Diagnosis, Epidemiology and Outcomes of Acute Kidney Injury

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Acute kidney injury is an increasingly common and potentially catastrophic complication in hospitalized patients. Early observational studies from the 1980s and 1990s established the general epidemiologic features of acute kidney injury: the incidence, prognostic significance, and predisposing medical and surgical conditions. Recent multicenter observational cohorts and administrative databases have enhanced our understanding of the overall disease burden of acute kidney injury and trends in its epidemiology. An increasing number of clinical studies focusing on specific types of acute kidney injury (*e.g.*, in the setting of intravenous contrast, sepsis, and major surgery) have provided further details into this heterogeneous syndrome. Despite our sophisticated understanding of the epidemiology and pathobiology of acute kidney injury, current prevention strategies are inadequate and current treatment options outside of renal replacement therapy are nonexistent. This failure to innovate may be due in part to a diagnostic approach that has stagnated for decades and continues to rely on markers of glomerular filtration (blood urea nitrogen and creatinine) that are neither sensitive nor specific. There has been increasing interest in the identification and validation of novel biomarkers of acute kidney injury that may permit earlier and more accurate diagnosis. This review summarizes the major epidemiologic studies of acute kidney injury and efforts to modernize the approach to its diagnosis.

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"The disease seems in general to come on suddenly. The peculiar symptom is a sudden diminution of secretion of urine, which soon amounts to a complete suspension of it. The affliction is probably at first considered as retention; but the catheter being employed, the bladder is found to be empty. . . after several days, the patient begins to talk incoherently, and shows a tendency to stupor. This increases gradually to perfect coma, which in a few days more is fatal. . . " John Abercombie (1780–1828), "Observations on ischuria renalis" (1)

Acute renal failure (ARF), now increasingly referred to as "acute kidney injury" (AKI), is characterized by sudden (*i.e.*, hours to days) impairment of kidney function. Descriptions of AKI date back to the ancient Greek period (2), when the diagnosis was possible only by observing a reduction in urine volume. The modern day conception of AKI has evolved alongside developments in pathology and clinical biochemistry, which have permitted clinicopathologic correlations and early diagnosis (3). Initial descriptions of AKI from the early 20th century centered around specific conditions, such as crush injuries (4), war nephritis (5), and falciparum malaria (6). Sir William Osler in 1912 described several recognizable causes of AKI under the heading of "acute Bright's disease," including sepsis, pregnancy, burns, and toxins (7).

AKI is now understood to be an increasingly common and potentially catastrophic complication in hospitalized patients. This review summarizes modern epidemiologic studies of AKI, attempted prevention and treatment strategies, and emerging methods for its early and accurate diagnosis.

Early Cohort Studies of AKI

Hou *et al.* in 1983 published one of the first prospective cohort studies of AKI (8). They focused on hospital-acquired disease and therefore excluded patients with established AKI on admission. Over a 5-mo period beginning in 1978, a total of 2216 consecutive medical and surgical admissions to Tufts-New England Medical Center were followed for the development of AKI. The definition of AKI in this study was based on an absolute increase in serum creatinine (SCr) depending on the admission SCr: increase in SCr of ≥0.5 mg/dl if admission SCr ≤1.9 mg/dl; increase of ≥1.0 mg/dl for admission SCr of 2.0 to 4.9; or an increase ≥1.5 mg/dl for SCr ≥5.0 mg/dl. Overall, 4.9% of patients met criteria for AKI. The major causes of hospital-acquired AKI were decreased renal perfusion (42%), major surgery (18%), contrast nephropathy (12%), and aminoglycoside antibiotics (7%). The crude in-hospital mortality rate was 32%, and the degree of kidney injury as assessed by change in SCr was noted to be important. In-hospital mortality was 3.8% in patients with an increase in SCr of 0.5 to 0.9 mg/dl, and increased progressively to 75% in patients with a ≥4.0 mg/dl

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increase who were not treated with renal replacement therapy. This study was also one of the first to establish the association between oliguria and mortality in patients with AKI (52% *versus* 17% with and without oliguria, $P < 0.01$).

Shusterman *et al.* performed a case-control study of hospital-acquired AKI in patients admitted over 1 mo to the Hospital of the University of Pennsylvania in 1981 (9). The definition of AKI was different from that used by Hou *et al.* 4 yr earlier in the same journal. AKI was defined as a >0.9 mg/dl increase in SCr with baseline SCr <2.0 mg/dl or >2.0 mg/dl increase in SCr with baseline SCr ≥2.0 mg/dl; the incidence was 1.9% among patients on medical, surgical, and gynecologic services. The 34 AKI cases were matched to 57 controls without AKI. From this small group of cases and controls, the authors found volume depletion, aminoglycoside use, septic shock, congestive heart failure, and intravenous contrast administration as risk factors for AKI. They also found a 10-fold increased odds of death and a doubling of the length of stay among patients with AKI.

Nash et al. updated their initial report of hospital-acquired AKI almost two decades later (10). Over a 4-mo period in 1996, they prospectively followed 4622 medical and surgical admissions at Rush Presbyterian-St. Luke's Medical Center for the development of AKI, defined as in their earlier study. They identified 332 patients (7.2% of admissions) who developed AKI, higher than the 4.9% in the original study performed at a different institution. The in-hospital mortality rate of 19.4% was lower, albeit not statistically significantly, than the 25% reported previously. The most common causes of AKI remained decreased renal perfusion (39%; defined broadly to include congestive heart failure, cardiac arrest, as well as volume contraction), nephrotoxin administration (16%), contrast administration (11%), and major surgery (9%).

Multicenter Cohort Studies of AKI

Initial cohort studies of AKI shed important light on the frequency, causes, and mortality associated with hospital-acquired AKI. No matter how carefully conducted, single-center studies are inherently limited in terms of sample size and external validity (*i.e.*, generalizability to AKI at other medical centers). Recognizing this limitation, investigators have launched multicenter epidemiologic investigations of AKI.

Liaño and Pascual conducted a prospective, 9-mo study of all AKI episodes in 13 tertiary-care hospitals in Madrid, Spain, beginning in 1991 (11). They defined AKI as a sudden rise in SCr of more than 2 mg/dl, excluding patients with preexisting chronic kidney disease (CKD) (defined as SCr >3 mg/dl). Unlike the Hou et al. (8) and Nash et al. (10) studies, hospital- and community-acquired cases of AKI were included. Of the 748 episodes of AKI (representing 0.4% of admissions, and 21 per 100,000 population), acute tubular necrosis (ATN) was the most frequent cause (45%, defined to include diverse causes, including surgery, nephrotoxin administration, sepsis, and renal hypoperfusion), followed by prerenal azotemia (21%, defined as the rapid recovery of kidney function following volume administration or restoration of cardiac output), acute onset chronic renal failure (12.7%, not defined), and urinary tract obstruction (10%). The crude in-hospital mortality rate was 45% overall and as high as 65.9% in patients requiring dialysis (which constituted 36% of all cases of AKI). In a follow-up study, Liaño *et al.* provided more details on the specific differences between AKI in and outside of the intensive care unit (ICU) (12). Compared with non-ICU patients, those admitted to the ICU were younger, more likely to die in-hospital (71.5% *versus* 31.5%), and more likely to have ATN from sepsis or renal hypoperfusion than nephrotoxin administration.

Brivet et al. focused on AKI occurring in the ICU in a 20-center, prospective, 6-mo study performed in France in 1991 (13). They included all patients with a rise in SCr to at least 3.5 mg/dl and/or blood urea nitrogen (BUN) to at least 100 mg/dl, or a 100% increase with preexisting CKD. Patients with severe CKD (baseline SCr >3.5 mg/dl) were excluded. Overall, 7% of ICU admissions developed AKI or had AKI on ICU admission. The major causes of AKI were attributed to sepsis (48%), hemodynamic alterations (32%), nephrotoxin administration (20%), and prerenal factors (17%). Overall in-hospital mortality was 58% and was higher in those with sepsis (73%) and delayed occurrence of AKI after admission (71%). Another group of French investigators (Guerin *et al.)* performed a similar prospective observational study beginning in 1996 (14). These authors found a 7.7% incidence of AKI in the ICU, defined as SCr more than 3.4 mg/dl or the need for dialysis (14). Overall in-hospital mortality was 66%, and 81% in patients with AKI that developed 1 wk after admission to the ICU.

The Program to Improve Care in Acute Renal Disease (PICARD) performed a 31-mo-long, prospective observational cohort study of patients at five academic medical centers in the United States from 1999 to 2001 (15). Eligible patients were those in the ICU for whom nephrologic consultation was obtained; AKI was defined as an increase in SCr ≥0.5 mg/dl if baseline ≤1.5 mg/dl, or an increase of ≥1.0 if baseline SCr was between 1.6 and 4.9. Unique to PICARD among AKI epidemiologic studies to date was the extensive clinical detail captured (>800 data elements per patient, including details on dialysis procedures) and limited biologic sample collection.

A total of 618 patients were enrolled in PICARD. One of the most illustrative findings in PICARD was the degree of heterogeneity of patients with AKI across the five medical centers in terms of baseline characteristics, processes of care, and in-hospital mortality. Even across five academic medical centers, in hospital mortality associated with AKI from ATN and nephrotoxins ranged from a low of 24% to a high of 62%. Substantial differences in process of care were also evident across the five sites in terms of dialysis modality. Despite the many differences, however, the presumed etiologies of AKI were relatively similar among institutions. Fully fifty percent of patients were labeled as having ATN with no specified precipitant. The next most common etiologies included nephrotoxin administration (26%), cardiac disease (20%, including myocardial infarction, cardiogenic shock, and congestive heart failure), ATN from hypotension (20%), ATN from sepsis (19%), unresolved prerenal factors (16%), and liver disease (11%). The PICARD cohort has been the subject of subsequent epidemiologic studies to derive prediction rules for mortality (16) and to explore the associations between dialysis modality (17) and timing of ini-

tiation and survival (18). The biologic samples from subsets of PICARD participants have been used to study urea volume of distribution (19), insulin resistance (20), cytokine levels (21), and oxidative stress (22) in patients with AKI.

The largest and most inclusive cohort study of AKI to date was conducted by the Beginning and Ending Supportive Therapy for the Kidney (BEST Kidney) investigators (23). They prospectively studied patients admitted to 54 ICUs across 23 countries over 15 mo beginning in September 2000. The target population was patients with severe AKI: inclusion criteria were treatment with renal replacement therapy or AKI defined as oliguria (<200 ml in 12 h) or BUN >84 mg/dl. Of 29,269 patients admitted to the ICUs, 1738 (5.7%) had AKI. The most common causes of AKI were septic shock (47.5%), major surgery (34%), cardiogenic shock (27%), hypovolemia (26%), and nephrotoxin administration (19%) (multiple causes were allowed on the data collection form, accounting for total >100%).

The overall in-hospital mortality rate in the BEST Kidney cohort study was 60.2%. As with PICARD, mortality varied widely across centers. Among countries contributing more than 100 patients to the cohort, in-hospital mortality ranged from 50.5% to 76.8%. A multivariable logistic regression model to identify independent correlates of in-hospital mortality yielded several previously identified risk factors also found in PICARD (16) and/or the French Study Group (13), including delayed AKI, age, sepsis, and a generic disease severity score that included BUN and urine output. Follow-up studies from the BEST Kidney multinational database have compared severity scoring systems for AKI-related mortality (24) and investigated the relationship between diuretic administration and mortality (25).

Administrative Database Studies

Medical administrative and claims databases afford investigators the opportunity to study AKI in vast numbers of patients over multiple years admitted to a wide spectrum of hospitals, including those not ordinarily represented in prospective cohort studies. The major limitation of most administrative databases is the lack of detailed clinical and laboratory information. The International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) codes for ARF (584.x) and renal replacement therapies (39.95) have been shown to be accurate for the identification of patients with severe AKI (defined as AKI requiring dialysis, or AKI-D), but less accurate for AKI not requiring dialysis (26).

Two studies to date have used large administrative and/or claims databases to study secular trends in the epidemiology of AKI in the United States. Xue *et al.* used inpatient claims data from a 5% sample of Medicare beneficiaries to investigate the incidence and mortality of acute renal failure between 1992 and 2001 (27). Waikar *et al.* used the Nationwide Inpatient Sample (NIS), a nationally representative database of hospital discharges, to study AKI from 1988 and 2002 (28). Using the same ICD-9-CM codes to identify AKI and a similar and partially overlapping study population, the two studies found a marked rise in the incidence and fall in the mortality associated with AKI and AKI-D. Among Medicare beneficiaries, the incidence of AKI rose from 14 to 35 per 1000 discharges between 1992 and 2001; in the NIS, which unlike the Medicare database includes patients under the age of 65, the incidence of AKI rose from 4 to 21 per 1000 discharges between 1988 and 2002. Both studies showed a statistically significant decline in mortality, in contrast to the prevailing wisdom and a recent systematic review, which suggest that mortality rates have remained unchanged over decades (29). Increasing incidence and declining mortality of AKI have also been demonstrated using a large database of critically ill patients admitted to ICUs in Australia and New Zealand (30).

Liangos *et al.* used the National Hospital Discharge Survey (NHDS), a nationally representative hospital discharge database different from the NIS database used by Waikar *et al.* (28), to study AKI in patients admitted in 2001 (31). Using the same diagnosis codes, they reported that 19 per 1000 discharges had AKI and that 21.3% died in-hospital, virtually identical to the findings in the NIS.

Both NIS and NHDS studies documented that patients with AKI have a median length of stay of 7 d and that approximately one fourth are discharged to skilled nursing facilities. Costs attributable to AKI were not reported in the NIS, NHDS, or the Medicare analyses. Costs were addressed in a study by Fischer *et al.* involving administrative data from 23 Massachusetts hospitals (32). They reported that uncomplicated ARF (*i.e.*, excluding patients in the ICU) had the third highest median direct hospital costs ($2600) after acute myocardial infarction and stroke.

The study from the NIS estimated the incidence of AKI at 288 per 100,000 U.S. population in 2002; the incidence of AKI-D was estimated to be 27 per 100,000 population. Other investigators have performed population-based epidemiology studies and estimated AKI-D rates of 45 per 100,000 (Manchester, United Kingdom) (33), 20 per 100,000 (Scotland) (34), and 8 per 100,000 (Australia) (35).

Hsu *et al.* used a large integrated administrative and laboratory database from Kaiser Permanente Northern California to estimate the community-based incidence of AKI using SCr-based definitions rather than administrative codes (36). They confirmed the finding of a rising incidence of AKI over time: between 1996 and 2003, the incidence of AKI not requiring dialysis increased from 323 to 522 per 100,000, whereas the incidence of AKI-D increased from 20 to 30 per 100,000 in keeping with estimates derived from the nationally representative NIS study (28).

The reasons for increased incidence of AKI are not entirely clear. Differing coding practices ("DRG creep") have been implicated in describing similar trends for other conditions but probably do not explain the increase in AKI incidence, as AKI requiring dialysis should be less susceptible to overcoding (and a corresponding increase in the incidence of AKI requiring dialysis was consistently observed). Moreover, the study by Hsu *et al.* (36) defined AKI using changes in SCr without depending on diagnosis codes. Alternatively, increasing severity of illness and comorbidity along with expanded use of invasive procedures in higher-risk patients could have contributed to these trends. Despite a general trend toward more

severely and chronically ill patients in hospital, mortality rates associated with AKI have declined. We do not think that differing coding practices can account for the decline in mortality, particularly among individuals with AKI requiring dialysis. Indeed, Waikar *et al.* demonstrated significant declines in mortality in stratified analysis of concomitant medical conditions (28). Whether better outcomes (perhaps more fairly described as slightly less terrible outcomes) are attributable to improved nephrology care, improved ICU and/or general hospital care, or other factors is unknown and warrants further study.

Epidemiology in Disease-Specific States

Estimates of the incidence of AKI and associated mortality have been performed in numerous conditions, including sepsis, contrast nephropathy, major surgery, and nephrotoxic antibiotic administration. Several of the largest of studies are summarized in Table 1. A striking and consistent finding is the marked increase in mortality associated with the development of AKI. Studies that have identified risk factors for the development of AKI or AKI-D using multivariable regression models are described in Table 2. Attempts at deriving risk factors or prediction rules for AKI-associated mortality are described in Table 3.

Small Changes in Serum Creatinine

In one of the first studies to examine the independent association between AKI and mortality, Levy *et al.* showed that, in patients undergoing radiocontrast procedures, an increase in SCr of ≥25% to at least 2 mg/dl was associated with a 5.5-fold higher odds of death, after adjustment for comorbid medical conditions (37). Recent studies have explored whether the association between AKI and mortality extends to less severe kidney injury, as assessed by smaller increases in SCr. In a consecutive sample of 19,982 adults admitted to an urban medical center, Chertow *et al.* found that patients with an increase in SCr of just 0.3 to 0.4 mg/dl had a 70% higher multivariable-adjusted odds of death than patients with little or no change in SCr (38). Other investigators have reported comparable findings in patients with congestive heart failure (39,40) and those undergoing cardiac surgery (41–44). Brown *et al.* studied 1391 undergoing coronary artery bypass graft to investigate the prognostic significance of varying cutoffs for perioperative increases in SCr (41). Compared with patients with less than 25% change in SCr, those with a 50% to 99% increase in SCr had a 6.6-fold increased risk of death at 90 d, adjusted for age and sex. These authors did not find a significant difference in mortality among patients with a 25% to 49% increase in SCr (hazard ratio = 1.80; 95% confidence interval [CI], 0.73 to 4.44).

In recognition of the potential clinical importance of small changes in kidney function and the need to standardize definitions of AKI for clinical and research purposes, the Acute Dialysis Quality Initiative has proposed the RIFLE criteria for the classification of AKI (45). The RIFLE criteria provide a graded definition of AKI severity, starting at the lowest stage ("Risk," defined as oliguria for over 6 h or an increase in SCr of at least 50%). Progressively more severe injury, as defined by an increase in SCr or duration and severity of oliguria, is denoted by "Injury" and "Failure." The final two stages correspond to the provision of renal replacement therapy and its duration for >4 wk ("Loss") or >3 mo ("ESRD"). The Acute Kidney Injury Network (46) has proposed a similar system that incorporates 3 stages of increasing disease severity. The criteria are identical to the first 3 stages of RIFLE, with the exception of a lower creatinine threshold (≥0.3 mg/dl increase in SCr) for "stage 1" AKI and the requirement that the SCr threshold be reached within 48 h.

Whether the RIFLE or AKIN criteria will be widely adopted in medicine will depend upon the demonstration of their utility and validity. Research has begun on the incidence and prognosis associated with the various stages of RIFLE (47–53). One large study of 5383 ICU admissions at a single center used an integrated database with physiologic and laboratory information to show that more than two-thirds of all patients had some evidence of AKI during admission and that more than one-half of patients with "Risk" progressed; the hazard ratio for in-hospital mortality according to maximum RIFLE classification was NS for "Risk," of borderline statistical significance for "Injury" (1.40; 95% CI, 1.02 to 1.88) and significant for "Failure" (HR = 2.7; 95% CI, 2.03 to 3.55) (53). The extent to which the RIFLE or AKIN criteria misclassify patients because of the urine output criterion has not been investigated sufficiently and remains to be determined in future studies.

AKI in the Setting of CKD

It is intuitive that an already damaged organ is at heightened risk of acute injury. Indeed, elevated baseline SCr has been consistently observed to be a risk factor for the development of AKI in a number of settings, including radiocontrast administration, cardiac surgery, and sepsis (Table 2). Patients with CKD constitute a large fraction of patients with AKI in cohort studies. One third of patients in the PICARD cohort had CKD stage IV or above (16). Similarly, in the BEST cohort, 30% of patients had impaired kidney function (defined as "any abnormal serum level of creatinine or creatinine clearance before hospitalization"), whereas 15% had unknown baseline kidney function (23). In the cohort study by Nash et al., 151 of 332 patients with AKI had SCr concentrations >1.2 mg/dl at baseline (10). Interestingly, patients with CKD have been reported in some studies to have lower in-hospital mortality than patients without CKD who develop AKI. This finding has been noted in large database studies as well as studies to identify predictors of mortality following AKI. For example, among patients included in the NIS, 22% of patients with CKD and AKI-D died in hospital, compared with 30% of patients without CKD (28). In the PICARD cohort, baseline CKD conferred a 43% (95% CI, 16% to 61%) lower adjusted odds of in-hospital mortality (16); CKD was not associated with lower mortality in the BEST Kidney cohort (23). Used as a continuous variable, higher baseline SCr has also been associated with lower mortality in studies examining outcomes after AKI (16,54). Reasons that may underlie this seemingly paradoxical finding include confounding by malnutrition (and lower SCr values from low muscle mass) and unrecorded differences in disease severity between those with and without CKD who develop AKI. The latter may reflect relatively less severe kidney injury required in patients with CKD to manifest AKI, as currently diagnosed.

The presence or absence of CKD likely influences long-term

Table 1. Incidence and mortality of acute kidney injury in selected conditions

Reference (year)	Setting	Definition of AKI	Incidence	In-hospital Mortality
Sepsis				
Yegenaga (92) (2004)	ICU admissions with sepsis/SIRS (n = 217)	SCr increase to >2 mg/dl	AKI: 13%; AKI-D: 6%	No AKI: 24%; AKI: 72%; AKI-D: 69%; no AKI: 28%
Hoste (93) (2003)	Surgical ICU admissions with sepsis (n = 185)	SCr increase from ≤1.0 to ≥2.0 mg/dl	AKI: 30%; AKI-D: 11%	AKI: 57%
Neveu (94) (1996)	ICU admissions with AKI and sepsis (n = 345)	100% increase in SCr to ≥3.5 mg/dl or BUN ≥100 mg/dl, or 100% increase in BUN or SCr	Not reported; 46% of all AKI was in the setting of sepsis	AKI from sepsis: 74% nonseptic AKI: 45%
Rangel-Frausto (95) (1995)	ICU admissions with sepsis/SIRS (n = 2527)	Acute SCr increase to >2 mg/dl, need for dialysis, or doubling of SCr	AKI: 9% for SIRS, 51% for culture + septic shock	3% to 46%, depending on severity; AKI mortality not reported
Percutaneous coronary intervention (PCI)				
Marenzi (96) (2004)	ST-elevation AMI treated with primary PCI (n = 208)	Increase in SCr >0.5 mg/dl	AKI: 19%; AKI-D: 3%	AKI: 31%; no AKI: 0.6%
Mehran (97) (2004)	PCI (n = 8357)	Increase in SCr ≥25% or ≥0.5 mg/dl	AKI: 13%	Not reported
Rihal (98) (2002)	PCI (n = 7586)	Increase in SCr ≥0.5 mg/dl	AKI: 3.3%; AKI-D: 0.3%	AKI: 22%; no AKI: 1%
McCullough (99) (1997)	PCI (n = 1826)	Increase in SCr >25%	AKI: 14%; AKI-D: 0.8%	No AKI: 1%; AKI: 7%; AKI-D: 36%
IV contrast for radiologic examination				
Mitchell (100) (2007)	CT angiography to rule out pulmonary embolism in the emergency department (n = 1224)	Increase in SCr >25% or 0.5 mg/dl within 7 d	AKI: 4% of entire cohort, 12% of those with 2 SCr measurements AKI-D: 0%	Not reported
Parfrey (101) (1989)	IV contrast for cardiac arteriography or CT examination (n = 220)	Increase in SCr >25%	AKI in + DM -CKD: 2.4% +DM + CKD: 8.8% -DM + CKD: 6.4%	Not reported
Cramer (102) (1985)	CT of the brain with (n = 193) and without (n = 233) IV contrast	Increase in SCr ≥50% to at least 1.2 mg/dl	AKI in IV contrast: 2.1% AKI no IV contrast: 1.3%	Not reported
Cardiac surgery				
Mehta (103) (2006)	Cardiac surgery (n = 449,524)	Need for dialysis	AKI: not reported AKI-D: 1.4%	No AKI-D: 2.3%; AKI-D: 43.6%
Brown (41) (2006)	Patients undergoing CABG (without valve replacement) (n = 1391)	Increase in SCr <25%, 25%–49%, 50%–99%, ≥100%	25–49%: 16% 50 – 99%: 7% ≥100%: 5%	90-day mortality adjusted HR, reference = <25% (increase in SCr) 25%–49%: 1.8 (50%–99%): 12.2 ≥100%: 5%: 30.8
Loef (43) (2005)	CABG or valvular surgery (n = 843)	Increase in SCr ≥25% within 7 d of surgery	AKI: 17.2%; AKI-D: 0.7%	No AKI: 1.1%; AKI: 14.5%; AKI-D: 83.3%
Thakar (104) (2005)	Open-heart surgery (n = 18,838)	Need for dialysis	AKI: not reported; AKI-D: 1.7%	Not reported
Bove (105) (2004)	Cardiopulmonary bypass/CABG (including valve replacement) (n = 5068)	Increase in SCr ≥100%	AKI: 3.4%; AKI-D: 1.9%	No AKI: 2.7%; AKI: 46.2%; AKI-D: 63.8%
Ryckwaert (106) (2002)	CABG or valvular surgery (n = 591)	Increase in SCr ≥20% within 3 d of surgery	AKI: 15.6%; AKI-D: 1.4%	No AKI: 1.0%; AKI: 12.0%; AKI-D: 37.5%
Chertow (107) (1998)	CABG or valvular surgery (n = 43,642)	Need for dialysis	AKI: not reported; AKI-D: 1.1%	30-day mortality; no AKI: 4.3%; AKI: not reported; AKI-D: 63.8%
Mangano (108) (1998)	CABG or valvular surgery (n = 2222)	Increase in SCr of ≥0.7 mg/dl to at least 2.0 mg/dl	AKI: 7.7%; AKI-D: 1.4%	No AKI: 0.9%; AKI: 19%; AKI-D: 63.8%
Nephrotoxic antibiotics				
Folwer (109) (2006)	Daptomycin (n = 124) or gentamicin + penicillin or vancomycin (n = 126)	Decrease in CrCl to <50 ml/min, or decrease in CrCl of 10 ml/min if below 50 at baseline	AKI, daptomycin: 11% AKI, gentamicin: 26.3%	Not reported
Bates (110) (2001)	Amphotericin B (n = 707) (64 received liposomal preparation)	Increase in SCr of ≥50% to at least 2.0 mg/dl (severe: peak SCr at least 3.0 mg/dl)	AKI: 30%; severe AKI: 13%	No AKI: 14%; AKI: 54%
Wingard (111) (1999)	Amphotericin B for aspergillosis (n = 239)	Increase in SCr of ≥100%	AKI: 53%; AKI-D: 14.5%	No AKI-D: 57%; AKI-D: 76%
Leehey (112) (1993)	Aminoglycosides (n = 243)	Increase in SCr of 0.5 mg/dl and 100% over baseline	AKI: 20.6%; AKI-D: 1.2%	Not reported
Smith (113) (1980)	Gentamicin and tobramycin (n = 146)	—	AKI: 19.2%	Not reported
Aortic aneurysm repair				
Prinssen (114) (2004)	Open (n = 174) or endovascular (n = 171) AAA repair	Increase in SCr ≥20%	AKI: 13% (both groups); AKI-D: not reported	Not reported
Ryckwaert (44) (2003)	Infra-renal aortic abdominal surgery (n = 215)	Increase in SCr ≥20%	AKI: 20%; AKI-D: 2.8%	No AKI:1.2%; AKI: 9.3%; AKI-D: 50%
Godet (115) (1997)	Thoracic or thoracoabdominal aortic surgery (n = 475)	Increase in SCr to >1.7 mg/dl or 30% over baseline	AKI: 25%; AKI-D: 8%	AKI (no dialysis): 38% AKI-D: 56%

AAA, abdominal aortic aneurysm; AKI, acute kidney injury; AKI-D, acute kidney injury requiring dialysis; AMI, acute myocardial infarction; BUN, blood urea nitrogen; CABG, coronary artery bypass grafting; CT, computed tomography; ICU, intensive care unit; PCI, percutaneous coronary intervention; PCN, penicillin; SCr, serum creatinine; IV, intravenous; —, not applicable.

Table 2. Predictors of the development of acute kidney injury

Reference (year)	Clinical Setting	N (%) With AKI Outcome	AKI Definition	Identified Risk Factors in Multivariable Models
Davidson (116) (1989)	Diagnostic cardiac catheterization	1162 (6)	Increase in SCr ≥0.5 mg/dl	Older age and baseline SCr ≥1.2
Rich (117) (1990)	Cardiac catheterization, age >70, including percutaneous coronary intervention	183 (11)	Increase in SCr ≥0.5 mg/dl	Contrast volume >200 ml, serum albumin <3.5 mg/dl, diabetes, serum sodium <135 mmol/L, SCr >1.5, NYHA class III or IV
Lautin (118) (1991)	Femoral arteriography	394 (22)	Increase in SCr >0.3 mg/dl and 20% over baseline	Diabetes, baseline SCr >1.5 mg/dl
McCullough (99) (1997)	Percutaneous coronary intervention	1826 (0.77)	Need for dialysis	Lower baseline CrCl, diabetes, contrast volume
Gruberg (119) (2001)	Percutaneous coronary intervention	7690 (0.66)	Need for dialysis	Non-Q-wave MI, saphenous vein graft intervention, peak postprocedural SCr, IABP, contrast volume, lower baseline CrCl
Rihal (98) (2002)	Percutaneous coronary intervention	7586 (3.3)	Increase in SCr ≥0.5 mg/dl	Older age, higher baseline SCr, CHF, DM, shock, MI, PVD, contrast volume
Mehran (97) (2004)	Percutaneous coronary intervention	8357 (13.1)	Increase in SCr ≥25% or ≥0.5 mg/dl	Hypotension, IABP, CHF, CKD, DM, age >75, anemia, contrast volume
Marenzi (96) (2004)	Percutaneous coronary intervention for acute MI	208 (19)	Increase in SCr >0.5 mg/dl	Age ≥75, anterior acute MI, time-to-reperfusion ≥6 h, contrast volume, IABP
Chertow (120) (1998)	Coronary artery bypass grafting	42,773 (1.1)	Need for dialysis	Valve surgery, lower preoperative CrCl, IABP, prior heart surgery, NYHA class IV, PVD, LVEF <35%, pulmonary rales, COPD, SBP ≥160 (CABG only)
Thakar (104) (2005)	Coronary artery bypass grafting	33,217 (1.7)	Need for dialysis	Female gender, CHF, IABP, COPD, insulin-requiring diabetes, previous cardiac surgery, emergency/valve surgery, higher preoperative SCr
Mehta (103) (2006)	Coronary artery bypass grafting	449,524 (1.4)	Need for dialysis	Higher preoperative SCr, older age, type of surgery (+/− valve), diabetes, recent MI, nonwhite race, chronic lung disease, prior CABG, NYHA class IV, cardiogenic shock
Chawla (121) (2005)	Sepsis	194 (18)	>75% increase in SCr (baseline ≤2.0 mg/dl) or >50% increase (baseline >2.0 mg/dl)	Low serum albumin, high A-a gradient, active cancer
Hoste (93) (2003)	Sepsis	185 (16)	Increase in SCr to at least 2 mg/dl	pH <7.3 and SCr >1.0 mg/dl on day of sepsis diagnosis
Yegenaga (92) 2004)	Sepsis	257 (11)	Increase in SCr to at least 2.0 mg/dl or urine output <400 ml/24 h	Older age, higher SCr, higher CVP, serum bilirubin >1.5 mg/dl
Chertow (16) (2006)	Established AKI	618 (64)	Need for dialysis	Younger age, oliguria, higher BUN, liver failure
Chertow (122) (1998)	Established AKI (placebo arm of RCT)	256 (57)	Need for dialysis or death	Oliguria, low serum albumin, acute MI, mechanical ventilation, arrhythmias
Godet (115) (1997)	Thoracoabdominal aortic surgery	475 (25)	Increase in SCr to at least 1.7 mg/dl or ≥30% increase if preexisting CKD	Age >50, preoperative SCr >1.3, ischemia duration >30 min, use of Cell-saver, >5 units pRBC transfusion
Bates (110) (2001)	Amphotericin B	643 (27)	Increase in SCr ≥50% to at least 2.0 mg/dl	ICU stay at initiation of therapy, use of cyclosporine, maximum daily dose of amphotericin B

AKI, acute kidney injury; A-a, alveolar-arterial; BUN, blood urea nitrogen; CABG, coronary artery bypass grafting; CHF, congestive heart failure; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CrCl, creatinine clearance; IABP, intra-aortic balloon pump; ICU, intensive care unit; MI, myocardial infarction; NYHA, New York Heart Association; PICARD, Program to Improve Care in Acute Renal Disease; RCT, randomized controlled trial; pRBC, packed red blood cells; PVD, peripheral vascular disease; SCr, serum creatinine.

outcome in survivors of AKI-D. In a population-based surveillance study of AKI from Calgary, among all patients with AKI who required maintenance dialysis 1 yr after hospital admission, 63% had preexisting CKD (median baseline SCr = 2.6 mg/dl) (55).

Because the presence of CKD influences the risk of AKI, its consequences, and the propensity for the development of end-stage renal disease, future studies of AKI epidemiology should use definitions that incorporate baseline CKD stage, as has been suggested by others (56,57). Likewise, prevention and intervention studies of AKI should be stratified on baseline kidney function.

Beyond Creatinine

Newer Markers of Glomerular Filtration Rate (GFR)

A reduction in GFR remains the *sine qua non* for the clinical diagnosis of AKI; however, SCr is an imperfect marker of GFR because of tubular secretion, the need for steady-state determi-

Table 3. Predictors of mortality after acute kidney injury

Reference (year)	Clinical Setting	Mortality, N (%)	AKI Definition	Identified Risk Factors for Mortality in Multivariable Models
Liaño (123) (1993)	Hospital	328 (53)	Increase in SCr to at least 2.0 mg/dl (baseline <1.5 mg/dl)	Coma, mechanical ventilation, hypotension, oliguria, jaundice, nephrotoxic etiology (protective), normal consciousness (protective)
Chertow (54) (1995)	ICU	132 (70)	Need for dialysis	Mechanical ventilation, malignancy, nonrespiratory organ system failure
Neveu (94) (1996)	ICU	345 (59)	Increase in SCr to at least 3.5 mg/dl or BUN to at least 100 mg/dl, or >100% increase in SCr	Sepsis as cause of AKI, occurrence of AKI during ICU stay, oliguria, mechanical ventilation, generic severity of illness score, preadmission health status
Paganini (124) (1996)	ICU	512 (67)	Need for dialysis	Male gender, mechanical ventilation, hematologic dysfunction, bilirubin >2.0 mg/dl, absence of surgery, higher SCr on first dialysis treatment, increasing number of failed organ systems, increased BUN from time of admission
Chertow (122) (1998)	Placebo arm of randomized controlled trial	256 (36)	Increase in SCr of ≥1.0 mg/dl	Male gender, mechanical ventilation, oliguria, acute myocardial infarction, stroke/seizure, hypertension (protective), low serum bicarbonate
Metnitz (125) (2002)	ICU	839 (63)	Need for dialysis	Mechanical ventilation, cardiopulmonary resuscitation, treatment of complicated metabolic acidosis/alkalosis, enteral nutrition (protective)
Mehta (126) (2002)	ICU	605 (52)	BUN ≥40 mg/dl or SCr ≥2.0 mg/dl; increase in SCr ≥1.0 mg/dl if preexisting CKD	Older age, male gender, nonrenal organ failure (respiratory, liver, and hematologic), lower SCr, higher BUN, oliguria, higher heart rate
Lins (127) (2004)	ICU	293 (51)	Increase in SCr to at least 2.0 mg/dl, or ≥50% increase in SCr if preexisting CKD	Older age, lower serum albumin, higher INR value, mechanical ventilation, CHF, higher serum bilirubin, sepsis, hypotension
Uchino (23) (2005)	ICU	1738 (60)	BUN >84 mg/dl or oliguria <200 ml in 12 h	Older age, delay between admission and inclusion into study, mechanical ventilation, generic severity of illness score, vasopressor use, metabolic diagnosis (protective), hematologic diagnosis, septic shock, cardiogenic shock, hepatorenal syndrome
Chertow (16) (2006)	ICU	618 (37)	Increase in SCr ≥0.5 or 1.0 mg/dl if baseline CKD	At diagnosis: older age, CKD stage IV (protective), high BUN, liver failure, sepsis

AKI, acute kidney injury; BUN, blood urea nitrogen; CHF, congestive heart failure; CKD, chronic kidney disease; ICU, intensive care unit; NYHA, New York Heart Association; RRT, renal replacement therapy; SCr, serum creatinine.

nations for accurate GFR estimates, and the confounding influences of muscle mass and changes in volume of distribution, the latter particularly in the setting of acute illness. Assessment of GFR by gold standards, such as iothalamate or inulin clearance, is cumbersome and impractical in the acute setting. The best studied alternative to SCr as an endogenous GFR marker is cystatin C. Cystatin C is a low molecular weight protein produced by all nucleated cells that is freely filtered by the glomerulus and then reabsorbed and metabolized by the proximal tubule. Several studies in AKI suggest that cystatin C may be superior to SCr for the earlier detection of reduced GFR (58–61). Like any circulating substance, serum levels of cystatin C are dependent not only on clearance but also on production rate and acute changes in the volume of distribution. Higher doses of corticosteroid and hyperthyroidism increase and hypothyroidism decreases serum cystatin C. Although previously a concern, (62), it does not appear that inflammation significantly alters serum cystatin C concentrations (63).

In a single study, cystatin C was compared with proatrial natriuretic peptide (1–98), a circulating prohormone of atrial natriuretic peptide that has been studied as an index of kidney function in patients with heart failure. In 29 critically ill patients with sepsis, Mazul-Sunko *et al.* reported that pro-ANP (1–98) was superior to cystatin C for the prediction of AKI (64). Confirmatory studies are needed.

Injury Markers

The new term AKI heralds a paradigm shift for our conceptualization of the syndrome previously called "acute renal failure." It is worth considering each of the three terms in turn. "Acute" refers to the temporal nature of the disease process and is designed to exclude the many, usually irreversible, causes of CKD. The recent RIFLE and AKIN classifications specify the time period as "abrupt" and "within 48 h." Whether the tempo of the rise in serum creatinine (or other biomarkers) is relevant in terms of prognosis of diagnosis remains to be evaluated. "Renal" refers of course to the organ sustaining the damage, but interestingly to only one of the many functions of the kidney, namely, GFR. A reduction in GFR is not always observed in cases of even severe parenchymal injury, as seen in cases of lupus nephritis. Also, reductions in GFR can be observed in cases of no evident pathology, as in some cases of prerenal azotemia. "Failure" refers to organ failure as assessed by a marker of GFR, namely, BUN or creatinine.

The new phrase AKI retains one word, harmlessly substitutes a synonym for another, but replaces "failure" with "injury." This last substitution may very well redefine the epidemiology of the syndrome. Currently, the diagnosis of "injury" rests on an elevation in serum creatinine, which is understood to be neither perfectly sensitive nor specific. Newer biomarkers under consideration aim in general to identify correlates of cellu-

Table 4. Human studies of urinary biomarkers for acute kidney injury

Biomarker	Clinical Conditions Studied	References
Neutrophil gelatinase-associated lipocalin (NGAL)	Cardiac surgery (adult)	68
	Cardiac surgery (pediatric)	67
	Percutaneous coronary intervention	69
	Delayed graft function	74
	Critically ill children	71
Kidney injury molecule-1 (KIM-1)	AKI (cross-sectional study)	81
	Human kidney biopsy series	82
	Established AKI	83
	Cardiac surgery (pediatric)	84
Interleukin-18 (IL-18)	AKI (cross-sectional study)	77
	Cardiac surgery	75
	Acute respiratory distress syndrome	76
	Delayed graft function	74
	Critically ill children	78
Fatty acid binding protein (FABP)	Coronary angiography	128
Na+/H+ exchanger isoform 3 (NHE-3)	AKI (cross-sectional study)	79
Endothelin-1	Intravenous contrast	129
	Cisplatin	130
N-acetyl-β-(D)-glucosaminidase (NAG)	Cardiac surgery	86, 131–135
	Cisplatin	130, 136–139
	ICU/AKI	140–142
	Aminoglycosides	139, 143–145
	Burn injury	146
	Russell's viper bite envenomation	147
	Bone marrow transplant	148
	Extracorporeal shock wave lithotripsy	149–151
	Birth asphyxia	152
	Intravenous contrast	153–157
	Amphotericin B	158
Adenosine deaminase binding protein	Cardiac surgery	134
	AKI (cross-sectional study)	159
	Cisplatin	160
	Cancer chemotherapeutics	161
Alanine aminopeptidase	Cisplatin	137–139
	Extracorporeal shock wave lithotripsy	149
	Intravenous contrast	153–157
	Aminoglycosides	139, 145
Leucine aminopeptidase	Extracorporeal shock wave lithotripsy	162
	Burn injury	163
Beta-galactosidase	Cisplatin	137
	Extracorporeal shock wave lithotripsy	150
α-glutathione S-transferase	Cardiac surgery	85, 131, 135, 164
	ICU/AKI	140, 141
	Abdominal aortic aneurysm repair	165
	Amphotericin B	158
π-glutathione S-transferase	Cardiac surgery	85, 131, 135
	ICU	140
	Abdominal aortic aneurysm repair	165
	Amphotericin B	158
	Intravenous contrast	166
γ -Glutamyl transpeptidase	ICU/AKI	140, 141
	AKI (cross-sectional study)	81
	Intravenous contrast	155, 157, 167
	Extracorporeal shock wave lithotripsy	149, 150, 162
Alkaline phosphatase	ICU	140
	AKI (cross-sectional study)	81, 142
	Extracorporeal shock wave lithotripsy	149
	Intravenous contrast	155, 167, 168
Lactate dehydrogenase	ICU	140
	Intravenous contrast	155
Neutral endopeptidase	Cardiac surgery	169
α 1-microglobulin	ICU/AKI	141
	Cardiac surgery	131–133, 135
	Intravenous contrast	153, 154
β 2-microglobulin	Cardiac surgery	134
	ICU/AKI	141
	Cisplatin administration	130, 136
	Intravenous contrast	156
	Burn injury	163
Retinol binding protein	Cardiac surgery	169
	ICU/AKI	141
	Birth asphyxia	152
	Aminoglycosides	144
	Cisplatin	137
Urinary cystatin C	ICU/AKI	141

ICU, intensive care unit.

lar (typically tubular cell) injury. Importantly, tubular cell injury may precede or not always lead to a reduction in GFR. The concept that injury to the tubule should cause such a decline in a morphologically and functionally distinct part of the nephron rests upon a series of downstream events, such as tubular obstruction by necrotic debris leading to backflow, creatinine absorption, tubuloglomerular feedback, and intense vasoconstriction from release of inflammatory mediators. What if biomarkers are able to identify tubular injury at a stage even before GFR begins to fall? Would such biomarkers be discarded as nonspecific because they can be elevated without a rise in serum creatinine or another marker of GFR? Perhaps AKI is more common and consequential than currently appreciated on the basis of proxies of GFR, such as SCr, BUN, or cystatin C. Not all cases of AKI, particularly those now identified on the basis of small and transient rises in SCr, reflect structural injury. In other words, markers of GFR may not be true gold standards against which all biomarkers should be judged. In the future, clinical investigators should consider biomarkers of AKI that reflect important consequences of the injury (*e.g.*, death, need for dialysis, hospital length of stay) whether or not they correspond to changes in SCr or other markers of GFR.

Early identification of kidney injury will be critical for future developments in treatment or prevention of AKI. Advances in the care of patients with stroke, myocardial infarction, and sepsis have been made possible by early intervention, which is in turn possible only with early diagnosis.

The earliest sign of ischemic or nephrotoxic AKI may not be a decline in GFR, in much the same way that a decrease in cardiac output or albumin synthesis are not early signs of cardiac or hepatic injury. Time-honored tests, such as urinary microscopy, urine osmolality, and fractional excretion of sodium or urea are nonspecific and insensitive, although careful and large prospective studies evaluating these parameters have not been conducted (65).

The biologic response of kidney tissue to ischemic or nephrotoxic injury may be used as early indicators of AKI. Urine has been investigated as a more promising biologic fluid than serum or plasma to identify the earliest markers of kidney injury. Urinary injury markers may be present in the urine because of impaired tubular reabsorption and catabolism of filtered molecules, release of enzymes or exosomes from tubular cells, and as a response of tubular cells to ischemic or nephrotoxic injury. Table 2 lists several promising urinary biomarkers that have been studied in humans in the context of AKI (not including kidney transplantation).

Neutrophil Gelatinase-Associated Lipocalin (NGAL)

NGAL is one of the best studied urinary biomarkers of AKI to date. Also known as lipocalin-2 or siderocalin, NGAL was first discovered as a protein in granules of human neutrophils; animal studies showed its promise as an early marker of ischemic and nephrotoxic kidney injury (66).

Mishra *et al.* prospectively obtained serial urine and serum samples from 71 children undergoing cardiopulmonary bypass (CPB) for surgical correction of congenital heart disease (67). Twenty children developed AKI, defined as a 50% increase in SCr. Urinary NGAL at just 2 h after CPB almost perfectly predicted which patients would go on to develop AKI. Two-hour NGAL levels more than 50 mg/L had 100% sensitivity and 98% specificity for the diagnosis of AKI, which was made 24 to 72 h after CPB. A measure of the diagnostic performance characteristics of a test is the area under the receiver operating characteristics curve (AUC-ROC), which ranges from 0.50 (no better than chance alone) to 1.0 (perfect test). In the setting of pediatric patients after CPB, the AUC-ROC for urinary NGAL at 2 h was a remarkable 0.998. In this study, serum NGAL was inferior to urinary NGAL for the identification of AKI. As encouraging as these results were, it should be noted that 29% of eligible patients were excluded because of perioperative use of ibuprofen, angiotensin-converting enzyme inhibitors, gentamicin, or vancomycin.

Other studies showed less impressive results. Wagener et al. reported results on urinary NGAL in 81 adult patients undergoing cardiac surgery; the only exclusion criterion was preexisting end-stage renal disease (68). Sixteen patients developed AKI, defined as a 50% increase in SCr. Urinary NGAL levels were consistently higher immediately postoperatively and at 1, 3, 18, and 24 h postoperatively in patients who went on to develop AKI. However, substantial overlap was noted between patients who did and did not develop AKI. The AUC-ROC for NGAL ranged from 0.67 (immediately after surgery) to 0.80 (18 h following surgery). At 3 h after surgery, urinary NGAL levels more than 213 mg/L had 69% sensitivity and 65% specificity for the diagnosis of AKI. Bachorzewska-Gajewska et al. measured urinary and serum NGAL in 35 patients undergoing elective percutaneous coronary intervention (69). No patient developed contrast nephropathy defined as an increase in SCr. Urinary NGAL was studied in 53 consecutive patients undergoing living or deceased donor kidney transplantation. NGAL levels (normalized to urine creatinine concentration) were significantly higher in deceased donor recipients with delayed graft function (DGF) (n = 10, median 3306 ng/mg creatinine) than after prompt graft function (n = 20, median 756 ng/mg creatinine). A cutoff of 1000 ng/mg creatinine had 90% sensitivity and 83% specificity for the identification of DGF; the AUC-ROC was 0.90. Not reported in this paper was the influence of the normalization of NGAL levels to urine creatinine or the non-normalized NGAL results. Urine creatinine is used as a proxy for urine flow rate to account for differences in the concentration in urine. This normalization approach has been validated in the setting of estimates of 24 h protein or albumin excretion (70), but not in the setting of AKI when the urinary creatinine concentration may decline because of low GFR. Zappitelli *et al.* studied urinary NGAL in 140 children admitted to the ICU requiring mechanical ventilation (71). Urine was collected daily for 4 d. The authors found on cross-sectional analysis that mean and peak urinary NGAL levels were higher in patients with worsening degrees of AKI (as judged by the pediatric RIFLE criteria (72). At 48 h before the development of AKI, urinary NGAL had an AUC-ROC of 0.79 for the subsequent development of AKI.

Interleukin-18 (IL-18)

IL-18 was found to mediate ischemic AKI and to be detectable in the urine of mice subjected to ischemic kidney injury (73). Urinary IL-18 has been studied by Parikh *et al.* in a variety of clinical settings, including delayed graft function (74), cardiac surgery (75), and acute respiratory distress syndrome (76) and in patients with and without acute and chronic kidney disease (77). The first AKI study of urinary IL-18 in humans was a cross-sectional comparison of ATN (n = 14), healthy controls (n = 11), prerenal azotemia (n = 8), urinary tract infection (n = 5), CKD (n = 12), and transplant recipients (n = 22) (77). The highest levels of urinary IL-18 were observed in patients with ATN and delayed graft function, with relatively little overlap from patients with prerenal azotemia, urinary tract infections, and CKD. The AUC-ROC from this cross-sectional cohort (for the identification of ATN, including delayed graft function) was 0.95, with a sensitivity of 85% and specificity of 88% at a cutoff of 500 pg IL-18/mg creatinine.

The NIH sponsored Acute Respiratory Distress Syndrome Network trial of low *versus* high tidal volume ventilation was the source of urine samples in a subsequent study of urinary IL-18 (76). Parikh et al. performed a nested case-control study in 138 of the 861 patients enrolled; exclusion criteria included a baseline SCr more than 1.2 mg/dl. Urinary IL-18 levels were higher in patients who developed AKI (defined as a 50% increase in SCr within 6 d of enrollment), and higher levels were associated with mortality. The AUC-ROC for IL-18 (not normalized to urine creatinine) was 0.73 at 24 h before AKI diagnosis. Parikh *et al.* also measured IL-18 in urine samples collected in the pediatric cardiac surgery cohort used to study NGAL (67). They measured IL-18 in all 20 cases of AKI and in 35 of the 51 non-AKI cases (matched according to race, gender, and age to AKI cases). Compared with NGAL, which increased 25-fold within 2 h and declined after 6 h of CPB, IL-18 increased at 4 to 6 h and remained elevated up to 48 h after CPB. The reported AUC-ROCs for IL-18 were 0.61 at 4 h, 0.75 at 12 h, and 0.73 at 24 h, lower than the 0.998 reported by Mishra for NGAL at 2 h after CPB. IL-18 was also studied by Washburn *et al.* (78) in critically ill children requiring mechanical ventilation (identical cohort as studied by Zappitelli *et al.* for NGAL71). They found on cross-sectional analysis that peak urinary IL-18 levels were higher in patients with worsening degrees of AKI (as judged by the pediatric RIFLE criteria (72)). However, in prospective analysis, IL-18 demonstrated no ability to predict the subsequent development of AKI (AUC-ROC = 0.54). Not surprising for a pro-inflammatory cytokine that plays an important role in sepsis, urinary IL-18 was significantly higher in patients with sepsis than in those without, and limited its diagnostic ability for the early identification of AKI in this cohort.

Na^+/H^+ Exchanger Isoform 3 (NHE3)

NHE3 is the most abundant sodium transporter in the renal tubule and is responsible for proximal reabsorption of up to 70% of filtered sodium and bicarbonate. du Cheyron *et al.* performed a cross-sectional study of 68 patients admitted to the ICU (79). They isolated membrane fractions from the urine and measured NHE3 concentrations using semiquantitative immunoblotting. NHE3 protein was undetectable in patients without AKI (n = 14), detectable at relatively low levels in prerenal azotemia (n = 17) and postrenal obstruction (n = 3), and was significantly elevated in ATN (n = 17; 6.6-fold higher than in prerenal azotemia). The same investigators also measured urinary retinol binding protein (RBP), the primary plasma transport protein for vitamin A, a molecule that gets filtered by the glomerulus and reabsorbed by the proximal tubule. Urinary RBP was significantly higher in patients with ATN than normal controls, but significant overlap was noted, particularly with prerenal azotemia.

Kidney Injury Molecule-1 (KIM-1)

KIM-1 was identified as a markedly upregulated gene in postischemic rat kidney using a polymerase chain reaction-based technique (80). The ectodomain of KIM-1 protein is shed from cells into the urine in rodents and in humans. Han *et al.* (81) demonstrated marked expression of KIM-1 in kidney biopsy specimens from 6 patients with acute tubular necrosis (ATN), and found elevated urinary levels of KIM-1 in 7 patients with ischemic ATN; urinary levels of KIM-1 were significantly lower in contrast nephropathy (n = 7) although the levels did correlate with severity of contrast-induced injury. Levels of urinary KIM-1 were lower in AKI not due to ATN (n = 9), CKD (n = 9), and were below limits of detection in normal subjects (n = 8). van Timmeren *et al.* stained for KIM-1 protein in tissue specimens from 102 patients who underwent kidney biopsy for a variety of kidney diseases and 7 patients who underwent nephrectomy for renal cell carcinoma (82). No tissue KIM-1 was found in patients with minimal change disease or in the tumor-free samples of renal cell carcinoma. In all other disease conditions, KIM-1 protein was identified in dedifferentiated proximal tubular cells and correlated with tubulointerstitial fibrosis and inflammation. In the subset of patients who underwent urine collection near the time of biopsy, urinary KIM-1 levels correlated with tissue expression of KIM-1. Urinary KIM-1 may therefore hold promise as a noninvasive assessment of the activity and prognosis of a variety of acute and CKDs. Liangos *et al.* studied urinary KIM-1 at the time of nephrology consultation in 201 patients with established AKI (83). Because non-AKI controls were not included in this study, diagnostic performance characteristics, such as sensitivity, specificity, or the AUC-ROC curve were not reported. KIM-1 demonstrated prognostic significance: elevated levels were significantly associated with the clinical composite endpoint of death or dialysis requirement, even after adjustment for disease severity or comorbidity. Urinary KIM-1 was also measured by Han *et al.* (84) in samples from the same pediatric cardiac surgery cohort that was used for prospective studies on urinary NGAL and IL-18. Urinary KIM-1 at 12 h after CPB had an AUC-ROC of 0.83 for the subsequent development of AKI, as defined as an increase in SCr of $\geq$50%.

Tubular Enzymes and Markers of Tubular Dysfunction

The apical surface of proximal tubular epithelial cells contains numerous microvilli that form the brush border and contain specific proteins to carry out the specialized functions of the proximal tubule. After kidney injury, these tubular enzymes can often be recovered in the urine. Several different classes of enzymes can be found: lysosomal proteins, such as N-acetyl-β-(D)-glucosaminidase (NAG), brush border enzymes, including g-glutamyltransferse (GGT) and alkaline phosphatase, as well as cytosolic proteins, such as α-glutathione s-transferase (GST) and π-GST. Furthermore, when proximal tubular epithelial cells are injured, they may not metabolize cystatin C properly, and intact cystatin may be shed into the urine. Similarly, injured cells may not completely reabsorb low molecular weight proteins that are freely filtered into the urinary space, such as α1 and β2-microglobulin.

In one of the most comprehensive studies performed to date, Westhuyzen *et al.* (140) compared the predictive value of a number of tubular enzymes for the subsequent development of AKI, defined as a 50% rise in SCr to at least 1.7 mg/dl. Four of 26 subjects developed AKI; baseline levels of GGT, AP, NAG, α-GST, and π-GST were higher in those who developed AKI compared with those who did not. GGT and π-GST had the best predictive value on their own, with AUC-ROC of 0.95 (95% CI, 0.79 to 1.0) and 0.93 (95% CI, 0.74 to 1.0), respectively. Changes in enzyme levels preceded detectable changes in timed creatinine clearance. However, when the authors attempted to develop cutpoints based on this small study and tested the generalizability of their results in a test population of 19 patients (4 of whom developed AKI), the sensitivity and specificity of these biomarkers were significantly reduced. Furthermore, the timing of AKI after study enrollment ranged from 12 h to 4 d in the original study population, so the precise timing of the rise in these markers relative to AKI is also unclear. Further studies are needed to determine how predictive these markers are for AKI in a larger population of patients.

Herget-Rosenthal *et al.* risk-stratified patients with nonoliguric AKI (defined as a doubling in creatinine from a baseline concentration of <106 μmol/L to at least 115 μmol/L) using tubular enzymes as biomarkers (141). They identified 73 subjects who met prespecified criteria for AKI; 26 of these individuals subsequently required dialysis. They measured urinary excretion of cystatin C, α1 and β2 microglobulin, α-GST, NAG, RBP, GGT, and lactate dehydrogenase on the day of study enrollment. On average, subjects required dialysis 4 d after study enrollment. Cystatin C and α1-microglobulin (markers of abnormal proximal tubule function) had the best predictive value for the need for dialysis, with AUC-ROC curve of 0.92 and 0.86, respectively. Of the tubular enzymes studied, NAG had the best predictive value, with an AUC-ROC of 0.81. Similarly, Chew *et al.* risk-stratified patients with AKI based on levels of tubular enzymes (142); levels of NAG and alkaline phosphatase were higher in patients with poor outcomes (defined as need for dialysis or death).

Tubular enzymes have been studied as markers of AKI for over two decades, yet they have not been adopted in widespread clinical use either as early diagnostic tests or surrogate endpoints for interventional studies. Some authors have suggested that tubular enzymes are overly sensitive because they tend to rise after injuries such as CPB without an associated rise in SCr (85,86). While tubular enzymes may not prove to be particularly valuable biomarkers, it is unclear that a change in SCr is a satisfactory standard against which to judge their merit. Well-designed and adequately powered clinical studies with appropriately chosen endpoints will be needed to settle these issues.

Other Markers

Keratinocyte-derived chemokine was found in a mouse model of renal ischemia-reperfusion injury to be elevated in serum and urine 3 h after injury (87). These investigators measured urinary levels of a structurally homologous molecule in humans, termed human growth-related oncogene-alpha (Gro-alpha), in a small pilot study of patients (n = 17) undergoing kidney transplantation, and found markedly higher levels among those with DGF following deceased donor transplantation. Zhou *et al.* have focused on urinary exosomes (small excreted vesicles that contain membrane and cytosolic proteins) as a potential source of novel AKI biomarkers (88). Exosomal fetuin-A was identified in preclinical rodent models of ischemic and cisplatin-induced AKI; a small pilot study in 9 humans showed exosomal fetuin-A to be present in the urine of ICU patients with AKI but not in healthy volunteers or ICU patients without AKI (88).

Availability of Multiple Biomarkers

The various biomarkers under clinical investigation will likely perform differently with respect to disease specificity (*e.g.*, sepsis *versus* nephrotoxic *versus* postoperative AKI), time course (early *versus* late markers), and prognostic characteristics (e.g., markers of incipient AKI *versus* markers of prognosis in established AKI). Whether a panel of biomarkers would provide complementary information and be practical in use compared with a single biomarker approach remains to be determined. Establishing the optimal test(s) will require prospective validation in large numbers of patients with a variety of causes of AKI. The possibility that injury biomarkers may be superior to SCr or other clearance-based markers for the identification of AKI will require investigators to test the creatinine-independent associations between biomarker levels and exposures (*e.g.*, CPB time, dose of nephrotoxin administration) and outcomes (*e.g.*, not only AKI as defined by change in SCr or cystatin C but mortality, complications, need for dialysis, and length of stay and other outcomes).

Interventional Studies

Prevention of AKI

Innumerable AKI prevention studies have been conducted over the past three decades, the vast majority of which have targeted persons anticipating exposure to radiocontrast, often persons at above average risk, owing to the presence of diabetes mellitus,

with or without underlying CKD. Volume expansion, diuretic agents, vasoactive drugs (including dopamine and related compounds aimed to augment renal blood flow), growth factors, and antioxidants have been the most widely studied, with some clinical trials showing dramatic results: up to a 90% reduction in AKI incidence. However, there are numerous methodologic problems with many of these studies. First, the majority of cases of AKI cannot be anticipated, so that we cannot generalize results obtained in the setting of radiocontrast or antibiotic or chemotherapy exposure to the more common setting of AKI complicating multisystem disease. Second, virtually all prevention studies are underpowered, regardless of the result (89). Thus, our confidence in the results, either negative or positive, is limited. Until we can effectively identify truly high-risk (*e.g.*, ≥20% to 30% incidence of clinically meaningful AKI) subjects, probably using a combination of clinical risk factors and one or more biomarkers (Availability of Multiple Biomarkers), our attention should be focused on studies aimed to reduce the consequences of established AKI.

Treatment of Established AKI

Clinical trials of pharmacologic therapies for established AKI have been uniformly negative to date. These have included reasonably well-designed and executed trials of atrial natiuretic peptide (90) and insulin-like growth factor-1 (91). One of the major design issues with these trials has been delayed enrollment long after the onset of kidney injury. For example, in the Auriculin Anaritide Acute Renal Failure study of atrial natiuretic peptide, the mean SCr at enrollment was greater than 4.5 mg/dl. This delay in study enrollment is likely attributable to our currently limited armamentarium of biomarkers for AKI; SCr, as has been discussed, is a marker of GFR rather than injury *per se* and therefore reflects severe and established injury.

Several clinical trials have focused on established and severe AKI, such as diuretics to attenuate renal injury and variations in dialysis prescription to improve renal recovery and overall survival. However, it is clear from recent epidemiology studies that even mild AKI is important clinically and that not all individuals with mild AKI progress to severe disease. Other markers of GFR (*e.g.*, cystatin C) or biomarkers of kidney injury and recovery may prove to be predictive tools in the much larger number of individuals with early or less severe AKI and allow for rigorously designed therapeutic trials.

Conclusion

AKI is an increasingly common and potentially catastrophic complication in hospitalized patients. Our understanding of the incidence and consequences of AKI has grown considerably, yet mortality rates remain unacceptably high despite significant advances in the care of the critically ill. The diagnostic approach to AKI has stagnated and rests today on the same biomarkers (BUN, creatinine) used for several decades. To improve the identification of patients at risk of AKI and their care in the years to come, novel approaches for early diagnosis and risk stratification are needed. Prevention and treatment strategies for AKI will be facilitated by ongoing basic and clinical science investigations in this critical field.

Disclosures

None.

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