Acute Kidney Injury: Definitions, Incidence, Diagnosis, and Outcome

2

Francis X. Dillon and Enrico M. Camporesi

2.1 Introduction

Surgeons, anesthesiologists, intensivists, radiologists, interventional cardiologists, and nephrologists, among others, are keenly interested in preserving renal function in patients undergoing surgical interventions or other procedures, as well as in intensive care unit (ICU) patients. The well-known strong association between acute kidney injury (AKI) and its sequel, chronic kidney disease (CKD) with mortality and with severe cardiac and other organ morbidity [1–5] makes practitioners even more mindful of kidney function in these patients. No effective new therapy for AKI has been introduced so far; thus better avenues for progress may be novel diagnostic tests and a clearer understanding of the factors associated with the development of AKI in both surgical and critically ill patients and how to prevent it.

Around 2000, the lack of novel pharmacologic strategies for AKI therapy seemed to awaken a critical mass of epidemiologists and nephrologists: worldwide a reassessment of the most fundamental questions about AKI was spurred, and nephrology literature from 2004 onward was eventually unfolded.

F.X. Dillon, MD (✉)
TEAMHealth Inc./Florida Gulf-to-Bay Anesthesia Associates LLC, Tampa General Hospital, 1 Tampa General Circle, Suite A327, Tampa, FL 33606, USA

Department of Surgery, University of South Florida, Tampa, FL 33606, USA
e-mail: fxdillon@gmail.com

E.M. Camporesi, MD
TEAMHealth Inc./Florida Gulf-to-Bay Anesthesia Associates LLC, Tampa General Hospital, 1 Tampa General Circle, Suite A327, Tampa, FL 33606, USA

Department of Surgery, University of South Florida, Tampa, FL 33606, USA

Department of Anesthesiology, Molecular Pharmacology and Physiology, University of South Florida, Tampa, FL 33606, USA
e-mail: ecampore@health.usf.edu

G. Landoni et al. (eds.), *Reducing Mortality in Acute Kidney Injury*,
DOI 10.1007/978-3-319-33429-5_2

The first most urgent questions were related on AKI definition, how best AKI could be classified, what is its etiology, and how best to prevent it. If indeed prevention is the only way of reducing the burden of AKI and of its sequelae (outside of renal replacement therapy [RRT]), then clarifying definition was the obligatory first step.

2.2 The Evolution of AKI Definition

The lack of uniformity in naming and defining AKI has been a serious impediment to progress in the field's epidemiology [6]. From the standpoint of nomenclature, the older term "acute renal failure" (ARF) was predominant until 2005 when the term AKI emerged. The term ARF is now obsolete as an acronym in medicine and nephrology.

The significance of this change in nomenclature was felt by many in the nephrology community to be of great, even revolutionary importance because generally the older references in the nephrology and critical care literature had often defined ARF less precisely than the newer term AKI would be defined. For example, in a 1999 review Nissenson defined ARF in the critical care setting as "the abrupt decline in glomerular filtration rate (GFR) resulting from ischemic or toxic injury to the kidney" [7]. Some authors defined ARF as azotemia with or without oliguria. Other authors had recorded increases in blood urea nitrogen (BUN) to diagnose ARF and omitted serum creatinine (sCr) measurements. In others, the timing of sCr or BUN samples was incompletely documented. Some authors noted rehydration as a precondition for diagnosing ARF, while others did not specify the presence or absence of rehydration as a part of this definition. In the seminal critical care paper in which the first exact definition of AKI was introduced, Bellomo et al. [8] noted that some 30 definitions of ARF had hitherto been used at different times in the literature.

From 2002 onward, three different consensus definitions, from three different workgroups, have emerged and become accepted, and the reader needs to be aware of the differences between them when comparing studies. No single consensus definition has yet emerged as the standard definition, but the use of KDIGO definition [9] (see below) is currently recommended for epidemiologic and research purposes.

2.2.1 The ADQI Workgroup Was Formed to Address a Lack of Consensus Over How Best to Treat AKI with RRT: Eventually, the Group Produced RIFLE, an Acronym Defining AKI by Its Severity in Stages

The Acute Dialysis Quality Initiative (ADQI) [8, 10] Workgroup was founded in 2000 by representatives from the US National Institutes of Health (NIH), American Society of Nephrology (ASN), and the Society of Critical Care Medicine (SCCM), among others. In 2004, its founding members identified a definition and classification system for AKI. It employed the mnemonic acronym RIFLE (for "risk,"

"injury," "failure," "loss" of renal function, and "end-stage" kidney disease). The various levels of AKI were defined according to azotemia (serum creatinine) *and* urinary output (UO) criteria (Table 2.1) [8]. Note that the most severe criteria in either the azotemia or oliguria columns should be applied when assigning a RIFLE stratum: i.e., one should use whichever criterion that assigns the most severe class of AKI.

2.2.2 The AKIN Diagnostic and Staging Criteria for AKI Emphasize Azotemia

The members of the Acute Kidney Injury Network (AKIN) first met in 2005 and proposed a diagnostic criterion for AKI [11] (see Table 2.2) in order to improve some of RIFLE drawbacks. The AKIN workgroup classified AKI into three degrees of severity called stages 1, 2, and 3 (Table 2.3). Note that, as the AQDI definition did, these resemble the "R," "I," and "F" strata, which also take into account creatinine increase over baseline as well as oliguria. The AKIN guideline also stipulates adequate fluid resuscitation prior to diagnosis of AKI.

Table 2.1 The acute dialysis quality initiative (ADQI) workgroup criteria and classification for AKI

RIFLE criterion[a]	GFR criterion	Urine output criterion	Sensitivity or specificity
Risk	Increased sCr × 1.5 or GFR decrease ≥25 %	UO <0.5 mL/kg h × 6 h	High sensitivity
Injury	Increased sCr × 2 or GFR decrease ≥50 %	UO <0.5 mL/kg h × 12 h	
Failure	Increased sCr × 3 or GFR decrease ≥75 % or sCr ≥4 mg/dL (acute rise of ≥0.5 mg/dL)	UO <0.3 mL/kg h × 24 h or anuria × 12 h	High specificity
Loss	Persistent ARF: complete loss of renal function >4 weeks		
End-stage	End-stage kidney disease		

Modified from Bellomo et al. [8]
GFR glomerular filtration rate, *UO* urine output, *sCr* serum creatinine, and *ARF* acute renal failure
[a]Select the highest (worst) RIFLE level using either the GFR or urine output criteria

Table 2.2 AKIN diagnostic criteria for AKI

An abrupt (within 48 h) reduction in kidney function defined as (one of the three below):
An absolute increase in serum creatinine of 0.3 mg/dl (26.4 μmol/l) *or*
A percentage increase in serum creatinine of 50 % (1.5-fold from baseline) *or*
A reduction in urine output (documented oliguria of <0.5 mL/kg h for >6 h)
Criteria to be applied in the context of the clinical presentation and following adequate fluid resuscitation

Modified from Molitoris et al. [11] and Mehta et al. [72]

Table 2.3 Staging of AKI according to AKIN

Stage	sCr criteria	Urine output criteria
1	A serum Cr increase of 0.3 mg/dl (26.4 μmol/L) *or* An increase of sCr 150–200 % from baseline	UO <0.5 mL/kg per hour for >6 h
2	A sCr increase of 200 % over baseline	UO <0.5 mL/kg per hour for >12 h
3	A sCr increase of 300 % over baseline *or* A sCr ≥4.0 mg/dL (354 μmol/L) with an acute increase ≥0.5 mg/dL (44 μmol/L) *or* A need for RRT	UO <0.3 mL/kg per hour for 24 h or anuria for 12 h

Modified from Mehta et al. [72]
sCr serum creatinine, *UO* urine output, and *RRT* renal replacement therapy

Table 2.4 Diagnosis and staging of AKI according to the KDIGO workgroup

The diagnosis of AKI is made by any one of the following:		
An increase in sCr by ≥0.3 mg/dl (≥26.5 μmol/l) within 48 h		
An increase in sCr ≥1.5 times baseline, which is known or presumed to have occurred within the prior 7 days		
UO <0.5 mL/kg h for at least 6 h		
Staging of AKI is done according to the following criteria:		
KDIGO stage	**sCr or eGFR increase**	**Urine output decrease**
1	sCr 1.5–1.9 times baseline *or* 0.3 mg/dl (26.5 μmol/L) increase	<0.5 mL/kg h for 6–12 h
2	sCr 2.0–2.9 times baseline	<0.5 mL/kg h for 12 h
3	sCr 3.0 times baseline *or* Increase in sCr to 4.0 mg/dL (353.6 μmol/L) *or* Initiation of RRT *or* In patients <18 years, decrease in eGFR to <35 mL/min per 1.73 m^2	<0.3 mL/kg h for 24 h *or* Anuria for 12 h

See Ref. [9] for the complete version
sCr serum creatinine, *UO* urine output, *RRT* renal replacement therapy, and *eGFR* estimated glomerular filtration rate. KDIGO guideline is reported in abbreviated form

2.2.3 The KDIGO Defines AKI Using Similar Azotemia and Oliguria Criteria and Includes a GFR Criterion for Patients Younger than 18 Years of Age

In 2003, the Kidney Disease: Improving Global Outcomes (KDIGO) was formed with the aim of implementing clinical practice guidelines for patients with kidney disease. In March 2012, KDIGO published its far-ranging guidelines for the evaluation and management of AKI (Table 2.4) [9].

2.2.4 The US National Kidney Foundation and Others Weigh in on These Three Definitions

A study group of the US National Kidney Foundation, called the NKF-KDOQI (National Kidney Foundation—Kidney Disease Quality Outcome Initiative), reported mixed sentiments about the KDIGO guidelines [12]. The initiative was a group of renal specialists who generally applauded the melding of ADQI, AKIN and KDIGO AKI definitions but was less enthusiastic about the recommendations for AKI management proposed in the KDIGO guidelines. The KDOQI's concern was that many of the management recommendations, though sensible or at least plausible as first-approaches, were unsubstantiated by well-powered controlled clinical studies [12]. Likewise, the Canadian Society of Nephrology (CSN) [13] and the European Renal Best Practices (ERBP) society [14] were hesitant to embrace the KDIGO guideline. By way of the struggle to define and clarify the definition of AKI, and to take the first steps to make the treatment of AKI more evidence-based, much information about the incidence and progression of AKI has been brought to light, even in the absence of any radically new science.

2.2.5 Summary of the Definitions of AKI

The importance of recounting these steps in the evolving definition of AKI is twofold: first, comparing research papers about AKI requires some understanding of the differences between the RIFLE, AKIN, and KDIGO definitions, since they vary in their respective criteria of azotemia, oliguria, estimated glomerular filtration rate (eGFR), and time intervals over which AKI must occur. Secondly, they have different names for each stage of severity. There is yet no consensus on which definition is predominant. The RIFLE acronym [8] is popular in the literature and in medical records, but the KDIGO definition [9, 12] implies future screening and initial management recommendations and is likewise popular. Any of these classifications can be utilized to stratify AKI severity and are used to report incidence and outcome. So far, no one has yet identified a better serum marker than creatinine or better functional criteria than oliguria and GFR to characterize AKI. All three are used one way or another in these three workgroup definitions, for classifying AKI. They are likely all robust and close enough to be reliably used presently.

2.3 The Incidence of AKI

Table 2.5 provides a summary of some relevant publications addressing the incidence of AKI among postoperative and medical inpatients. Various risk factors associated with AKI are also briefly summarized.

Table 2.5 Some studies describing the incidence and risk factors associated with acute kidney injury (AKI)

Study	Type of analysis	*N*	How AKI is defined in the study	Variables associated with AKI	Clinical setting	Main findings
Walsh et al. (2013) [15]	Retrospective	33,330	↑sCr per AKIN definition within 7 days	↓MAP (>55 mmHg)	*Noncardiac surgery* adults	7.4 % pts. developed AKI
Lehman et al. (2010) [18]	Retrospective multivariate logistical regression	16,728	↑sCr per AKIN definition within 48 h	↓MAP (≤80 mmHg) AKI risk related to lowest MAP and duration of ↓BP	*ICU adults*	AKI ↑ for any MAP ≤80 mmHg OR 1.03 (3 %) per each mmHg <80 AKI incidence 50 % for MAP ≤50 mmHg AKI ↑ for each additional hour MAP was decreased below: 70 mmHg (2 %) 60 mmHg (5 %) 50 mmHg (22 %)
Weingarten et al. (2012) [14]	Retrospective case control	9171	↑sCr per AKIN definition within 72 h	↑BMI general anesthesia ↑N of antihypertensive medications CVD PVD DM Transfusion Preoperative anemia	*Major adult orthopedic surgery* Unilateral knee, hip, or shoulder replacement Bilateral knee replacement	AKI developed in 1.82 % Of those with AKI 12.0 % had sCr elevation at 3 months

Kheterpal et al. (2007) [16]	Prospective observational	15,102	CrCl ≤50 mL/min (C&G) within 7 days	Age >59 years ↑BMI, ESLD High-risk surgery PVD COPD	*Noncardiac, general surgery, adult*	0.8 % pts. developed AKI 0.1 % required RRT
Abhela et al. (2009) [17]	Retrospective cohort study; simple binary logistic regression	1166	↑sCr per AKIN definition within 48 h	ASA status RCRI score high-risk surgery ischemic cardiac disease CHF	*ICU adult patients*	7.5 % met AKI criteria
Tujjar et al. (2015) [19]	Retrospective	199	Oliguria within 24 h ↑sCr per AKIN definition within 48 h	Age CKD Higher epinephrine dose In-hospital cardiac arrest hypotension Low admission CrCl High cumulative fluid balance	*Resuscitated cardiac arrest pts., adult*	43 % of pts. developed AKI Pts. with AKI had higher mortality AKI did not predict 3-month neurologic outcome
Harris et al. (2015) [22]	Retrospective	136	RIFLE criteria	Diabetes ↑APACHE III score sepsis	*High-risk adult vascular surgery pts.*, both operative and non-operative management	48 % of pts. developed AKI Pts. with AKI had ↑ short- and long-term mortality and hospital length of stay

(continued)

Table 2.5 (continued)

Study	Type of analysis	*N*	How AKI is defined in the study	Variables associated with AKI	Clinical setting	Main findings
Uchino et al. (2005) [20]	Prospective observational	29,269	ARF defined as oliguria of ≤200 mL in 12 h or BUN ≥84 mg/dL	Causes (%): Sepsis 47.5 Surgery 34.3 CHF 26.9 ↓Vol 25.6 Drug 19.0 Hepatorenal 5.7 Obstructive 2.6 Other 12.2[a]	Pts. admitted to ICUs in multiple countries for *multiple reasons*	5.7 % of pts. developed AKI and 4.3 % needed RRT
Venot et al. (2015) [55]	Case-control	10,911 (3728 sepsis; 510 septic shock)	KDIGO category	55.9 % of septic pts. *without* DM got AKI 72.5 % of septic pts. *with* DM got AKI	*ICU sepsis pts. with or without DM*	Septic pts. *without* DM: 13.8 % had RRT Septic pts. *with* DM: 20.6 % had RRT

AKIN Acute Kidney Injury Network, *Pts*. patients, *OR* odds ratio, *BP* blood pressure, *ARF* acute renal failure, *CKD* chronic kidney disease, *MAP* mean arterial pressure (mmHg), *C&G* Cockcroft and Gault equation for estimating creatinine clearance (CrCl) from serum creatinine (sCr), *BMI* body mass index, *CVD* cerebrovascular disease, *PVD* peripheral vascular disease, *DM* diabetes mellitus, *ESLD* end-stage liver disease, *ASA* American Society of Anesthesiology, *CHF* congestive heart failure/cardiogenic shock, ↓*Vol* intravascular hypovolemia, *BUN* blood urea nitrogen, *RCRI* Revised Cardiac Risk Index

[a]Percentages add to ≥100 % because more than one etiology of AKI might have been listed in Uchino et al. [20]

It is clear from these studies that elective adult patients undergoing planned, especially noncardiac procedures have a lower incidence of AKI as compared to more severely ill categories of patients [14–22]. For example, AKI has been reported to occur in 0.8 % of patients undergoing low-risk surgeries [16], in 1.82 % of patients undergoing orthopedic procedures (shoulder, hip, and knee) [14], and in 7.4 % of patients undergoing any noncardiac intervention [15], while the incidence of AKI is much higher in patients undergoing high-risk (7.5 %) [17] or urgent/emergent surgical procedures (hazard ratio for AKI 1.9 [20]) [15, 16, 18], in ischemic and congestive heart failure patients (hazard ratio for AKI 2.0 [17]), in survivors after cardiac arrest (43 %) [19], in patients admitted to ICU for sepsis (10–20 %) [20, 21], and in both elective or emergent high-risk vascular surgery patients (48 %) [22]. *The greatest risk of AKI is borne by those with preexisting CKD* which is tenfold over the risk of patients who do not have a diagnosis of CKD [23].

2.4 Improving the Diagnosis of AKI: From Creatinine Clearance to the New Biomarkers

Practical assessment of day-to-day kidney function in patients is done implicitly, with simple measurement of UO and sCr, comparing it with a baseline (premorbid) value. According to many authors, however, the benchmark or "gold standard" for measuring renal function is the GFR [24], defined as the amount of blood filtrate per minute emerging from the glomeruli into the proximal tubule lumen, for both kidneys. The practicality of obtaining GFR remains controversial, yet some authors have addressed the complex issue of using serum creatinine as a proxy for actual GFR measurements [25]. Endre et al. [25] noted that the two measurements are not the same, of course, and argued that AKI definitions might do well to avoid GFR criteria. However, they suggested that the estimation of GFR with shorter collection times (e.g., 2–4 h) might indeed be practical and make actual GFR, in association with biomarkers of renal injury, sensitive and feasible on a daily basis. Discussion here will merely address that acceptance of spot sCr and the use of eGFR equations like Cockroft-Gault and MDRD are the nearly universally accepted means of estimating GFR.

Normal GFR, in the absence of CKD, is defined as greater than or equal to 90 mL/min 1.73 m^2 of body surface area (BSA). If CKD has been diagnosed, a patient with a GFR ≥90 mL/min 1.73 m^2 would be said to have KDIGO CKD stage G1. A GFR between 60 and 89 mL/min 1.73 m^2 is said to be mildly decreased (KDIGO stage G2 CKD). Note that this pertains to CKD, not AKI.

2.4.1 The Most Promising Novel Biomarkers of AKI: uAlb/uCr, CysC, NGAL, IL-18, and KIM-1

Though well accepted as a noninvasive marker of GFR, sCr has limitations. It is known to vary with muscle mass, age, gender, liver function, and nonrenal

gastrointestinal elimination [26]. Its measurement may be also confounded by exogenous creatinine ingestion. Most importantly, it is well known that sCr is a late indicator of kidney injury [27–29] and that also the reduction in sCr lags as an indicator of improvement in renal function [30]. Moreover, hemodilution may cause a reduction in sCr indicating falsely an improvement in renal function. Finally, its production is decreased in sepsis, unfortunately, just when its use as a marker of AKI makes it a focus of clinical attention [31].

As the need arises to identify AKI earlier and more sensitively than serum creatinine, other biomarkers have been proposed [32]. Table 2.6 shows some features of recently studied biomarkers, including the overall quality of the indicator (i.e., its sensitivity and specificity) as quantitated by its receiver-operator characteristic (ROC) area under the curve (AUC) [33–35]. An AUC value which approaches 1.0 indicates high sensitivity and specificity.

Five of these new biomarkers are among the most promising and will be discussed briefly: urine albumin/creatinine ratio (uAlb/uCr), cystatin-C (CysC), neutrophil gelatinase-associated lipocalin (NGAL), interleukin-18 (IL-18), and kidney injury molecule-1 (KIM-1) [36].

Some authors have merely reexamined the sensitivity and specificity of urine albumin in conjunction with urine creatinine in an attempt to increase the sensitivity and specificity of the two markers, already available in most routine clinical lab panels. Tziakas et al. [29] found the ratio of urinary albumin to creatinine (*uAlb/uCr*) to have a significant predictive value for AKI with an AUC of 0.725, superior to some more modern biomarkers under investigation. Others reported the use of albumin-creatinine ratio as a biomarker of increased risk for cardiovascular morbidity and mortality and all-cause mortality [37].

CysC is a post-gamma-globulin protein first described in 1984 [38]. It belongs to a large class of cysteine proteinase inhibitors. These inhibitors are found in all tissues and bodily fluids, and the enzymes which they inhibit are normally stored in lysozymes produced primarily by nucleated cells throughout the body. It is a small (13 kDa), nonglycosylated, basic protein consisting of 120-amino acid residues [39].

Recent evidence suggests that CysC may be as useful as creatinine or, more so, as a marker for glomerular filtration and AKI. For purposes of assessing renal function, CysC is useful due to its low molecular weight, electrostatic (charge) characteristics, and physical stability: all of these make it easily filtered by the glomerulus. Moreover, its serum concentration is independent of gender, age, or muscle mass, all confounding factors when using creatinine to assess GFR. CysC or the gene coding for it (*CST3*) has also been studied as a biomarker for coronary artery disease [40], congestive heart failure (CHF) [41], squamous cell carcinoma of the head and neck [39], Alzheimer's disease [42, 43], and age-related macular degeneration [43]. This is relevant because the assay for CysC may become more widely used and less expensive and possibly included in clinical laboratory panels in the future.

NGAL, also known as human neutrophil lipocalin (HNL), lipocalin 2, siderocalin, or 24p3, is a small, 25 kDa monomer peptide or a 45 kDa dimer peptide [37]. It is linked covalently with gelatinase (matrix metalloproteinase 9, MMP-9). Its

Table 2.6 Some recent investigations describing novel diagnostic biomarkers of AKI

Study	Type of analysis	Novel biomarker investigated	*N*	Comparison indicator(s)	Setting	AUC (ROC)	Main findings
Tziakis et al. (2015) [29]	Prospective	uNGAL, IL-18, uCysC, pCysC	805	uACR, spot	AKI developing in STEMI and NSTEMI patients	uACR, 0.725	uACR threshold of ≥66.7 μg/mg most accurate, more so than uNGAL or u, pCysC
Hoek et al. (2003) [73]	Prospective cross-sectional analysis	CysC	123	GFR: [^{125}I] iothalamate clearance vs. estimated CysC clearance vs. CrCl (C&G)	Outpatients of a nephrology clinic	CysC, 0.931 C&G, 0.938 Cl, 0.848; both CysC/C&G better than Cl ($p=0.006$) comparison of CysC/C&G, $p=0.815$	Bland-Altman analysis[a] shows that this formula is superior to any other measure in the study[b]: GFR = −4.32 + (80.35/CysC)
Kym et al. (2015) [74]	Prospective cohort study	CysC	85	BUN, sCr, uCr, CysC, CysC-eGFR, AST, LDH, CPK, lactate, myoglobin	Burn patients admitted to ICU	For AKI: LDH, 0.746 lactate, 0.718 sCr, 0.717 CysC, 0.555 For early AKI: LDH, 0.833 sCr, 0.816 AST, 0.790	CysC not useful in predicting AKI in burn patients. LDH, lactate, sCr good LDH, sCr, AST, and Mb good early

(continued)

Table 2.6 (continued)

Study	Type of analysis	Novel biomarker investigated	*N*	Comparison indicator(s)	Setting	AUC (ROC)	Main findings
Stevens et al. (2008) [27]	GFR-estimating equations developed by least squares linear regression. Variables: CysC, sCr, age, sex, race	CysC	3418	GFR: [^{125}I] iothalamate clearance or [^{51}Cr] EDTA clearance vs. sCr/CysC estimated GFR or both	CKD patients	–	CysC alone provides GFR estimates more accurate than sCr alone and nearly as accurate as sCr, age, sex, and race
Nejat et al. (2010) [75]	Prospective	CysC	444	sCr	Pts. admitted to ICUs (with and without preexisting AKI)	sCr, 087 CysC, 0.78 ($p<0.0001$)	In pts. without AKI on ICU admission, the on-entry analyte concentrations were predictive of RRT need (AUC 0.84 for CysC and 0.77 for sCr)
Cruz et al. (2010) [76]	Prospective observational	pNGAL	301	↑sCr (≥50 %) ↓UO (≤0.5 mL/kg h for 6 h)	Adult ICU pts	AKI, 0.78 RRT, 0.82	Correlation of NGAL with AKI severity ($R=0.554$)
Wang et al. (2015) [77]	Prospective cohort study	NGAL	123	NGAL percentile correlation with mortality and MODS	ICU patients with sepsis or septic shock	NGAL predicts mortality (AUC 0.6385)	Mortality 32 % in 12 months
Zhou F (2015) [78]	Meta-analysis	NGAL	4066 (pooled)	NGAL used to predict cardiac surgery-associated AKI	Cardiac surgery pts.	0.86	uNGAL/pNGAL early predictor of AKI especially in neonates/children

Parikh et al. (2013) [52]	Prospective, multicenter cohort study	KIM-1	1219 adults + 319 children	LFABP, NGAL, and composites of the three biomarkers measured at different times	Patients enrolled after cardiac surgery	Adults: urine KIM-1 (6–12 h), 0.78 Children: urine IL-18 (0–6 h) and urine LFABP (from day 2), 0.78	LFABP much more early predictor (6 h) than KIM-1 (2 days)
Nisula et al. (2015) [59]	Prospective cohort study	IL-18	1439	sCr, NGAL	ICU patients	Highest AUC: 0.586 for AKI, 0.667 for stage 3, 0.655 for RRT, 0.536 for 90-day mortality	IL-18 alone felt to be insufficiently accurate
Liu et al. (2013) [79]	Meta-analysis	IL-18	4512 (pooled)	sCr	ICU, ER, cardiac surgery, after contrast	0.70 (overall) 0.68–0.76 (cardiac surgery) 0.62–0.70 (ICU) 0.75–0.82 (children) 0.62–0.70 (adults)	Better predictor of AKI in children than adults, better in cardiac surgery, overall acceptable

Pts. patients, *STEMI/NSTEMI* ST-elevation/non-ST-elevation myocardial infarction, *Mb* myoglobin, *uACR* urine albumin to creatinine ratio, *uCysC/pCysC* urine/plasma cystatin-C, *GFR* glomerular filtration rate (GFR), *C&G* Cockcroft and Gault equation for estimating creatinine clearance (CrCl) from serum creatinine (sCr), *IL-18* interleukin-18, *KIM-1* kidney injury molecule-1, *LFABP* liver fatty acid binding protein, *pNGAL* plasma neutrophil gelatinase-associated lipocalin, *NAG* N-acetyl-β-D-glucosaminidase, *uNGAL* urinary neutrophil gelatinase-associated lipocalin, *uKIM-1* urinary kidney injury molecule-1, *ICU* intensive care unit, *MODS* multi-organ dysfunction syndrome, *ROC* receiver operating characteristic curve, *AUC* area under the curve

[a]Bland-Altman analysis is a statistical test designed to tell if two clinical measurement methods of a single variable are in agreement throughout the range of measurement. It complements the ROC, which is better at comparing various sets of criteria or combinations of tests used in concert to try to establish a binary (i.e., yes-or-no) disease state [80, 81]

[b]The equation estimates GFR in mL/min, using a value of CysC in mg/dL. The most widely used assay is an immune-nephelometric assay with a range of 0.23–7.25 mg/L (17.2–543.0 nmol/L). See Stevens et al. [27]

function is thought to be as a modulator of early inflammation, where it is thought to inhibit bacterial growth, scavenge iron and induce epithelial growth. Plasma NGAL is freely filtered by the glomerulus and then largely reabsorbed by proximal tubular cells. More importantly though, upon renal tubular injury NGAL reabsorption is decreased and NGAL synthesis in epithelial cells of the loop of Henle and of distal tubule segments is strongly upregulated. This makes it an early, sensitive indicator of kidney injury of many etiologies, including diabetic nephropathy [44], ureteral obstruction, nephrotic syndrome and interstitial nephritis, as shown in a variety of animal models and in human disease [45]. It is possible that NGAL might be developed into an early-responding biomarker. In an interesting head-to-head prospective observational study comparing NGAL, CysC, creatinine, and other markers, Ralib et al. [46] measured levels of all these biomarkers beginning at presentation in the emergency room (ER). The study was performed on a small ($n = 77$) cohort of patients admitted to the ER with conditions likely to result in AKI (hypotension, ruptured abdominal aortic aneurysm, etc.) and who were followed at very short intervals: 0, 4, 8, and 16 h and 2, 4, and 7 days in the ICU. Of all the biomarkers, only plasma NGAL diagnosed AKI correctly at all time points, including at presentation, and urinary NGAL was best at predicting the composite outcome of mortality or dialysis. Among the sea of candidate biomarkers NGAL merits following as other investigators study it.

IL-18 is a 24 kDa, nonglycosylated polypeptide member of the IL-1β interleukin superfamily of inflammatory cytokines [47]. Its precursor is produced in mononuclear cells in the blood and processed by caspase and then IL-18 is secreted outside the cell to assist in innate and acquired immune responses. This is done by inducing IFN-γ production from T lymphocytes and macrophages and by enhancing cytotoxicity of natural killer [42]. IL-18 is also produced in most endothelial cells of the gastrointestinal tract and kidney (tubular epithelial cells, mesangial cells, and podocytes) [48], thus its potential value as a marker of AKI.

KIM-1 is a larger molecule, a 104 kDa type I transmembrane glycoprotein that contains both an immunoglobulin-like domain and a mucin domain in its extracellular portion [49, 50]. It is expressed at baseline in low levels in healthy proximal tubule cells in the kidney. It is thought to promote apoptotic clearance after ischemia and reperfusion injury of the kidney [49]. Indeed, after kidney ischemia or toxicity, KIM-1 is highly upregulated and released into the extracellular space and urine [49–51], where it is a putative marker of kidney injury.

All these biomarkers have acceptable but not outstanding sensitivities and specificities (AUC values) when used alone (see Table 2.6). An early trend in the literature is of combining two or more biomarkers to increase the composite AUC and thus the overall diagnostic strength of the test [52]. Indeed, a 2014 review of 32 different urine biomarkers, used to predict the progression of acute kidney injury following cardiac surgery, showed that the most sensitive and specific (thus greatest AUC) biomarker was the combination of IL-18 and KIM-1. They had an AUC of 0.93 in predicting an AKIN 3 (RIFLE "F") stage or death [32].

Which of these new biomarkers will enter into common use (in addition to sCr, which is already widely accepted and embedded in several versions of eGFR

equations and should be probably preserved as the standard)? The answer will be determined by the following factors: (1) the biomarker must be excellent in terms of sensitivity and specificity (as measured by AUC) alone or in combination with other biomarkers; (2) it must be fast, leading, not lagging, as a marker (of both onset and recovery of AKI); (3) it must be inexpensive with regard to time, convenience of sampling, labor, ingredients, and assay complexity; (4) it must be accepted by the medical community, the workgroups, and the payers; in other words it must be an acknowledged improvement over the eGFR status quo using sCr; and (5) it must be suitable to health institutions by appearing in an eGFR equation like MDRD; therefore, (6) according to the National Institute of Health (NIH) [53] any candidate biomarker value must be inserted into a so-called IDMS-traceable eGFR equation. An isotope dilution mass spectrometry (IDMS)-traceable equation is an eGFR equation (e.g., MDRD) that is "traceable to" or calibrated by IDMS, an extremely precise means of quantitating GFR. In other words, any eGFR equation must essentially be grounded in creatinine assays that are super-accurate, by way of IDMS calibration.

A detailed discussion of this issue is beyond the scope of this chapter but it is treated exhaustively by Myers et al. [54].

2.5 Outcome Following AKI

As mentioned, a number of published studies (summarized in Table 2.5) addressed the incidence of AKI in various clinical settings, e.g., total joint arthroplasty in elective patients [14], ICU patients [20], cardiology patients monitored for hypotension in the ICU [16], patients with intraoperative hypotension [15], noncardiac general surgery patients with preexisting normal kidney function [18], patients with sepsis or diabetes or both [20, 55, 56], patients resuscitated from cardiac arrest [19], high-risk vascular surgery patients [22], etc. Several authors were able to incorporate long-term outcomes (primarily mortality) in their surveys of AKI patients. Table 2.7 summarizes some of the more widely known studies in which outcome following AKI was examined.

Overall, patients experiencing AKI after surgery have significant increases in mortality. In a very large study including 65,043 patients undergoing major noncardiac surgery, an eightfold increase in 30-day mortality was reported in those who developed postoperative AKI [16]. AKI markedly increases mortality also in ICU patients. Several studies show a clear correlation between the degree of AKI (according to the AKIN and RIFLE criteria) and mortality [57, 58]. In a large retrospective study of 22,303 patients from 22 ICUs, Osterman et al. [57] found a mortality of 10.7 % in patients without AKI, of 20.1 % (odds ratio [OR] 2.59) in those with AKIN stage 1 (RIFLE "R") AKI, of 25.9 % (OR 3.24) in those with stage 2 ("I") AKI, and of 49.6 % (OR 9.38) in those with stage 3 ("F") AKI.

However, an independent association of the various stages of AKI with ICU mortality is harder to demonstrate. In the study by Osterman et al. [57], only AKI stage 3 was independently associated with increased ICU mortality. Stage 2 AKI

Table 2.7 Some recent investigations reporting AKI outcomes

Study	Type of analysis	AKI criteria	*N*	Comparison indicators	Setting	Important findings
Ricci et al. | (2008) [58]	Meta-analysis	RIFLE	71,000 (pooled)	AKI vs. non-AKI: ICU, hospital, 28-, 30-, 60-, and 90-days mortality	Mostly ICU pts	Pooled OR for death compared to non-AKI: "Risk" 2.40 "Injury" 4.14 "Failure" 6.37
Hildebrand et al. (2015) [82]	Retrospective	AKI needing RRT	188	RRT vs. no RRT need	Parturients cared over a 15-year period	RRT incidence 1/10,000 Among those needing RRT: 4.3 % died 3.9 % on RRT 4 months later
Uchino et al. (2005) [20]	Prospective observational	↑sCr per AKIN definition within 48 h	29,269	AKI vs. non-AKI:	ICU pts.	Pts. who developed AKI had higher SAPS II and APACHE II scores and higher ICU, hospital, and 6-months mortality AKI was an independent risk factor for hospital mortality (OR 3.12, 95 % CI 1.41–6.93, $P = 0.005$)
Rimes-Stigare et al. (2015) [83]	Prospective observational	RRT or ↑sCr (×1.5) or sCr ≥4.0 mg/dL (354 μmol/L)	97,782 (5273 with AKI)	Patients who had AKI were more likely to die (MRR 2.87)	ICU pts.	20 % of AKI pts. were dead within 4 days AKI survivors had a 7-fold ↑risk of developing CKD and a 22-fold ↑ risk of ESRD compared with non-AKI pts

Osterman et al. (2008) [57]	Retrospective	↑sCr per RIFLE criteria or need for RRT	22,303 (7898 with AKI)	AKI vs. non-AKI	ICU patients without preexisting CKD	ICU mortality (OR) 10.7 % without AKI (1.0) 20.1 % "risk" (2.59) 25.9 % "injury" (3.24) 49.6 % "failure" (9.38) Only AKI-"failure" was independently associated with ICU mortality AKI-"injury" not associated with mortality AKI-"risk" associated with a reduced risk of mortality (see text)
Nisula et al. (2013) [84]	Prospective multicenter study	KDIGO criteria	1568 (635 with AKI)	Follow-up at 6 months of AKI pts. admitted to ICU vs. ICU pts. without AKI	ICU pts.	35.3 % of pts. with AKI as compared to 16.5 % of pts. without AKI were died within six months AKI patients had lower quality-of-life indices six months later

Pts. patients *ICU* intensive care unit, *OR* odds ratio ,*CI* confidence interval, *AKI* acute kidney injury, *RRT* renal replacement therapy, *MRR* mortality rate ratio, *CKD* chronic kidney disease, *ESRD* end-stage renal disease

was not independently associated with increased ICU mortality. Surprisingly, stage 1 AKI and RRT were independently associated with reduced ICU mortality. The authors acknowledged that because AKIN criteria allowed including all patients on RRT as AKI stage 3, and because some 583 persons began to receive RRT before their AKI had actually progressed to AKI stage 3, the picture may be confused.

The 6-month outcomes of surviving AKI patients in a large Finnish study using the KDIGO AKI definition have been recently reported [59]. Among 933 patients studied, 224 patients (35.3 %) with AKI died within 6 months, as compared with 154 (16.5 %) patients without AKI. Surviving AKI patients had lower quantitative quality-of-life indices 6 months later, as opposed to those who did not have AKI. Surprisingly though, their self-reported assessments of well-being were equivalent to survivors without AKI.

2.6 Summary and Discussion

The reexamination of AKI from a standpoint of its definition, classification, and diagnosis began around 2000 when the first definitions of AKI were propounded.

Paired with improvements in the definition of AKI was the problem of how to diagnose it. The traditional, "gold standard" methods (clearances of various inert compounds such as phenol red and inulin) had long ago evolved to more practical spot assays of serum creatinine and albumin. The problems with creatinine are, however, that it is a late (24–48 h), indirect indicator of kidney injury [27, 28], and that its production times are impaired in sepsis (a high-risk condition for the kidney) [60] and they also decrease in cachexia or extremes of age.

From this conundrum came a new starting point. Better understanding of AKI has led to discrimination between the various mechanisms of kidney injury. Apart from preexisting CKD [2, 23], sepsis is the most powerful risk factor in developing AKI [20, 56, 61, 62]. As a rule, AKI will develop predictably in about 19 % of patients with "moderate" sepsis (fever or hypothermia with infection, tachycardia, tachypnea, and leukocytosis), 23 % of patients with severe sepsis (the above plus lactatemia, oliguria, or mental status changes), and 51 % of patients with septic shock (all the above plus systolic blood pressure less than 90 mmHg after fluid resuscitation) when blood cultures are positive [56, 62, 63]. Better knowledge about this type of kidney injury may lead to better diagnosis of at-risk patients and more rapid therapy of sepsis. Likewise better biomarker-led diagnosis of septic AKI might result in intervention hours or days before azotemia or oliguria develop. Novel biomarkers, such as IL-18, are differentially sensitive to AKI caused by different mechanisms. IL-18 is thought to increase in early (3 h) sepsis-induced AKI as opposed to a slower rise in AKI from ischemia in hypotensive states [61, 64, 65]. Indeed, it is thought that the pathophysiological mechanisms for AKI from sepsis or non-septic etiologies (e.g., ischemia) are completely different [61]. With research targeted at the most harmful intermediaries in the septic process, therapeutic or preventative drugs or biologics may be found to protect the kidney in systemic inflammatory response syndrome (SIRS) and sepsis.

Other approaches might prevent or mitigate AKI in patients at risk for renal ischemia. As shown in the papers by Lehman et al. [18], Osterman et al. [57], and Raimundo et al. [66], huge databases of ICU time-series blood pressure readings and other clinical data have been mined to show the most sensitive criterion for adequate perfusion of the kidney in ICU and surgical patients. The time-honored 90 mmHg systolic threshold may soon, in routine clinical practice, be replaced by the more sensitive and specific 55 mmHg mean pressure as the commonly taught threshold for immediate intervention with vasopressor medication or fluids. Other hemodynamic and respiratory factors appear to contribute to the risk of AKI with unclear mechanisms: obesity, hyperuricemia, low indexed systemic oxygen delivery, hyperlactatemia, elevated central venous pressure, and the use of mechanical ventilation have been shown to be important but ill-defined factors [57, 66].

The ischemia-reperfusion paradigm so widely invoked in studies of stroke and myocardial infarction may likewise provide a framework for studying AKI from causes other than sepsis. However, it is generally felt that AKI from sepsis (but also, e.g., after cardiopulmonary bypass) is via other, largely inflammatory pathways. Accordingly, the mere restoration or improvement of renal perfusion will be insufficient to reverse kidney damage [67]. Other authors, using a combinatorial systems biology and proteomic approach, have identified the glutaminergic signaling pathway, induced by overactivation of *N*-methyl-D-aspartate receptors, as perhaps the inciting factor in AKI [68].

Lastly, bioinformatics approaches enable wide surveys of thousands of genes [69, 70] that are activated or repressed in AKI, as well as epigenetic changes that occur with AKI [71]. New candidate gene products and pathways discovered from this research will, it is hoped, open avenues to explore and to better prevent and mitigate AKI in the future.

References

1. Chawla LS, Amdur RL, Shaw AD et al (2014) The association between AKI and long-term renal and cardiovascular outcomes in United States veterans. Clin J Am Soc Nephrol 9:448–456
2. Go AS, Chertow GM, Fan D et al (2004) Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. N Eng J Med 351:1296–1305
3. Lafrance JP, Miller DR (2010) Acute kidney injury associates with increased long-term mortality. J Am Soc Nephrol 21:345–352
4. James MT, Ghali WA, Knudtson ML et al (2011) Associations between acute kidney injury and cardiovascular and renal outcomes after coronary angiography. Circulation 123:409–416
5. Tsagalis G, Akrivos T, Alevizaki M et al (2009) Renal dysfunction in acute stroke: an independent predictor of long-term all combined vascular events and overall mortality. Nephrol Dial Transplant 24:194–200
6. Farley SJ (2007) Acute kidney injury/acute renal failure: standardizing nomenclature, definitions and staging. Nat Clin Pract Nephrol 3:405

7. Niessenson AR (1998) Acute renal failure: definition and pathogenesis. Kidney Int Suppl 66:S7–S10
8. Bellomo R, Ronco C, Kellum JA et al (2004) Acute renal failure—definition, outcome measures, animal models, fluid therapy and information technology needs: the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. Crit Care 8:R204–R212
9. Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group (2012) KDIGO clinical practice guideline for acute kidney injury. Kidney Int Suppl 2:1–138
10. Ronco C, Kellum JA, Mehta R (2001) Acute dialysis quality initiative (ADQI). Nephrol Dial Transplant 16(8):1555–1558
11. Molitoris BA, Levin A, Warnock DG et al (2007) Improving outcomes of acute kidney injury: report of an initiative. Nat Clin Pract Nephrol 3:439–442
12. Palevsky PM, Liu KD, Brophy PD et al (2013) KDOQI US commentary on the 2012 KDIGO clinical practice guideline for acute kidney injury. Am J Kidney Dis 6:649–672
13. Fliser D, Laville M, Covic A et al (2012) A European Renal Best Practice (ERBP) position statement on the Kidney Disease Improving Global Outcomes (KDIGO) clinical practice guidelines on acute kidney injury: part 1: definitions, conservative management and contrast induced nephropathy. Nephrol Dial Transplant 27:4263–4272
14. Weingarten TN, Gurrieri C, Jarett PD et al (2012) Acute kidney injury following total joint arthroplasty: retrospective analysis. Can J Anaesth 59(12):1111–1118
15. Walsh M, Devereaux PJ, Garg AX et al (2013) Relationship between intraoperative mean arterial pressure and clinical outcomes after noncardiac surgery. Anesthesiology 119:1–9
16. Kheterpal S, Tremper KK, Englesbe MJ et al (2007) Predictors of postoperative acute renal failure after noncardiac surgery in patients with previously normal renal function. Anesthesiology 107:892–902
17. Abhela FJ, Botelho M, Fernandes V et al (2009) Determinants of postoperative acute kidney injury. Crit Care 13:R79
18. Lehman LW, Saeed M, Moody G, Mark R (2010) Hypotension as a risk factor for acute kidney injury in ICU patients. Comput Cardiol 37:1095–1098
19. Tujjar O, Mineo G, Dell'Anna A et al (2015) Acute kidney injury after cardiac arrest. Crit Care 19:169
20. Uchino S, Kellum JA, Bellomo R et al (2005) Acute renal failure in critically ill patients: a multinational, multicenter study. JAMA 294:813–818
21. Honore PM, Jacobs R, Hendrickx I et al (2015) Prevention and treatment of sepsis-induced acute kidney injury: an update. Ann Intensive Care 5:51
22. Harris DG, Koo G, McCrone MP et al (2015) Acute kidney injury in critically ill vascular surgery patients is common and associated with increased mortality. Front Surg 2:8
23. Chawla LS, Eggers PW, Star RA et al (2014) Acute kidney injury and chronic kidney disease as interconnected syndromes. N Eng J Med 371:58–66
24. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Workgroup (2013) KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney Int Suppl 3:1–150
25. Endre ZH, Pickering JW, Walker RJ (2001) Clearance and beyond: the complementary roles of GFR measurement and injury biomarkers in acute kidney injury (AKI). Am J Physiol Renal Physiol 301:F697–F707
26. Shemesh O, Golbetz H, Kriss JP et al (1985) Limitations of creatinine as a filtration marker in glomerulopathic patients. Kidney Int 28:830–838
27. Stevens LA, Coresh J, Schmid CH et al (2008) Estimating GFR using serum cystatin C alone and in combination with serum creatinine: a pooled analysis of 3418 individuals with CKD. Am J Kidney Dis 51:395–406
28. Dai X, Zeng Z, Fu C et al (2015) Diagnostic value of neutrophil gelatinase-associated lipocalin, cystatin C, and soluble triggering receptor expressed on myeloid cells-1 in critically ill patients with sepsis-associated acute kidney injury. Crit Care 19:223

29. Tziakas D, Chalikias G, Kareli D et al (2015) Spot urine albumin to creatinine ratio outperforms novel acute kidney injury biomarkers in patients with acute myocardial infarction. Int J Cardiol 197:48–55
30. Vaidya VS, Ramirez V, Ichimura T et al (2006) Urinary kidney injury molecule-1: a sensitive quantitative biomarker for early detection of kidney tubular injury. Am J Physiol Renal Physiol 290:F517–F529
31. Doi K, Yuen PS, Eisner C et al (2009) Reduced production of creatinine limits its use as a marker of kidney injury in sepsis. J Am Soc Nephrol 20:1217–1221
32. Arthur JM, Hill EG, Alge JL et al (2014) Evaluation of 32 urine biomarkers to predict the progression of acute kidney injury after cardiac surgery. Kidney Int 85:431–438
33. Bamber D (1975) The area above the ordinal dominance graph and the area below the receiver operating characteristic curve. J Math Psychol 12:387–415
34. Hanley JA, McNeil BJ (1982) The meaning and use of the area under a receiver operating characteristic (ROC) curve. Radiology 143:29–36
35. Zweig MH, Campbell G (1993) Receiver-operating characteristic (ROC) plots: a fundamental evaluation tool in clinical medicine. Clin Chem 39:561–577
36. Ferguson MA, Vaidya V, Bonventre JV (2008) Biomarkers of nephrotoxic acute kidney injury. Toxicology 245:182–193
37. Vart P, Scheven L, Lambers Heerspink HJ et al (2016) Urine albumin-creatinine ratio versus albumin excretion for albuminuria staging: a prospective longitudinal cohort study. Am J Kidney Dis 67(1):70–78
38. Brzin J, Popovic T, Turk V et al (1984) Human cystatin, a new protein inhibitor of cysteine proteinases. Biochem Biophys Res Commun 118:103–109
39. Strojan P, Oblak I, Svetic B et al (2004) Cysteine proteinase inhibitor cystatin C in squamous cell carcinoma of the head and neck: relation to prognosis. Br J Cancer 90:1961–1968
40. Kiyosue A, Hirata Y, Ando J et al (2010) Plasma cystatin C concentration reflects the severity of coronary artery disease in patients without chronic kidney disease. Circ J 74:2441–2447
41. Ruan ZB, Zhu L, Yin YG et al (2014) Cystatin C, N-terminal probrain natriuretic peptides and outcomes in acute heart failure with acute kidney injury in a 12-month follow-up: insights into the cardiorenal syndrome. J Res Med Sci 19:404–409
42. Kaur G, Levy E (2012) Cystatin C in Alzheimer's disease. Front Mol Neurosci 5:79
43. Butler JM, Umar Sharif U, Ali M et al (2015) A missense variant in CST3 exerts a recessive effect on susceptibility to age-related macular degeneration resembling its association with Alzheimer's disease. Hum Genet 2015 134(7):705–715
44. Liu F, Yang H, Chen H et al (2015) High expression of neutrophil gelatinase-associated lipocalin (NGAL) in the kidney proximal tubules of diabetic rats. Adv Med Sci 60:133–138
45. Kuwabara T, Mori K, Mukoyama M et al (2009) Urinary neutrophil gelatinase-associated lipocalin levels reflect damage to glomeruli, proximal tubules, and distal nephrons. Kidney Int 75:285–294
46. Ralib A, Pickering JW, Shaw GM et al (2014) The clinical utility window for acute kidney injury biomarkers in the critically ill. Crit Care 18:601
47. Okamura H, Tsutsui H, Toshinori K et al (1995) Cloning of a new cytokine that induces IFN-γ production by T cells. Nature 378:88–91
48. Yano T, Nozaki Y, Kinoshita K et al (2015) The pathological role of IL-18Rα in renal ischemia/reperfusion injury. Lab Invest 95:78–91
49. Ichimura T, Bonventre JV, Bailly V et al (1998) Kidney injury molecule-1 (KIM-1), a putative epithelial cell adhesion molecule containing a novel immunoglobulin domain, is up-regulated in renal cells after injury. J Biol Chem 273:4135–4142
50. Bailly V, Zhang Z, Meier W et al (2002) Shedding of kidney injury molecule-1, a putative adhesion protein involved in renal regeneration. J Biol Chem 277:39739–39748
51. Zwiers AJM, de Wildt SN, vanRosmalen J et al (2015) Urinary neutrophil gelatinase-associated lipocalin identifies critically ill young children with acute kidney injury following intensive care admission: a prospective cohort study. Crit Care 19:181

52. Parikh CR, Thiessen-Philbrook H, Garg AX et al (2013) Performance of kidney injury molecule-1 and liver fatty acid-binding protein and combined biomarkers of AKI after cardiac surgery. Clin J Am Soc Nephrol 8:1079–1088
53. http://www.niddk.nih.gov/health-information/health-communication-programs/nkdep/lab-evaluation/gfr/creatinine-standardization/recommendations/Pages/recommendations.aspx. Webpage accessed 22 Jan 2016
54. Myers GL, Miller WG, Coresh J et al (2006) Recommendations for improving serum creatinine measurement: a report from the Laboratory Working Group of the National Kidney Disease Education Program. Clin Chem 52(1):5–18
55. Venot M, Weis L, Clec'h C et al (2015) Acute kidney injury in severe sepsis and septic shock in patients with and without diabetes mellitus: a multicenter study. PLoS One 10(5):e0127411
56. Rangel-Frausto MS, Pittet D, Costigan M et al (1995) The natural history of the systemic inflammatory response syndrome (SIRS): a prospective study. JAMA 273:117–123
57. Osterman M, Chang R, Riyadh ICU Program Users Group (2008) Correlation between the AKI classification and outcome. Crit Care 12:R144
58. Ricci Z, Cruz D, Ronco C (2008) The RIFLE criteria and mortality in acute kidney injury: a systematic review. Kidney Int 73:538–546
59. Nisula S, Yang R, Poukkanen M et al (2015) Predictive value of urine interleukin-18 in the evolution and outcome of acute kidney injury in critically ill adult patients. Br J Anaesth 114:460–468
60. Umbro I, Gentile G, Tinti F et al (2016) Recent advances in pathophysiology and biomarkers of sepsis-induced acute kidney injury. J Infect 72(2):131–142
61. Zarjou A, Agarwal A (2011) Sepsis and acute kidney injury. J Am Soc Nephrol 22:999–1006
62. Schrier RW, Wang W (2004) Acute renal failure and sepsis. N Engl J Med 351:159–169
63. Riedemann NC, Guo RF, Ward PA (2003) The enigma of sepsis. J Clin Invest 112:460–467
64. Bellomo R, Bagshaw S, Langenberg C, Ronco C (2007) Pre-renal azotemia: a flawed paradigm in critically ill septic patients? Contrib Nephrol 156:1–9
65. Bagshaw SM, Langenberg C, Haase M et al (2007) Urinary biomarkers in septic acute kidney injury. Intensive Care Med 33:1285–1296
66. Raimundo M, Crichton S, Syed Y et al (2016) Low systemic oxygen delivery and BP and risk of progression of early AKI. Clin J Am Soc Nephrol 10(8):1340–1349
67. Landoni G, Baiardo Redaelli M, Pisano A (2016) Dopamine derivatives and acute kidney injury: the search for the magic bullet continues … and leads to new (magic?) targets. Nephrol Dial Transplant 31(4):512–514
68. Husi H, Sanchez-Nino MD, Delles C et al (2013) A combinatorial approach of proteomics and system biology in unravelling the mechanisms of acute kidney injury (AKI): involvement of NMDA receptor GRIN1 in murine AKI. BMC Syst Biol 7:110
69. Boyd JH, McConechy M, Walley KR (2014) Acute organ injury is associated with alterations in the cell-free plasma transcriptome. Intensive Care Med Exp 2:7
70. Stafford-Smith M, Li YJ, Mathew JP et al (2015) Genome-wide association study of acute kidney injury after coronary bypass graft surgery identifies susceptibility loci. Kidney Int 88(4):823–832
71. Tang J, Zhuang S (2015) Epigenetics in acute kidney injury. Curr Opin Nephrol Hypertens 24:351–358
72. Mehta RL, Kellum JA, Shah SV et al (2007) Acute Kidney Injury Network: report of an initiative to improve outcomes in acute kidney injury. Crit Care 11(2):R31
73. Hoek FJ, Kemperman AW, Krediet RT (2003) A comparison between cystatin C, plasma creatinine and the Cockcroft and Gault formula for the estimation of glomerular filtration rate. Nephrol Dial Transplant 18:2024–2031
74. Kym D, Cho YS, Yoon J et al (2015) Evaluation of diagnostic biomarkers for acute kidney injury in major burn patients. Ann Surg Treat Res 88:281–288
75. Nejat M, Pickering JW, Walker RJ et al (2010) Rapid detection of acute kidney injury by plasma cystatin C in the intensive care unit. Nephrol Dial Transplant 25:3283–3289

76. Cruz DN, deCal M, Garzotto F et al (2010) Plasma neutrophil gelatinase-associated lipocalin is an early biomarker for acute kidney injury in an adult ICU population. Intensive Care Med 36:444–451
77. Wang B, Chen G, Zhang J et al (2015) Increased neutrophil gelatinase-associated lipocalin is associated with mortality and multiple organ dysfunction syndrome in severe sepsis and septic shock. Shock 44:234–238
78. Zhou F, Luo Q, Wang L, Han L (2016) Diagnostic value of neutrophil gelatinase-associated lipocalin for early diagnosis of cardiac surgery-associated acute kidney injury: a meta-analysis. Eur J Cardiothorac Surg 49(3):746–755
79. Liu Y, Guo W, Zhang J et al (2013) Urinary interleukin 18 for detection of acute kidney injury: a meta-analysis. Am J Kidney Dis 62:1058–1067
80. Bland JM, Altman DG (1986) Statistical methods for assessing agreement between two methods of clinical measurement. Lancet 1(8476):307–310
81. Altman DG, Bland JM (1983) Measurement in medicine: the analysis of method comparison studies. The Statistician 32:307–317
82. Hildebrand AM, Liu K, Shariff SZ et al (2015) Characteristics and outcomes of AKI treated with dialysis during pregnancy and the postpartum period. J Am Soc Nephrol 26(12):3085–3091
83. Rimes-Stigare C, Frumento P, Bottai M et al (2015) Evolution of chronic renal impairment and long-term mortality after de novo acute kidney injury in the critically ill: a Swedish multicentre cohort study. Crit Care 19:221
84. Nisula S, Vaara ST, Kaukonen KM et al (2013) Six-month survival and quality of life of intensive care patients with acute kidney injury. Crit Care 17:R250