 days. *IGFBP7,* Insulin-like growth factor-binding protein 7; *TIMP-2,* tissue inhibitor metalloproteinases 2.

However, the injury reduces the functioning renal mass and produces a progressive increase in kidney frailty with a remarkable susceptibility to future injuries. This process may be the gateway to CKD. Molecules expressed in the process of an injury, may be biomarkers of the event, but they also may represent the expression of a defensive mechanism against the very same event. Although cell-cycle arrest biomarkers can be involved in the pathogenic mechanisms of the injury, it is likely that they represent a pathway of defense. They may operate a protection of tubular cells from a progressive damage perpetuated by multiplication of damaged cell with altered DNA or senescent phenotype. Biomarkers also may alert the clinician in the very early phase of the process.[34] These molecules even could be considered also as therapeutic targets to be antagonized or in some case even stimulated with synergistic actions to favor recovery. The biomarker molecule in this scenario may become not only theragnostic, allowing to follow the results of therapeutic actions, but it even could be considered as a therapeutic molecule to be used in the right time window of the process of injury and recovery.

CONSTITUTION OF NEPHROCHECK RAPID RESPONSE TEAM

After the discovery of several AKI biomarkers over the years, the recent validation and routine clinical application of NephroCheck has put in our hands a tool to detect patients at high risk of AKI and improve their outcomes.[53–57] The aim is to integrate the performance of NephroCheck into a rapid clinical response from a multidisciplinary team that eventually will reduce episodes of AKI, severity, and number of dialysis needed (Fig. 11.7). Among ICU patients those with sepsis and major high-risk surgeries, including

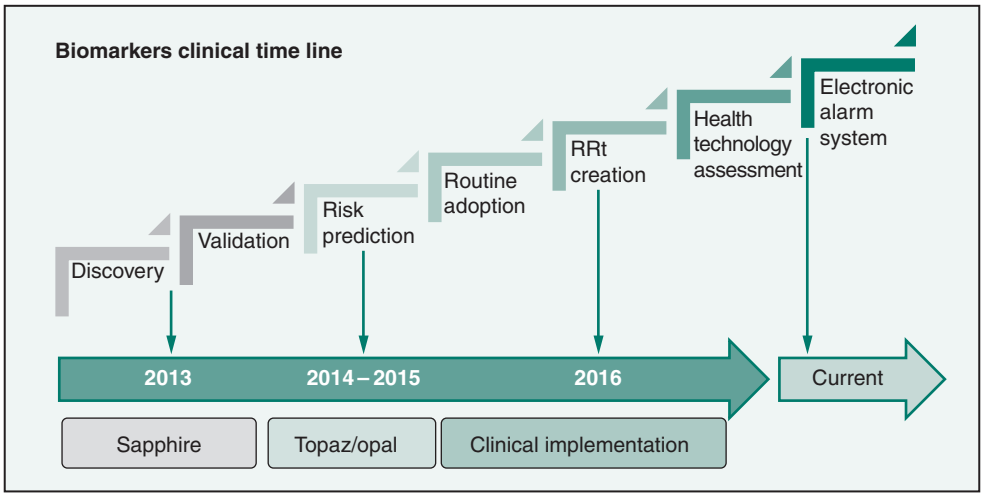

FIGURE 11.7 Evolution from biomarker discovery to routine adoption for the NephroCheck molecule combination. *RRt,* Rapid response team.

CPB operations, are considered the high-risk group for AKI development.[1,43] The other risk factors for AKI are age >65 years, diabetes mellitus, CKD, exposure to nephrotoxins including contrast media, nonsteroidal antiinflammatory drugs (NSAIDs), angiotensin-converting enzyme inhibitors (ACEIs), angiotensin II receptor blockers (ARBs), or antibiotics, known previous episode of AKI, sepsis, use of vasopressors, mechanical ventilation, volume, and kind of resuscitation fluid.[12,44,45]

Looking for a hospital's routine clinical application, a NephroCheck Rapid Response Team (NRRT) has been suggested[57] to drive the decision progress that will affect the patient's clinical benefit. To favor the practical implementation of guidelines and routine adoption of the biomarkers, a careful health technology assessment (HTA) should be made to elucidate the potential benefits of this approach. At the same time, we must take advantage of current technology using alarm systems and sniffers in the management of electronic medical records to facilitate practical implementation of biomarkers-driven renal protection programs.[58] A multidisciplinary HTA process recently has provided vital information to key decision makers and stakeholders.[58] The cost of routine adoption of biomarkers and biomarker-driven policies can be afforded because of reduction of incidence and severity of AKI cases and their relevant costs to the society, not only as immediate expenditure but also as future costs related to management of CKD patients who progressed from an AKI episode.

The proper performance of biomarkers depends on the training of personnel and the presence of a well-coordinated multidisciplinary team. A rapid response team (RRt) may educate caregivers (allied health staff, providers, and others) in the early recognition of the patient at risk for AKI and to alert the specialists for appropriate and timely processes of care. This may result in a reduction of hospital length of stay, morbidity, and mortality.[49–52] The advent of specialized teams (RRt for trauma, stroke, and chest pain) for the care of medical and surgical emergencies has changed substantially hospital medicine and improved patient safety. In some clinical scenarios, it is difficult to identify patients who are going to progress to full-blown AKI after kidney stress. Early identification would enable physicians to modify the exposure and patient susceptibility to avoid further complications. As the golden hour has been recognized to act before the established acute myocardial infarction (AMI) or stroke, a critical time window of less than 12 hours should be considered to prevent permanent and severe kidney damage. An NRRT has been created and put into practice in San Bortolo hospital (Vicenza). Candidate patients to undergo NephroCheck testing are critically ill or high-risk patients in ICU and cardiac surgery. Low-, high-, and very high-risk patients are identified according to the NephroCheck nomogram and the reported discrete values (<0.3, 0.3–2.0, >2.0 ng/mL). The result, available after 20 minutes, prompts the nephrologist and critical care physician (CCP) with an electronic alert.

If NephroCheck is ≤0.3 (ng/mL), a low-risk condition is detected and monitoring continues with standard AKI prophylaxis. A NephroCheck >0.3 (ng/mL) triggers an early renal consultation.[57] The multidisciplinary team is activated with recommendation to implement KDIGO guidelines immediately and to pay special attention to patients' individual susceptibilities and exposures responsible for a potential AKS. The team will evaluate diuresis, fluid balance, and possible need for early renal replacement therapy or support while recommendations will include close monitoring, avoiding nephrotoxic agents, and ensuring hemodynamic stability (conservatory preventive management).

If NephroCheck is ≥2 ng/mL, the immediate response should include discontinuation of nephrotoxins, avoidance of contrast media, avoidance of fluid overload, and achievement of hemodynamic stability even if vasopressors or additional monitoring are needed (aggressive preventive management). All of these actions should be done as soon as the NephroCheck value arrives (Fig. 11.8). Finally, patients must be identified clinically or electronically based on their risk profile for immediate complications and for long-term effects (progression to CKD or end-stage renal disease [ESRD]). This would not only allow appropriate care to critically ill patients but also would provide guidance to providers regarding who needs long-term follow-up and care to avoid AKI-associated complications. A follow-up is necessary to check for AKI resolution, new onset, or worsening of preexisting CKD and, accordingly, to individualize frequency and duration of patient monitoring.

CONCLUSION

Biomarkers seem to be useful tools in clinical routine to identify patients at risk for AKI, to make an early diagnosis of AKI, to classify severity of AKI, to detect progression or resolution of the kidney attack, and to evaluate response to therapy. Their predictive value has increased dramatically, and today we can make a diagnosis of AKI only based on these molecular criteria even in presence of still-normal classic parameters such as urine output or SCr. There seems to be a cost-benefit ratio justifying the use of these expensive biomarkers in critically ill patients especially to identify a status of kidney stress. In these circumstances biomarkers represent an index of increased susceptibility to insults and high risk to develop AKI. The ADQI consensus group proposed the use of biomarkers to diagnose AKI with kidney damage even in the absence of dysfunction. Urine and plasma NGAL are good predictive markers for AKI, as well as efficient tests to predict the need of RRT and mortality in septic and high-risk cardiac surgery patients. In the same line is the recent validation of discrete limits of cell-cycle arrest biomarkers (TIMP-2 and IGFBP-7) to rule out AKI or to identify high-risk conditions for AKI. High levels of TIMP-2 and IGFBP-7 describe a condition of kidney stress and they are highly predictive of mild to severe AKI. Biomarker levels may change over time, allowing identifying different phases of the syndrome such as increased susceptibility and risk, subclinical kidney damage, tissue regeneration and recovery, or progression toward CKD. Subclinical AKI may be diagnosed only with the use of biomarkers, because classic criteria are still within normal range. AKI biomarkers are useful also to identify conditions of partial recovery, maladaptive repair, and progression toward CKD. Specific biomarkers may represent a molecular signature for every type of insult (e.g., ischemia, sepsis, toxins). Moving from clinical to molecular diagnosis of AKI allows developing individual criteria and decision-making frameworks for the etiologic variants of AKI. An evident cost-benefit ratio may be achieved by the application of biomarkers in specific environments. Implementation of routine use of biomarkers triggering specific alert conditions and rapid response teams (e.g., NRRT) may help prevent development of AKI, decreasing severity and number of dialysis treatments. If dialysis is avoided even in a limited cohort of patients or progression to CKD can be blocked, the financial advantage of biomarkers will become evident for healthcare providers beyond any immediate clinical and individual benefit.

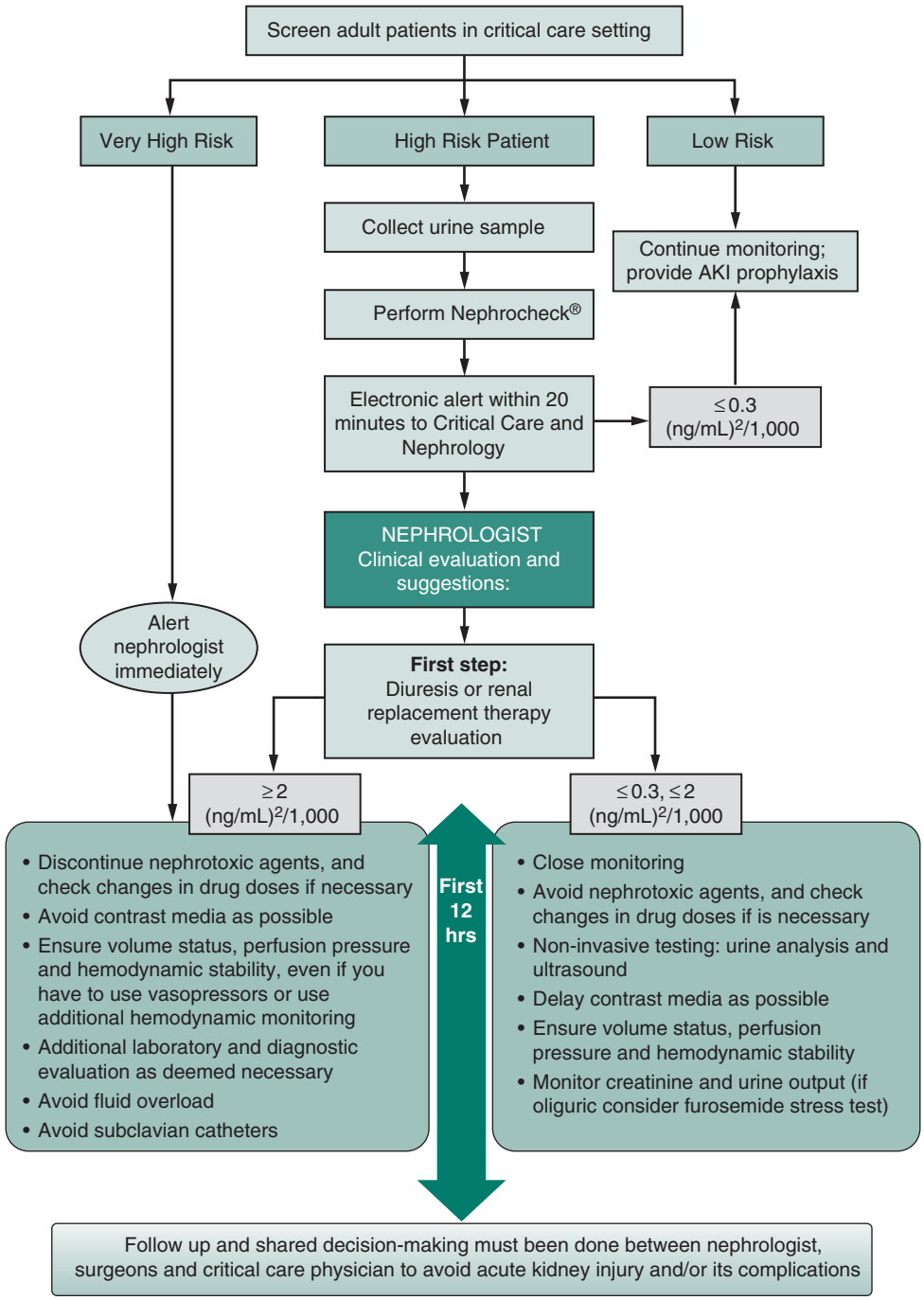

FIGURE 11.8 Practical algorithm for the clinical routine adoption of acute kidney injury biomarkers and relevant actions from a rapid response team.

Key Points

1. For many years, the diagnosis of acute renal failure (ARF) has been mostly clinical and based on evident signs and symptoms such as uremia and oliguria.
2. RIFLE diagnostic criteria were introduced in 2004, allowing to describe the presence of acute kidney injury (AKI) and to define its clinical stage, based upon serum creatinine level (SCr) and urine output (UO).
3. SCr and UO criteria also have been used to develop other scoring systems such as Acute Kidney Injury Network (AKIN) and Kidney Disease Improving Global Outcome (KDIGO).
4. Current practice suggests that RIFLE, AKIN, and KDIGO diagnostic criteria used to assess the

presence of AKI and its severity are insufficient to illustrate the complexity of the AKI syndrome. In particular, current methods are suboptimal, poorly accurate, and often timely inadequate in detecting the presence of an early kidney injury.

5. New AKI biomarkers can be used to rule out AKI and to assess high-risk conditions or the presence of subclinical forms of AKI.
6. NGAL or cell cycle arrest biomarkers seem to be highly sensitive and specific diagnostic tools that would be highly valuable in conjunction with existing markers of AKI for better classifying renal injury as well as dysfunction, with important consequences on prevention and organ protection.
7. AKI diagnosis has finally moved from clinical to molecular level with potential benefits for the patients.
8. Given the reliability of AKI biomarkers, the creation of a multidisciplinary biomarker-driven response team is recommended strongly to implement preventive and protective measures.

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

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