KDIGO CLINICAL PRACTICE GUIDELINE FOR ACUTE KIDNEY INJURY

Online Appendices A-F
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ABBREVIATIONS AND ACRONYMS

ACCP	American College of Chest Physicians
ACE-I	Angiotensin-converting enzyme inhibitor(s)
AKD	Acute kidney diseases and disorders
AKI	Acute kidney injury
AKIN	Acute Kidney Injury Network
ARB	Angiotensin-receptor blocker(s)
ARF	Acute renal failure
ATN	Acute tubular necrosis
AUC	Area under receiver-operator characteristic curve
BUN	Blood urea nitrogen
CI-AKI	Contrast-induced acute kidney injury
CKD	Chronic kidney disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CRRT	Continuous renal replacement therapy
CSA-AKI	Cardiac surgery-associated acute kidney injury
CT	Computed tomography
CVP	Central venous pressure
eGFR	Estimated glomerular filtration rate
ERT	Evidence Review Team
ESRD	End-stage renal disease
FE	Fractional excretion
GFR	Glomerular filtration rate
HF	Hemofiltration
HGF	Hepatocyte growth factor
HIV	Human immunodeficiency virus
HR	Hazard ratio
ICU	Intensive-care unit
IHD	Intermittent hemodialysis
IL	Interleukin
KDIGO	Kidney Disease: Improving Global Outcomes
KIM-1	Kidney injury molecule 1
L-FABP	L-type fatty acid binding protein
LOS	Length of stay
MDRD	Modification of Diet in Renal Disease
MI	Myocardial infarction
MRA	Magnetic resonance angiography
MRI	Magnetic resonance imaging
NAG	*N*-acetyl-beta-D-glucosaminidase
NKD	No known kidney disease
NKF	National Kidney Foundation
NSF	Nephrogenic Systemic Fibrosis
OR	Odds ratio
PET	Positron emission tomography
RCT	Randomized controlled trial
RIFLE	Risk, Injury, Failure; Loss, End-Stage Renal Disease
RR	Relative risk
RRT	Renal replacement therapy
SCr	Serum creatinine
SLED	Sustained low-efficiency dialysis

SRI	Simplified renal index
TCC	Tunneled cuffed catheter
TNF	Tumor necrosis factor
VEGF	Vascular endothelial growth factor

APPENDIX A: BACKGROUND

Acute and Chronic Kidney Disease

In principle, acute kidney injury (AKI) is one of a number of conditions that acutely affects kidney structure and function. For simplicity, we refer to these conditions as acute kidney diseases and disorders (AKD), in contrast to chronic kidney disease (CKD), and illustrate the relationship of AKI, AKD, and CKD in Figure 1. Whereas CKD has a well-established conceptual model and definition that has been useful in clinical medicine, research, and public health,[1-3] the definition for AKI is evolving, and the concept of AKD is relatively new. A conceptual model and definition of AKI and AKD could also be useful. This diagram has implications for the definitions of AKI and AKD. First, AKI is a subset of AKD. Thus, the definition for AKD must include the criteria included for the definition for AKI as well as other criteria. Second, AKI and AKD can occur in patients with CKD. Thus, the definitions for AKI and AKD must include criteria that enable the diagnosis to be made in patients with pre-existing CKD. This guideline includes a conceptual model and definition of AKI (Chapter 2.1) as well as an operational definition of AKD for use in the diagnosis of AKI (Appendix B).

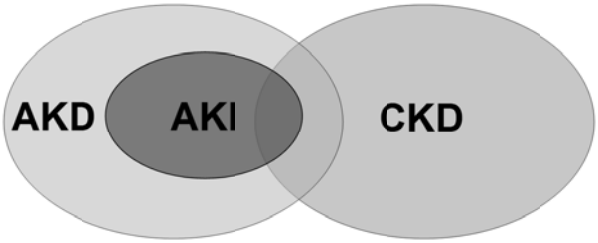


Figure 1. Conceptual model for integration of AKI, CKD, and AKD.

Overlapping ovals show the relationships among AKI, AKD, and CKD. AKI is a subset of AKD. Both AKI and AKD without AKI can be superimposed upon CKD. Individuals without AKI, AKD, or CKD have no known kidney disease (NKD), not shown here. AKD, acute kidney diseases and disorders; AKI, acute kidney injury; CKD, chronic kidney disease.

Conceptual Model of AKI

The current conceptual model of AKI was introduced at the Acute Kidney Injury Network (AKIN) conference in Vancouver in 2006 (Figure 2),[4] and is analogous to the conceptual model of CKD.[1] This model is also applicable to AKD. Circles on the horizontal axis depict stages in the development (left to right) and recovery (right to left) of AKI. AKI (in red) is defined as reduction in kidney function, including decreased glomerular filtration rate (GFR) and kidney failure. The criteria for the diagnosis of AKI and the stage of severity of AKI are based on changes in serum creatinine (SCr) and urine output as depicted in the triangle above the circles. Kidney failure is a stage of AKI highlighted here because of its clinical importance. Kidney failure is defined as a GFR <15 ml/min per 1.73 m^2 body surface area or requirement for renal replacement therapy (RRT), although it is recognized that RRT may be required earlier in the evolution of AKI.

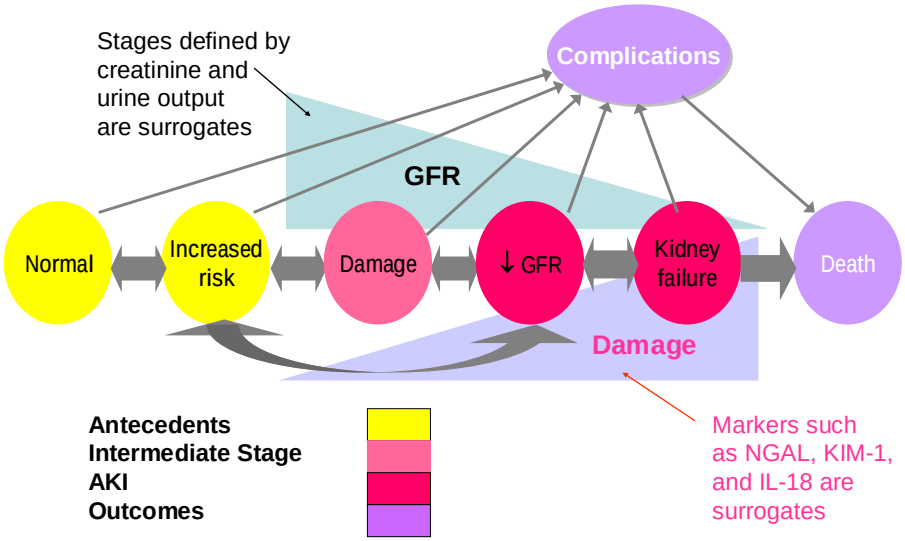


Figure 2. Conceptual models for AKI.

Red circles represent stages of AKI. Yellow circles represent potential antecedents of AKI, and the pink circle represents an intermediate stage (not yet defined). Thick arrows between circles represent risk factors associated with the initiation and progression of disease that can be affected or detected by interventions. Purple circles represent outcomes of AKI. "Complications" refers to all complications of AKI, including efforts at prevention and treatment, and complications in other organ systems. Adapted with permission from American Society of Nephrology[4] conveyed through Copyright Clearance Center, Inc.

Kidney damage (in pink) refers to an intermediate stage of early subclinical pathology or alterations in function other than GFR. The curved arrow indicates that this stage may occur in some, but not all, patients. In principle, markers reflect the severity of structural impairment, which increases in number and severity with increased severity of AKI. The stage of damage is emphasized because of the importance of ongoing research to identify earlier manifestations of AKI, including traditional markers of kidney damage (e.g., urine chemistries, microscopy),[5] and emerging markers.[6-10]

Antecedents (in yellow) of AKI include increased risk in certain patient groups. Patients are at increased risk as a result of *exposure factors* to a variety of known and unknown factors that are capable of directly initiating kidney damage or decreasing GFR, or *susceptibility factors* that affect the outcome after exposure to an initiation factor. In some cases, susceptibility factors represent a continuum of normal, e.g., those with older age. Patients with failure of organs other than the kidneys would represent another high-risk group for AKI.

Outcomes (in purple) of AKI include fatal or nonfatal complications in organ systems other than kidneys, or death from kidney failure. Complications may occur from AKI or its treatment, or from attempts at treatment or prevention in patients at increased risk. Nonrenal outcome factors affect the development, severity, and resolution of complications in other organ systems (including multisystem organ failure). It has long been recognized that AKI is associated with increased mortality; there is increasing evidence that AKI also leads to distant organ injury (e.g., lung, heart, gut), and *vice versa*. Death specifically limits the utility of using

solely kidney disease end-points to study the effects of AKI, because nonsurviving patients are censored from further study.

Horizontal arrows between stages represent risk factors for development or recovery of AKI. Development and progression of AKI are indicated by left-to-right arrows. Risk factors for *development* of AKI include *exposures* and *susceptibility factors*, as discussed above. *Progression factors* increase the risk for progression from damage to AKI and development of higher stages of AKI, including kidney failure. Conversely, recovery of AKI is signified by reverse arrows, right to left. The nomenclature for *recovery factors* is still undefined. Recovery of AKI may be complete, partial, or absent. Kidney failure for >3 months is chronic kidney failure and, in the USA, satisfies conditions for the designation of end-stage renal disease (ESRD). GFR <60 ml/min per 1.73 m^2 or kidney damage for ≥3 months is defined as CKD. AKI that leads to CKD (including ESRD) is an increasingly recognized phenomenon.[11, 12]

The proposed model also encompasses the concept of prerenal azotemia: GFR decrease without kidney damage (left-to- right curved arrow), with reversibility (right-to-left curved arrow). These pathways could also be used to define AKI caused by acute urinary tract obstruction with prompt relief. These concepts will be reevaluated as AKI biomarkers are developed and validated.

Level of GFR and Increase in SCr

Figure 3 shows factors affecting SCr, including GFR and other physiologic process (non-GFR determinants), including creatinine generation by muscle catabolism and diet, renal tubular secretion of creatinine, extrarenal elimination by the gut, and the distribution volume of creatinine (not shown in the figure). The level of GFR can be estimated from SCr and other easily measured clinical variables that are surrogates for the unmeasured non-GFR determinants. Estimating equations are defined as regressions in which measured GFR is related to SCr and other variables, and provide more accurate GFR estimates than estimates from SCr alone. Estimating equations are developed in the steady state of creatinine balance when GFR and non-GFR determinants are stable; hence, GFR estimates are more accurate in the steady state.

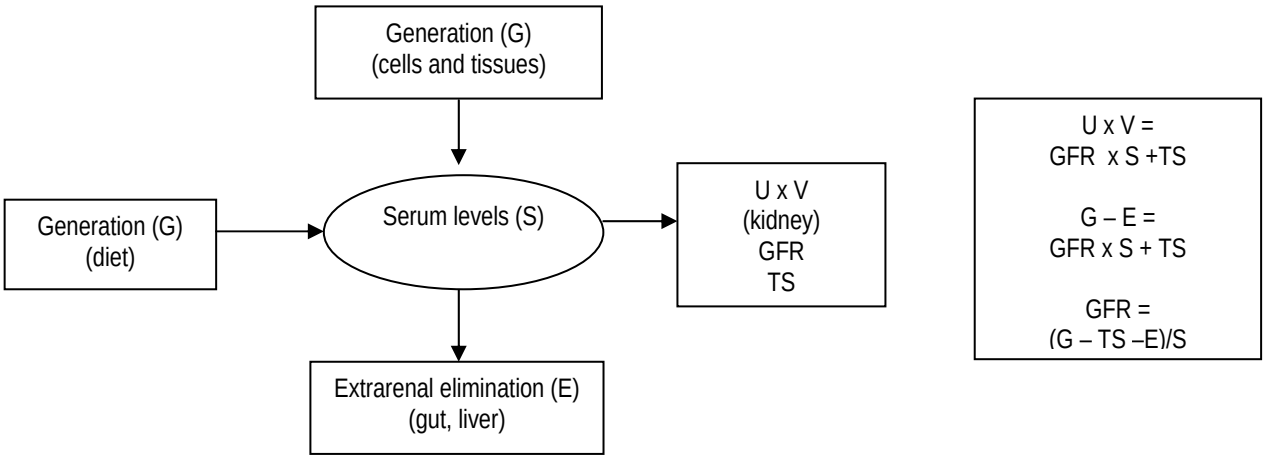


Figure 3. Determinants of the serum level of creatinine.

The serum level (S) of creatinine is determined by its generation (G) from cells (muscle) and diet (protein, especially cooked meat), extrarenal elimination (E) by the gut, and urinary excretion (U x V) by the kidney. Urinary excretion is the sum of filtered load (GFR X P) and tubular secretion (TS). In the steady state, urinary excretion equals generation and extrarenal elimination. By substitution and rearrangement, GFR can be expressed as the ratio of the non-GFR determinants (G, TS, and E) to the serum level. Adapted with permission from American Society of Nephrology[13] conveyed through Copyright Clearance Center, Inc.

Figure 4 shows the relationship between GFR, SCr, and GFR in the nonsteady state. Prior to a decrease in GFR, the filtered load of creatinine equals generation, leading to stable creatinine balance and SCr. Following a decrease in GFR, the reduction in creatinine filtration leads to a positive creatinine balance and a rising serum level until the filtered load once again equals generation, resulting in a new steady state. During the nonsteady state, when SCr is rising, estimated GFR overestimates measured GFR. In the new steady state, estimated GFR again approximates measured GFR. Conversely, after restoration of GFR (not shown), SCr decreases to its previous levels. While SCr is decreasing, estimated GFR underestimates measured GFR. When the new steady state is attained, estimated GFR again approximates measured GFR.

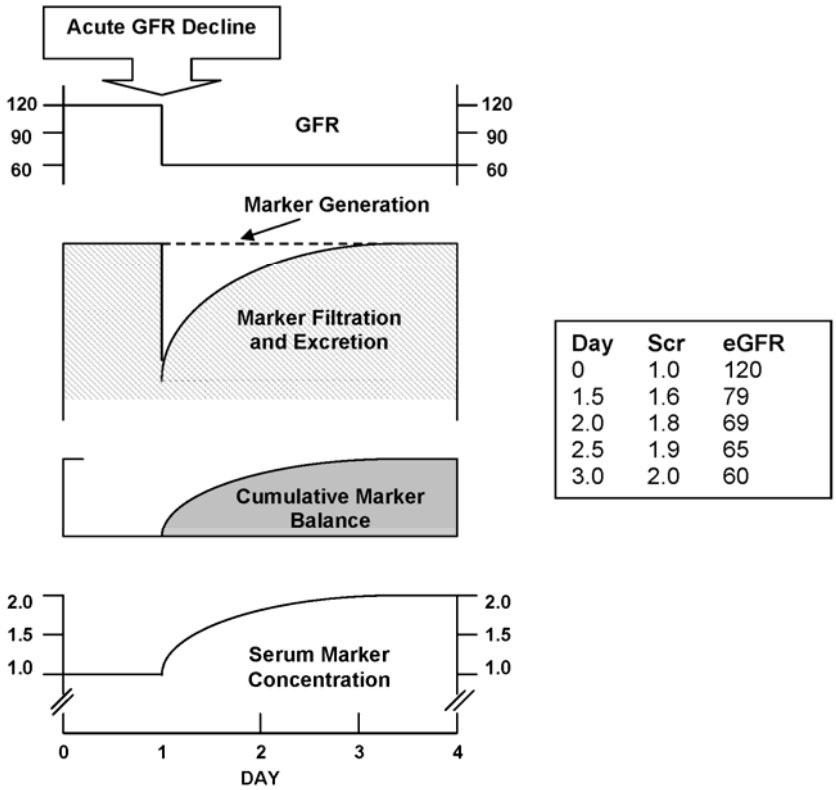


Figure 4. Effect of an acute GFR decline on generation, filtration, excretion, balance, and SCr (mg/dl).

After an acute GFR decline, generation of creatinine is unchanged, but filtration and excretion are reduced, resulting in retention of the marker (a rising positive balance) and a rising serum level (nonsteady state). During this time, estimated GFR (eGFR) is lower than measured GFR (mGFR). Although GFR remains reduced, the rise in serum level leads to an increase in filtered load (the product of GFR times the serum level) until filtration equals generation. At that time, cumulative balance and the plasma level plateau at a new steady state. In the new steady state, eGFR approximates mGFR. GFR expressed in units of ml/min per 1.73 m^2. Tubular secretion and extrarenal elimination are assumed to be zero. Adapted with permission from American Society of Nephrology[13] conveyed through Copyright Clearance Center, Inc.

As shown in Figure 4, there is an inverse relationship between GFR and SCr in the steady state. If the non-GFR determinants of SCr are constant, and the coefficient relating SCr to GFR is 1.0, then a 1.5-, 2.0-, and 3.0-fold increase in SCr would correspond to a decrease in GFR by 33%, 50%, and 67%, respectively. Using the Modification of Diet in Renal Disease (MDRD) Study equation, the coefficient relating SCr and GFR is –1.154, so a 1.5-, 2.0-, and 3.0-fold increase in SCr correspond to a decrease in GFR by 37%, 55%, and 72%, respectively. Using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation, the coefficient relating SCr to GFR is slightly more steep (–1.209) above SCr values of 0.9 mg/dl (79.6 µmol/l) in men and 0.7 mg/dl (61.9 µmol/l) in women, leading to higher estimated glomerular filtration rate (eGFR) values; a 1.5-, 2.0-, and 3.0-fold increase in SCr correspond to a decrease in GFR by 39%, 57%, and 74%, respectively. At SCr values <0.9 mg/dl (79.6 µmol/) in men and 0.7 mg/dl (61.9 µmol/l) in women, percent decrease in eGFR after an increase in SCr is lower.

Two limitations of this general approach are worth noting. First, theoretical models relating the rate of rise in SCr to decrease in GFR suggest that the empirical thresholds for stages of AKI do not represent unique reductions in the level of GFR in AKI.[14] More work will be necessary to determine the whether changes to the definition and thresholds given here would be more accurate compared to measured GFR or more predictive of adverse outcomes. Second, GFR estimates are likely to be less accurate in AKI than CKD, not only to considerations of the nonsteady state, as discussed above, but due to greater variability among patients and over time in the non-GFR determinants of SCr. GFR estimates have not been well studied in AKI, and we anticipate that they are likely to provide only a rough approximation of measured GFR. Nonetheless, they are likely to be a more accurate estimate of GFR than SCr alone, and it is useful to express SCr in GFR terms, especially in those with pre-existing CKD or in those who may develop CKD.

Epidemiology of AKI

The epidemiology of AKI is difficult to ascertain due to the differences in definitions and classifications and the patient populations studied, as mentioned above. The epidemiology of AKI is different whether it occurs in the general population, the hospitalized population, or in critically ill patients admitted to the intensive-care unit (ICU).

Community-acquired AKI

Hsu et al.[15] evaluated an adult cohort of beneficiaries of the health-care delivery system Kaiser Permanente of Northern California over an 8-year period from 1996 till 2003, and found that the use of acute RRT increased from 195 patients per million population per year (pmp/y) in the period 1996-1997 to 295 pmp/y in the period 2002-2003. In addition, the incidence is greater in men than in women (356 vs. 240 pmp/y in the period 2002-2003), and increases with age until the ninth decade (in the period 2002-2003, for patients <50 years: 103 pmp/y; patients 60-69 years: 815 pmp/y; patients 70-79 years: 1232 pmp/y; and patients 80-89 years: 625 pmp/y). Between the years 1996-2003, there was also an increased incidence of AKI not requiring dialysis from 323 to 522 per 100 000 person-years.

A good illustration of the importance of case mix and possibly local practice on the use of RRT can be seen when comparing three population studies performed in Scotland during more or less the same time period.[16-18] In a study covering a population of 523 000 in the Grampian region, Ali et al.[16] found an incidence of acute RRT of 183 pmp/y. Metcalfe et al.[17] covered 1 112 200 people in the Grampian, Highland, and Tayside regions and found an incidence of 203 pmp/y, while Prescott et al.[18] covered 5 054 800 people in the whole of Scotland and found an incidence of 286 pmp/y.

Ali et al.[16] reported a population incidence of AKI in Northern Scotland of 2147 per million population. Sepsis was a precipitating factor in 47% of patients. Risk, Injury, Failure; Loss, End-Stage Renal Disease (RIFLE) classification was useful for predicting recovery of renal function, requirement for RRT, length of hospital stay for survivors, and in-hospital mortality. Although no longer statistically significant, subjects with AKI had high mortality at 3 and 6 months as well. AKI, defined as an acute elevation in SCr occurring outside the hospital, was noted in about 1% of all hospital admissions. In a Spanish study the incidence of community-acquired AKI was 209 cases pmp/y.[19] De novo AKI in African Americans

occurred in 0.7% of all admissions over a 1-year period; community-acquired AKI was 3.5 times more frequent than hospital-acquired AKI in this series.[20]

Community-acquired AKI may also occur in massive disasters after earthquakes, war casualties, or other causes of crush syndromes.[21] In children postinfectious glomerulonephritis and, in particular, diarrhea-associated hemolytic-uremic syndrome are common causes of AKI. The latter occurred in 0.7 cases per 100 000 population per year in the UK.[22] In the developing world, herbs and infections remain the most common etiological factors in the medical subgroup of AKI.[23] AKI is a challenging problem in Africa because of the burden of disease (especially human immunodeficiency virus [HIV]-related AKI in sub-Saharan Africa, diarrheal disease, malaria, and potentially nephrotoxic traditional medicines, postobstetric and postsurgical complications, late presentation of patients to health-care facilities), and the lack of resources to support patients with established AKI in many countries. The pattern of AKI is vastly different from that in more developed countries and there are no reliable statistics about the incidence of AKI in Africa. AKI in hospitalized antiretroviral therapy–naive patients infected with HIV-1 is associated with a six-fold higher risk of in-hospital mortality.[23, 24] In Asia, infectious diarrheal diseases, malaria, leptospirosis, intravascular hemolysis due to G6PD-deficiency, snakebites, and insect stings constitute over 60% of AKI.[23, 25, 26] Nephrotoxicity caused by traditional medicines and accidental ingestion of toxic plants, but also accidental occupational exposure in industrial workplaces (e.g., chromic acid), or after suicidal or homicidal use (e.g., copper sulphate, ethylene dibromide, and ethylene glycol) is common.

There is little reliable information on the epidemiology of AKI in Latin America.[27] Transmissible diseases such as leptospirosis, malaria, dengue, diarrhea, among others, are recognized as important causes of AKI in these areas. On the other hand, in large cities and university hospitals in Latin American, the AKI spectrum is similar to that seen in developed countries.

Hospital-acquired AKI

The incidence of hospital-acquired AKI is about 5-10 times higher than that of community-acquired cases, despite the fact that all surveys of hospital-acquired AKI underestimate its true incidence. This underestimation is due to the fact that some cases (e.g., terminal patients) are not screened or referred for treatment for AKI. A study in the late 1970s that defined hospital-acquired AKI as an increase in SCr with respect to baseline values reported an incidence of 4.9%.[28] Two decades later, both incidence and prevalence had nearly doubled.[29] In both studies, patients with underlying CKD were approximately three times more likely to develop AKI than patients with normal renal function. In one assessment of 311 unselected hospitalized patients with AKI, only 22% were referred to a nephrologist. Referral rates were influenced by age and comorbidities of patients at presentation,[30] and by referral patterns to the site of care (e.g., district general hospital, tertiary referral center, general ICU, cardiothoracic ICU). In contrast with most ICU patients who suffer from acute tubular necrosis (ATN) in the setting of multiorgan failure, general hospital admissions will reflect the wider spectrum of AKI. The age profile, site of care and mortality rate of patients with isolated AKI differs from that of patients with AKI in the context of multiorgan failure, as does the etiology and pathophysiology of the condition in a comparative study between AKI patients admitted in the ICU and other settings.[31] For example, the ICU patients were younger, had more acute-on-

chronic renal failure, and had significantly more ATN than the non-ICU group. The causes of ATN were also different, with sepsis and postsurgical ATN being more frequent and nephrotoxic causes less frequent in the ICU patients, compared to the non-ICU population.

Liangos et al.[32] analyzed the 2001 National Hospital Discharge Survey, identifying patients with AKI on the basis of International Classification of Diseases, Ninth Revision (ICD-9) codes. Among the approximately 330 210 discharges included in the database, AKI was coded as a discharge diagnosis with a frequency of 19.2 per 1000 hospitalizations. This corresponds to an estimated 558 000 cases of AKI per year on the basis of a national estimate of slightly more than 29 million hospital discharges annually. Approximately 7.5% of patients with AKI were identified as requiring RRT. AKI was more commonly coded for in older patients; men; black individuals; and the setting of CKD, congestive heart failure, chronic lung disease, sepsis, and cardiac surgery.

Waikar et al.[33] evaluated the incidence of AKI using the 1988 to 2002 Nationwide Inpatient Sample, a USA-based administrative database, containing a representative sample of discharges from acute-care, nonfederal hospitals. The incidence of "coded" AKI rose from 61 per 100 000 population in 1988 to 288 per 100 000 population in 2002. For AKI requiring dialysis, the percentage of annual discharges increased from 0.03% in 1988 to 0.20% in 2002, translating to an increase in the incidence rate from 4 per 100 000 population in 1988 to 27 per 100 000 population in 2002.

There is also some evidence of an increased incidence of AKI over the last decade, particularly among older individuals. Data from hospitalized Medicare beneficiaries in the USA[34] (5 403 015 discharges between 1992 and 2001 from the 5% sample of Medicare claims) revealed that for 1992 to 2001, the overall incidence rate of AKI was 23.8 cases per 1000 discharges, with rates increasing by approximately 11% per year. Older age, male gender, and black race were strongly associated with AKI. Despite a shift in the etiology of hospital-acquired AKI over the past few decades, prerenal conditions manifesting as reduced rates of renal perfusion remain the leading cause (approximately 40% of cases). The incidence of postoperative AKI has decreased from 18% to 9%, and new etiologies—such as AIDS nephropathy, and AKI following liver, heart and bone marrow transplantation—have emerged. The trend in developed countries towards an increasing incidence of AKI in hospitalized patients has also been observed in emerging countries in Asia, Africa, and Latin America.[24, 27, 35, 36]

AKI in critically ill patients

Severe AKI requiring admission to an ICU occurs in 11 patients per 100 000 population per year and in these critically ill patients AKI occurs in up to 30% of all ICU admissions and is usually a manifestation of a multiorgan failure syndrome.[37] When the more "liberal" RIFLE definition is applied, approximately two-thirds of ICU patients develop an episode of acute kidney dysfunction. In a retrospective cohort study in seven intensive care units in a single tertiary-care academic center, the occurrence of AKI in 5383 critically ill patients admitted during a 1-year period was explored.[38] AKI occurred in a staggering 67% of patients, with 12% achieving a maximum class of R, 27% I, and 28% F. Of the 1510 patients who reached R, 56% progressed to either I or F. It is even possible that this high incidence is likely an underestimate due to the underreporting of terminal patients who are not considered for treatment for AKI.

The period prevalence of AKI in ICU patients was estimated in 23 countries and the differences in etiology, illness severity, and clinical practice were characterized. The impact of these differences on patient outcomes was also determined.[39] Between September 2000 and December 2001, a total of 29 269 critically ill patients were hospitalized in the participating ICUs of 54 hospitals across North and South America, Europe, Asia, and Australia. A case definition for AKI of a urine output <200 ml in 12 hours or a blood urea nitrogen (BUN) concentration of ≥84 mg/dl (30 mmol/l) was used. Of these critically ill patients admitted during the study period, 1738 (5.7%; 95% confidence interval [CI] 5.5-6.0%) had AKI during their ICU stay, including 1260 who were treated with RRT. The most common contributing factor to AKI was septic shock (47.5%; 95% CI 45.2-49.5%). Approximately 30% of patients had preadmission kidney dysfunction.

AKI occurs in approximately 20% of patients with bacteremia but increases to 50% of patients with concurrent septic shock.[40] Mortality in patients with sepsis-associated AKI (~70%) is greater than in patients with AKI unrelated to sepsis (~45%). In recent multicenter studies including more than 160 000 patients very similar results were found. First, Ostermann and Chang analyzed 41 972 patients admitted to 22 ICUs in the UK and Germany between 1989 and 1999 as part of the Riyadh Intensive Care Programme database.[41] AKI defined by RIFLE occurred in 15 019 (35.8%) patients: 7207 (17.2%) with R, 4613 (11%) I, and 3199 (7.6%) F. A recent analysis of the North East Italian Prospective Hospital Renal Outcome Survey on Acute Kidney Injury estimated the AKI incidence in 19 ICUs in northeastern Italy.[42] Of 2164 ICU patients who were admitted during the study period, 234 (10.8%; 95% CI 9.5-12.1%) developed AKI; 19% were classified as R, 35% I, and 46% F. Pre-existing kidney disease was present in 36.8%. The most common causes of AKI were prerenal causes (38.9%) and sepsis (25.6%).

More recently, Bagshaw et al. have reported on data from the Australian New Zealand Intensive Care Society Adult Patient Database.[43] They evaluated 120 123 patients admitted from 1 January 2000 to 31 December 2005 from 57 ICUs across Australia. RIFLE criteria for AKI on the day of admission occurred in 36.1% of patients with a maximum RIFLE category of R in 16.3%, I in 13.6%, and F in 6.3%. Taking these studies together, the ICU period prevalence of AKI of 36% would seem a reliable estimate. Uchino et al.[44] focused on the predictive ability of the RIFLE classification in a cohort of 20 126 patients admitted to a teaching hospital for >24 hours over a 3-year period. The authors used the electronic laboratory database to classify patients into RIFLE-R, I, and F, and followed them to hospital discharge or death. Nearly 10% of patients achieved a maximum RIFLE-R, 5% I, and 3.5% F. There was a nearly linear increase in hospital mortality with increasing RIFLE class, with patients at R having more than three times the mortality rate of patients without AKI. Patients with I had close to twice the mortality of R, and patients with F had 10 times the mortality rate of hospitalized patients without AKI. On performing multivariate logistic regression analysis to test whether RIFLE classification was an independent predictor of hospital mortality, the investigators found that class R carried an odds ratio (OR) of hospital mortality of 2.5, I of 5.4, and F of 10.1.

In conclusion, AKI is a prevalent problem and its incidence is clearly increasing both in the developed and developing world. More aggressive medical and surgical interventions in an

aging population that has more pre-existing comorbid conditions have altered the spectrum of AKI and explain the increasing incidence.[45]

Prognosis of AKI

AKI affects both short-term and long-term outcomes. AKI results in multiple-organ dysfunction and can complicate underlying disease. Emerging evidence suggests that CKD and cardiovascular disease may be accelerated by AKI.

Short-term prognosis of AKI

Waikar et al.[33] analyzed a large database of hospitalized patients, the National Inpatient Sample. This database is the largest all-payer administrative database of USA hospitalizations. Examining data from 1988 to 2002, they observed an increase in the percentage of annual discharges with AKI from 0.4% in 1988 to 2.1% in 2002. Correcting for census data, they estimated that the USA population-adjusted incidence of AKI increased from 61 per 100 000 population in 1988 to 288 per 100 000 population in 2002. When they limited the analysis to AKI that required RRT, the rates increased from 0.03% of hospital discharges in 1988 to 0.20% in 2002, corresponding to population-adjusted rates of 4 per 100 000 population in 1988 to 27 per 100 000 population in 2002.

The immediate outcomes in the international observational study in critically ill patients with AKI reported by Uchino et al.[39] were very poor. ICU mortality was 52%, with an additional 8% mortality in the hospital after ICU discharge, giving an overall hospital mortality of 60.3% (95% CI 58.0-62.6%). Dialysis dependence at hospital discharge was 13.8% (95% CI 11.2-16.3%) for survivors. As mentioned before, increasing RIFLE severity grades correspond with increasing mortality in these patients.[46, 47] In the single-center cohort study of Hoste et al.[38] patients with a maximum score of R had a mortality rate of 8.8%, compared to 11.4% for I, and 26.3% for F. On the other hand, patients who had no evidence of AKI had a mortality rate of 5.5%. Furthermore, RIFLE-I (hazard ratio of 1.4) and RIFLE-F (hazard ratio of 2.7) were independent predictors of hospital mortality after controlling for other variables known to predict outcome in critically ill patients. In the study by Ostermann and Chang,[41] hospital mortality rates were RIFLE-R 20.9%, I 45.6%, and F 56.8%, respectively, compared to 8.4% among patients without AKI. The independent risk factors for hospital mortality were age (OR 1.02); APACHE II score on admission to ICU (OR 1.10); presence of pre-existing ESRD (OR 1.17); mechanical ventilation (OR 1.52); RIFLE class R (OR 1.40), I (OR 1.96) and F (OR 1.59); maximum number of failed organs (OR 2.13); admission after emergency surgery (OR 3.08); and nonsurgical admission (OR 3.92). Interestingly, RRT for AKI was not an independent risk factor for hospital mortality. Also, in the study by Bagshaw et al.[43] AKI was associated with an increase in hospital mortality (OR 3.29, 95% CI 3.19-3.41; P <0.0001) and hospital mortality stratified by RIFLE category was 17.9% for R, 27.7% for I, and 33.2% for F. By multivariable analysis, each RIFLE category was independently associated with hospital mortality (OR: R 1.58, I 2.54, and F 3.22).

It is tempting to speculate that the significantly higher mortality rates in the first study by Uchino et al.[39] compared to the second[41] and the most recent one[43] reflect an improvement in outcome over the last years. However, it should be considered that the data in the first study

were collected 5-10 years earlier. In addition, given that these studies were conducted in very different places, it is difficult to conclude that mortality is decreasing.

By contrast, Ympa et al.[48] found that mortality of AKI patients treated with RRT remained more or less constant between the years 1970-2004. However, these findings are probably biased by the fact that the baseline characteristics of hospitalized patients have changed over the years. Patients treated more recently are more severely ill, older, and have more underlying disease. When corrected for severity of illness, age, and other organ dysfunctions, Desegher et al.[49] showed that, at least in a single ICU, outcomes following RRT have improved over a 10-year period.

Although mortality may have decreased, the 2001 National Hospital Discharge Survey found that AKI code was associated with an adjusted prolongation of hospital length of stay (LOS) by 2 days (P <0.001) and an adjusted OR of 4.1 for hospital mortality and of 2.0 for discharge to short- or long-term care facilities. In the USA at least the presence of an ICD-9-CM code for AKI in discharge records is associated with prolonged LOS, increased mortality, and, among survivors, a greater requirement for posthospitalization care. Overall, these findings suggest that AKI is associated with increased in-hospital and posthospitalization resource utilization. In the Medicare Sample Beneficiary Standard Analytical File for the years 1992 through 2001,[34] hospital mortality was 32.9% in patients who had AKI and required RRT and 27.5% in patients who had AKI and did not require RRT, as compared to 4.6% in patients without AKI. Mortality rates also were higher among patients in whom AKI was coded as a secondary diagnosis (32.6%) as compared to patients in whom AKI was the primary diagnosis (15.2%). AKI also was associated with an increased mortality in the first 90 days after hospital discharge (34.5%) as compared to patients who were discharged without an AKI diagnosis (13.1%). Although these results are very similar to those reported by Liangos et al. during this same period, these authors observed a decrease in hospital mortality from 40.4% in 1988 to 20.3% in 2002 for all patients with AKI and a corresponding decrease in mortality from 41.3% in 1988 to 28.1% in 2002 among patients who had AKI and required renal support. Adjusting for demographic factors, comorbidities, and other clinical parameters in a multivariable model, the OR for in-hospital mortality during the final 5-year interval (1998 to 2002) was 0.40, as compared to the preceding 5-year interval, for all patients with AKI and 0.47 for the subgroup of patients who required RRT. Despite the trend for lower mortality of AKI patients AKI is still an important negative prognostic factor, particularly in critically ill patients. So, the nephrological idiom that patients “die with AKI and not from AKI” certainly no longer holds true.

Long-term outcome of AKI: general outcome and renal recovery

The longer-term outcomes of AKI have been less well-characterized than hospital outcomes. Very recently, the relationship between long-term mortality and AKI, during hospitalization after various cardiothoracic surgery procedures between 1992 and 2002, was retrospectively analyzed.[50] AKI was defined by the RIFLE classification. Long-term survival up to 10 years after the AKI hospitalization was analyzed with a risk-adjusted Cox proportional hazards regression model. Survival was worse among patients with AKI and was proportional to its severity, with an adjusted hazard ratio (HR) of 1.23 (95% CI 1.06-1.42) for the least severe RIFLE R class and 2.14 (95% CI 1.73-2.66) for the RIFLE F class compared to patients without AKI. Remarkably, patients with complete renal recovery after AKI still had an

increased adjusted HR for death of 1.28 (95% CI 1.11-1.48) compared to patients without AKI. A similar analysis by the same group of authors, but focusing on patients with AKI after major surgery, confirmed that survival up to 5 years follow-up was worse among patients with AKI and was proportional to its severity with an adjusted HR of 1.18 (95% CI 1.08-1.29) for the RIFLE R class and 1.57 (95% CI 1.40-1.75) for the RIFLE F class, compared to patients without AKI (P <0.001). As in the cohort after postcardiac surgery also in this study, patients with complete renal recovery after AKI still had an increased adjusted HR for death of 1.20 (95% CI 1.10-1.31) compared to patients without AKI (P <0.001).

Coca et al.[12] published a systematic review of all evaluable studies regarding the long-term risk of adverse outcomes after AKI, summarizing the literature from 1985 to 2007. The investigators included all studies of survivors of AKI with at least a 6-month follow-up period and examined outcomes of mortality and the subsequent development of cardiovascular disease or CKD. Forty eight studies that contained a total of 47 017 participants were reviewed; 15 studies reported long-term data for patients without AKI. The incidence rate of mortality was 8.9 deaths per 100 person-years in survivors of AKI and 4.3 deaths per 100 person-years in survivors without AKI (rate ratio 2.59; 95% CI 1.97-3.42). AKI was associated independently with mortality risk in six of six studies that performed multivariate adjustment (adjusted rate ratio 1.6-3.9). Only two studies examined cardiovascular end points after AKI. At 1 year after AKI, 15.4% (56 of 377) of survivors of AKI and 7.0% (817 of 11 755) of survivors without AKI had a myocardial infarction (MI) (relative risk [RR] 2.05; 95% CI 1.61-2.61). One of the two studies examined the risk of MI at three points of follow-up (0.5, 1, and 5 years) and the increased risk of MI persisted over time (RR 1.6, 1.85, and 1.75 at each time, respectively). Studies published subsequently to the Coca review showed similar risk relationships (Table 1).

Few studies have evaluated long-term quality of life in survivors of AKI. Noble et al.[51] studied a cohort of 16 patients who had survived an episode of AKI and respiratory failure that required RRT. These 16 individuals were the survivors of an original cohort of 117 patients. Among this original cohort, 79.4% died before hospital discharge. Eight of the 24 patients who survived to hospital discharge subsequently died after a median of 5 years (range 6 months to 15 years). Quality of life was assessed using the SF-36 in 12 of the 16 surviving patients. Scores for overall physical health and seven of the eight domains (physical functioning, role physical, bodily pain, general health, vitality, social functioning, and role emotional) were significantly lower than population norms. Only the scores for overall mental health and the domain score for mental health were not significantly different from the general population. Although CKD is a widely known risk factor for AKI,[28, 52] until recently much less is known about clinical outcomes, especially long-term outcomes, among patients who have CKD and experience superimposed AKI (acute-on-chronic renal failure).

Table 1. Overview table of observational studies of AKI as a predictor for mortality

Citation	N	Population/Setting	Study design	Single/Multicenter	Relative risk RR or HR (95% CI)	Absolute risk
Arnaotakis[53] 2007 US	267 pts	Aortic arch surgery with deep hypothermic circulatory arrest	Retrospective	Single	Stage R vs. no AKI: nd Stage I vs. no AKI: nd Stage F vs. no AKI: nd	30 day Mortality Stage 0: 3% Stage R: 9% Stage I: 12% Stage F: 38%
Lopes[54] 2008 Portugal	82 pts	Haematopoietic cell transplantation	Retrospective	Single	Hazard Ratio for Mortality Stage R vs. no AKI: 1.62 (0.47-5.6) Stage I + Stage F vs. no AKI: 1.64 (1.06-2.54)	nd
Bihorac[55] 2009 US	10,518 pts	Discharged after a major surgery between 1992-2002. No history of CKD.	Retrospective	Multicenter	Hazard Ratio for Mortality Stage R vs. no AKI: 1.18 (1.08–1.29) Stage I vs. no AKI: 1.43 (1.29–1.59) Stage F vs. no AKI: 1.57 (1.40–1.75)	nd
Chen[56] 2009 Taiwan	121 pts	Sepsis patients from June 2003-January 2004	Retrospective	Single	OR (95% CI) No AKI: 1 Stage R: 1.330 (0.538-3.292) Stage I: 5.444 (1.692-17.519) Stage F: 6.319 (1.799-22.203)	In-hospital mortality No AKI: 34% Stage R: 40.6% Stage I: 73.7% Stage F: 76.5%
Perez Valdivieso[57] 2008 Spain	903 pts	Patients with nephrology consultation requested because of suspicion of AKI	Prospective	Single	Hazard Ratio for Mortality Stage R vs. no AKI: 5.08 (2.19–11.76) Stage I vs. no AKI: 7.64 (3.56–16.37) Stage F vs. no AKI: 10.57 (5.13–21.79)	In-hospital mortality, n (%) No AKI: 11 (4.2%) R: 23 (21%) I: 50 (27%) F: 116 (33%) (P <0.001 across all)
Bagshaw[58] 2008 Canada	9,449 pts	Critically ill trauma patients	Retrospective	Multicenter	Hospital Mortality Adjusted OR Stage R: 1.69 Stage I: 1.88 Stage F: 2.29 Crude OR Stage R: 2.25 (1.84-2.74) Stage I: 2.23 (1.78-2.78) Stage F: 3.86 (2.61-5.71)	In-hospital mortality No AKI: 8% Stage R: 16% Stage I: 16% Stage F: 25%
Daher[59] 2008 Brazil	722 pts	Patients with AKI admitted to an infectious diseases ICU	Retrospective	Single	OR for Hospital Mortality Stage I: 1.00 Stage F: 1.66 (0.34-817) Stage L: 4.70 (1.05-20.9)	In-hospital mortality Stage I: 38% Stage F: 50% Stage L: 74%
Cruz[42] 2007 Italy	2164 pts	ICU patients	Prospective	Single	OR for ICU mortality Stage I vs. R: 2.2 (0.8 to 6.0) Stage F vs. R: 4.8 (1.4 to 17.1)	ICU mortality Stage R: 20% Stage I: 29% Stage F: 50% (P= 0.001 across all)

Ali[16] 2007 UK	5321 pts	All patients with S_{Cr} >150 µmol/l [>1.7 mg/dl] (male) or >130 µmol/l [>1.47 mg/dl] (female) over a 6-mo period in 2003	Retrospective	Single	nd	AKI In hospital mortality Stage R: 28 (27%) Stage I: 71 (30%) Stage F: 56 (41%) (P=0.035 across all) 90 d mortality (n %) Stage R: 37 (35%) Stage I: 94 (40%) Stage F: 65 (48%) (P= 0.132 across all) 6-mo mortality (n %) Stage R: 48 (46%) Stage I: 112 (48%) Stage F: 76 (56%) (P= 0.224 across all) ACRF Group In-hospital mortality (n %) Stage R: 3 (25%) Stage I: 8 (44%) Stage F: 24 (41%) (P= 0.517 across all) 90 d mortality (n %) Stage R: 4 (33%) Stage I: 11 (61%) Stage F: 28 (48%) (P=0.325 across all) 6-mo mortality (n %) Stage R: 4 (33%) Stage I: 14 (78%) Stage F: 37 (64%) (P= 0.045 across all)

Macedo et al.[60] have reviewed the important topic of renal recovery after AKI and included studies on the epidemiology of recovery in their review up to 2008. The reviewers proposed that a standardized definition for renal recovery is needed; it appears further that the majority of studies addressing renal recovery includes only critically ill patients requiring dialysis and considers renal recovery as dialysis independency at hospital discharge. However, a significant proportion of AKI patients are not in the ICU, are not dialyzed, and may require alternate definitions for assessing renal recovery. Patients with incomplete renal recovery after AKI are probably underrepresented in most epidemiologic studies. The authors further discussed the emerging evidence that an AKI episode can lead to CKD and can accelerate the progression to ESRD. When risk factors for AKI are assessed, CKD is found to be a significant and consistent risk for the development of AKI.[61, 62] However, whether AKI causes CKD is unknown. As summarized,[63] early studies estimating long-term risk after an episode of AKI consisted of small prospective observational studies of incident patients with AKI. The studies consistently found a decrease in GFR months after the initial insult, even with full restoration of renal blood flow. The reduction in GFR was seldom less than 50 ml/min from baselines of about 100 ml/min and was therefore ignored, and the effect on long-term mortality was frequently underestimated. In the systematic review of Coca et al.,[12] the incidence rate of CKD after an episode of AKI was 7.8 events per 100 patient-years, and the rate of ESRD was 4.9 events per 100 patient-years. However, the authors pointed out that the RR for CKD and ESRD after AKI was unobtainable, because of lack of follow-up of appropriate controls without AKI.

The report by Wald et al.[64] provides valuable insights into the complex complications faced by survivors of an episode of severe AKI. Using linked administrative health databases covering the entire province of Ontario, Canada, the authors addressed the long-term risks of death and dialysis dependence among individuals who developed acute kidney injury requiring acute temporary dialysis during hospitalization. During a 10-year period between 1996 and 2006, they identified 18 551 individuals with AKI requiring dialysis, which corresponds to an approximate yearly incidence of 19 per 100 000 population—lower than the estimate of 24.4 per 100 000 population reported in Northern California between 1996 and 2003.[15] After excluding 3321 individuals who had previous AKI, dialysis, or kidney transplantation in the preceding 5 years, and 202 who had extreme lengths of hospital stay, the authors identified 15 028 patients with a first hospitalization for AKI requiring dialysis. More than 40% of these individuals died during hospitalization, in keeping with previous reports of the grave implications of severe AKI. Nearly half of these patients recovered kidney function for at least 30 days following hospitalization, attesting to the remarkable ability of the kidneys to repair and regenerate even after severe, dialysis-requiring injury. Another 23% of patients required further dialysis within 30 days of discharge, but it is not reported how many of those required chronic dialysis.

The final study cohort included 4066 survivors, 3769 (92.7%) of whom were matched to control patients and observed for a median of 3 years after discharge. Even among this selected cohort of survivors, mortality rates exceeded 10% per year. One of every 12 survivors of AKI requiring acute dialysis required subsequent initiation of chronic dialysis despite being dialysis-free at 30 days after discharge. These findings are noteworthy even without considering the next step in the analysis, which was to compare this incidence rate against that of matched individuals without AKI. From the perspective of a clinician caring for an individual with severe AKI, the findings by Wald et al. provide an important quantitative

estimate that can be shared with affected patients and their families: even in the best of circumstances—meaning survival during hospitalization and recovery of kidney function sufficient to stop dialysis for a month—there is almost a 10% chance of requiring chronic dialysis in the next few years.

As commented upon by Waikar and Winkelmayer,[65] the chronic dialysis incidence rate reported by Wald et al.[64] is 72 times higher than that reported for the general population in the USA in 2006 (366 per 1 million person-years).[66] This finding has important implications for the postdischarge care of patients successfully treated with acute temporary dialysis: follow-up care with a nephrologist for secondary prevention is absolutely necessary. These findings also highlight the magnitude of the problem of AKI as a cause of ESRD: extrapolating from the data of Wald et al., a rough estimate of the yearly incidence of ESRD due to AKI is 0.3 per 100 000 population, which is approximately one-third of the incidence of ESRD secondary to cystic kidney disease. The true magnitude is even higher because this estimate does not consider the 3481 individuals excluded from the final cohort due to the need for dialysis during the 30 days following hospitalization. If only 30% of those individuals developed ESRD by the definition used by Wald et al., then the yearly incidence would be 1.0 per 100 000, accounting for approximately 3% of the overall yearly incidence of ESRD in the USA.

Based on this analysis, Waikar and Winkelmayer[65] concluded that AKI is therefore a non-negligible cause of ESRD. Amdur et al.[67] used a United States Department of Veterans Affairs database to ascertain long-term renal function in 113 272 patients. Of these, 44 377 had established CKD and were analyzed separately. A cohort of 63 491 patients was hospitalized for acute MI or pneumonia and were designated as controls. The remaining 5404 patients had diagnostic codes indicating AKI or ATN. SCr, eGFR, and dates of death over a 75-month period were followed. Renal function deteriorated over time in all groups, but with significantly greater severity in those who had AKI and ATN compared to controls. Patients with AKI, especially those with ATN, were more likely than controls to enter Stage 4 CKD, but this entry time was similar to that of patients who initially had CKD. The risk of death was elevated in those with AKI and CKD compared to controls, after accounting for covariates. Relatively little is known about clinical outcomes, especially long-term outcomes, among patients who have CKD and experience superimposed AKI, previously called acute-on-chronic renal failure). Observational studies show that AKI superimposed on CKD leads to ESRD at a higher frequency than does AKI alone.[16, 34, 62]

Hsu et al.[68] recently tracked 39 805 members of an integrated health-care delivery system in northern California who were hospitalized during 1996 through 2003 and had prehospitalization eGFR <45 ml/min per 1.73 m^2. Superimposed AKI was defined as having both a peak inpatient SCr greater than the last outpatient SCr by ≥50% and receipt of acute dialysis. Overall, 26% of CKD patients who suffered superimposed AKI died during the index hospitalization. There was a high risk for developing ESRD within 30 days of hospital discharge that varied with preadmission renal function, being 42% among hospital survivors with baseline eGFR 30-44 ml/min per 1.73 m^2 and 63% among hospital survivors with baseline eGFR 15-29 ml/min per 1.73 m^2. Compared to patients who had CKD and did not experience superimposed AKI, those who did had a 30% higher long-term risk for death or ESRD. Thus, it appears, as evidenced by this large community-based cohort of patients with CKD, that an episode of superimposed dialysis-requiring AKI was associated with very high risk for

nonrecovery of renal function. Dialysis-requiring AKI also seemed to be an independent risk factor for long-term risk for death or ESRD.

Prognosis of AKI in geriatric and pediatric patients

Although it is well established that age is a major risk factor for developing AKI, it is not well known whether age is an important prognostic predictor for renal recovery after an episode of AKI. A systematic review and meta-analysis of studies published in English between 2000 and 2007 was performed.[69] Recovery of kidney function (defined as independence from dialysis therapy, decrease in SCr level to less than a defined threshold, or return to baseline kidney function in patients older or younger than 65 years) was analyzed. Overall, 31.3% of surviving elderly patients did not recover kidney function compared to 26% of younger patients (pooled RR 1.28; 95% CI 1.06-1.55; P <0.05). The increased risk of nonrecovery in the elderly remained greater in several subgroups examined through sensitivity analyses, including those stratified by type of dialysis support, time of assessment of recovery (short- vs. long-term), and definition of renal recovery.

There is thus impaired recovery of kidney function after AKI in aged individuals. And "age" should be cognizant as a potential effect modifier in the prognosis after AKI. In a pediatric patient population, Askenazi et al.[70] reported on the 3- to 5-year longitudinal follow-up of 245 children who had AKI and were treated at the Texas Children's Hospital between January 1998 and June 2001. A total of 174 (71%) survived to hospital discharge. An additional 32 children died after discharge and 16 were dialysis-dependent long-term, leaving 126 potential pediatric participants. Among this population, only 29 could be located and evaluated, 17 (59%) of whom had at least one sign of kidney injury, including microalbuminuria, hyperfiltration, decreased GFR, and hypertension. Thus, also in the pediatric population, survivors of AKI have high risks for ongoing kidney injury and require long-term follow-up.

Although the data derived from large databases are thus very suggestive for the thesis that AKI is one of the "new" causes of ESRD, this area of research still presents several methodological challenges that have not been sufficiently discussed in the literature. These are related to the current consensus definitions of AKI; the determination of "baseline" kidney function before the AKI episode; and the possibility that observed associations between AKI and future adverse events are confounded by differences in the severity of baseline CKD.[71, 72] To help fill this major gap in knowledge, the National Institutes of Health recently sponsored an Acute Kidney Injury Natural History Consortium to directly address this issue (http://grants.nih.gov/ grants/guide/rfa-files/RFA-DK-07-009.html).[72]

Cost of AKI

Korkella et al.[73] retrospectively not only assessed the long-term outcome of patients requiring RRT in terms of 6-month and 5-year mortality, but also the quality of life and costs of intensive care in these patients. Mortality in the ICU and in the hospital was 34% and 45%, respectively. Mortality was 55% at 6 months and 65% at 5 years. Kidney function recovered in 82% of the survivors during hospitalization. Loss of energy and limitations of physical mobility assessed by Nottingham Health Profile were the most frequently reported complaints

at 6 months. Functional ability, as assessed by the Activities of Daily Living score, was fairly good at 6 months. The cost per AKI 6-month survivor was calculated to be $80 000.

Manns et al.[74] estimated the cost of continuous renal replacement therapy (CRRT) and intermittent hemodialysis (IHD) in the ICU and explored the impact of renal recovery on subsequent clinical outcomes and costs among AKI survivors. The patient cohort included all patients who developed AKI and required dialysis between April 1, 1996, and March 31, 1999. The cost of performing CRRT ranged from Canadian $3486 to Canadian $5117 per week, depending on the modality and the anticoagulant used, and it was significantly more expensive than IHD (Canadian $1342 per week). Survivors with renal recovery spent significantly fewer days in hospital (11.3 vs. 22.5 days; P <0.001) and incurred less health-care costs (Canadian $11 192 vs. $73 273; P <0.001) over the year after hospital discharge compared to survivors who remained on dialysis.

More recently costs, resource use, and mortality rate of patients who developed AKI following cardiac surgery and classified according to the RIFLE criteria were determined.[75] Total and departmental level costs, LOS, and requirement for RRT were higher in AKI patients compared to controls. Statistically significant differences in all costs, mortality rate, and requirement for RRT were seen in the patients stratified into RIFLE classes R, I, and F. Even patients with class R had a 2.2-fold greater mortality, a 1.6-fold increase in ICU LOS, and 1.6-fold increase in total postoperative costs compared to controls. It was concluded overall that costs, LOS, and mortality are higher in postoperative cardiac surgery patients who develop AKI, using RIFLE criteria, and that these values increase as AKI severity worsens.

An additional study, using hospital case-mix data sets from 23 hospitals as reported by the Massachusetts Division of Health Care Finance and Policy during 1999 and 2000, attempted to analyze the costs and LOS of “uncomplicated” AKI, defined as AKI not associated with nonrenal organ failure.[76, 77] The patient cohort in this study was restricted to 2252 adults whose principle hospital diagnosis was AKI and who did not receive care in an ICU or require mechanical ventilation. Patients with uncomplicated AKI incurred median direct hospital costs of $2600, had a median hospital LOS of 5 days, and had a hospital mortality rate of 8%. These values all were greater than those associated with hospitalizations for heart failure, pneumonia, gastrointestinal hemorrhage, cellulitis, or bronchitis and asthma, and were exceeded only by hospitalizations for circulatory disorders with acute MI and complications (direct hospital cost $3600; LOS 5 days; mortality 24%) and cerebrovascular disorders except transient ischemic attack (direct hospital cost $2700; LOS 4 days; mortality 11%).

Summary

From this literature survey, it is clear that the incidence of AKI is high in the community as well as the hospitalized population. In particular, critically ill patients very frequently develop AKI in as part of the multiorgan failure syndrome. Based on large data sets, this incidence is increasing over the last decades.

The immediate and long-term prognosis depends on a number of both patient and nonpatient-related factors. Recent analysis strongly suggests that the renal prognosis of AKI is not “an all or none” phenomenon. Recovery of kidney function is often suboptimal and may

lead to progression to severe CKD and even ESRD, in particular when acute-on-chronic kidney injury occurs. Finally, the costs of management of AKI patients are very high.

APPENDIX B: DIAGNOSTIC APPROACH TO ALTERATIONS IN KIDNEY FUNCTION AND STRUCTURE (SUPPLEMENTARY MATERIAL)

This chapter provides supplementary material on the systematic diagnostic approach to alterations in kidney function and structure based on the conceptual models of AKI and CKD.

Similarities between AKI and CKD

The conceptual models and definitions for AKI and CKD have many similarities.[1, 2, 4] Both conditions are characterized primarily by decreased kidney function, which can lead to kidney failure and death, as well as fatal and nonfatal complications in other organ systems. In both conditions, decreased kidney function may be preceded by kidney damage. However, the current state of knowledge of markers of kidney damage is limited, especially for AKI, and in many patients, the conditions are diagnosed solely by decreased GFR.

Both conditions are common, harmful, and treatable, and—to a certain extent—preventable. The risk profile for both conditions is similar, including individuals of older age with underlying hypertension, diabetes, or other serious comorbid conditions, who are exposed to drugs with toxicity to the kidney, procedures, or systemic injury (see below).[1] Each condition appears to be a risk factor for the development of the other, and each condition appears to worsen the prognosis of the other. It has been known for many years that CKD is a risk factor for development of AKI.[28, 52] It has now been recognized that many patients with AKI do not fully recover kidney function after an episode of AKI, leading to CKD.[68] This may be especially important in patients with advanced CKD, in whom an episode of AKI may lead to chronic renal failure, requiring dialysis and transplantation (ESRD).

Both AKI and CKD are defined according to a time course. For AKI, the time course relates to the interval over which the condition evolves: an increase in SCr over 2-7 days (see Chapters 2.1 and 2.4). Conditions which evolve more slowly do not meet this definition. For CKD, the time course relates to the interval over which the condition must persist: kidney damage or decreased GFR for more than 3 months.[1, 2] Conditions which have not persisted for this long do not meet this definition.

Definitions of AKI, CKD and AKD

AKI and CKD were defined by separate work groups according to different criteria. The definition for each is based on alterations in kidney function or structure. AKI and CKD have many causes which may lead to alterations of kidney function and structure that do not meet the criteria for the definition of either AKI or CKD, yet patients with these diseases and disorders may need medical attention to restore kidney function and reverse damage to kidney structure to avoid adverse outcomes. A uniform and systematic nomenclature could enhance understanding and communication about these diseases and disorders, and lead to improved medical care, research, and public health. For these reasons, the Work Group proposed an operational definition for acute kidney diseases and disorders (AKD) to provide an integrated clinical approach to patients with abnormalities of kidney function and structure.

Table 2 compares the definitions for AKI, CKD, and AKD. We have also included an operational definition of "no known kidney disease" (NKD) for those who do not meet these criteria, with the understanding that clinical judgment is required to determine the extent of the evaluation that is necessary to assess kidney function and structure. In the following sections, we will elaborate on each component of these definitions.

Table 2. Definitions of AKI, CKD, and AKD

	Functional criteria	Structural criteria
AKI	Increase in SCr by 50% within 7 days, *OR* Increase in SCr by 0.3 mg/dl (26.5 µmol/l) within 2 days, *OR* Oliguria	No criteria
CKD	GFR <60 ml/min per 1.73 m^2 for >3 months	Kidney damage for >3 months
AKD	AKI, *OR* GFR <60 ml/min per 1.73 m^2 for <3 months, *OR* Decrease in GFR by ≥35% or increase in SCr by >50% for <3 months	Kidney damage for <3 months
NKD	GFR ≥60 ml/min per 1.73 m^2 Stable SCr	No damage

GFR assessed from measured or estimated GFR. Estimated GFR does not reflect measured GFR in AKI as accurately as in CKD. Kidney damage assessed by pathology, urine or blood markers, imaging, and—for CKD—presence of a kidney transplant. NKD indicates no functional or structural criteria according to the definitions for AKI, AKD, or CKD. Clinical judgment is required for individual patient decision-making regarding the extent of evaluation that is necessary to assess kidney function and structure.

AKD, acute kidney diseases and disorders; AKI, acute kidney injury; CKD, chronic kidney disease; GFR, glomerular filtration rate; NKD, no known kidney disease; SCr, serum creatinine.

GFR and SCr

CKD, AKD, and AKI are defined by parameters expressing the level of kidney function. Table 3 gives examples of each condition based on GFR and different magnitudes of increase in SCr.

To illustrate the relationship of changes in SCr to changes in eGFR, we simulated changes in eGFR that would result from changes in SCr corresponding to the Kidney Disease: Improving Global Outcomes (KDIGO) definition of AKI in the CKD-EPI cohort. The CKD-EPI cohort includes subjects with a wide range of age and kidney function, including individuals with and without kidney disease, diabetes, and a history of solid-organ transplantations. In these individuals, GFR was measured using a standardized method, SCr was calibrated to standardized creatinine, and eGFR was computed using the MDRD Study equation for standardized SCr.[78, 79] Figure 5 shows the distribution of initial level of SCr, eGFR, and measured GFR, stratified according to eGFR. Figure 6 and Figure 7 show the distribution in eGFR that would result if SCr increased to levels that correspond to the KDIGO definition for AKI (see Chapter 2.1). Figure 6 shows an increase in SCr to 1.5, 2.0, and 3.0 times the initial level (corresponding to AKI Stages 1, 2, and 3, respectively). As mentioned earlier, these increases in SCr correspond to a decline in eGFR by 37%, 55%, and 72%, respectively. As expected, higher AKI stages are associated with greater changes in eGFR and lower final eGFR. For each AKI stage, changes in eGFR are larger in subjects with higher initial eGFR, while final eGFR is lower in subjects with lower baseline eGFR. Figure 7 shows an increase in SCr by 0.3 mg/dl (26.5 µmol/l) above the initial level. The percent reduction and

change in eGFR are greater in subjects with higher initial eGFR, while the final eGFR is lower in subjects with lower initial eGFR. Figure 8 shows the relationship of these changes in eGFR to the definition and stages of AKI. Not all patients with AKI would meet the eGFR criteria for the definition of AKD.

Table 3. Examples of AKI, CKD, and AKD based on GFR and increases in SCr

Baseline GFR (ml/min per 1.73 m^2)	Increase in SCr during 7 consecutive days	GFR during next 3 months	Diagnosis
≥60	>1.5 x	NA	AKI
≥60	<1.5 x	<60	AKD without AKI
≥60	<1.5 x	≥60	NKD
Baseline GFR (ml/min per 1.73 m^2)	**Change in SCr during next 7 days**	**GFR during 3 next months**	**Diagnosis**
<60	>1.5 x	NA	AKI + CKD
<60	<1.5 x	>35% decrease	AKD without AKI + CKD
<60	<1.5 x	<35% decrease	CKD

GFR assessed from measured or estimated GFR. Estimated GFR does not reflect measured GFR in AKI as accurately as in CKD.
AKD, acute kidney diseases and disorders; AKI, acute kidney injury; CKD, chronic kidney disease; GFR, glomerular filtration rate; NKD, no known kidney disease; SCr, serum creatinine.

GFR/SCr Algorithm

Figure 9 provides a diagnostic algorithm based on a sequential approach through three questions: i) Is GFR decreased or is SCr increased (according to the criteria in Table 3)?; ii) Is SCr increasing or GFR decreasing (according to the criteria in Table 3)?; and iii) Does the decrease in GFR or increase in SCr resolve within 3 months? Based on a "yes" or "no" response to these three sequential questions, all combinations of AKI, AKD, and CKD can be identified. In this section, we review the algorithm and illustrate its use for classification of patients with acute and chronic kidney disease in two previously reported cohorts.

The answer to Question 1 requires ascertainment of an index GFR/SCr as well during the prior 3 months. The index GFR/SCr can be assigned as any of the GFR/SCr measures during the interval of observation. The answer classifies patients into three categories: NKD, AKD, and CKD. Question 2 requires repeat ascertainment of kidney function after the index measure. "No" indicates that the increase in SCr or decrease in GFR after the index measure does not meet AKI or AKD criteria; "Yes-D" indicates that increase in SCr and decrease in GFR meets the AKD criteria but not AKI criteria; and "Yes-I" indicates that increase in SCr meets AKI criteria. Question 3 requires repeat ascertainment of GFR/SCr 3 months after the index measure. "Yes" indicates GFR >60, indicating NKD. No indicates GFR <60, and based on prior level of GFR, may indicate stable, new, or worse CKD.

The Grampian cohort is a population-based sample of patients with elevated SCr (>1.7 mg/dl [>150 µmol/l] in men or >1.5 mg/dl [>133 µmol/l] in women) in northeast Scotland.[16] Figure 10 shows the distribution of index SCr and corresponding eGFR computed using the MDRD Study equation. Figure 11 shows the classification of patients according to the KDIGO GFR/SCr algorithm. Based on the index SCr, 77% had CKD and 23% had AKD. Of those with

CKD, 3% had AKI superimposed upon CKD, 77% had CKD, and 20% did not have a follow-up SCr. Of those with presumed AKD, 29% had AKI, 34% had AKD without AKI, and 37% did not have a follow-up SCr. A 3- to 6-month follow up showed that 78% of those labeled AKD still had eGFR<60, indicating that they probably had CKD, and that the AKD episode was the first presentation. In the remaining 22%, impaired kidney function resolved, indicating that these patients probably had had a mild acute episode not satisfying the KDIGO criteria. Thus, in this clinical population with elevated index SCr, CKD appears to be more common than AKD; AKD without AKI and AKI appear to be approximately equally likely.

The University of Pittsburgh cohort, a subset of 943 ICU patients from a larger cohort,[38] includes consecutive patients with more than one SCr measurement and an ICU stay greater than 24 hours. In this subset, 346 patients (36.7%) had AKD using GFR criteria and 546 patients (57.9%) had AKI by SCr or urine output criteria. Eleven patients (1.1%) had AKD without AKI.

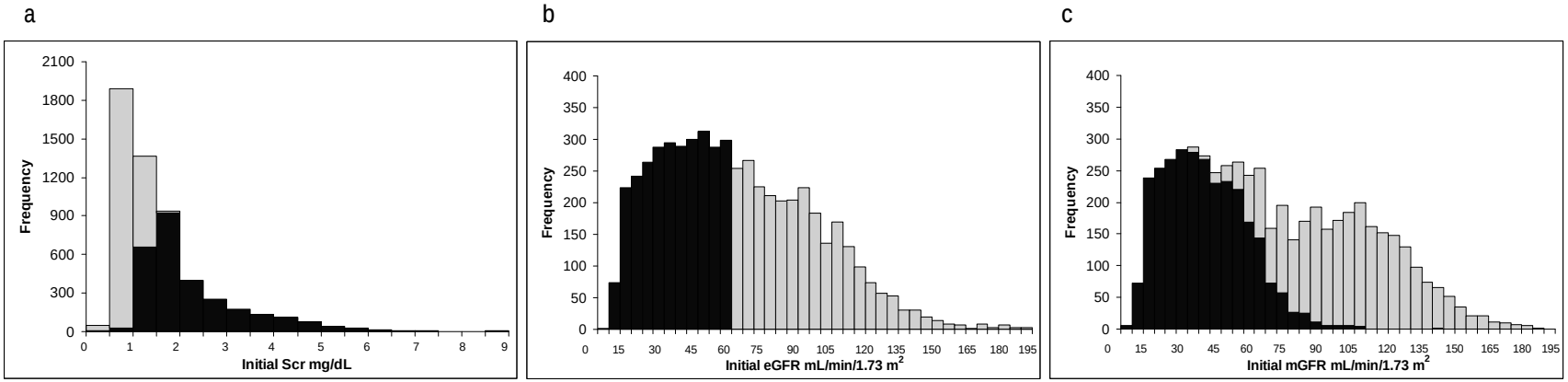


Figure 5. CKD-EPI cohort distribution of initial level of SCr, eGFR, and mGFR.

Light and dark bars indicate subjects with baseline eGFR ≥60 ml/min per 1.73 m^2 and eGFR <60 ml/min per 1.73 m^2, respectively (n = 5511). eGFR, estimated glomerular filtration rate; mGFR, measured glomerular filtration rate; SCr, serum creatinine. (Lesley Inker, personal communication).

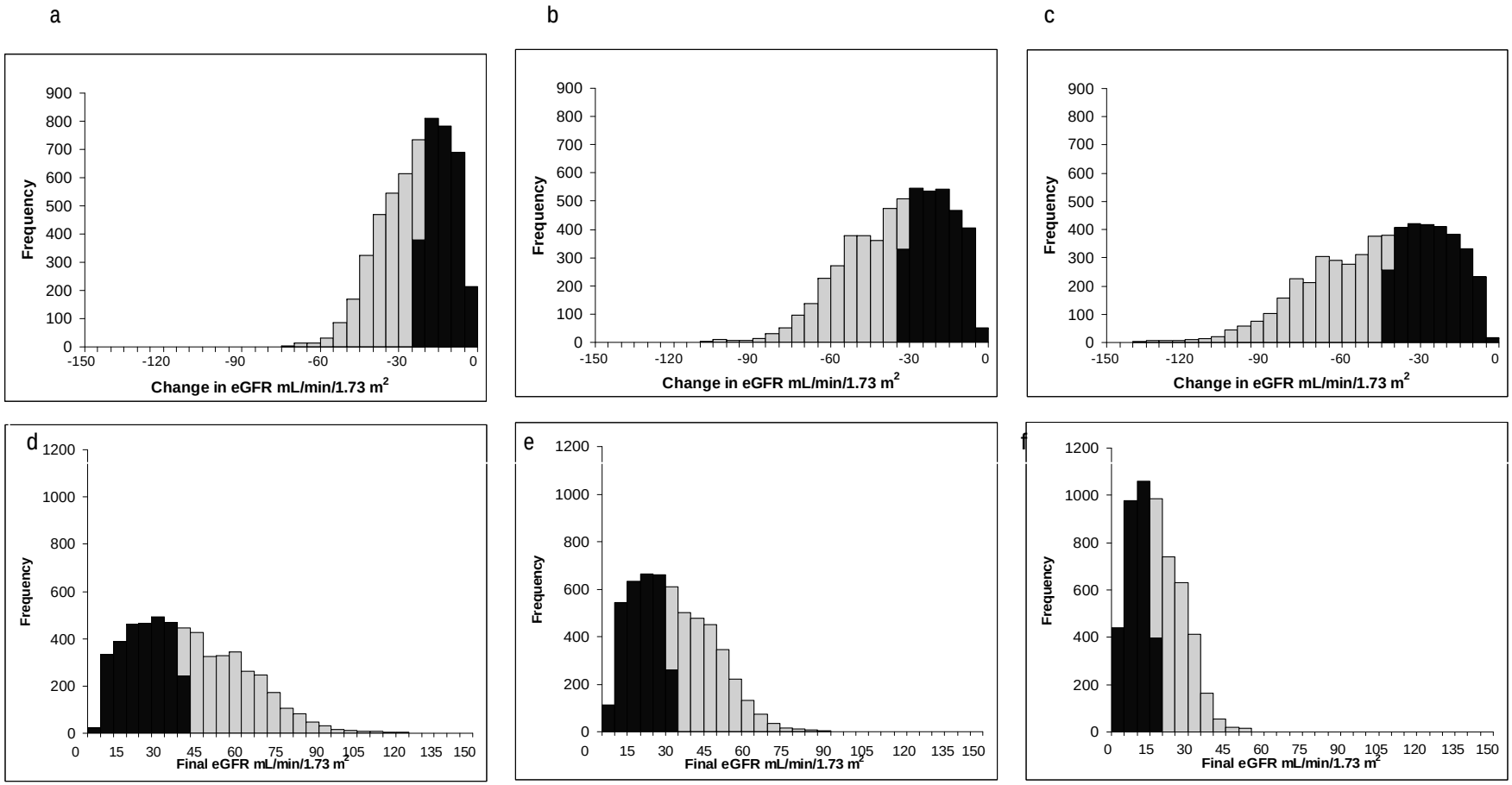


Figure 6. CKD-EPI cohort distribution in eGFR corresponding to increases in SCr to 1.5, 2.0, and 3.0 times the initial level.

Panels a, b and c show the distribution of changes in eGFR, while panels d, e and f show the distribution of final eGFR corresponding to changes in SCr to 1.5, 2.0, and 3.0 times the initial level, respectively. Light and dark bars indicate subjects with baseline eGFR ≥60 ml/min per 1.73 m^2 and eGFR <60 ml/min per 1.73 m^2, respectively (n = 5511). eGFR, estimated glomerular filtration rate; SCr, serum creatinine. (Lesley Inker, personal communication).

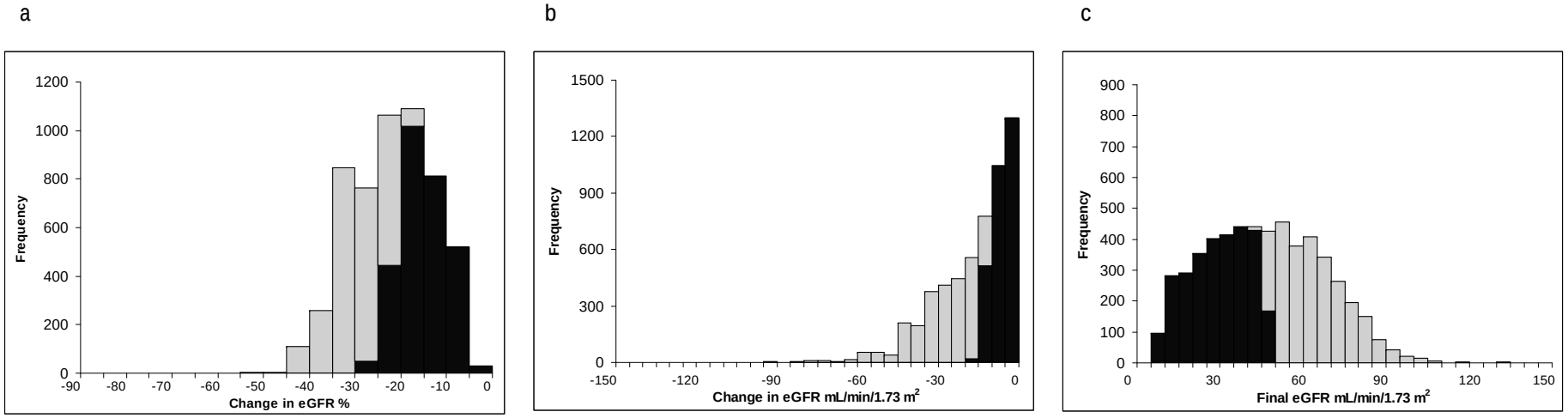
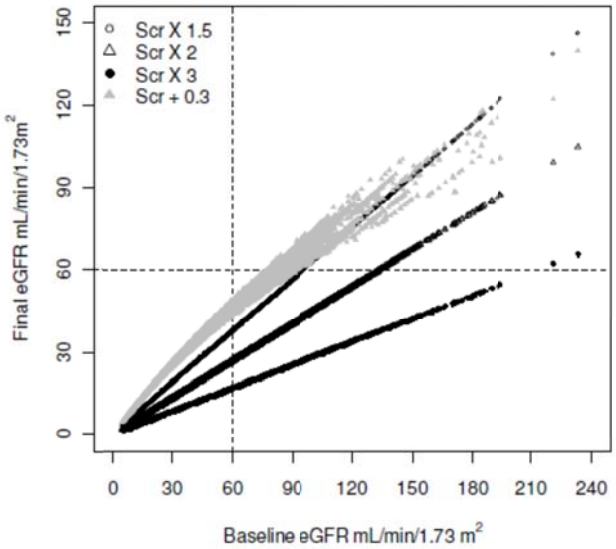
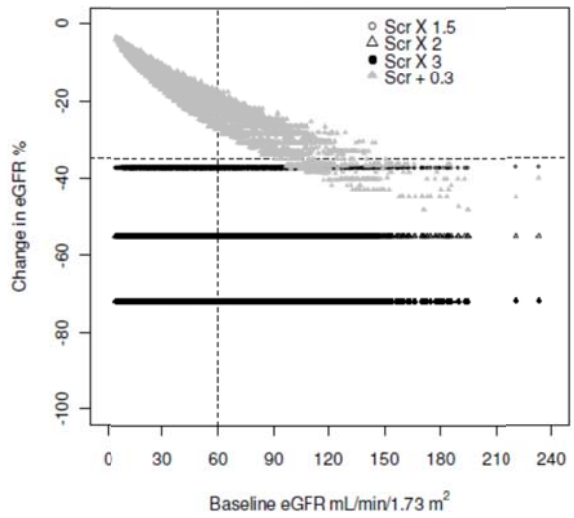


Figure 7. CKD-EPI cohort distribution in eGFR corresponding to an increase in SCr by 0.3 mg/dl (26.5 µmol/l) above the initial level.

Panel a shows the percent reduction in eGFR, panel b shows the change in eGFR, and panel c shows the final eGFR corresponding to increases in SCr by 0.3 mg/dl (26.5 µmol/l). Light and dark bars indicate subjects with baseline eGFR ≥60 ml/min per 1.73 m^2 and eGFR <60 ml/min per 1.73 m^2, respectively (n = 5511). eGFR, estimated glomerular filtration rate; SCr, serum creatinine. (Lesley Inker, personal communication).



a



b

Figure 8. CKD-EPI cohort changes in eGFR and final eGFR corresponding to KDIGO definition and stages of AKI.

Panels a and b show the final eGFR and the percent changes in eGFR, respectively, corresponding to the KDIGO definition and stages of AKI. The horizontal line in panel a and b indicates the threshold value for AKD (<60 ml/min per 1.73 m^2 and >35% reduction in initial GFR, respectively). Points above the horizontal line indicate subjects who meet the SCr criteria for the definition of AKI but do not meet eGFR criteria for the definition of AKD. AKD, acute kidney disorder/disease; AKI, acute kidney injury; eGFR, estimated glomerular filtration rate; KDIGO, Kidney Disease: Improving Global Outcomes; SCr, serum creatinine. (Lesley Inker, personal communication).

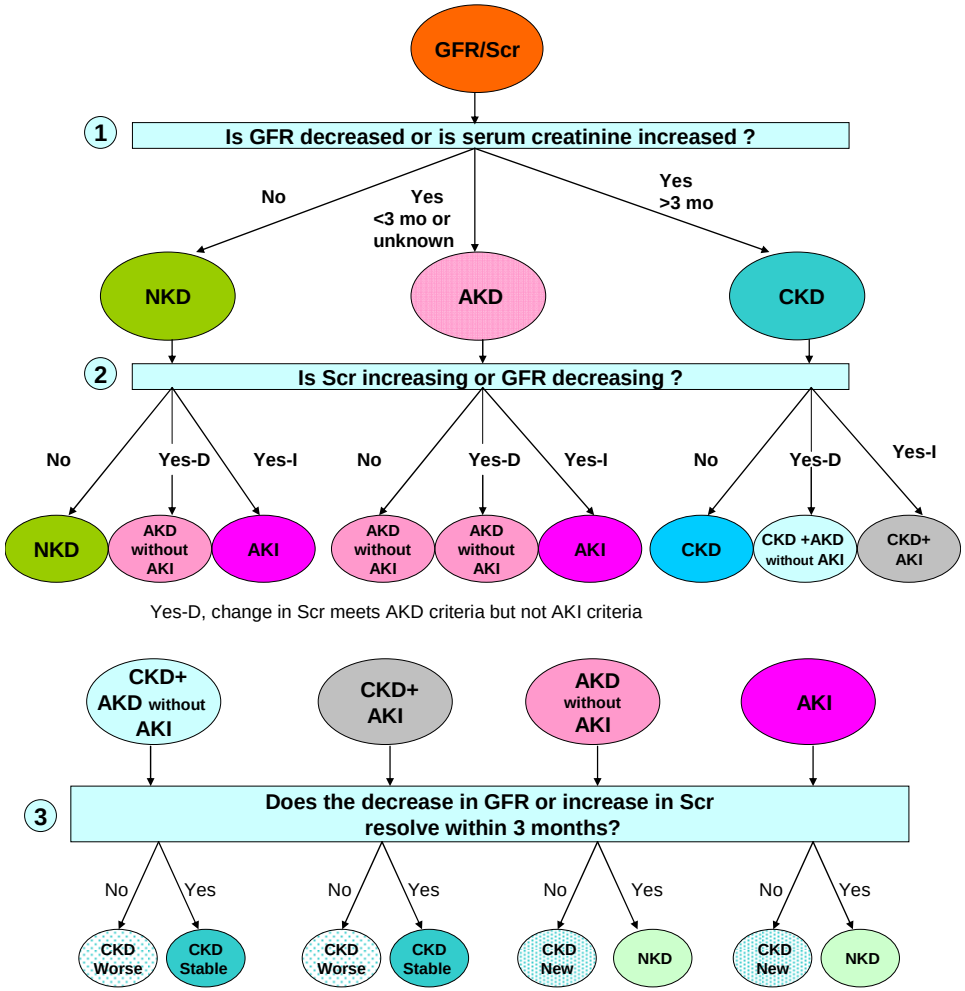


Figure 9. GFR/SCr algorithm.

See text for description. AKD, acute kidney disease/disorder; AKI, acute kidney injury; CKD, chronic kidney disease; GFR, glomerular filtration rate; NKD, no known kidney disease; SCr, serum creatinine.

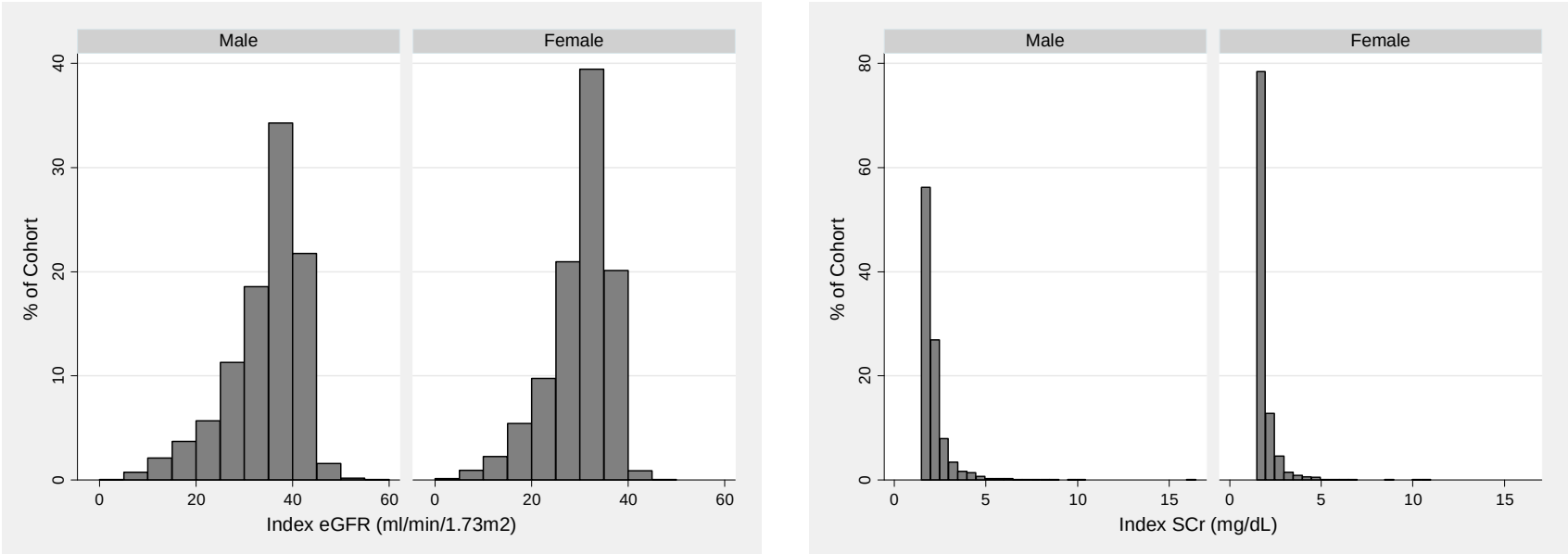


Figure 10. Grampian cohort distribution of index SCr and eGFR in men and women.
eGFR, estimated glomerular filtration rate; SCr, serum creatinine.

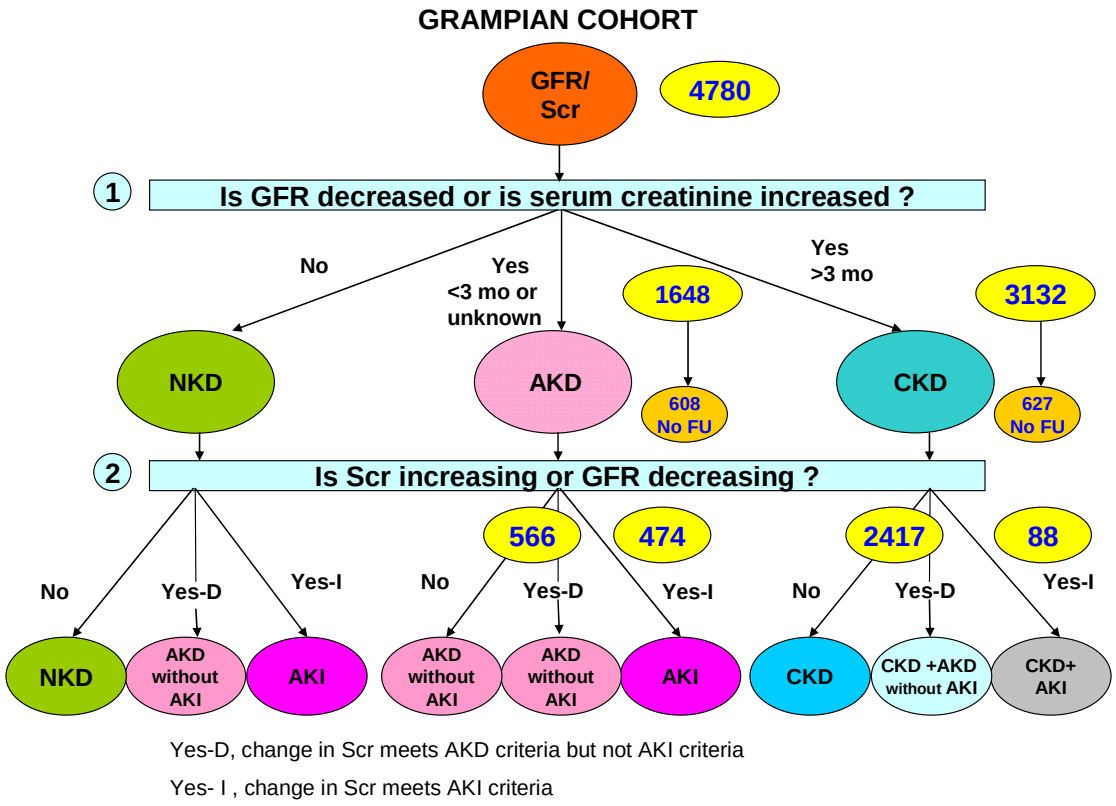


Figure 11. Grampian cohort classification according to KDIGO GFR/SCr algorithm.

Study sample includes patients with index SCr >1.7 mg/dl (>150 µmol/l) in men or >1.5 mg/dl (>133 µmol/l) in women in the Grampian region of Scotland. The number and proportion of patients with AKI, AKD, CKD and AKI superimposed on CKD are shown. Among 5321 with elevated index SCr in the original report, 430 were not included because baseline SCr was not available. Another 324 were excluded from 5321 as they were on long-term RRT, 202 were visitors with no further follow up and 15 were duplicates. KDIGO classification was applied retrospectively to groups of patients. AKD, acute kidney disease/disorder; AKI, acute kidney injury; CKD, chronic kidney disease; GFR, glomerular filtration rate; KDIGO, Kidney Disease: Improving Global Outcomes; NKD, no known kidney disease; RRT, renal replacement therapy; SCr, serum creatinine. (Alison MacLeod, personal communication).

Oliguria as a Measure of Kidney Function

Although urine flow rate is a poor measure of kidney function, oliguria generally reflects a decreased GFR. If GFR is normal (approximately 125 ml/min, corresponding to approximately 107 ml/kg/h for a 70-kg adult), then reduction in urine volume to <0.5 ml/kg/h would reflect reabsorption of more than 99.5% of glomerular filtrate. Such profound stimulation of tubular reabsorption usually accompanies circulatory disturbances associated with decreased GFR. Oliguria is unusual in the presence of a normal GFR and is usually associated with the non–steady state of solute balance and rising SCr sufficient to achieve the criteria for AKI. As a corollary, if GFR and SCr are normal and stable over an interval of 24 hours, it is generally not necessary to measure urine flow rate in order to assess kidney function.

In principle, oliguria (as defined by the criteria for AKI) can occur without a decrease in GFR. For example, low intake of fluid and solute could lead to urine volume of less than 0.5 ml/kg/h for 6 hours or 0.3 ml/kg/h for 24 hours. On the other hand, severe GFR reduction in CKD usually does not lead to oliguria until after the initiation of dialysis.

As described in Chapter 2.1, the thresholds for urine flow for the definition of AKI have been derived empirically and are less well substantiated than the thresholds for increase in SCr. Urinary diagnostic indices, such as the urinary concentrations of sodium and creatinine and the fractional reabsorption of sodium and urea, remain helpful to distinguish among causes of AKI, but are not used in the definition (see Chapter 2.4).

Kidney Damage

Table 4 describes measures of kidney damage in AKD and CKD. Kidney damage is most commonly ascertained by urinary markers and imaging studies. Most markers and abnormal images can indicate AKD or CKD, based on the duration of abnormality. One notable exception is small kidneys, either bilateral or unilateral, indicating CKD, which are discussed separately below. Kidney damage is not a criterion for AKI; however, it may be present. Renal tubular epithelial cells and coarse granular casts, often pigmented and described as “muddy brown”, remain helpful in distinguishing the cause of AKI, but are not part of the definition.

Small Kidneys as a Marker of Kidney Damage

Loss of renal cortex is considered a feature of CKD, and is often sought as a specific diagnostic sign of CKD. Kidney size is most often evaluated by ultrasound. The normal cortical thickness is approximately 3 cm, and normal adult kidney length is approximately 11-12 cm. Reduction in cortical thickness to less than 2 cm and kidney length to less than 9 cm is considered abnormal.[80]

Table 4. Markers of kidney damage in AKD and CKD

Markers	AKD	CKD
Pathology	X	X
Urinary markers		
RBC/casts	X	X
WBC/casts	X	X
RTE/casts	X	X
Fine and coarse granular casts	X	X
Proteinuria	X	X
Blood markers (tubular syndromes)	X	X
Imaging		
Large kidneys	X	X
Small kidneys	–	X
Size discrepancy	–	X
Hydronephrosis	X	X
Cysts	X	X
Stones	X	X
History of kidney transplantation	–	X

Kidney damage is not required for diagnosis of AKI. In the presence of AKI, findings of kidney damage do not indicate a separate diagnosis of AKD.

AKD, acute kidney diseases and disorders; CKD, chronic kidney disease; RBC, red blood cells; RTE, renal tubular epithelial cells; WBC, white blood cells.

Integrated Approach to AKI, AKD, and CKD

Clinical evaluation is necessary for all patients with alterations in kidney function or structure. The expectation of the Work Group is that the diagnostic approach will usually begin with assessment of GFR and SCr. However, evaluation of kidney function and structure is not complete unless markers of kidney damage—including urinalysis, examination of the urinary sediment, and imaging studies—have been performed. Table 5 shows a summary of the diagnostic approach using measures for kidney function and structure. Based on interpretation of each measure separately, the clinical diagnosis indicated by an "X" can be reached.

Table 5. Integrated approach to interpret measures of kidney function and structure for diagnosis of AKI, AKD, and CKD

Diagnosis	Measures			
	GFR/SCr	Oliguria	Kidney damage	Small kidneys
AKI	X	X		
AKD	X		X	
CKD	X	X	X	X

X indicates that the measures can contribute to the diagnosis indicated.

AKD, acute kidney diseases and disorders; AKI, acute kidney injury; CKD, chronic kidney disease.

RESEARCH RECOMMENDATIONS

- Studies are needed to investigate incidence, prevalence, risk factors, and outcomes for AKD in a variety of populations (Table 6).

Table 6. Research recommendations related to the definitions of AKI, AKD, and CKD

Population	Predictor (range, threshold)	Comparator	Outcomes (definition, metric, time point)	Study design
Various	AKI and CKD risk factors	No AKI or CKD risk factors	AKD prevalence	Cross-sectional
Various	AKI and CKD risk factors	No AKI or CKD risk factors	AKD incidence	Longitudinal (Cohort)
Various	AKD	Not AKD	AKI incidence, CKD incidence, Kidney failure incidence, death	Longitudinal (Cohort)

APPENDIX C: RISK DETERMINATION

The evaluation of factors which influence the development, course, and outcome of AKI, should be made at four levels: before a contemplated exposure, after exposure to an insult, upon the development of, and after recovery from AKI (Figure 12).

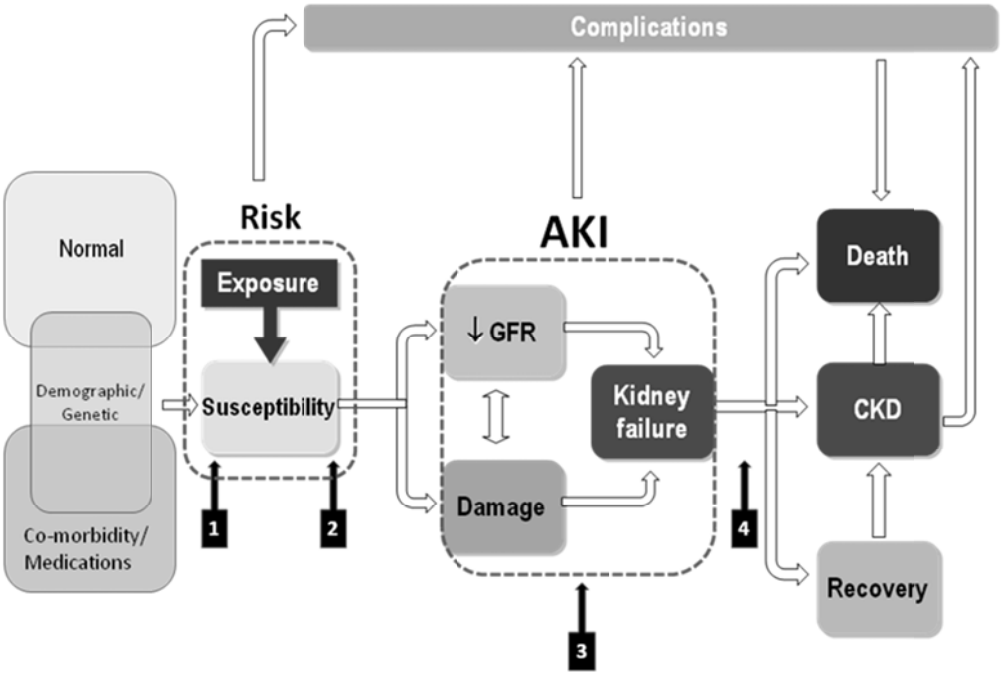


Figure 12. Suggested levels of risk assessment with relevance to AKI.
AKI, acute kidney injury; CKD, chronic kidney disease; GFR, glomerular filtration rate.

Level 1: Risk Assessment before Exposure to an Insult

Patients considered for deliberate exposure to procedures or therapies that have the potential of inducing kidney injury should be stratified according to three parameters:

a) The presence of susceptibility factors in common to most AKI settings, or "shared risk factors" including dehydration, older age, female gender, CKD, and certain other comorbidities. Our knowledge in this area is fairly well evidence-based (see reviews[81-83]), although our understanding of these factors primarily comes from large retrospective studies and may be subject to certain biases.

b) The presence of exposure-specific, patient-related susceptibility factors, such as the preoperative cardiac function in cardiac surgery or myeloma in radiocontrast nephrotoxicity. The available information on such factors is limited to a few hospital-based studies which, though evidence-based, cannot be extrapolated to dissimilar exposures.

c) The type and intensity of the exposure. The same individual may be stratified in a high-risk category if exposed to a certain insult, yet in a lower category when exposed to another. Risk-stratification should be seen as a relative parameter that changes with exposure factors. Information on such patient/exposure interactions is often addressed in scoring systems, designed and validated for specific settings as cardiac, aortic, or abdominal surgery, procedures involving the use of radiocontrast media, or the administration of nephrotoxic drugs. In the absence of such a scoring system, clinical judgment is a reasonable alternative.

Shared susceptibility factors

Dehydration/volume depletion

Extracellular volume contraction is the most consistent, and indeed most readily modifiable, risk factor for the development of AKI upon exposure to almost any insult. Evaluation of the volume status by adequate history-taking, physical examination, and laboratory data is certainly the most important single measure a physician may observe for the sake of prevention of AKI. True dehydration (loss of water) should be treated with hypotonic fluids (free water via the enteral route or i.v. dextrose in water), whereas volume depletion (reduced circulating plasma volume) should be treated with isotonic fluids.

Hypoalbuminemia

Hypoalbuminemia was found to be an independent risk factor for AKI and for mortality in patients who developed AKI.[84]

Advanced age

The definition of "advanced age" varies in different studies, starting from 65-75 years.[62, 69, 85, 86] Older age has been associated, in many studies, with the risk of developing hospital-acquired AKI[87] or community-acquired AKI.[85] This was reported with a wide spectrum of insults, including exposure to radiocontrast material,[86] aminoglycosides,[88] or cardiac surgery.[89] The negative effect of advanced age extends throughout the subsequent phases of AKI, including long-term sequelae.[62, 69, 90] There are certain conditions leading to AKI where the effect of age is not apparent, as in tumor lysis syndrome[91] or crush-induced AKI in massive disasters.[21]

There are no studies on the effect of age in the pediatric range, though the course of certain disorders, such as postinfectious glomerulonephritis, hemolytic uremic syndrome, and interstitial nephritis suggests that children are less likely to develop AKI with such intrinsic parenchymal diseases. Low and very low birth-weight neonates are at significant risk of AKI upon exposure to hypoxia. Such risk seems to correlate with genetic factors that are described in the next section.

Female gender

Contrary to most chronic kidney disorders, it is the female gender that carries a higher risk for AKI. This has been documented by large observational studies in hospital-acquired AKI, including cardiac surgery[92] or exposure to radiocontrast material[86] or aminoglycosides,[88] hence the inclusion of female gender as a risk factor in several validated predictive scores.[86, 89]

In many studies, this gender effect extended as a risk factor for CKD at 1 year.[93] This was not the case, however, in a population-based study in the Calgary (Canada) Health Region, where male patients admitted to multidisciplinary and cardiovascular surgical intensive care units had a higher chance of death or CKD at 1 year.[85]

Males consistently predominated in reports on the incidence of AKI complicating infection with HIV,[94] malaria,[95] leptospirosis,[96] and other community-acquired AKIs. The reasons for such gender differences are unclear.

Black race

Black race was reported as a risk factor in HIV-associated AKI.[93, 97] Yet this effect was *not* confirmed in hospital-acquired AKI under different settings,[91, 92] nor in its 5-year outcome.[98]

Previous AKI

Some reports have listed previous AKI as a risk factor for subsequent episodes of AKI. It is unclear, however, if undiagnosed CKD, rather than AKI per se, was indeed the risk factor entailed in subsequent susceptibility. Further study will be needed to address this question.

Chronic comorbidities

CKD

CKD is the most consistent pre-existing condition associated with a high risk of AKI in almost every relevant study addressing hospital- or community-acquired AKI, in the setting of almost every reported exposure.[60, 85-89, 91, 93, 94, 99, 100] While the definition of CKD includes many parameters, most prevalent of which is proteinuria, this has been largely neglected in most observational studies where data on urine analysis were generally lacking. The parameters most often alluded to for the definition of CKD were SCr or eGFR.

Even minor elevation of SCr, or decline of GFR, constitutes a risk that increases with the level of SCr.[101] This is included in several scoring models that provide more than double scoring points for SCr levels above 2.1 mg/dl (185.6 µmol/l).[89] There are no studies that associate risk with etiology of CKD, but given the independent risk of diabetes, it is likely that patients with diabetic kidney disease are at a higher risk.

Pre-existing CKD increases the risk of nonrecovery from AKI. In a large, community-based study in Northern California comprising 39 805 patients with CKD Stage 3B or higher, the risk for ESRD or death 30 days after hospital discharge was increased by 30% as a direct consequence of an episode of AKI.[68] A similar trend was observed in longer-term observations on hospital-acquired AKI extending for many years.[12]

Diabetes mellitus

In addition to its well-known deleterious effect of AKI superimposed on CKD,[102] diabetes mellitus is reported to be an important risk factor for AKI in community[85] as well as hospital[87] settings, particularly in association with cardiac surgery[89, 100] or exposure to radiocontrast media.[86] In a large hospital-based study, it was insulin-requiring, rather than non–insulin-requiring diabetes that carried a risk of AKI associated with cardiac surgery, with a relatively modest contribution (1/17) to the total risk score.[89] Regardless of insulin requirement, diabetes is a risk factor for poor 1-year outcomes, including ESRD and death.[85]

Heart disease

Expectedly, data on cardiac function are mostly available in hospital-based studies, specifically those addressing percutaneous or surgical interventions for ischemic, valvular, or aortic disease.[89, 92, 98, 100, 103-108] Cardiac dysfunction was also reported as a risk factor for radiocontrast nephropathy in a study comprising 8358 patients,[86] a prospective study of 180 pooled cases of hospital-acquired AKI,[87] and a large community-based retrospective study on a total population of one million individuals.[85] Several studies showed that previous and/or multiple cardiac interventions, or the need for preoperative intra-aortic balloon counterpulsation were additional risk factors.[89]

In many studies, the evidence of cardiac dysfunction was clinical. In those where more sophisticated evaluation was reported, impaired left ventricular systolic function was consistently incriminated. Ejection fraction was the most reliable criterion, with a threshold of 35% in cardiac surgery[89] to 50% in contrast-induced nephropathy.[109] The increased risk with cardiac dysfunction extends to long-term sequelae, including ESRD and death at 1 year.[85]

Pulmonary disease

Chronic obstructive lung disease is an acknowledged risk factor for AKI in patients undergoing cardiac surgery, being included in several predictive risk-scoring systems.[89] Assisted ventilation is associated with an exceptionally high risk for AKI in hospital-acquired[110] as well as community-acquired[59] infections.

Other comorbidities

Chronic liver disease was a risk factor for the development of AKI in HIV-infected individuals, particularly those coinfected with HCV,[94] and in nephrotoxicity with certain aminoglycosides.[88] Multiple myeloma is a known risk factor for AKI, particularly following the exposure to volume depletion, cytotoxic drugs, or radiocontrast material.[111, 112] Cancer,[113] connective-tissue disease, and alcoholism[85] were reported as risk factors for incomplete recovery from AKI at 1 year.

Pre-exposure medication

The beneficial or detrimental impact of angiotensin-converting enzyme inhibitors (ACE-I) is controversial. Two recent studies in postcardiac surgery AKI came to opposite conclusions. The first study by Benedetto et al.[114] used a propensity score–based analysis of 536 patients undergoing coronary artery bypass graft on cardiopulmonary bypass, among which 281 received ACE-I preoperatively. In this study, the incidence of AKI was 6.4% in patients who received preoperative ACE inhibitors and 12.2% in patients who did not (P <0.02). The incidence of AKI requiring dialysis was 2.4% in the treatment group and 6.3% in controls (P <0.03).

By contrast, Arora et al.,[115] in a retrospective cohort study of 1358 adult patients undergoing cardiac surgery, found that preoperative use of ACE-I or angiotensin receptor blockers (ARB) was associated with a 27.6% higher risk for AKI postoperatively. This study recommended even to stop these drugs in order to reduce the incidence of AKI.

Kiski et al.[116] found that patients treated with renin-angiotensin aldosterone system blockade before exposure to radiocontrast agents developed significantly more contrast-

induced acute kidney injury (CI-AKI) within 72 hours and 30 days. Even after adjustment for confounding comorbidities, treatment with ACE-I or angiotensin II receptor type 1 blockers turned out to be an independent risk predictor.

However, a recent randomized prospective trial performed in stable outpatients did not show any difference in incidence of CI-AKI between patients who did or did not discontinue renin-angiotensin aldosterone system blockers before contrast-media administration.[117] Therefore, although there is currently insufficient evidence to support discontinuation of these medications, further study is warranted given the widespread use of these agents in clinical practice.

Specific exposures

There are a number of common exposures that are known to be associated with a high incidence of AKI. Among the most important are sepsis, cardiac surgery, and radiocontrast media. We discuss sepsis throughout the guideline and the risk factors for CI-AKI are detailed in Chapter 4.1.

Epidemiology of AKI Following Cardiac Surgery

Cardiac surgery is one of the most commonly performed procedures in the developed world. In the USA alone, there were over 646 000 cardiac surgeries performed in 2005.[118] One of the most feared complications of this surgery is AKI. The incidence of AKI in this setting varies depending on the definition used and the specific population studied. Even considering only the most severe form, defined by the need for RRT, AKI rates after cardiac surgery range between 0.33%[119] and 9.5%[120]. Besides patient- and procedure-related factors, local practice patterns may partially explain this nearly 30-fold difference.[118] Given the poor outcomes associated with postoperative AKI, a paradigm shift from being reactive to being proactive needs to be invoked.

In view of the lack of consensus on the definition of cardiac surgery-associated acute kidney injury (CSA-AKI) in the literature, most studies that report on its epidemiology describe cohorts with different severity grades of AKI. In addition, cohorts may differ in baseline characteristics which may be procedure-related (see section below on risk factors). Both the variations in the definition of CSA-AKI, and the difference in baseline characteristics explain the wide range in reported incidence of CSA-AKI. Only few studies have used the RIFLE and/or AKIN classification in cardiac surgery patients, and these papers focused on the mortality risk and not on the impact of the incidence of CSA-AKI.[121-123] For example, Heringlake et al.[121] found that the incidence of a 50%, 100%, or 150% increase in SCr (graded as R, I, and F according to the RIFLE system) were 9% (2-40%), 5% (0.8-30%), and 2% (0.6-33%), respectively, with an overall incidence of 15.4% (3.1-75%). All three studies found a relation between short-term mortality and the RIFLE class.[121-123]

Risk Factors of AKI Following Cardiac Surgery

The risk factors (susceptibilities) for AKI following cardiac surgery are the same as for any other form of AKI, and have been discussed in Chapter 2.2. Besides these susceptibilities, quite specific exposure factors for the development of AKI following cardiac surgery have been observed in most clinical series. Multiple risk factors for CSA-AKI have been identified,

mostly in multicenter retrospective observational trials. Most studies defined risk factors for the development of CSA-AKI based on the need for RRT, whereas some single-center studies defined CSA-AKI by 25-100% increase in SCr. Obviously, these observational data are biased by the retrospective nature of most studies and the absence of a strict guideline for initiation of RRT (for a summary of these studies, see Hoste et al.).[124] A summary of risk factors for CSA-AKI identified in several studies is extensively reviewed elsewhere.[125]

Table 7. Risk factors associated with acute renal failure

Patient-related	Procedure-related
Female gender	Length of CPB
Chronic obstructive pulmonary disease	Cross-clamp time
Diabetes	Off-pump *versus* on-pump
Peripheral vascular disease	Nonpulsatile flow
Renal insufficiency	Hemolysis
Congestive heart failure	Hemodilution
LV ejection fraction <35%	
Need for emergent surgery	
Cardiogenic shock (IABP)	
Left main coronary disease	

CPB, cardiopulmonary bypass; IABP, intra-aortic balloon pump; LV, left ventricular.
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Table 7 summarizes these risk factors.[125] Ten patient-related risk factors and six procedure-related risk factors were identified. As for many other causes of AKI, presurgery exposure to nephrotoxic drugs (nonsteroidal anti-inflammatory drugs), medication interfering with the hemodynamic response to surgery (preoperative ACE-I/ARB), or agents such as contrast media (Chapter 4.1), may contribute to the spectrum of CSA-AKI. The impact of off-pump vs. on-pump coronary artery bypass graft surgery is discussed in greater detail in Chapter 3.9.

ACE-I/ARB

Two relatively recent papers, one retrospective cohort study[115] and one systematic review including three randomized trials,[126] explored the clinically important issue of whether ACE-I/ARB should be stopped before cardiac surgery. Arora et al. concluded that, among multiple other risk factors, an independent and significant association of AKI and preoperative use of ACE-I/ARB was found. The systematic review,[126] although concluding that the current available evidence is low, also recommended that stopping ACE-I or ARB before cardiac surgery may reduce the incidence of AKI. These drugs may contribute to lowering of the systemic vascular resistance/vasoplegia postoperatively, thereby making their omission before cardiac surgery a rational strategy to avoid this postoperative vasodilation.

Preoperative CKD: As with many other types of AKI, preoperative CKD is perhaps the most predictive risk factor, with the risk for dialysis requiring AKI approaching 10-20% in patients with a baseline preoperative SCr 2.0-4.0 mg/dl (177-354 µmol/l). In patients with a preoperative SCr >4.0 mg/dl (354 µmol/l), the risk for AKI rises to 25-28% (for summary, see Rosner and Okusa).[125]

Risk Models

Efforts have been made to modify these risk factors into clinically applicable tools. Chertow et al.[127] published a risk model in predicting AKI after cardiac surgery using 40 000 patients who underwent cardiac bypass or valvular surgery in 43 Veterans Administration Hospitals in Virginia. A risk-stratification algorithm was formulated on the basis of interactions between potential risk factors. Although there were inherent flaws in the study cohort, specifically a lack of females and African-American patients, this algorithm formed the basis of future AKI risk-predictive tools. In an attempt to improve on prior methodological limitations, Thakar et al.[89] formulated and validated a clinical risk score to predict post–cardiac surgery AKI requiring RRT. Using a cohort of 33 217 patients who underwent cardiac surgery at the Cleveland Clinic between 1993 and 2002, a scoring system was derived based on 13 preoperative factors. Each of the 13 risk factors was weighted and the sum of the scores, ranging from 0 to 17, allowed for stratification of postoperative risk of AKI from low to high. The lowest-risk group (score 0-2) had a risk for AKI requiring RRT of 0.4%. In contrast, the high-risk stratum (score 9-13) had a RRT risk of 21.5%. One year later, Mehta et al.,[128] using data from the Society of Thoracic Surgeons database in 449 524 patients, published a bedside tool for predicting the risk for postoperative dialysis use after cardiac surgery. Two new models were developed. Wijeysundera et al.[129] developed and validated a simplified renal index (SRI) based on patients who underwent cardiac surgery under cardiopulmonary bypass at two Canadian centers. The potential advantages of the SRI is that the index has discriminatory characteristics similar to the other scoring systems, while employing only eight variables. Secondly, SRI assessed preoperative renal function using eGFR, rather than SCr. It is interesting to note that other studies have also substantiated the utility of eGFR, rather than SCr, in predicting clinical outcomes after cardiac surgery.

Recently, the Thakar score and the Wijeysundera scores were externally validated.[130] For evaluation of the performance of both models, discrimination and calibration were measured. The frequency of AKI after cardiac surgery was 3.7% in the cohort used to validate the Thakar score and 3.8% in the cohort used to validate the Wijeysundera score. Discrimination of both models was excellent. Calibration, however, was poor, with underestimation of the risk for AKI except for patients within the very-low-risk category. The performance of both models clearly improved after recalibration.

Although most risk-prediction models focus on the need for RRT after cardiac surgery using preoperative factors, other investigators have tried to extend the continuum of risk prediction while incorporating intraoperative and postoperative variables. Brown et al.[131] published a prediction rule that identified risk for severe renal insufficiency (eGFR <30 ml/min) after cardiac surgery in patients with normal preoperative renal function. Eleven similar preoperative variables were found to be associated with an increased risk of severe renal insufficiency after surgery.

Finally, Palomba et al.[132] published the Acute Kidney Injury after Cardiac Surgery score based on a cohort of patients who underwent elective cardiac surgery in a single Brazilian center. The score incorporated preoperative, intraoperative, and postoperative variables in the development of AKI not requiring dialysis after cardiac surgery. In addition to the mentioned preoperative risk factors, cardiopulmonary bypass time of more than 120 minutes and a

postoperative central venous pressure of higher than 14 cm H_2O were found to be significant risk factors for AKI after cardiac surgery. The emergence and evolution of prediction models for AKI after cardiac surgery over the past few years has facilitated clinical decision-making and risk stratification. In addition, these models may aid in designing clinical trials for the prevention of AKI, specifically targeting the most vulnerable patient population.

Risk-prediction scores

Scoring systems (Table 8) have been developed in specific clinical settings to integrate the relative weights of shared as well as specific susceptibilities with specific exposures. The latter includes the nature and duration of surgery[87, 104] or cardiopulmonary bypass,[89] the type[109] and dose[99] of a radiocontrast material, or the blood level and duration of treatment with an aminoglycoside.[88] Other exposures have not been addressed in the same detail. However, there are many case-control studies which indicate that the nature and administered dose of a toxic plant[133] or a snake venom,[134] the site and multiplicity of a burn or trauma,[135] the size of a tumor associated with the tumor lysis syndrome,[91] the load of infective agent such as HIV[94] or plasmodium ,[95, 136] must be taken into consideration for risk stratification, even in the absence of validated specific scoring systems.

Risk scores in cardiac surgery have taken the lead (as discussed above), with at least five predictive scoring systems in different subpopulations.[130] According to the Cleveland Clinic system,[89] based on 15 838 cases and validated on 17 379 cases in the same institution, one point is added for female gender, congestive heart failure, left ventricular ejection fraction <35%, chronic obstructive pulmonary disease, insulin-requiring diabetes, and several operative parameters. Two points are counted for a SCr 1.2-2 mg/dl (106.1-176.8 µmol/l), and five points to values above 2.0 mg/dl (176.8 µmol/l). The maximum total score according to this system is 17.

A simple scoring system was proposed for noncardiac surgeries on the basis of a retrospective analysis of 15 102 cases.[137] This system is based on seven major risk factors namely age, emergent surgery, liver disease, body mass index, high-risk surgery, peripheral vascular occlusive disease, and chronic obstructive pulmonary disease necessitating chronic bronchodilator therapy. Patients having three of these factors have a RR of 16 for developing postoperative AKI compared to patients having none.

Mathematical equations have been derived and validated for prediction of aminoglycoside nephrotoxicity. In one study that included 214 patients, older age, female gender, and pre-existing CKD or liver disease were the main risk factors. There was no significant impact of diabetes, dehydration, serum bicarbonate, bacteremia, urinary tract infection, duration of therapy and, surprisingly, total aminoglycoside dose, or the use of clindamycin, frusemide, or cephalothin.[138] However, this model has not been confirmed in other studies. Finally, risk assessment for CI-AKI is discussed in Chapter 4.2.

Table 8. Overview table of observational studies of prediction equations for AKI

Author Year Country	Population	Outcome	Study design
Prediction equations for predicting AKI			
Candela-Toha[130] 2008 Spain	External validation of Thakar and Wijeysundera in 1780 patients with cardiac surgeries at a University Hospital in Madrid, Spain from 2002-2006	AKI	Retrospective cohort Single-center
Thakar[89] 2005 US	33,217 patients with open-heart surgery at the Cleveland Clinic Foundation from 1993-2002	AKI requiring dialysis	Retrospective cohort Single-center
Wijeysundera[129] 2007 Canada	20,131 cardiac surgery under cardiopulmonary bypass patients at two hospitals in Ontario, Canada from May 1999-July 2004.	RRT	Retrospective cohort Multicenter
McCullough[139] 2007 US	1,826 consecutive patients undergoing coronary intervention at William-Beaumont Hospital, Michigan from December 1993-August1994.	RRT	Retrospective cohort Single-center
Mehran[86] 2004 US	8,357 patients who underwent PCI possibly at Columbia Medical Center, New York, New York, over a period of 6 years(dates unspecified).	CI-AKI	Retrospective cohort Presumed single-center
Skelding[107] 2007 US	External validation of William Beaumount score in 3,213 patients from the Mayo Clinic PCI Registry who underwent PCI at the from July 1, 2000 to June 30, 2003	CI-AKI	Retrospective cohort
Ghani[140] 2009 Kuwait	247 patients undergoing PCI in Kuwait from March to May 2005	CI-AKI	Prospective cohort Single-center
Drawz[87] 2008 US	540 hospitalized patients in three hospitals in Cleveland, Ohio since January 1, 2003	Hospital-acquired AKI	Case-controlled

Level 2: Risk Assessment after Exposure

The objective of assessment at this level is to determine additional risk factors, over and above those described at level 1, that would not be disclosed without the challenge of actual exposure. This can be done by evaluating the patient's response in terms of vital signs, evolution and severity of an inflammatory response, and other parameters that are very well organized in the ICU through a disease-severity score such as the Acute Physiology and Chronic Health Evaluation scoring system. While the latter has not proven sufficiently predictive of the *severity* or *outcome* of AKI, its correlation with the *incidence* of AKI is well documented.[141] This apparent controversy is resolved by realizing that additional parameters have to be taken into consideration when AKI actually occurs, as explained in Appendix D.

Genetic factors

Genetic factors have been shown to correlate with the severity of acute illness, by regulating the vascular reactivity or inflammatory response. Several polymorphisms that alter the immune response have been associated with AKI in experimental models[142] and in several case-control studies. Neonatal AKI has been associated with polymorphism of tumor necrosis factor (TNF),[143] interleukin (IL)-6,[144] heat-shock protein-72,[145] and vascular endothelial growth factor (VEGF)[146] but not the angiotensin-aldosterone genes[147] that have been incriminated in other studies.[148]

Similar data have been reported for adults with sepsis, cardiopulmonary bypass, and radiocontrast media as prototype exposures. In several studies, it was shown that the incidence of AKI was significantly increased with gene polymorphisms associated with increased production of TNF, IL-6, and IL-8, or decreased production of IL-10.[141, 149, 150]

Specific genetic impact

In addition to the "broad-spectrum" gene polymorphisms, several gene mutations have been associated with the incidence of AKI in specific conditions. The most striking example in this context is glucose-6-phosphate dehydrogenase deficiency, particularly common in malaria-endemic regions. In these cases, a negative selection of this mutation has occurred over the years, due to inability of plasmodia to survive in affected red blood cells.[151] AKI has been consistently reported in such individuals upon exposure to other infections such as typhoid, typhus, and hepatitis A as a consequence of intravascular hemolysis.[152] This observation may justify measurement of G6PD in patients with these infections, particularly in malaria-endemic areas, as a part of Level II risk assessment.

An emerging risk factor for the development of microagiopathies (e.g., hemolytic uremic syndrome, thrombotic thrombocytopenic purpura) in several infections is a genetic mutation leading to deficiency of a disintegrin and metalloproteinase with a thrombospondin type 1 motif (ADAMTS)-13.[153] Rhabdomyolysis associated with certain infections, particularly when associated with hyperpyrexia, may be attributed to carnitine palmitoyltransferase II deficiency.[154]

Genetic factors without overt phenotypic expression

Many studies have shown a probable association with certain single- or multiple-gene polymorphisms, yet without a clear phenotype that can be detected at the bedside or with

routine laboratory testing. A recent meta-analysis of 16 studies[155] showed that only one polymorphism, apolipoprotein E (APO-E) e2/e3/24, was associated with increased incidence of AKI in multiple studies. Gene polymorphisms involving NADPH oxidase and haptoglobin were sporadically associated with AKI. The potential of these observations to evolve into biomarkers usable for risk stratification remains questionable.

Level 3: Risk Assessment after Development of AKI

Prognostic criteria involved in shaping disease severity or outcome have been extensively studied in hospital-acquired—and, less elaborately, in community-acquired—AKI. Many scoring systems have been developed and validated for predicting outcomes, including insult-related as well as patient-related factors. These are described in detail in Appendix D.

Level 4: Risk Assessment for Delayed Sequelae

Since hospital mortality due to AKI remains alarmingly high,[156] the usual end-point of earlier studies was the immediate outcome of a single episode; death vs. survival. It was believed that the majority of survivors would regain normal kidney structure and function, only a few having persistent kidney injury.[157] This concept been called into question by recent studies (Table 9), which show that recovery may indeed be less likely than expected, with as many as one-third of patients still dialysis-dependent at 1 year.[158] Other sequelae may require up to 20 years to detect, such as cardiovascular events and death (Table 10).[12]

CKD

Multiple studies confirm that AKI is an independent risk factor for de novo development of CKD in patients who had undergone cardiac[124] or aortic surgery,[159] exposed to radiocontrast material,[109] aminoglycosides,[138] or an episode of HUS[160] with an overall average incidence of 7.8 events per 100 patient-years, according to a recent meta-analysis comprising 47 017 participants.[12] In this and other studies, the duration and severity of AKI according to RIFLE or AKIN criteria, or the need for dialysis,[64, 93] correlated with the subsequent incidence of CKD. In other analyses, the etiology of AKI and its duration do not seem to contribute to the correlation between AKI and long-term mortality and/or later CKD.[85, 161] While mild AKI is associated with a 70% increase in risk of hospital mortality, long-term survival was nearly three-fold less in patients with mild to moderate AKI as compared to their non-AKI counterparts.[161] In a recent retrospective 75-month follow-up of 5404 cases in a USA Veterans database with diagnostic codes indicating “acute renal failure” or “acute tubular necrosis”, the risk of reaching Stage 4 CKD was significantly higher than that in 63 491 controls.[67]

Table 9. Long-term outcome studies of AKI

Reference	Patients with CKD excluded from study (threshold reported if yes)	AKI definition	Follow-up (y)		Mortality (%)		Renal outcomes		Lost to follow-up (%)
			Mean/Median	Maximum	In-hospital or 30-d	Hospital survivors (time reported)	CKD (%)	ESRD (%)	
Abosaif et al.[46]	No	RIFLE	NA	0.5	52	13 (0.5 y)	NA	NA	0
Ahlstrom et al.[162]	No	RRT	4	6.4	41[a]	70 (5 y)	NA	NA	41
Akposso et al.[163]	No	SCr >1.35[b] mg/dl	NA	12	40	77 (6 y)	NA	NA	53
Ali et al.[16]	No	RIFLE	0.5	0.5	34	27 (0.5 y)	NA	NA	NA
Alric et al.[164]	No	↑SCr >20%	2.4	5	24[a]	NA	16[c]	NA	64
Askenazi et al.[70]	Yes (not defined)	↑SCr >0.3 mg/dl	NA	5	29	20 (3-5 y)	12[d]	9	0/77[ˇ]
Bagshaw et al.[165]	No	SCr ≥1.7 mg/dl	NA	1	24	5.5 (1 y)	NA	NA	0
Bagshaw et al.[85]	No	RRT	NA	1	59	27.5 (1 y)	NA	9, 14[f]	0
Bahar et al.[166]	No	RRT	6	13	80	41 (10 y)	15[g]	24	0
Barratt et al.[167]	No	RRT or SCr >6.8 mg/dl	NA	5	75	56 (5 y)	69[h]	6	0
Benoit et al.[168]	No	RRT	NA	0.5	62	24 (0.5 y)	NA	NA	25
Bhandari et al.[169]	Yes (not defined)	RRT or SCr >6.8 mg/dl	NA	5	41	59 (5 y)	NA	17	NA
Brivet et al.[170]	SCr >3.4 mg/dl	SCr >3.5 mg/dl or ↑SCr ≥100%	NA	0.5	58[i]	13 (0.5 y)	28[j]	NA	43
Chertow et al.[171]	No	RRT	NA	1	70	19 (1 y)	NA	33	2
Cosentino et al.[172]	No	RRT	NA	1	NA	NA	NA	35	NA
Dahlberg et al.[173]	No	RRT	NA	13	55	29 (3 y)	NA	25	NA
El-Shahawy et al.[174]	SCr >2.0 mg/dl	↑SCr ≥1 mg/dl	NA	1	NA	46.5 (1 y)		NA	NA
Frost et al.[175]	No	RRT	NA	5	46[a]	37 (5 y)	NA	NA	NA
Gonwa et al.[176]	No	RRT	NA	1	6[a]	7.4 (1 y)	NA	16	NA
Gopal et al.[177]	No	SCr >3.4 mg/dl	2.8	5	66	33 (2.8 y)	NA	NA	39
Gruberg et al.[178]	No (all patients in study with CKD; SCr ≥1.8 mg/dl)	↑SCr ≥25%	NA	1	9	19.2 (1 y)	NA	18[b]	0
Gupta et al.[179]	No	↑SCr >1 mg/dl	3	NA	NA	19 (3.2 y)	NA	NA	NA
Hamel et al.[180]	No	RRT	NA	0.5	NA	73 (6 y)	NA	NA	0
Hein et al.[120]	No	RRT	3	NA	6.3	14 (3 y)	NA	NA	5
Jones et al.[181]	No	RRT	NA	0.5	62	4.5 (0.5 y)	NA	9	1

Reference	Patients with CKD excluded from study (threshold reported if yes)	AKI definition	Follow-up (y)		Mortality (%)		Renal outcomes		Lost to follow-up (%)
			Mean/Median	Maximum	In-hospital or 30-d	Hospital survivors (time reported)	CKD (%)	ESRD (%)	
Kaltenmaier et al.[182]	No	RRT	NA	0.5	44[a]	42 (0.5 y)	NA	NA	NA
Khan et al.[30]	SCr ≥2.25 mg/dl	SCr ≥3.4 mg/dl	NA	2	NA	69 (2 y)	NA	NA	0
Korkeila et al.[73]	No	RRT	NA	5	45	35 (5 y)	NA	15	0
Landoni et al.[183]	No	RRT	3.5	NA	67	14 (3.5 y)	NA	9	5
Liano et al.[184]	SCr >1.4 mg/dl	SCr >2 mg/dl	7	22	55	50 (10 y)	19[k]	2	5[c]
Lindsay et al.[185]	SCr >1.2 mg/dl	↑SCr ≥50%	NA	1	NA	9.5 (1 y)	NA	NA	15
Lins et al.[186]	SCr >2.0 mg/dl	SCr >2 mg/dl	NA	1	51	22 (1 y)	NA	12	NA
Loef et al.[187]	No	↑SCr ≥25%	NA	8.3	15	16 (8.3 y)	NA	NA	10
Luckraz et al.[188]	No	RRT	NA	5	42	9.5 (5 y)	NA	5	1
McCarthy et al.[189]	No	RRT	NA	1	68,[m] 48[n]	35,[m] 43[n] (1 y)	NA	22,[m] 4[n]	0
Miler et al.[190]	No	NA	NA	12.5	24	6 (NA)	47[o]	NA	29
Morgera et al.[191]	No	RRT	2.5	NA	69	42 (5 y)	31[p]	10	10,[q] 47[r]
Noble et al.[51]	No	RRT	5	17	79	33 (NA)	NA	9	7
Paramesh et al.[192]	Yes (not defined)	RRT	6	NA	NA	40 (1 y)	46[t]	23	0
Rihal et al.[193]	No	↑SCr ≥0.5 mg/dl	NA	5	23.5	15.2 (5 y)	NA	NA	6.5
Rocha et al.[194]	GFR <90 ml/min	RIFLE	3	10	NA	49.5 (5 y)	NA	NA	0
Schiffl[195]	SCr >1.3 mg/dl	RRT	1	1	47	34 (1 y)	NA	1	2
Soares et al.[113]	No	Bellomo criteria	NA	0.5	64	24 (0.5 y)	26[t]	8.5	NA
Sraer et al.[196]	No	↑SCr >50%	1.5	8	40	63 (5 y)	NA	5	NA
Topkara et al. [340]	No	RRT	NA	7	NA	42.2 (7 y)	NA	NA	NA
Turney et al. [341]	Yes (not defined)	RRT or SCr >6.8 mg/dl	NA	1	NA	49.5 (1 y)	8[b]	NA	NA
Welten et al.[159]	CCr <30 ml/min	↓GFR >10%	6 (3)	10	8	38 (10 y)	NA	NA	NA
Wong et al.[197]	No	RRT	NA	1	69	12 (1 y)	NA	NA	7

Note: Bellomo criteria are SCr level greater than 1.44 mg/dl and urea level greater than 48 mg/dl and/or urine output less than 800 ml/d or less than 200 ml per 6 h. If there was a CKD baseline, the AKI definition was increase in SCr level greater than 0.72 mg/dl or urea level greater than 24 mg/dl and/or urine output less than 800 ml/d or less than 200 ml per 6 h.
Conversion factors for units: SCr in mg/dl to µmol/l, ×88.4, GFR and CCr in ml/min to ml/s, ×0.01667.

a. Percentage of deaths in 30 to 100 days.
b. In patients with normal baseline renal function (ΔSCr >50% or 0.72 mg/dl in patients with baseline CKD).
c. SCr level greater than 130 mmol/l in patients with normal baseline kidney function.
d. CCr less than 90 ml/min.
ˇ. Zero percent loss to follow-up for the ESRD or death end points and 77% loss to follow-up for the CKD end point.
f. Nine percent ESRD in patients with normal baseline kidney function and 14% in those with baseline CKD.
g. Kidney function did not recover to normal.
h. Renal impairment necessitated continued review in a nephrology outpatient clinic.

i. Only in patients who had dialysis-requiring AKI.
j. SCr level greater than 1.7 mg/dl.
k. SCr level greater than 1.4 mg/dl.
°. SCr level greater than 110 mmol/l.
m. Cohort between 1977 and 1979.
n. Cohort between 1991 and 1992.
o. Impaired renal function.
p. Not defined.
q. Entire cohort.
r. Loss to follow-up for assessment of kidney function.
¹. Estimated GFR less than 60 ml/min/m^2 for at least 3 months.

Δ, change; AKI, acute kidney injury; CKD, chronic kidney disease; CCr, creatinine clearance; ESRD, end-stage renal disease; GFR, glomerular filtration rate; NA, not available; RIFLE, Risk, Injury, Failure, Loss, End-stage Kidney disease; RRT, renal replacement therapy; SCr, serum creatinine. Reprinted with permission.[12]

Table 10. Mortality rates and risk ratios in survivors of AKI

Subgroup	No. of studies	Deaths/person-years (deaths/100 person-years)		No. of studies showing harm		Rate ratio	Heterogeneity (I^2)
		AKI	No AKI	Point estimate >1	Lower bound 95% CI >1		
Overall	15	685/7665 (8.9)	3739/87 014 (4.3)	15	12	2.59 (1.97-3.42)	86%
Definition of AKI							
At least mild	3	250/3972 (6.3)	340/9908 (3.4)	3	3	1.67 (1.41-1.98)	0%
At least moderate	6	325/2928 (11.1)	2980/67 488 (4.4)	6	4	2.73 (1.81-4.14)	90%
Severe (RRT)	7	148/1079 (13.7)	590/13 351 (4.4)	7	6	3.04 (2.13-4.33)	60%
Clinical setting							
Critical illness	2	48/347 (13.8)	173/3743 (4.6)	2	1	2.41 (1.50-3.85)	0%
Cardiac surgery	3	97/1335 (7.3)	327/11 956 (2.7)	3	3	3.72 (1.49-6.94)	85%
PCI	4	218/1670 (13.1)	2793/66 350 (4.2)	4	4	2.89 (2.32-3.61)	49%
Nonrenal transplant	3	92/1632 (5.6)	204/2884 (7.1)	3	1	1.89 (0.9-3.96)	82%
Left ventricular assist device	2	59/581 (10.2)	79/1582 (5.0)	2	2	2.15 (1.53-3.03)	0%
Aortic surgery	1	171/3 840 (4.5)	163/5290 (3.1)	1	1	1.45 (1.17-1.79)	NA
Duration							
Transient v none	2	201/2298 (8.7)	301/9645 (3.1)	2	2	2.54 (2.10-3.06)	0%
Persistent v none	2	124/1370 (9.1)	301/9645 (3.1)	2	2	2.46 (1.68-3.60)	49%
Persistent v transient	3	186/2150 (8.7)	232/2923 (7.9)	2	1	1.15 (0.84-1.57)	45%

Note: Mild AKI defined as increase in creatinine level greater than 25% or decrease in creatinine clearance greater than 10%; moderate AKI, increase in creatinine level greater than 50%, greater than 100%, greater than 1.0 mg/dl, or creatinine level greater than 1.7 mg/dl; severe AKI, need for RRT; transient AKI, Welten et al.[159] defined it as worsening of creatinine clearance greater than 10% at day 1 or day 2, but recovery within 10% of baseline value by day 3; Liano et al.[184] defined it as serum creatinine value of 1.4 mg/dl or greater at the time of hospital discharge; Loef et al.[187] defined it as a 25% or greater increase in postoperative serum creatinine value that returned to preoperative level at hospital discharge; persistent AKI, Welten et al. 34 defined it as a greater than 10% decrease in creatinine clearance without recovery to within 10% of baseline value by day 3; Liano et al.[184] defined it as AKI serum creatinine value greater than 1.4 mg/dl at hospital discharge; Loef et al.[187] defined it as a 25% or greater increase in postoperative creatinine level that did not return to preoperative level at hospital discharge.

AKI, acute kidney injury; CI, confidence interval; NA, not available; PCI, percutaneous coronary intervention; RRT, AKI requiring dialysis. Reprinted with permission.[12]

Lo et al.[198] recently examined the long-term sequelae of AKI in a retrospective analysis of the large Kaiser Permanente database using the years 1996-2003. This analysis explored AKI and its correlation with long-term kidney disease and mortality in comparison with enrollees of the same health-care organization who did not develop AKI and served as controls. The study focused on patients with estimated GFR >45 ml/min per 1.73 m^2 at baseline. As compared to controls, patients who suffered dialysis-dependent AKI during their hospitalization had a 28-fold increased risk of developing CKD Stage 4 or Stage 5. There was also more than a two-fold risk of long-term death in this group. Although major differences existed between cohorts in terms of baseline characteristics, and this is a source of bias, at the very least, AKI appeared to be an important risk factor for long-term CKD and mortality.

The impact of AKI etiology was addressed several years ago in a comprehensive observational study that showed that acute vasculitis and postinfectious glomerulonephritis were associated with a worse prognosis, while viral and allergic drug-induced, interstitial nephritides were associated with the best prognosis. Incomplete resolution in those with tubular necrosis varied from 3% to 30% (Figure 13).[199] In a recent study, persistent microalbuminuria was found in 32% of children 3 years after recovering from an episode of D+ HUS, compared to 5% in controls.[200]

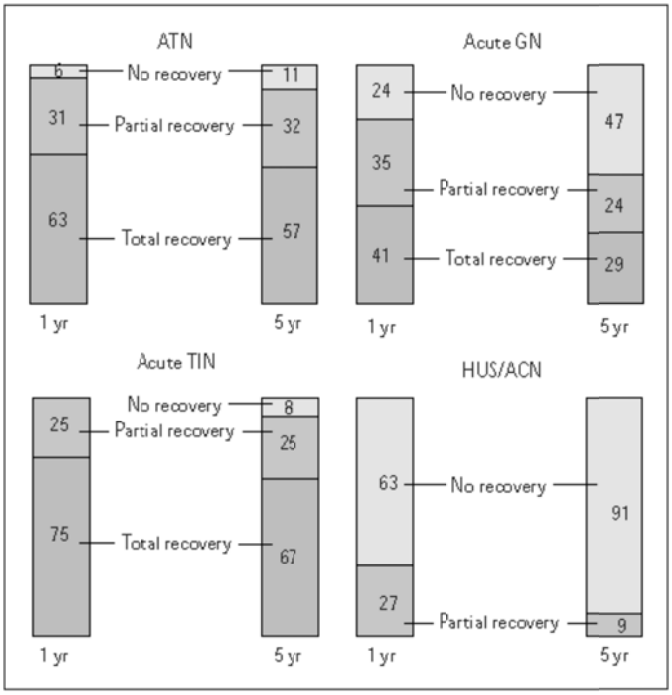

Figure 13. Recovery of kidney function in 227 patients, 1 and 5 years after AKI, due to different biopsy-confirmed causes.

ACN, acute cortical necrosis; ATN, acute tubular necrosis; GN, glomerulonephritis; HUS, hemolytic uremic syndrome; TIN, tubulointerstitial nephritis. Reprinted with permission.[201]

ESRD

The incidence of ESRD in AKI survivors has been reported from as few as 1% to as many as 64% at 1 year, depending on the study population,[199, 202] and averaged 4.9 events per 100 patient-years in longer follow-up.[12] In an attempt to survey the chronic consequences of AKI, the National Institute of Diabetes and Digestive and Kidney Diseases has funded a prospective study composed of a consortium of several institutions: AKI-ASSESS. The results of their work are several years away.[63]

MI

AKI was an independent risk factor for subsequent MI, with an average RR of 2.05 (95% CI 1.61-2.61).[12]

Mortality

In a meta-analysis of 48 studies,[12] incident all-cause mortality was 8.9 deaths per 100 patient-years following a single episode of AKI, compared to 4.3 deaths per 100 patient-years in controls (rate ratio 2.59; 95% CI 1.97 to 3.42) (Figure 14). AKI was associated independently with mortality risk in six of six studies that performed multivariate adjustment (adjusted rate ratio, 1.6-3.9). A similar conclusion was made in a large study using USA Veterans database.[67] In a prospective observational study, 5-year mortality following AKI correlated with surgery, incomplete recovery, need for dialysis and comorbidity (Figure 15). A retrospective study of 2973 patients with AKI after cardiothoracic surgery between 1992 and 2002, without a history of CKD, and who were discharged from the hospital, investigated the 10-year survival.[50] Patient survival was determined through the National Social Security Death Index. Long-term survival was analyzed with a risk-adjusted Cox proportional hazards regression model. As in many similar studies, survival was worse among patients with AKI and was proportional to its severity, with an adjusted HR of 1.23 (95% CI 1.06-1.42) for the least-severe RIFLE risk class and 2.14 (95% CI 1.73-2.66) for the RIFLE F class compared to patients without AKI. Survival was worse among all subgroups of cardiothoracic surgery with AKI, except for valve surgery. Importantly, patients with complete renal recovery after AKI still had an increased adjusted HR for death of 1.28 (95% CI 1.11-1.48) compared to patients without AKI. The authors conclude that the risk of death associated with AKI after cardiothoracic surgery remains high for 10 years regardless of other risk factors, even for those patients with apparent complete renal recovery.

Study name	Clincial Setting	Comparison	Statistics for each study			Death / Total		Rate ratio and 95% CI	
			Rate ratio	Lower limit	Upper limit	AKI	Non-AKI		Relative weight
Abosaif	Critically Ill	> 50%	1.52	0.33	6.92	10 / 33	2 / 10		2.42
Bagshaw	Critically Ill	≥ 1.7	2.53	1.54	4.14	38 / 314	171 / 3733		7.05
Gonwa	Liver Txp	RRT	1.60	0.95	2.69	16 / 94	140 / 1317		6.90
Gruberg	PCI	> 25%	1.77	1.13	2.79	36 / 137	39 / 263		7.32
Gupta	PCI	> 1 mg/dl over baseline	4.38	3.51	5.46	83 / 303	1624 / 25958		8.61
Hein	Cardiac Surgery	RRT	4.03	2.88	5.65	41 / 359	188 / 6639		8.02
Kaltenmaier	LVAD	RRT	3.29	1.85	5.85	17 / 75	36 / 522		6.52
Landoni	Cardiac Surgery	RRT	29.17	1.73	492.61	13 / 126	1 / 147		0.86
Lindsay	PCI	> 50%	3.64	2.20	6.04	17 / 171	131 / 4800		6.98
Loef	Cardiac Surgery	> 25%	1.90	1.35	2.67	43 / 850	138 / 5170		7.99
Rihal	PCI	> 0.5 mg/dl	3.64	2.91	4.56	82 / 720	999 / 31952		8.59
Rocha	Lung Txp	> 50%	1.12	0.78	1.61	67 / 1165	53 / 1035		7.89
Topkara	LVAD	RRT	2.54	1.66	3.89	42 / 308	43 / 801		7.49
Welten	Aortic Surgery	> 10% decl in CC	1.57	1.27	1.95	171 / 2985	163 / 4475		8.64
Wong	Liver Txp	RRT	6.28	2.60	15.16	9 / 25	11 / 192		4.72
			2.59	1.97	3.42	685 / 7665	3739 / 87014		

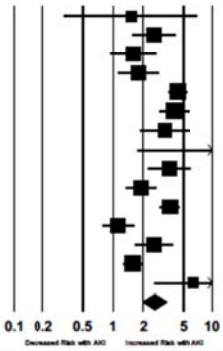

Figure 14. Pooled rate ratio for long-term mortality for survivors of AKI.

Overall RR, 2.62; 95% CI 1.99-3.45; I2 = 86%. AKI, acute kidney injury; CC, creatinine clearance; CI, confidence interval; LVAD, left ventricular assist device; PCI, percutaneous coronary intervention; RRT, renal replacement therapy; Txp, transplantation. Reprinted with permission.[12]

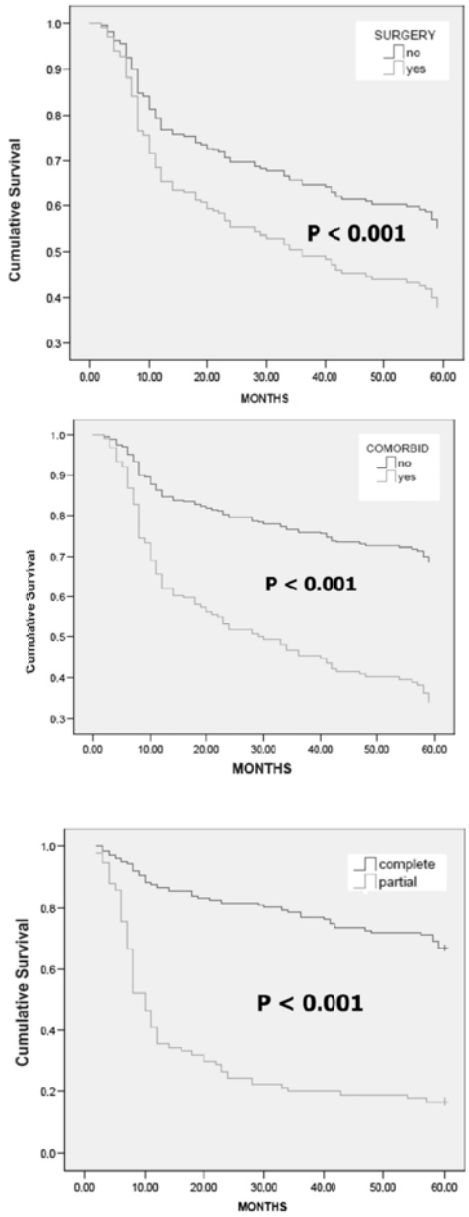

Figure 15. Factors in the long-term outcome of AKI.

Reprinted with permission from The European Renal Association-European Dialysis and Transplant Association.[98]

A large retrospective community-based observational study of 3769 patients with AKI who received dialysis treatment found that long-term mortality was 10.01 per 100 patient-years, similar to that in matched controls (10.85 per 100 patient-years).[64] However, matching was performed on the basis of a 22-variable propensity score for AKI and dialysis. Thus, the results indicate that survival among patients with AKI treated with dialysis is similar to patients without AKI but with other disease processes that result in similar severity of illness. This would apparently indicate that severe AKI is associated with a similar outcomes compared to other forms of severe acute illness.

Other risk factors for long-term sequelae

In addition, practically all the risk factors described for the development of AKI seem to apply for long-term sequelae. This has been shown for advanced age,[62, 69] female gender in hospital-acquired AKI,[93] pre-existing CKD,[12, 68] heart disease,[85] diabetes,[85] and a few other comorbidities.[12, 98]

Pediatric Considerations

Children typically do not have the comorbid conditions noted above for adult patients. However, the epidemiology of AKI in children has changed over the past decade, from primary kidney disease, such as HUS, to diseases in which the kidneys are affected as a result of another systemic disease or its treatment.[203-205] However, no prospective study exists to evaluate the rate of AKI development in matched controls exposed to the same multiple potential AKI causes to truly identify who is at risk. Critically ill children with multiorgan dysfunction or exposed to nephrotoxic medications represent the most prevalent pediatric cohorts who develop AKI.[203] The rates of AKI development in pediatric ICUs depend upon the populations studied and the AKI definition used, ranging from 4.5% (all admitted patients with AKI defined as a doubling of SCr, where worse organ dysfunction, thrombocytopenia, neurological dysfunction, nephrotoxic mediations and hypoxemia were risk factors for AKI)[206] to 82% (only children receiving invasive mechanical ventilation and receiving one or more vasoactive medications, with AKI defined by a 25% decrease in estimated SCr).[207, 208] Mortality is higher for children with AKI, especially those with multiorgan failure.[103] Thus, we suggest all children with any of these risks factors be monitored closely for the development of AKI. Early AKI detection is crucial, as even small increases in SCr may be associated with pediatric patient morbidity and mortality.[209]

Conclusions

The risk factors for AKI are like a proverbial iceberg, the tip of which is all we can see: dehydration, older age, female gender, possibly black race in community-acquired AKI, pre-existing CKD, and a number of other comorbid conditions including diabetes, heart, lung or liver disease, malignancy and paraproteinemias. We can also vaguely see, underneath the surface, some features that reflect hidden characters: phenotypic expressions of genetic disparities. Certain patient responses to exposure variables may reflect these genetic factors, often collectively measured by critical-illness scores such as APACHE.

While the study of risk factors for AKI continues to be exciting and challenging, the benefit of more knowledge will remain limited to specific situations where intervention is still possible. These include:

a) Prior to exposure to a planned intervention which may be avoided or modified.
b) After exposure to an insult, where modifiable risk factors may still provide targets for intervention. In most cases, though, close follow-up may be the only possible action in the hopes of early detection and management of AKI.
c) After surviving an episode of AKI, where closer follow up is indicated for high-risk subjects—including those with residual kidney damage—for detection of CKD, and applying relevant measures to slow progression, avert development of cardiovascular disease, and reduce the chances of premature death.

APPENDIX D: EVALUATION AND GENERAL MANAGEMENT GUIDELINES FOR PATIENTS WITH AKI

After AKI has been diagnosed, multiple issues require attention. First, the etiology of AKI should be evaluated and, in particular, reversible cause or causes that might be correctable should be identified. Second, SCr and urine output should be monitored to perform staging. This might require some time until the SCr peak or the required observation period for urine output is reached. Third, acute and chronic comorbid conditions can influence the outcome of AKI, leading to further kidney injury and increasing the risk of the development of CKD. For example, the use of nephrotoxic drugs, which might increase kidney damage, have to be weighed against the potential benefit of the drugs. In addition, planned procedures (e.g., imaging studies, surgery) with a potential risk for further kidney injury have to be balanced against their potential benefit. These procedures might require further prophylactic management or modification. Fluid status has to be monitored very carefully, since it is important for maintaining global hemodynamics, ensuring optimal kidney perfusion, enhancing kidney recovery, and preventing further kidney damage. In turn, the decreased kidney function during AKI influences therapeutic options and management of acute and chronic comorbid conditions. Drug therapy becomes more complicated, since dosage of drugs has to be adapted to decreased kidney function. Maintaining the desired fluid status, especially to prevent tissue and lung edema, might be hampered by the decreased urine output and might even require RRT. The latter, by itself, may introduce multiple complications in the patient's management. Finally, patients after AKI have an increased risk for CKD and should be staged for the severity and evaluated for the etiology of AKI.

The evaluation and treatment of patients with AKI requires understanding of separate but related concepts of diagnosis, comorbid conditions, severity of disease, complications of disease, and risks for loss of kidney function and mortality.

Evaluation to Determine the Cause, with Special Attention to Reversible Causes

Clinical history and examination of patients with AKI gives information about the underlying cause of AKI, comorbid conditions, and complications. Medical history should include information about fluid loss or sequestration, previous urea, SCr, and electrolyte results, previous health checks, systemic conditions (e.g., diabetes, hypertension, ischemic heart or peripheral artery disease, chronic heart failure, jaundice), previous urinary symptoms (pyelonephritis, urinary tract infection), recent procedures (surgery, angiography, other radiological procedures), known infections (e.g., HIV, hepatitis), and known immunosuppressive therapy (transplant patients, patients with malignancies). Drug history should include over-the-counter formulations and herbal remedies or recreational drugs. The social history should include exposure to waterways, sewage systems, and rodents (malaria, leptospirosis, hantavirus).

Physical examination should include evaluation of fluid status, signs for acute and chronic heart failure, infection, and sepsis (see Recommendations 2.3.1-2.3.3). Ophthalmic examination may reveal plaques suggestive of atheroemboli (Hollenhorst plaques, i.e., intraluminal retinal cholesterol/fibrin deposits), or findings compatible with bacterial endocarditis, vasculitis or malignant hypertension. Neck examination for jugular venous

pressure and carotid pulses and sounds may be helpful in detecting heart failure, aortic valve disease, or vascular disease. Cardiovascular examination for rate, rhythm, murmurs, gallops, and rubs may be helpful in detecting the presence of heart failure and possible sources of emboli. Lung examination can assist in determining the presence of either heart failure or a pulmonary-renal syndrome associated with AKI. Abdominal examination can reveal findings compatible with vascular disease (e.g., bruits, palpable abdominal aortic aneurysm), masses that could be malignant, enlarged or tender kidneys, distended bladder, possible sources of bacteremia, or evidence of liver disease or of intra-abdominal hypertension. Examination of the extremities for symmetry and strength of pulses and edema can be helpful. Skin examination may reveal palpable purpura (vasculitis), a fine maculopapular rash (drug-induced interstitial nephritis), livedo recticularis, purple toes, and other embolic stigmata (atheroemboli). If neurological signs are present, systemic disorders such as vasculitis, thrombotic microangiopathy, subacute bacterial endocarditis, and malignant hypertension warrant consideration. Peripheral neuropathy in the presence of AKI raises the possibility of nerve compression caused by rhabdomyolysis, heavy-metal intoxication, plasma cell dyscrasia, or acute polyneuropathy of the critically ill patient. Pelvic examination in females and rectal examination in both females and males may detect an obstructive cause of AKI.

Monitoring of Intra-abdominal Pressure

Markedly raised intra-abdominal pressures (>20 mm Hg) may occur after trauma, abdominal surgery, or secondary to massive fluid resuscitation. The mechanism remains unclear but may be due to increased renal venous pressure and vascular resistance. There is no widely accepted gold standard for intra-abdominal pressure measurement. Bladder pressure can be used as an intra-abdominal pressure estimate, provided it is measured in a reproducible way. Automated continuous intra-abdominal pressure monitoring has recently become available. This measurement may be particularly useful in the sometimes abrupt decline in GFR in patients with severe heart failure; this form of hemodynamically mediated AKI is often called the cardiorenal syndrome. The kidneys are intricately involved in fluid and electrolyte homeostasis, and are critical to the body's compensatory mechanisms responsible for the pathophysiologic changes in heart failure. In advanced heart failure, however, the kidney may be unable to compensate properly, and, in fact, several of the compensatory mechanisms that are active can be counterproductive. This can ultimately worsen both the heart failure and the kidney dysfunction, potentially leading to cardiorenal syndrome, present in 20-30% of patients admitted to the hospital for acute decompensated heart failure.[210] It has been suggested that high intra-abdominal pressure or increased renal vein pressure plays a role in the decreased renal perfusion in severe heart failure.

Fluid Status

Patients should be evaluated for fluid responsiveness. Fluid status plays a major role in the diagnosis of the underlying cause, prevention/progression, and therapy of AKI.[211] Volume depletion will compromise kidney perfusion, contributing to the progression of AKI or being the cause of it. On the other hand, volume overload can also compromise kidney function as discussed above and can be difficult to correct in patients with AKI. Fluid overload can cause multiple problems, and may lead to increased hospital mortality.[212, 213] Fluid management is therefore one of the mainstays for patients with established AKI and assessment of the fluid status is mandatory. A variety of measures to assess fluid status in a patient with AKI are

available. However, not all the methods are applicable to every patient and situation, so good clinical judgment is needed to determine the best method.

The medical history of patients with AKI should include careful attention to loss or sequestration of extracellular fluid volume and to symptoms of heart failure. Intense thirst, salt craving, orthostatic syncope, nonfluent speech, and muscle cramps often are symptoms of extracellular fluid loss. Review of available hemodynamic data (vital signs, central venous pressure, etc.) input and output, and daily body weight give invaluable information about the fluid status of the patient. Physical examination for assessing fluid status of a patient is difficult, because the physical signs often have limited sensitivity and specificity. The presence of a dry mucosal membrane, impaired capillary refill time, absence of axillary moisture, furrowed tongue or decreased turgor of skin over the forehead and sternum may indicate fluid loss or sequestration. In a meta-analysis, dry mucosal membrane and furrowed tongue had the highest sensitivity for detecting volume depletion.[214] Assessment of the jugular venous pressure with the patient reclining at 45° gives an estimate of right atrial pressure. The normal jugular venous pressure is between 0-3 cm above the sternal angle, which corresponds to a right atrial pressure of approximately 4-8 cm water. If the jugular venous pressure is difficult to visualize, gentle pressure over the liver to increase venous return can be helpful (the hepatojugular reflux). Recording the patient's daily body weight in conjunction with fluid balance charts and clinical examination can help estimate fluid balance. In critically ill patients, invasive hemodynamic monitoring (central venous and/or Swan-Ganz catheterization) is often necessary. However, the most important question the physician faces is whether fluid infusion will lead to improvement of general hemodynamics, which will, in turn, increase kidney blood flow and GFR.

The effect of volume infusion is determined by the Frank-Starling relationship, which relates stroke volume and cardiac preload.[215] In the first steep part of the curve, the stroke volume is highly dependent on preload, whereas in the second, flat part of the curve the preload has minimal impact on stroke volume (Figure 16). If the heart is working on the first part of the curve (point A in the figure) volume resuscitation will increase stroke volume and improve cardiac output. In contrast, if the heart is working on the second flat part of the curve (point B), volume infusion will not lead to improvement of cardiac output and fluid infusion can exert adverse effects (e.g., tissue edema). As mentioned above, signs of volume depletion or measurement of the central venous pressure or the pulmonary artery occlusion/wedge pressure can be misleading and often do not predict the effect of volume infusion, especially in critically ill ICU patients.[216] The reason why these static measures of preload are not always a reliable predictor of volume responsiveness, is that multiple Frank-Starling curves exist. At a given level of cardiac preload, it will depend on the contractility of the ventricle as to whether there might be an increase in stroke volume or not.[215] The only way to find that out is to induce a change in cardiac preload to determine at which part of the Frank-Starling curve the patient's heart is working. There are multiple ways to induce such a change and the easiest one is the administration of a test dose of 500 ml of crystalloid fluid and to monitor the hemodynamic changes. This method could be criticized, because the change in preload is not readily reversible, especially in the setting of AKI.[211] An alternative is the passive leg raising test, where the legs of the patient are passively lifted from the horizontal position and blood is transferred from the lower extremities to the intrathoracic compartment. The effect of the consecutive increase in preload can be monitored and used to guide subsequent fluid

therapy.[217] Another way of assessing fluid responsiveness is by recording the effect of mechanical ventilation on hemodynamics. The cyclic changes of ventricular preload by mechanical ventilation will result in greater cyclic changes in ventricular stroke volume, when the heart works on the steep portion of the Frank-Starling curve. Thus, higher variation in the arterial pulse pressure (>13%) as a measure for stroke volume will indicate volume responsiveness.[218]

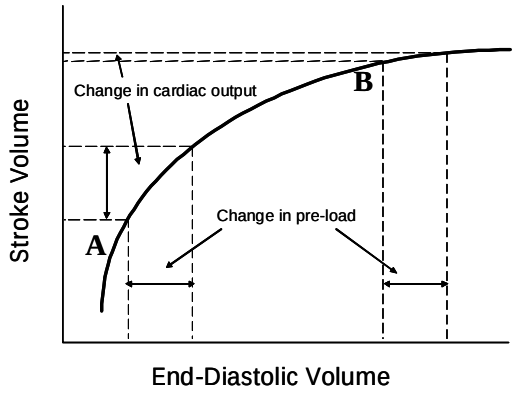

Figure 16. Starling curve: Frank-Starling relationship.

The position on the curve determines the effect of fluid loading. For a patient at point "A", fluid loading results in an increase in end diastolic volume (preload) which results in a large increase in stroke volume and, therefore, cardiac output. When at position "B", however, the same change in preload has a negligible effect on stroke volume. Note that each patient will have a unique Starling curve (more or less steep) that will define their individual relationship.

Laboratory parameters that should be measured besides SCr, BUN, and electrolytes are shown in Table 11. Additionally, urinary dipstick, urine microscopic examination, and urinary indices may be helpful in determining the underlying cause of AKI.

Table 11. Blood and serum findings pointing to specific causes of AKD

Laboratory finding	Observed in AKI due to:
Anemia	Pre-existent CRF, hemorrhage, hemolysis
Anemia with rouleaux formation	Plasma cell dyscrasia
Eosinophilia	Atheroemboli, acute interstitial nephritis or polyarteritis nodosa, parasitic infections
Leukopenia	SLE
Thrombocytopenia	SLE, Hantavirus infection, DIC, rhabdomyolysis, advanced liver disease with hypersplenism, "white clot syndrome" due to heparin administration
Thrombocytopenia, reticulocytosis, elevated LDH, schistocytes on peripheral smear, low ADAMTS13 levels	Thrombotic microangiopathy
Coagulopathy	Liver disease, DIC, antiphosholipid antibody syndrome
Hyperkalemia >5.5 mEq/l	Various causes
Marked hyperkalemia	Tumor lysis syndrome, hemolysis, use of NSAIDs, ACE-I or ARB
Marked hyperkalemia, hyperphosphatemia, hypocalcemia, elevated serum uric acid and CK, AST, and LDH	Rhabdomyolysis
Marked hyperkalemia, hyperphosphatemia, hypocalcemia, very high serum uric acid, normal or marginally elevated CK	Acute uric acid nephropathy, tumor lysis syndrome, heat stroke
Hypercalcemia	Malignancy, sarcoidosis, vitamin-D intoxication etc.
Widening of serum anion and osmolal gap*	Ethylene glycol or methanol intoxication, CKD .
Marked acidosis, anion gap >5-10 mEq/l	Ethylene glycol poisoning, rhabdomyolysis, lactic acidosis from sepsis
Hypergammaglobulinemia	SLE, bacterial endocarditis and other chronic infections
Paraprotein (M-gradient), hypergammaglobulinemia	Myeloma
Serum-free monoclonal light chains or urine electrophoresis showing free light chains	Myeloma, low-grade plasma cell dyscrasias (even in the absence of serum abnormalities)
Elevated serum IgA	IgA nephropathy
Elevated antinuclear antibodies	Autoimmune diseases including SLE, scleroderma, mixed connective tissue disease, Sjögren's syndrome etc.
Elevated anti-double stranded DNA antibodies	SLE
Elevated anti-C1q antibodies	SLE, MPGN, some cases of IgA nephropathy
Elevated ANCA titer	Wegener's granulomatosis, microscopic polyangiitis
Antiglomerular basement membrane antibodies	Anti-GBM nephritis, Goodpasture syndrome
Cryoglobulins	Hepatitis C and other infections, lymphoproliferative disorders

* Mild metabolic acidosis occurs frequently as a consequence of AKI and is often associated with a modest (5-10 mEq/l) increase in the anion gap.

ACE-I, angiotensin-converting enzyme inhibitors; ADAMTS13, a disintegrin and metalloprotease with thrombospondin-1–like domains; ARB, angiotensin-receptor blockers; AST, asparagine aminotransferase; CK, creatinine kinase; CRF, chronic renal failure; DIC, disseminated intravascular coagulation, LDH, lactate dehydrogenase; MPGN, membranoproliferative glomerulonephritis; NSAID, nonsteroidal anti-inflammatory drugs; SLE, systemic lupus erythematosus.

Urine Analysis, Sediment, and Urinary Diagnostic Indices

Urine analysis, sediment, and urinary diagnostic indices are important to aid the early diagnosis of AKI, differential diagnosis, severity of AKI, and prognosis of the patient with AKI.

Urine volume

Urine volume in AKI can vary from oliguria (i.e., <0.5 ml/kg/h) or even anuria to extreme polyuria. In most patients with AKI in the ICU, an indwelling urinary catheter allows accurate measurement of hourly urine output, a parameter useful in monitoring the initial response to fluid resuscitation until the intravascular fluid volume of the patient is adequately restored. Once this state is reached, hourly urine volumes are less useful in guiding management and increased urine flow should not be regarded as a primary treatment goal. If a patient has established oligoanuric AKI, the urinary catheter should be removed to reduce the risk of infection. Severe AKI can exist despite normal urine output (i.e., nonoliguria), but changes in urine output can occur long before biochemical changes are apparent. Nonoliguric AKI is nowadays more common than oliguric AKI, particularly in ICU patients, because of the more frequent monitoring via daily SCr changes and/or earlier intervention with fluid loading and diuretics. Importantly, urine output becomes an unreliable measure of kidney perfusion in the setting of AKI, and reliance on urine output to guide fluid therapy can result in under- or over-resuscitation.

Anuria is seen with cessation of glomerular filtration (e.g., rapidly progressive glomerulonephritis, acute cortical necrosis, or total renal arterial or venous occlusion) or complete urinary tract obstruction. Brief (<24- to 48-hour) episodes of oligoanuria occur in some cases of AKI. Prerenal causes of AKI nearly always present with oliguria, although nonoliguric forms have been reported.[219] Postrenal and renal causes of AKI can present with any pattern of urine flow. The presence of alternating anuria and polyuria is an uncommon but classic manifestation of urinary tract obstruction, e.g., due to a stone that changes its position. In rare cases, unilateral obstruction can lead to anuria and AKI; vascular or ureteral spasm, mediated by autonomic activation, is thought to be responsible for the loss of function in the nonobstructed kidney.

Urine dipstick and microscopic examination

Routine dipstick and microscopic analysis of urine are often helpful in determining the cause of AKI (Table 12). Generally, a normal urinanalysis in the setting of AKI suggests a prerenal or postrenal cause and an abnormal urinalysis a “renal” cause. However, patients with a prerenal cause for AKI can have a significant number of casts (due to the precipitation of Tamm-Horsfall protein in concentrated, acidic urine) and cellular elements in their urine in addition to small urine volumes, high specific gravity, and acidic urine. Urinary protein measurement by dipstick is specific for albumin. Small amounts of protein found by dipstick, with larger amounts found by laboratory urinary protein tests (such as sulfosalicylic acid) suggest the presence of light chains. If the dipstick reaction for protein is moderately or strongly positive in the setting of AKI, quantification is indicated. The presence of more than 1-2 g/d of urine protein suggests a glomerular cause of AKI.

Table 12. Urinary indices

Indices	Prerenal	Renal
Urine sediment	Hyaline casts	Abnormal
Specific gravity	>1.020	~1.010
Urine osmolality (mOsm per kg H_2O)	>500	<350
U_{Na} (mmol/l)	<20	>40
Fractional excretion		
Sodium (%)	<1	>2
Urea (%)	<35	>35
Uric acid (%)	<7	>15
Lithium (%)	<7	>20
Low molecular weight proteins	Low	High
Brush border enzymes	Low	High

Examination of the urine sediment is of great value in AKI. Gross or microscopic hematuria suggests a glomerular, vascular, interstitial, or other structural renal cause (e.g., stone, tumor, infection or trauma) of AKI and is rarely seen with more typical forms of AKI. RBC casts in the urine sediment strongly suggest a glomerular or vascular cause of AKI, but have also been observed with acute interstitial nephritis. Studies of the urinary red cell morphology in AKI of different causes are lacking. Lack of urinary red cells, despite a positive dipstick reaction for blood, is typical of AKI induced by myoglobinuria or hemoglobinuria.

The performance of the urinary sediment examination was recently examined in the setting of AKI.[220] The cause of AKI was assessed at two time points: i) before urine microscopy examination; and ii) after patient discharge or death (final diagnosis). A urinary scoring system was created on the basis of casts and renal tubular epithelial cells to differentiate "renal" from prerenal causes of AKI. The urinary sediment scoring system was highly predictive of the final diagnosis of ATN. In patients with a high pretest probability of renal AKI, any casts or renal tubular epithelial cells (score ≥2) resulted in a very high positive predictive value and low negative predictive value for a final diagnosis of renal AKI. In patients with a low pretest probability of renal AKI (initial diagnosis of a prerenal state), lack of casts or renal tubular epithelial cells on urinary sediment examination had a sensitivity of 73% and specificity of 75% for a final diagnosis of prerenal azotemia. The negative predictive value of absence of casts or renal tubular epithelial cells in patients with low pretest probability of disease was 91%.

However, it is important to appreciate that these categories remain clinical diagnoses, since no gold standard was applied, and one could argue that urine sediment merely increases "diagnostic confidence". Indeed, the diagnostic value of urinary sediment was not confirmed in a recent systematic review on urinary microscopy in patients with septic AKI.[221] Because of substantial heterogeneity, no formal quantitative analysis could be performed, since urinary microscopy was described in only seven publications analyzed in this review (26%). The majority were small, single-center reports and showed serious limitations. For example, only 52% of patients were septic, only 54% of patients had AKI, many studies failed to include a control group, time from diagnosis of sepsis or AKI to measure of urinary tests was variable, and there were numerous potential confounders. A few reports of urinary microscopy described

muddy brown/epithelial cell casts and renal tubular epithelial cells in patients with septic acute renal failure (ARF), whereas others described a normal urinary sediment. This systematic review concluded that the scientific basis for the use of urinary biochemistry indices and urinary microscopy is weak, at least in patients with septic AKI.

Large numbers of white blood cells and, in particular, leukocyte casts on urinalysis suggests either pyelonephritis or interstitial nephritis. Eosinophiluria (>1% urine white blood cells) is nonspecific. However, this finding is diagnostically valuable when AKI occurs in a setting compatible with either allergic interstitial nephritis (drug exposure, fever, rash, peripheral eosinphiluria) or cholesterol embolism. Collecting duct cells and total casts in urine detected by cytodiagnostic quantitative assessment are increased in AKI but as illustrated by the above-mentioned systematic review,[221] lacks sufficient sensitivity, specificity, and predictive power for routine clinical use.

Crystals in the urine sediment should be assessed by an experienced microscopist using fresh, warm urine, polarizing microscopy, and knowledge of the urine pH. A large number of uric acid crystals suggest acute uric acid nephropathy or tumor lysis syndrome. Oxalate crystals are compatible with ethylene glycol intoxication, jejunoileal bypass, or massive doses of vitamin C underlying AKI. Drug-induced crystals can result from sulfonamides, indinavir, and triamterene.

In the setting of prerenal azotemia, tubular function is intact and renal vasoconstriction is associated with enhanced tubular sodium reabsorption. Thus, when creatinine accumulates in the blood due to a fall in GFR secondary to renal vasoconstriction with intact tubular function, the fractional excretion (FE) of filtered sodium (FE_{Na} = [(urine sodium x plasma creatinine)/(plasma sodium x urine creatinine)]) is less than 1%. A paradoxically high FE_{Na}, despite the presence of prerenal azotemia, occurs during diuretic treatment, within the preceding 24 hours, with glycosuria. Finally, renal vasoconstriction in a patient with advanced CRF may not be expected to be associated with a FE_{Na} of less than 1% because of chronic adaptation.

A reduced effective circulating volume also stimulates antidiuretic hormone release. Antidiuretic hormone results in increased distal water and urea reabsorption. Thus, a low FE_{urea} (<35%) is more sensitive and specific than FE_{Na} in differentiating between prerenal and renal causes of AKI, especially when diuretics have been administered.[222] The diagnostic accuracy of this combination of FE_{Na} and FE_{urea} was prospectively explored recently in 99 patients hospitalized at a tertiary-care center who developed a 30% increase in SCr concentration from baseline within 1 week.[223] Patients were classified as having transient or persistent changes in renal function according to the clinical context and whether SCr returned to baseline within 7 days. Each group also was subdivided according to exposure to diuretics. FE_{urea} of ≤35% and FE_{Na} of ≤1% were then analyzed for their ability to predict transient, presumably prerenal, azotemia. Sensitivity, specificity, and receiver-operator characteristic curves were generated for each index test. Sensitivity and specificity of FE_{urea} were 48% and 75% in patients who did not receive diuretics and 79% and 33% in patients administered diuretics. Sensitivity and specificity of FE_{Na} were 78% and 75% in patients not administered diuretics and 58% and 81% in those administered diuretics. Receiver-operator characteristic curves did not identify better diagnostic cutoff values for FE_{urea} or FE_{Na}. This study concluded that in patients without

diuretic use, FE_{Na} is better able to distinguish transient from persistent azotemia. In patients administered diuretics, this distinction cannot be made accurately by means of FE_{Na} or FE_{urea} and thus cannot be used as an alternative tool because it lacks specificity. Further investigations of the concomitant use of both urinary parameters are thus warranted, especially since the underlying assumption in this study that "transient" equates to "prerenal" is rather dubious. Another caveat is that a low FE_{Na} does not always indicate prerenal azotemia, and can be observed in the early stages of obstruction, acute glomerulonephritis, pigment nephropathy, and intrinsic AKI, induced by radiocontrast materials. This may be related to the early presence of severe renal vasoconstriction and intact distal tubule function, which can occur in the presence of proximal tubule injury.

The above- mentioned systematic review[221] has also explored the diagnostic accuracy of traditional urinary parameters in septic patients. Urinary biochemistry or derived indices were reported in 24 articles (89%). Urinary sodium, FE_{Na}, urinary-plasma creatinine ratio, urinary osmolality, urinary-plasma osmolality ratio, and serum urea-creatinine ratio showed variable and inconsistent results. In general, it can thus be concluded that, although useful as a first approach, the "classical" urinary parameters are not always reliable to make a clear distinction between the different forms of AKI.

New Biomarkers in the Early Diagnosis, Differential Diagnosis, and Prognosis of AKI

As outlined in detail in previous chapters, AKI has mainly been diagnosed by changes in SCr concentration, which reflect mainly changes in GFR. In addition to the change in SCr, an abrupt decrease of urinary output has been incorporated in the definition and classification of AKI. The latter parameter is probably more useful in the ICU than in the hospital, non-ICU, and community settings. Unfortunately, SCr does not accurately reflect the GFR in patients with AKI because they are not at steady state; furthermore, acute changes in SCr lag behind the stage of kidney damage, which presumably precedes the stage of decrease in GFR. In addition, in sepsis, one of the main causes of AKI in critically ill patients, creatinine production may be decreased as has recently been observed in an animal model of sepsis.[224] These data suggest that evaluation of kidney injury by SCr alone underestimates the early diagnosis of kidney injury, fails early diagnosis of sepsis-induced AKI, and could also lead to a further incorrect assessment of treatment efficacy.

Several candidate biomarkers for diagnosis of AKI have been proposed and are in various stages of development and validation. It is widely acknowledged that a single biomarker may be unable to diagnose all aspects of a complex multifactorial process such as AKI, and that a panel of biomarkers may be necessary. However, besides the analytical problems associated with each individual biomarker, there is also a problem of SCr as the gold standard in the evaluation of these biomarkers. As recently underlined by Waikar et al,[225] many biomarker studies published to date begin by reciting creatinine's imperfections as a biomarker—nonspecificity due to prerenal azotemia, nonsensitivity due to renal reserve—and then go on to judge the performance of the biomarker under study against the same "gold standard" whose imperfections engendered the need to discover a novel and superior biomarker! The real gold standard for the AKI biomarkers is whether they can be used to define and risk-stratify AKI and related complications, facilitating early diagnosis and interventions to improve clinical outcomes. If novel AKI biomarkers can be proved superior for these purposes, then they may

even replace SCr changes and urine output as our primary clinical tools to diagnose AKI and monitor response to therapy.[4]

Nonetheless, it should be pointed out that the definitions of AKI based on changes in SCr and urine output already risk-stratify patients quite well (see Chapter 2.1); the real problems with these definitions is that they are based on a maximum SCr change, which may take days to achieve, or urine output which, although more timely, is neither sensitive nor specific for AKI. Furthermore, although alternative classification schemes have been proposed based on absolute changes in SCr, which better reflect the physiology of glomerular function and may be more timely,[225] they have not been shown to correlate with clinical outcomes. Neither have anatomic or imaging based criteria been shown to correlate with outcome. Thus, it is in the clinical context of AKI defined and classified by maximum changes in SCr and urine output, that we are seeking biomarkers to detect AKI earlier and perhaps more accurately.

New biomarkers are likely to be useful in facilitating early diagnosis, guiding targeted intervention, and monitoring disease progression and resolution.[226, 227] However, AKI is a complex and heterogeneous process, and the identification of biomarkers should not be limited to initial injury alone, but should include markers of risk, injury propagation, and resolution of injury. It can be argued that markers of early resolution will be equally as important as markers of initial injury.[228] Desirable characteristics and expectations from an ideal biomarker for AKI are listed in Table 13, adapted from two recent reviews;[229, 230] clearly, it is unlikely that any biomarker will be classified as ideal under these criteria.

Table 13. Characteristics of an ideal biomarker for AKI

- Noninvasive
- Easily detectable in accessible samples like serum or urine
- Highly sensitive and specific for AKI, also in the presence of concomitant injury involving other organs
- Rapidly and reliably measurable
- Capable of early detection of AKI
- Able to give insight into etiology, nature, and duration of insult
- A marker of injury in addition to marker of function
- Predictor of AKI severity and reversibility
- Helpful in monitoring course and the response to interventions
- Useful as surrogate end-point for clinical interventional studies
- Unaffected by other biological variables
- Inexpensive

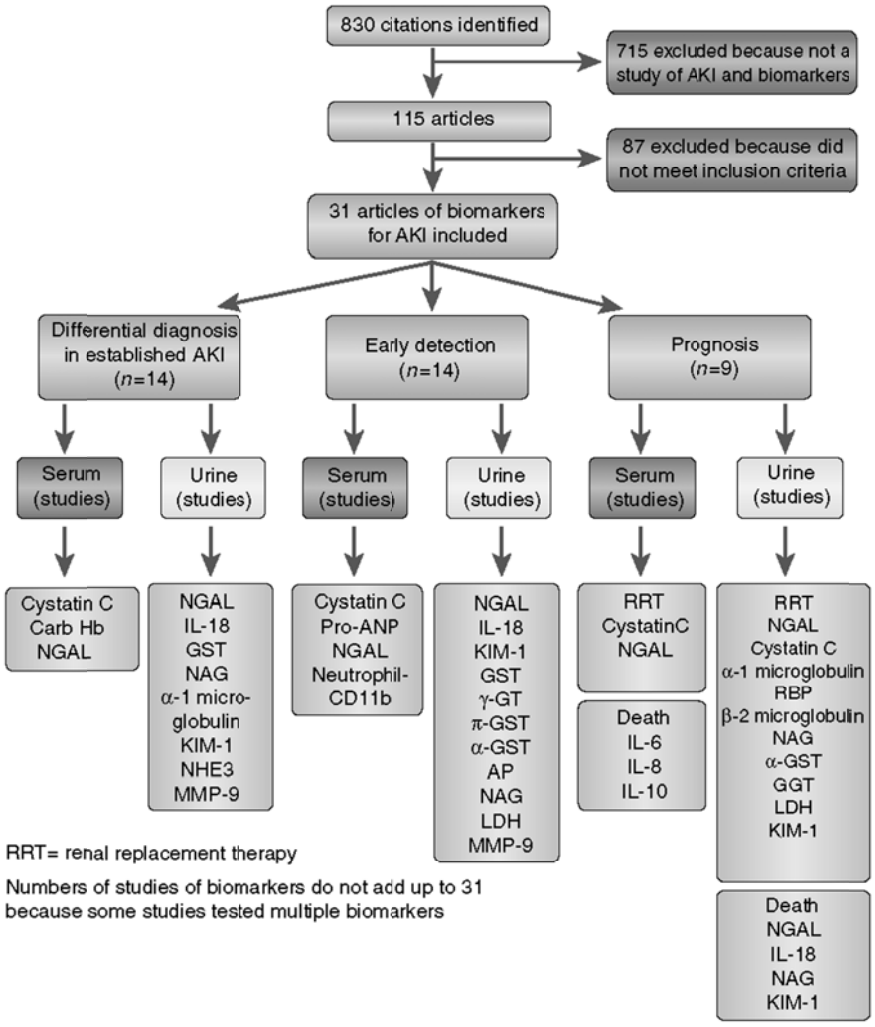

Figure 17. Biomarkers used in early detection, prognosis, or differential diagnosis of AKI.

AKI, acute kidney injury; AP, alkaline phosphatase; Carb-Hb, Carbamylated Hb, GGT, γ-glutamyltransferase; GST, glutathione-S-transferase; GT, glutamyl transpeptidase; IL, interleukin; KIM-1, kidney injury molecule-1; LDH, lactate dehydrogenase; MMP-9, matrix metalloproteinase-9; NAG, *N*-acetyl-β-D-glucosaminidase; NGAL, neutrophil gelatinase-associated lipocalin; NHE3, sodium hydrogen exchanger 1; Pro-ANP, prohormone of atrial natriuretic peptide; RBP, retinol-binding protein; RRT, renal replacement therapy. Reprinted by permission from Macmillan Publishers Ltd: Kidney International. Coca SG, Yalavarthy R, Concato J, et al. Biomarkers for the diagnosis and risk stratification of acute kidney injury: a systematic review. Kidney Int 73: 1008-1016, 2008 [231]; Accessed http://www.nature.com/ki/journal/v73/n9/full/5002729a.html

Figure 17, taken from the systematic review by Coca et al.[231] summarizes a number of studies performed on serum and urine samples with different biomarkers either used in the differential diagnosis in established AKI, or the early detection or prognosis of AKI. This systematic review included, in total, 31 studies that evaluated 21 unique serum and urine biomarkers. Twenty-five of the 31 studies were scored as having "good" quality. The results of the studies indicated that serum cystatin C, urine IL-18, and urine kidney injury molecule-1 (KIM-1) performed best for the differential diagnosis of established AKI. Serum cystatin C and urine neutrophil gelatinase–associated lipocalin (NGAL), IL-18, glutathione-S-transferase-p,

and c-glutathione-S-transferase performed best for early diagnosis of AKI. Urine N-acetyl-b-D-glucosaminidase, KIM-1, and IL-18 performed the best for mortality risk prediction after AKI.[231]

As discussed by Kanagasundaram,[232] it is crucial, when examining the evolving literature, to bear in mind what the potential candidate biomarker is actually reflecting; plasma cystatin C, for instance, is a measure of kidney functional status (a "quick creatinine") whereas others, such as urinary NGAL and urinary IL-18, are products of the pathologic derangements that occur in AKI[233] and indicate active kidney damage (a "troponin of the kidney"). Still others, such as plasma NGAL or IL-6 may simply identify a pathophysiologic state that is commonly associated with the development of AKI (an "LDL cholesterol" for the kidney).

Basic and clinical research in this field is evolving rapidly. Although the Work Group felt that this research is very promising, the evidence is not yet sufficient for recommendations as to which biomarkers should be used or how to use them. This brief narrative review will therefore summarize selected recent studies performed with the most promising biomarkers in AKI. Many recent excellent and detailed reviews, including discussion of biomarkers that are not covered here, are available.[226, 227, 229, 230, 232, 234-241] In particular, the review by Moore et al.[237] details not only the characteristics and function of the most studied biomarkers but also the analytical techniques, threshold values, and performance characteristics in different settings of AKI.

Plasma and/or urine cystatin C

Cystatin C is synthesized and released into plasma by all nucleated cells at a constant rate, and its small size and positive charge at physiologic pH makes it freely filtered at the glomerulus. While plasma cystatin C is used to estimate GFR, urine cystatin C is a biomarker of tubular cell integrity. This is because normally functioning renal tubular epithelial cells take up cystatin C and it cannot normally be measured in urine. Although cystatin C is generally considered less subject to the nonrenal variables that impact creatinine, recent studies suggest that cystatin C levels may, in fact, be affected by various anthropometric measures as well as inflammatory processes, use of corticosteroids, and changes in thyroid function, thereby potentially confounding its interpretation.[242] In human studies, plasma cystatin C can predict the development of AKI[243] and the requirement for RRT,[244] although its superiority over SCr has not been a universal finding.[245] For example, a recent study explored the potential usefulness of a single serum cystatin C level for predicting a composite outcome of dialysis requirement or in-hospital death in a cohort of 200 hospitalized patients with an established diagnosis of AKI and compared its performance characteristics to SCr, BUN, and timed urine output. It appeared that serum cystatin C performs similarly to SCr, BUN, and urine output for predicting adverse outcomes.[246] Serum cystatin C has also been analyzed when compared to plasma NGAL and more conventional markers in cardiac surgery patients.[247] Compared to the ICU admission postoperative SCr, the contemporaneous plasma NGAL and serum cystatin C were found to have good predictive value for the subsequent development of AKI. However, the accuracy of cystatin C diminished after patients with preexisting renal impairment were excluded from analysis, suggesting that it did not only indicate evolving AKI but was also an independent risk factor for it, being a reflection of the strong, predisposing effects of CKD. Beyond AKI, both plasma NGAL and cystatin C carried excellent prognostic value for the composite outcome of kidney replacement therapy or hospital mortality. Koyner et al.[248] found

urinary cystatin C, together with urinary NGAL, a very promising early (within 6 hours after surgery) biomarker of AKI in adult cardiac surgery patients. There is now an international standard for cystatin C determination which should be used in clinical research going forward to allow comparison across studies.[249, 250]

Plasma and/or urine NGAL

NGAL is a ubiquitous 25-KDa protein, covalently bound to gelatinase from human neutrophils, which is expressed at very low concentrations in various human tissues, including the kidney, trachea, lungs, stomach and colon.[251] NGAL expression increases greatly in the presence of inflammation and injured epithelia, and this includes renal damage after ischemia reperfusion injury and nephrotoxicity.[252] Plasma and/or urine NGAL levels have been shown to predict AKI in settings as diverse as percutaneous coronary intervention,[253] pediatric[7] and adult[254] cardiac surgery, and septic[255] and nonseptic[256] critically ill children. A recent systematic review and meta-analysis on the diagnostic and prognostic value of either plasma or urine NGAL found that the diagnostic accuracy of plasma/serum NGAL was similar to that of urine NGAL. Age was identified as an effective modifier of NGAL value with a better predictive ability in children compared to adults. Overall, NGAL was found to be a potentially useful prognostic tool for prediction of RRT initiation and in-hospital mortality.[257] An accompanying editorial[258] pointed, however, to several important limitations of the existing knowledge on NGAL (and other biomarkers) as they emerged from the meta-analysis. Most of the studies were single-centered with low numbers of included patients and also low numbers of outcome end-points, a relatively "homogenous population of relatively noncomplex forms of AKI" were studied, the already known difficulties of AKI definition using SCr, analytical problems in many studies with "home-grown" enzyme-linked immunosorbent assay to measure NGAL with wide ranges of "normal" values, and finally, potential publication bias.

Demonstration of robust sensitivity and specificity in a heterogeneous ICU population would strengthen the concept of NGAL as a biomarker for AKI. Cruz et al.[259] performed such a study assessing the diagnostic accuracy of plasma NGAL both for the early detection of AKI and the need for RRT in an heterogeneous adult ICU population. Interestingly, the plasma NGAL was found to be elevated in all ICU patients whether they had AKI or not; 67% of patients developed AKI within 24 hours of admission, and only 37 patients progressed to a more severe RIFLE class following the development of AKI. Moreover, median plasma NGAL levels of patients who developed AKI within 24-48 hours were not statistically significant compared to those of non-AKI patients ($P = 0.13$). As expected, plasma NGAL levels correlated with overall disease severity as assessed by ICU severity scoring systems, but it is clear that plasma NGAL levels did not help in identifying patients at risk of AKI. Given that all these patients were admitted to an ICU environment, some of them still developed AKI and a small percentage continued to progress despite treatment. Interestingly Cruz et al.[259] did not find differences in plasma NGAL between patients with sepsis and those without. This is in contrast to the findings reported by Bagshaw et al.[260] who found that septic AKI was associated with significantly higher plasma and urine NGAL at enrollment compared to nonseptic AKI ($P < 0.001$). Urine NGAL remained higher in septic compared to nonseptic AKI at 12 and 24 hours after enrollment in the study. Plasma NGAL showed fair discrimination for AKI progression (area under receiver-operator characteristic curve [AUC] 0.71), and RRT (AUC 0.78). Although urine NGAL performed less well (AUC 0.70, 0.70), peak urine NGAL predicted AKI progression better in nonseptic AKI (AUC 0.82). Peak plasma NGAL and peak

urine NGAL showed fair diagnostic performance discriminating between septic and nonseptic AKI (AUC 0.77; 95% CI 0.63-0.90 and AUC 0.70; 0.59-0.82). Once again, the "sicker" patients demonstrated higher NGAL levels and, although not quite reaching statistical significance, showed rises in more conventional markers of kidney function.

In critically ill children,[255]it was demonstrated that plasma NGAL is increased in sepsis and septic shock even in the absence of AKI. This was not unexpected regarding the fact that NGAL is released from activated neutrophils. Also, a larger trial of 451 critically ill adults demonstrated that urine NGAL, though independently associated with AKI, yielded only very moderate discrimination at 48 hours.[261] As pointed out in an editorial[229], although NGAL estimations may predict AKI occurring within 24 hours (and maybe even within 48 hours), they are not truly specific in that the other multiple problems and comorbidities critically ill patients have can also elevate NGAL. This may also explain the fact that predictive ability of NGAL for AKI was found to be far better in children (AUC 0.930; 95% CI 0.883-0.968) than in adults (AUC 0.782; 95% CI 0.689-0.872) in the above mentioned meta-analysis.[257]

The sensitivity and specificity of a single measurement of urine NGAL and other urinary proteins (*N*-acetyl-beta-D-glucosaminidase [NAG], α1-microglobulin α1-acid glycoprotein) to detect AKI were prospectively investigated in an emergency-room setting.[262] The a posteriori diagnosis of AKI was based on the RIFLE criteria. At a cutoff value of 130 g per gram creatinine, sensitivity and specificity of NGAL for detecting AKI were 0.90 (95% CI 0.73-0.98) and 0.995 (CI 0.990-1.00), respectively, and positive and negative likelihood ratios were 181.5 (CI 58.33-564.71) and 0.10 (CI 0.03-0.29); these values were superior to those for NAG, α1-microglobulin, α1-acid glycoprotein, FE_{Na}, and SCr. In multiple logistic regression, urine NGAL was highly predictive of clinical outcomes, including nephrology consultation, RRT, and admission to the ICU (OR 24.71 [CI 7.69-79.42]). Very recently, Haase-Fielitz et al.[263] observed that the predictive value of plasma NGAL in cardiac surgery varied according to the AKI definition used and was higher for more severe AKI.

Interleukins

IL-18 is a proinflammatory cytokine that is induced in the proximal convoluted tubule and is detected in urine following AKI. Rising urinary IL-18 levels are predictive of AKI in a general critically ill pediatric population,[264] in critically ill patients with acute respiratory distress syndrome,[8] and after adult and pediatric cardiac surgery.[10] Elevated urinary IL-18 is more specific for ischemic AKI and its levels are not deranged in CKD, urinary tract infections, or nephrotoxic AKI.[265] However, Haase et al.[266] did not find IL-18 to be a useful early predictor of AKI in a group of 100 adult patients undergoing cardiac surgery. By contrast, plasma IL-6 and IL-8 values identify AKI early in children undergoing cardiopulmonary bypass surgery.[267] Similar results were found for adults with community-acquired pneumonia in which IL-6 predicted the development of AKI even in patients clinically at low risk.[268]

KIM-1

KIM-1, also known as TIM-1 (T cell immunoglobulin mucin domains-1) as it is expressed at low levels by subpopulations of activated T cells is a transmembrane protein with extracellular mucin and immunoglobulin domains. KIM-1 is not detectable in the normal human and rodent kidney but is increased in expression more than any other protein in the injured kidney and is localized predominantly to the apical membrane of the surviving

proximal epithelial cells (for review, see Bonventre).[269] Human studies have confirmed the promise of KIM-1 for the diagnosis and prediction of outcome of AKI.[6, 227, 270-272]Recently a rapid direction immunochromatographic lateral flow 15-minute assay for detection of both urinary KIM-1 (rat) or KIM-1 (human) has been developed.[273] Using this assay, the KIM-1 band intensity was significantly greater in urine from patients with AKI than in urine from healthy volunteers. The KIM-1 dipstick also enabled temporal evaluation of kidney injury and recovery in two patients who developed postoperative AKI, following cytoreductive surgery for malignant mesothelioma with intraoperative local cisplatin administration.

Urinary L type fatty acid binding protein (L-FABP)

L-FABP binds selectively to intracellular free unsaturated fatty acids and lipid peroxidation products during hypoxic tissue injury. Urinary L-FABP has recently been shown to be a potential biomarker for the detection and assessment of AKI. Recently urinary L-FABP has been reported as an early marker of AKI in clinical studies where AKI was caused by acute tubular necrosis, sepsis, cardiac surgery, and nephrotoxins, including radiocontrast agents.[274-278] In these studies, urinary L-FABP was shown to reach high levels before the elevation of SCr. Ferguson et al.[279] have demonstrated in a cross-sectional study that urinary L-FABP is an excellent biomarker of AKI, and may be useful in predicting dialysis-free survival. The Japanese Ministry of Health, Labour and Welfare recently approved urinary L-FABP as a biomarker of renal tubular injury.

Biomarkers in combination

It is possible that, from future studies, a panel of biomarkers will emerge combining various markers in order to optimize the features of each (Figure 18). However, the complicated process of how to combine biomarkers for optimal clinical utility remains a hurdle.

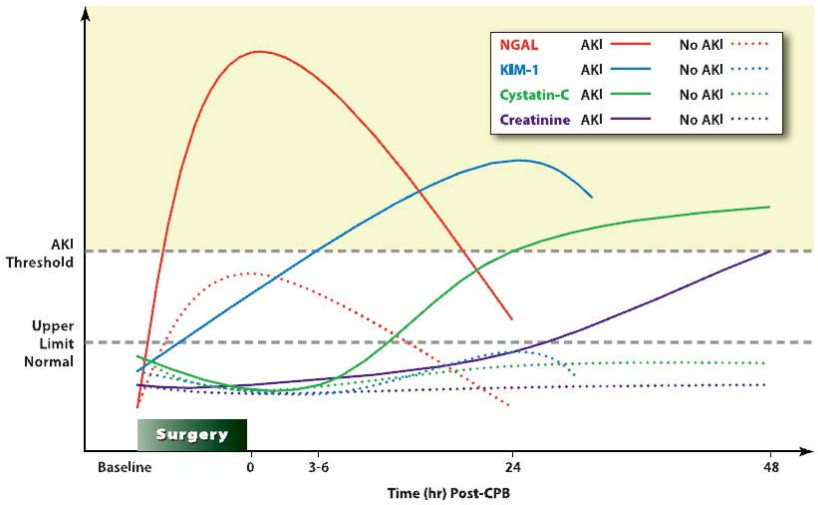

Figure 18. The theoretical evolution of the time course of several biomarkers in AKI following cardiac surgery.
AKI, acute kidney injury; KIM-1, kidney injury molecule 1; NGAL, neutrophil gelatinase–associated lipocalin. Reprinted with permission[235]

The combined diagnostic utility of urinary KIM-1, NAG, and NGAL was evaluated for the early detection of postoperative AKI in a prospective study of 90 adults undergoing cardiac surgery.[280] AUCs for KIM-1 to predict AKI immediately and 3 hours after operation were 0.68 and 0.65; for NAG, 0.61 and 0.63; and for NGAL, 0.59 and 0.65, respectively. Combining the three biomarkers enhanced the sensitivity of early detection of postoperative AKI to AUCs of 0.75 and 0.78, respectively. The performance of combining biomarkers was even better among 16 early postoperative AKI patients with AUCs of 0.80 and 0.84, respectively. In another study[227] of nine different biomarkers (KIM-1, NGAL, IL-18, hepatocyte growth factor [HGF], cystatin C, NAG, VEGF, chemokine interferon-inducible protein 10, and total protein) a logic regression model combining four biomarkers resulted in a greater AUC (0.94) compared to any individual biomarker. This study involved a cross-sectional comparison of 204 patients with or without AKI. Age-adjusted levels of urinary KIM-1, NAG, HGF, VEGF, and total protein were significantly higher in patients who died or required RRT when compared to those who survived and did not require RRT. Relevant to these studies is the investigation of Haase-Fielitz et al.[247] on the early use of plasma biomarkers in adult cardiac surgical patients (urine NGAL having already been studied in this setting).[254] As already discussed earlier in the section on cystatin C, the contemporaneous plasma NGAL and serum cystatin C levels were found to have better predictive value for the subsequent development of AKI.

Ho et al.[234] applied proteomics to the analysis of urine for biomarker discovery in a prospective cohort study of individuals undergoing cardiopulmonary bypass surgery. There were several notable findings in the study. First, regardless of whether AKI developed, all subjects had early evidence of tubular dysfunction and stress, shown by early β2-microglobulinuria. Systemic markers of inflammation, such as the proinflammatory cytokine IL-6 and several chemokines, were also increased in both groups at each time measured. Second, in patients who went on to develop AKI, the urinary proteome became more complex, suggesting either a second phase of injury or progression of injury. In these individuals, α1-microglobulin and NGAL were identified as early as 1 hour into the bypass procedure and remained increased at postoperative days 3 to 5 in patients with AKI, compared to patients who did not develop AKI. Third, and perhaps most interesting, proteomic analysis identified two high-intensity peaks for which the appearance postoperatively was associated with lack of development of AKI. One of these peaks was subsequently determined to be hepcidin-25, which was preferentially found in urine on postoperative day 1 of patients who did not go on to develop AKI. Because hepcidin is a regulator of iron homeostasis, these data again invoke the importance of free iron in the pathogenesis of ischemic and toxic AKI.

In a very recent study,[281] a combination of urinary biomarkers (γ-glutamyltranspeptidase and alkaline phosphatase) were used to identify and triage patients for an intervention study testing whether early treatment (within 6 hours of injury) with a high dose of erythropoietin could prevent the development of AKI in ICU patients. Although the combined elevation of γ-glutamyltranspeptidase and alkaline phosphatase identified patients with worse outcomes, the tests were poor in predicting AKI, with a combined AUC of only 0.54.

Conclusions

It is clear that, for the time being, these new biomarkers have primary roles as research tools. It is also obvious that an early diagnosis of AKI may allow timely diagnostic and therapeutic interventions in which the initiating insult may have been long over by the time

AKI is actually diagnosed using SCr. Close linkage between the index insult and time of diagnosis may be particularly important if other confounding insults are likely, as is clearly the case in the critical-care setting.[232] As far as the clinical utility of these biomarkers is concerned, most of the literature has emerged from relatively small single-center studies and from homogenous patient populations. Large multicenter prospective studies are required for further validation of the use of AKI biomarkers (alone and in combination panels) in heterogeneous patient populations and for defining cut-off values for diagnosis and outcomes of AKI.[4] The key unanswered question remains whether biomarkers will add anything to management beyond the information provided using our conventional, crude, and creatinine-based diagnosis and other aspects of clinical assessment. Indeed, it is hoped that biomarkers will feature in future clinical practice guidelines for AKI, although they currently have no better diagnostic performance than the classical clinical and routine biological parameters.[282, 283]

Imaging Procedures

Ultrasonography is mandatory in patients with AKI if obstructive nephropathy is suspected. It exhibits high sensitivity (90-98%) but a lower specificity (65-84%) for the detection of urinary tract obstruction. However, it is not a reliable method for identifying the anatomic site of obstruction. Sensitive ultrasonographic findings to rule out postrenal azotemia are a post–void residual bladder urine below 50 ml and absence of pelvicalyceal dilation. Patients with highly distensible collecting systems or with pyelocaliectasis may be misdiagnosed as having hydronephrosis. False-negative findings have also been reported in patients with very early (<8-hour) obstruction. In many other false-negative cases, the patients were of an older age and the obstructing process, usually prostatic carcinoma or retroperitoneal fibrosis, encased the retroperitoneal ureters and renal pelvis, preventing their dilation. In the elderly, partial obstruction may be obscured by volume depletion. When there is a strong suspicion of obstruction, the ultrasonographic examination should be repeated after volume repletion. Increased ultrasonographic renal size without hydronephrosis may occur with acute glomerulonephritis, with infiltration by amyloid or malignancy, in diabetes, and in renal vein thrombosis. The finding of reduced renal size and increased echogenicity points to CKD. Even if the kidneys are reduced in size, the possibility of a prerenal cause of AKI or acute-on-chronic kidney injury must always be considered. Ultrasound contrast media can improve the diagnostic capabilities in AKI by allowing the visualization of altered kidney blood flow and of kidney perfusion defects.

Renal Doppler ultrasonography studies have been suggested to differentiate prerenal cause from renal AKI. Partly as a result of intrarenal vasoconstriction, ischemic AKI usually produces a reduction in renal blood flow. Increases of the resistance index to >0.75 have been described in 91% of kidneys with ischemic AKI, compared to prerenal azotemia, which is typically associated with a RI <0.75. However, the resistance index results overlap between these two major causes of acute decreased renal function, and high resistance indexes are also observed in acute obstruction, which markedly reduces its usefulness to obtain a specific diagnosis.

i.v. urography nowadays is largely abandoned in patients with AKI in particular, given the need for potentially nephrotoxic contrast media. A plain radiograph of the abdomen (sometimes called KUB : “kidney, ureter and bladder”) is a mandatory investigation in any

patient in whom an obstructive cause of AKI is suspected, since it can detect even small radio-opaque stones and ureteral stones not found by ultrasound. The presence and site of obstruction is accurately diagnosed by antegrade or retrograde pyelography. If obstruction is present, a ureteral stent or percutaneous nephrostomy can be placed in the same session.

A computed tomography (CT) scan performed without contrast media is of comparable diagnostic value to the renal ultrasound but is more costly and less convenient. However, CT is superior in the evaluation of ureteral obstruction, since it can delineate the level of obstruction and define retroperitoneal inflammatory tissue (in retroperitoneal fibrosis) or a retroperitoneal malignant mass.

Magnetic resonance imaging (MRI) is not usually used for evaluation of AKI. An altered corticomedullary relationship is frequently recognized in patients with AKI but also in other acute kidney diseases on T-weighed images. When postrenal AKI is suspected, MRI is valuable in assessing hydronephrosis and detecting the cause and site of obstruction. Magnetic resonance angiography (MRA) can be useful for detecting abnormalities in the renal artery and vein. In particular, the diagnosis of acute renal cortical necrosis becomes more reliable with Gd-enhanced MRI. The “rim sign” is characteristic for this infrequent cause of AKI. In view of the increasingly reported incidence of the syndrome of nephrogenic systemic fibrosis in patients who have been exposed to Gd-containing contrast media, and such cases have also been described in patients with AKI (see Chapter 4.3), it is not recommended to use Gd-containing compounds, unless unavoidable, in patients with a GFR <30-40 ml/min.

Renal angiography can be indicated when renal artery occlusion (by embolization, thrombosis, or a dissecting aneurysm) is suspected based on the clinical history (e.g., in a patients with atrial fibrillation and acute flank pain) or on duplex scanning, to confirm the exact anatomy of the occlusion and to assess the potential for intervention. However, in this setting, MRA or spiral CT is superior. Hepatic or renal angiography may also be useful in diagnosing polyarteritis nodosa.

Although Doppler ultrasound, MRI, MRA, and CT are used more frequently in the evaluation of thromboembolic disease and acute cortical necrosis, renal venography may be indicated to confirm a clinical or duplex ultrasound suspicion of renal vein thrombosis. When a diagnosis of acute renal artery occlusion is considered, renal angiography should be obtained urgently, as early surgical or thrombolytic therapy may be necessary to salvage the kidney. However, where the complete occlusion occurs in a background of chronic occlusive disease, sufficient collateral blood supply may be provided and even delayed intervention can result in recovery of renal function.

Nuclear imaging in AKI

The functional assessment of the kidney by nuclear medicine procedures is based on the use of radioisotopes bound to nonmetabolized molecules with known pharmacokinetics. Renal scintigraphy is usually applied for the assessment of renal function expressed as GFR, effective renal plasma flow or, more generally, kidney perfusion. Newer methods rely on positron emission tomography (PET), which allows the generation of images with higher resolution and absolute quantitation of biological processes such as transport activities, enzyme activities, or angiotensin receptors.[284] Study of renal blood flow using ^{99}mTc-MAG3 scan may be helpful in

the setting of AKI, but is not widely used. While the renal uptake in the first 1-2 minutes is normal in prerenal azotemia, it is expected to be reduced in vascular and parenchymal diseases and in ATN.[285] After 20 minutes, the uptake is increased in cases with prerenal azotemia, vascular disease, and ATN, and is expected to be reduced in obstructive uropathy and parenchymal renal disease. Excretion of the radioisotope is reduced in AKI, regardless of the cause. Radioisotope investigations are thus not very useful in the differential diagnosis of AKI. PET provides significantly better spatial resolution than conventional scintigraphy and, in addition, has the capacity to provide data on the function and molecular composition of an organ. The combination of PET and CT scanning provides an opportunity to add functional and quantitative data with anatomical and spatial information to be able to localize lesions. Tracers used for PET scans are either limited to the tissue such as Rb-82, N-13, and Cu-62 pyruvaldehyde bis(*N*-4-methylthiosemicarbazone) (category II) or can freely diffuse between the blood pool and the tissue, like O-15 (category I). Potential clinical uses for PET scans in the future, based on the results of few studies of kidney imaging, include determination of renal blood flow and GFR; diagnosis of renal artery stenosis; determination of the function of tubular peptide, cation, and anion transporters; tissue activity of enzymes such as angiotensin-converting enzyme; and regulation of receptors such as angiotensin type 1 receptors within the kidney. In particular, the changes in expression of molecules such as reactive oxygen species that control cell response and repair after injury in the setting of AKI could potentially be determined by PET scanning.[286, 287]

Renal Biopsy

These examinations should reveal the underlying cause of AKI and should enable specific treatment for patient with specific causes for AKI. If the cause of AKI is not clear after careful evaluation, renal biopsy should be considered, especially in patients in whom prerenal and postrenal causes of AKI have been excluded, and the cause of intrinsic renal AKI is unclear. Renal biopsy is particularly useful when clinical assessment, urinalysis, and laboratory investigation suggest diagnoses other than sepsis, or ischemic or nephrotoxic injury that may respond to specific therapy, e.g., rapidly progressive glomerulonephritis, and allergic interstitial nephritis. Renal biopsy should also be considered in AKI when there are symptoms or signs of a systemic illness, such as persistent fever or unexplained anemia. Unexpected causes of AKI, such as myeloma, interstitial nephritis, endocarditis or cryoglobulinemia, or cholesterol emboli may be revealed by renal biopsy in these situations.

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

Determination of the Underlying Cause or Causes of AKI

AKI is a clinical syndrome with a variety of causes. These include prerenal, renal, and postrenal causes. To reduce the severity of AKI and facilitate recovery, it is important to identify possible reversible causes of AKI (Table 14).

Table 14. Causes of AKI

Causes of AKI due to decreased kidney perfusion (prerenal)
• *Decreased intravascular fluid volume*: Extracellular fluid loss (burns, diarrhea, vomiting, diuretics, salt-wasting renal disease, primary adrenal insufficiency, gastrointestinal hemorrhage), extracellular fluid sequestration (pancreatitis, burns, crush, injury, nephrotic syndrome, malnutrition, advanced liver disease)
• *Decreased cardiac output*: Myocardial dysfunction (MI, arrhythmias, ischemic heart disease, cardiomyopathies, valvular disease, hypertensive disease, severe cor pulmonale)
• *Peripheral vasodilation*: Drugs (antihypertensive agents), sepsis, miscellaneous (adrenal cortical insufficiency, hypermagnesemia, hypercapnia, hypoxia)
• *Severe renal vasoconstriction*: Sepsis, drugs (nonsteroidal anti-inflammatory agents, ß-adrenergic agonists), hepatorenal syndrome
• *Mechanical occlusion of renal arteries*: Thrombotic occlusion, miscellaneous (emboli, trauma [e.g., angioplasty])
Causes of AKI due to parenchymal or vascular diseases
• *Renal vascular disorders*: Vasculitis, malignant hypertension, scleroderma, thrombotic thrombocytopenic purpura, hemolytic-uremic syndrome, disseminated intravascular coagulation, mechanical renal artery occlusion (surgery, emboli, thrombotic occlusion), renal vein thrombosis
• *Glomerulonephritis*: Postinfectious, membranoproliferative, rapidly progressive glomerulonephritis (idiopathic, polyarteritis nodosa, systemic lupus erythematosus, Wegener's syndrome, microscopic polyarteritis, Goodpasture's syndrome, Henoch-Schonlein purpura, drugs
• *Interstitial nephritis*: Drugs (penicillin, sulfonamide, rifampin, ciprofloxacin, phenindiones, cimetidine, proton pump inhibitors [omeprazole, lansoprazole], azathioprine, phenytoin, captopril, thiazides, furosemide, bumetanide, allopurinol, NSAIDs including selective cyclooxygenase-2 inhibitors, 5-aminosalicylates), hypercalcemia
• *Infections*: Nonspecific due to frank septicemia or systemic anti-inflammatory response syndrome, specific organisms (Legionella, Leptospira, Rickettsia, Hantavirus, Candida, malaria), specific organ involvement (bacterial endocarditis, visceral abscess, pyelonephritis)
• *Infiltration*: Sarcoid, lymphoma, leukemia,
• *Connective-tissue disease*
• *Tubular necrosis*: Renal ischemia (prolonged prerenal), Nephrotoxins (aminoglycosides, radiocontrast agents, heavy metals, organic solvents, other antimicrobials), pigmenturia, (myoglobinuria, hemoglobinuria), miscellaneous
• *Intratubular*: Crystal deposition (uric acid, oxalic acid), methotrexate, acyclovir, triamterene, sulfonamides, indinavir, tenofovtransplant rejectionir, protein deposition (light chains, myoglobin, hemoglobin)
Causes of AKI due to urinary tract obstruction (postrenal)
Extrarenal: Ureteral/pelvic, intrinsic obstruction (tumor, stone, clot, pus, fungal ball, papilla), extrinsic obstruction (retroperitoneal and pelvic malignancy, fibrosis, ligation, abdominal aortic aneurysm)
Bladder: Prostate hypertrophy/malignancy, stones, clots, tumor, neurogenic, medication
Urethral: Stricture, phimosis

AKI, acute kidney injury; MI, myocardial infarction; NSAID, nonsteroidal anti-inflammatory drug. Reprinted with permission.[288]

Causes of AKI due to decreased kidney perfusion (prerenal causes)

Prerenal causes range from obvious renal hypoperfusion in patients with hypotension or hemorrhage to more subtle renal hypoperfusion, such as that seen in patients with heart failure or cirrhosis. A high ratio of urea nitrogen to creatinine, a low urinary output, and a fractional excretion of urinary sodium of less than 1% are suggestive, but not diagnostic, of a prerenal cause. Hypovolemia leading to renal hypoperfusion is the most common prerenal cause of decreased glomerular filtration, which may be exacerbated by vasoconstriction via prostanoids, cytokines, and activation of renal vasoactive hormones in the setting of sepsis, or by vasoconstrictors such as vasopressors and aminoglycoside antibiotics. Importantly, prerenal causes of AKI are not benign and can lead to renal failure and death. In the setting of normal kidney function, volume depletion alone will result in decrease GFR and azotemia with little, if any, evidence of cellular damage. This condition is usually completely reversible. However, in

critically ill and injured patients and in those with underlying CKD, the prerenal state may be poorly tolerated and may lead to direct renal parenchymal injury.

Specific causes of AKI due to parenchymal or vascular diseases

ATN can be caused by a toxic or ischemic injury to the kidney and was once considered the most common intrinsic mechanism of AKI. However, most patients with AKI do not have widespread tubular necrosis, despite severe loss of renal function. Sepsis, the leading cause of AKI, is well known to be associated with very minimal changes on histopathology. Nevertheless, most toxins, such as antibiotics, intravascular contrast media, and nonsteroidal anti-inflammatory drugs, lead to renal tubular cell injury.

Differences in the clinical setting and presentation, particularly in the history, physical examination, and urinalysis, will usually distinguish between typical AKI (e.g., sepsis) and specific diseases such as acute interstitial nephritis, or acute glomerulonephritis and/or acute vasculitis. Care must be taken to make a specific diagnosis when possible because the treatment and prognosis of each may differ. Unlike prerenal and postrenal causes of AKI, the decrement in GFR in intrinsic AKI is directly linked to kidney damage (though the change in GFR and the degree of cellular injury need not correlate) and not the result of reduced renal perfusion or elevated pressures in the renal conduits. Since urea reabsorption is not preferentially increased, urea and creatinine concentrations rise in parallel and the BUN/creatinine ratio is usually preserved (10-20:1). Similarly, because the impaired kidney function results from direct kidney injury, the urinalysis is usually abnormal. Specific findings on dipstick and microscopic examination of the urine provide important clues to the location of the parenchymal injury responsible for the kidney dysfunction. In some cases, despite a careful history, physical exam, urinalysis, and additional specific tests, the type of the kidney disorder (tubular, vascular, glomerular, interstitial) remains undefined and a percutaneous kidney biopsy will be needed to determine the cause.

Causes of AKI due to urinary tract obstruction (postrenal causes)

Obstructions distal to the collecting system, such as nephrolithiasis, prostatic hypertrophy, or operative injury, represent the most common postrenal causes of AKI. Once a diagnosis of AKI is established, the patient’s history, physical findings, laboratory tests, and imaging procedures usually answer the remainder of the above questions and identify a specific etiology of AKI.

Management of Factors That Relate to Kidney Injury and Complications Related to Decreased Kidney Function

Complications of AKI (Table 15) can increase mortality and the risk for persistent decline of the kidney function. Therefore diagnosis and treatment of these complications is important.

Table 15. Complications of AKI

Complication	Clinical and laboratory findings	Consequence	Treatment
Hyperkalemia	Electrocardiogram abnormalities (high T), tremor	Cardiac dysfunction, arrhythmia	Volume in combination with diuretics, β2 sympathmimetics, calcium, insulin/glucose, bicarbonate, dialysis
Volume overload	Dyspnoe, pulmonary edema, heart insufficiency, hypertension, tissue edema	Impairment of gas exchange, cardiac dysfunction, impairment of wound healing, increased risk of infection	Diuretics, dialysis
Acidosis	Increased respiration, negative base excess	Cardiac dysfunction, hypotension, increased risk of infection	Bicarbonate, dialysis
Encephalopathy/neuropathy	Dizziness, confusion, weakness, paresthesias	Prolonged duration of mechanical weaning	Dialysis
Thrombocytopathy	Bleeding, anemia	Increased blood transfusion	Dialysis
Anemia	Pale skin, decreased hemoglobin	Hemodynamic impairment, increased blood transfusion	Blood transfusion, correct iron deficiency
Decreased immune response	–	Increased risk of infection	Dialysis?
Myopathy	Decreased muscle mass	Prolonged duration of mechanical weaning	
Pleural effusion	Shortness of breath, abnormal chest exam/X-ray	Impairment of gas exchange	Dialysis

Drugs

Many drugs are risk factors for the development of AKI (Table 16) and therefore should be avoided in patients with AKI.

Table 16. Drug-associated risk factors for AKI

Primary etiology	Drug	Clinical or laboratory findings	Treatment
Decreased kidney perfusion	Diuretics, NSAIDs, ACE-I, cyclosporin, tacrolimus, radiocontrast media, interleukin-2, vasodilators (hydralazine, calcium-channel blockers, minoxidil, diazoxide)	Benign urine sediment, FE_{Na} <1%, UOsm >500	Suspend or discontinue medication, volume replacement as clinically indicated
Thrombotic microangiopathy	Cyclosporin, tacrolimus, mitomycin C, conjugated estrogens, quinine,5-fluorouracil, ticlopidine, clopidogrel, interferon, valaciclovir, gemcitabine, bleomycin	Fever, microangiopathic, hemolytic anemia, thrombocytopenia	Discontinue medication, provide supportive care, plasmapheresis if indicated
Cholesterol emboli	Heparin, warfarin, streptokinase	Fever, microangiopathic, hemolytic anemia, thrombocytopenia	Discontinue medication, provide supportive care, plasmapheresis if indicated
Tubular toxicity	Aminoglycosides, radiocontrast media, cisplatin, nedaplatin, methoxyflurane, outdated tetracycline, amphotericin B, cephaloridine, streptozocin, tacrolimus, carbamazepine, mithramycin, quinolones, foscarnet, pentamidine, i.v. gammaglobulin, fosfamide, zoledronate, cidofovir, adefovir, tenofovir, mannitol, dextran, hydroxyethylstarch	FE_{Na} >2%, UOsm <350, urinary sediment with granular casts, tubular epithelial cells	Discontinue medication, provide supportive care
Rhabdomyolysis	Lovastatin, ethanol, codeine, barbiturates, diazepam	Elevated CPK, ATN urine sediment	Discontinue medication, provide supportive care
Severe hemolysis	Quinine, quinidine, sulfonamides, hydralazine, triamterene, nitrofurantoin, mephenytoin	High LDH, decreased hemoglobin	Discontinue medication, provide supportive care
Immune-mediated interstitial inflammation	Penicillin, methicillin ampicillin, rifampin, sulfonamides, thiazides, cimetidine, phenytoin, allopurinol, cephalosporins, cytosine arabinoside, furosemide, interferon, NSAIDs, ciprofloxacin, clarithromycin, telithromycin, rofecoxib, pantoprazole, omeprazole, atazanavir	Fever, rash, eosinophilia, urine sediment showing pyuria, white-cell casts, eosinophiluria	Discontinue medication, provide supportive care

Primary etiology	Drug	Clinical or laboratory findings	Treatment
Glomerulopathy	Gold, penicillamine, captopril, NSAIDs, lithium, mefenamate, fenoprofen, mercury, interferon-α, pamidronate, fenclofenac, tolmetin, foscarnet	Edema, moderate to severe proteinuria, RBCs, RBC casts possible	Discontinue medication, provide supportive care
Intratubular obstruction (crystalluria and/or renal lithiasis)	Aciclovir, methotrexate, sulfanilamide, triamterene, indinavir, foscarnet, ganciclovir	Sediment can be benign with severe obstruction, ATN might be observed	Discontinue medication, provide supportive care
Ureteral obstruction (secondary to retroperitoneal fibrosis)	Methysergide, ergotamine, dihydroergotamine, methyldopa, pindolol, hydralazine, atenolol	Benign urine sediment, hydronephrosis on ultrasound	Discontinue medication, decompress ureteral obstruction by intrarenal stenting or percutaneous nephrostomy

ACE-I, angiotensin-converting enzyme inhibitors; ATN, acute tubular necrosis; CPK, creatinine phosphokinase; FE_{na}, fractional excretion of sodium; LDH, lactic dehydrogenase; NSAID, nonsteroidal anti-inflammatory drugs; RBC, red blood cell; UOsm, urinary osmolality.

APPENDIX E: RISKS WITH GADOLINIUM-BASED CONTRAST AGENTS

Nephrotoxicity of Gd Chelates

Perazella et al.[289] have summarized studies showing Gd-induced nephrotoxic AKI, compared to CI-AKI[290-294] (Table 17). Studies in patients with underlying kidney disease demonstrate the importance of renal clearance in determining the pharmacokinetic profile of Gd chelates.[295]

Table 17. Studies supporting nephrotoxicity of Gd-based contrast agents

Reference	Study	Contrast agent	Dosage (mmol/kg)	Renal function ([Cr] in mg/dl)	Result
Sam et al., 2003[294]	n = 195 with CKD, no control group CIN >1.0 mg/d at 48 h with oligoanuria	Gadopentetate	0.28	CrCl <80 ml/min, CG 38.2 ± 16 ml/min, mean [Cr] 2.6	CIN: 7/195, MRA: 3/153 (1.9%), DSA: 4/42 (9.5%)
Erley et al., 2004[292]	Randomized prospective, n = 21, CIN >50%, decrease in GFR	Gadobutrol = 10 Iohexol = 11	0.57 ± 0.17	[Cr] >1.5 or CrCl <50 ml/min per 1.73 m^2, mean [Cr] 3.4	CIN: GBC: 5/10 (50%) RC: 5/11 (45%)
Briguori et al., 2006[290]	Retrospective, n = 25 (historical controls, n = 32), CIN ≥0.5 mg/dl within 48 h or dialysis within 5 d	Gadodiamide = 8 Gadobutrol = 17 3:1 mixture with RC	0.60 ± 0.30 0.28 to 1.23	[Cr] >2 mg/dl or CrCl <40 ml/min, mean [Cr] 2.3	CIN: GBC: 7/25 (28%); RC: 2/32 (6.5%)
Ergun et al., 2006[291]	Retrospective, n = 91, [Cr] measured pre-GBC, days 1, 3, and 7, and 1 mo, CIN ≥0.5 mg/dl within 72 h	Gadopentetate, gadodiamide, dotarem	0.20	Stages 3 and 4 CKD mean [Cr] 33 ml/min, range CrCl 15 to 58, mean [Cr] 4.0	CIN: 11/91 (12.1%); CKD Stage 4: 9/11 with CIN
Kane et al., 2008[293]	Retrospective, n = 163, [Cr] measured pre-GBC and within 7 d, CIN ≥0.5 mg/dl within 7 d	GBC agent, GBC + RC mixture, RC alone	GBC-76 ml, GBC + RC mixture-55 + 37 ml, RC-102 ml	Stages 3 to 5 CKD GBC [Cr] 2.77, GBC + RC [Cr] 2.63, RC [Cr] 2.48	CIN: GBC: 5.3% GBC + RC: 10.5%; RC: 20.6%
Total	N/A	N/A	Average dosage ~0.41 (0.20 to 0.60)	Average mean [Cr] ~3.02, range 2.60 to 4.00	CIN: GBC: 5.3 to 50.0%; RC: 6.5 to 45.0%

CG Cockcroft-Gault; CIN, contrast-induced nephropathy; CKD, chronic kidney disease; [Cr], serum creatinine concentration; CrCl, creatinine clearance; DSA, digital subtraction angiogram; GBC, gadolinium-based contrast agents; GFR, glomerular filtration rate; MRA, magnetic resonance angiography; RC, iodinated radiocontrast.

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Perazella et al.,[296] after summarizing the pharmacokinetics of Gd in kidney function, concluded that caution should be exercised in the use of Gd chelates in patients with CKD, and possibly even more so in patients with CKD and diabetes. These agents have small volumes of distribution, approximately 0.3 l per kilogram body weight, and are eliminated unchanged via

glomerular filtration. The Gd-based contrast agents have a normal mean terminal half-life ($T_{1/2}$) of approximately 1.3-1.6 hours. More than 95% of an injected dose is eliminated within 24 hours, with 3% being eliminated in the feces. In ESRD, $T_{1/2}$ is increased up to 30 hours in patients with a GFR <5 ml/min. However, the relatively small molecular weight (500 Da), small volume of distribution (0.28 l/kg), and negligible protein binding make Gd chelates ideal for removal with IHD. In one study, the $T_{1/2}$ of Gd chelates in nondialyzed patients with ESRD was prolonged at 34.3 hours, but decreased significantly to 2.6 hours in those receiving IHD.[289, 297] Peritoneal dialysis is not effective for Gd-chelate removal ($T_{1/2}$ of 52.7 hours).[298] In view of the accumulation of Gd in renal failure, it is prudent to employ the lowest Gd-chelate dose possible to achieve adequate image quality in high-risk patients. There is no evidence that these maneuvers would be efficacious, but the similarities of Gd-chelate ‘‘nephrotoxicity’’ to that of typical iodine-CI-AKI make these suggestions tenable.

Whether higher doses of Gd chelates (>0.3-0.4 mmol/kg) or the use of higher-osmolality Gd-chelate agents increase the nephrotoxic risk (as is noted when using iodine contrast media) is uncertain, since the nephrotoxic potential of Gd chelates at different doses or osmolalities has not been systematically examined.

Nephrogenic Systemic Fibrosis (NSF)

NSF is a devastating disorder involving severe fibrosis, predominantly of the skin with subsequent extensive limitation in mobility and use of extremities. Systemic involvement of the liver, heart, lungs, diaphragm, and skeletal muscle has also been reported. NSF may result in fatal or debilitating systemic fibrosis.[289, 296, 297, 299, 300] The proximate cause of NSF is currently unknown, but there is little doubt that exposure to Gd chelates is probably the most important pathogenic factor.

The most significant risk factors for developing NSF are chronic or significant acute kidney disease (usually necessitating dialysis), and the administration of Gd-containing contrast agents.

A recent comprehensive review[300] states that the first evidence of a link between Gd-based contrast agents, in particular gadodiamide, and the development of NSF became apparent in the first half of 2006, but the association between the administration of Gd diethylene triamine pentacetic acid salt and the development of NSF was not made until the second half of 2006.[301]

A recent review[302] summarizes the characteristics of the presently available Gd contrast media (Table 18).

Table 18. Currently marketed Gd chelates used for MRI

Name	Acronym	Gd-DTPA	Gd-EOB-DTPA	Gd-BOPTA	MS325	Gd-DTPA-BMA	Gd-DTPA-BMEA	Gd-HP-DO3A	Gd-BT-DO3A	Gd-DOTA
	Generic Name	Gadopentetate dimeglumine	Gadoxetic acid, disodium salt	Gadobenate dimeglumine	Gadofosveset, Trisodium Salt	Gadodiamide	Gadoverset-amide	Gadoteridol	Gadobutrol	Gadoterate meglumine
	Trade Name	Magnevist	Primovist	MultiHance	Vasovist	Omniscan	OptiMARK	ProHance	Gadovist	Dotarem
Company		Bayer-Schering	Bayer-Schering	Bracco	EPIX	GE-Healthcare	Covidien	Bracco	Bayer-Schering	Guerbet
Year of first introduction		1988	2006	1997	2006	1993	2001	1992	2003	1989
Chemical structure		Open-chain	Open-chain	Open-chain	Open-chain	Open-chain	Open-chain	Macrocyclic	Macrocyclic	Macrocyclic
Charge		Di-ionic	Di-ionic	Di-ionic	Tri-ionic	Nonionic	Nonionic	Nonionic	Nonionic	Ionic
Concentration (M)		0.5	0.25	0.5	0.25	0.5	0.5	0.5	1.0	0.5
Osmolality at 37°C (mOsm per kg H_2O)		1960	688	1970	825	789	1110	630	1603	1350
Viscosity (mPa/s) at 37°C		2.9	1.19	5.3	2.06	1.4	2.0	1.3	4.96	2.0
Formulation		Free DTPA (1 mmol/l)	Ca-EOB-DTPA (trisodium salt) 1.5 mmol/l	No formulation	Fosveset (0.325 mmol/l)	Ca-DTPA-BMA (caldiamide) (Na^+ salt) (25 mmol/l)	Ca-DTPA-BMEA (Na^+ salt) (50 mmol/l)	$[Ca\text{-}HP\text{-}DO3A]_2$ (Ca^{2+} salt) 0.5 mmol/l	Ca-BT-DO3A (Na^+ salt) 1.0 mmol/l	No formulation
Hydrophilicity (log P butanol/water)		-3.16	-2.11	-2.33	-2.11	-2.13	N/A	-1.98	-2.0	-2.87
log Ktherm		22.1	23.5	22.6	22.06	16.9	16.6	23.8	21.8	25.6
log Kcond		17.7	18.7	18.4	18.9	14.9	15.0	17.1	14.7	19.3
Kinetic stability[a]		Low	Medium	Medium	Medium	Low	Low	High	High	High
Approving Body		EMEA, FDA	EMEA, FDA	EMEA, FDA	EMEA, FDA	EMEA, FDA	EMEA, FDA	EMEA, FDA	EMEA	EMEA

a. Low indicates long-time index (defined by Laurent et al.[303]) less than 0.3, medium indicates long-time index from 0.3 to 0.95, and high indicates long-time index greater than 0.95.
EMEA, European Agency for the Evaluation of Medicinal Products; FDA, Food and Drug Administration; N/A, not available. Data compiled from Idee et al., 2006 and Port et al., 2008.[304, 305]
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In February 2007, the European Medicines Agency contraindicated the use of gadodiamide in patients who have a GFR <30 ml/min, and 4 months later, a caution for its use in patients who have a GFR between 30-60 ml/min was added (EMEA. Public assessment report. http://www.esur.org/fileadmin/NSF/Public_Assessment_Report_NSF_Gadolinium_26_June_2007.pdf; last accessed April 20, 2011)

For the first time in the history of radiology, renal function was introduced into the summary of product characteristics, which was new for European radiologists and it became necessary to determine the GFR in all patients before using the above-mentioned agents. In the USA, the Food and Drug Administration, on May 23, 2007, requested that vendors add warnings about the risk for developing NSF to the full prescribing information on the packaging for all Gd-based contrast agents (gadopentetate dimeglumine, gadodiamide, gadoversetamide, gadoteridol, gadobenate dimeglumine; see www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm225375.htm; last accessed Mar 28, 2011).[306] The new labels highlighted and described the risk for NSF following exposure to a Gd-based contrast agent in patients who had acute or chronic severe renal insufficiency (GFR <30 ml/min per 1.73 m^2), and patients who had AKI of any severity due to hepato-renal syndrome or in the perioperative liver transplantation period. In such patients, the use of a Gd-based contrast agent should be avoided unless the diagnostic information is essential and/or not possible to obtain by the use of non–contrast-enhanced MRI.

In patients who have AKI, the American College of Radiologists MRI Safety group[307] recommended that administration of any Gd-based contrast agent should be refrained from, unless a risk-benefit assessment for a particular patient indicates that the benefits clearly outweigh the potential risks. When a risk-benefit assessment warrants administration of a Gd-based contrast agent to a patient who has AKI (or CKD Stages 3-5), consideration should be given to administering the lowest dose that would provide the diagnostic benefit being sought. A half dose, if clinically acceptable, should be considered the default standard dose for such patients. The study should be monitored during its execution, and before contrast-agent administration, to ensure that the administration of the Gd-based contrast agent is still deemed necessary and indicated at that time. Postponing the examination in patients who have AKI until renal function has recovered should also be considered, if clinically feasible. The name of the patient, name and specific brand of the Gd-based contrast agent, dose, route, and rate of administration should all be explicitly specified on the order, along with the date and signature of the requesting physician.

APPENDIX F: DETAILED METHODS FOR GUIDELINE DEVELOPMENT

Aim

The overall aim of the project was to create a clinical practice guideline with recommendations for AKI using an evidence-based approach. After topics and relevant clinical questions were identified, the pertinent scientific literature on those topics was systematically searched and summarized.

Overview of Process

KDIGO guidelines focus on topics related to the prevention of—or management of individuals with—kidney diseases. General information on the KDIGO guideline development process is available at http://www.kdigo.org/clinical_practice_guidelines/MethodsDevelopment.php.

The development of this particular guideline includes many sequential and concurrent steps:

- Appoint the Work Group and Evidence Review Team (ERT), which were responsible for different aspects of the process.
- Confer to discuss process, methods, and results.
- Develop and refine topics.
- Triage topics to systematic review or narrative review.
- Define specific populations, interventions or predictors, and outcomes of interest for systematic review topics.
- Create and standardize quality assessment methods.
- Create data extraction forms.
- Develop literature search strategies and run searches.
- Screen abstracts and retrieve full articles based on predetermined eligibility criteria.
- Perform “reverse engineering”, i.e., use of existing systematic reviews to refine questions.
- Extract data and perform critical appraisal of the literature.
- Grade quality of the outcomes of each study.
- Tabulate data from articles into summary tables.
- Grade the quality of evidence for each outcome and assess the overall quality and findings of bodies of evidence with the aid of evidence profiles.
- Write recommendations and supporting rationale statements.
- Grade the strength of the recommendations based on the quality of the evidence and other considerations.
- Conduct peer review by KDIGO Board of Directors in December, 2009 and the public prior to publication in 2011.

Creation of Groups

The KDIGO Co-Chairs appointed the Co-Chairs of the Work Group, who then assembled the Work Group to be responsible for the development of the guideline. The Work Group consisted of domain experts, including individuals with expertise in adult and pediatric nephrology, critical care medicine, internal medicine, cardiology, radiology, infectious diseases, and epidemiology. For support in evidence review, expertise in methods, and guideline development, the National Kidney Foundation (NKF) contracted with the ERT based primarily at the Tufts Center for Kidney Disease Guideline Development and Implementation at Tufts Medical Center in Boston, Massachusetts, USA. The ERT consisted of physician-methodologists with expertise in nephrology and internal medicine, and research associates and assistants. The ERT instructed and advised Work Group members in all steps of literature review, critical literature appraisal, and guideline development. The Work Group and the ERT collaborated closely throughout the project.

Systematic Review General Process

The first task of the Work Group was to define the overall topics and goals for the guideline. The Work Group Co-Chairs drafted a preliminary list of topics and the Work Group identified the key clinical questions and triaged topics for systematic and narrative review. The Work Group and ERT further developed and refined each systematic review topic, specified screening criteria, literature search strategies, and data extraction forms. The ERT performed literature searches, organized abstract and article screening, coordinated methodological and analytic processes of the report, defined and standardized the search methodology, performed data extraction, and summarized the evidence. Throughout the project, the ERT offered suggestions for guideline development, led discussions on systematic review, literature searches, data extraction, assessment of quality and applicability of articles, evidence synthesis, grading of evidence and guideline recommendations, and consensus development. With input from the Work Group, the ERT finalized the selection of eligible studies, performed all data extraction, and summarized data into summary tables. The ERT also created preliminary evidence profiles (described below). The Work Group members reviewed all included articles, data extraction forms, summary tables, and evidence profiles for accuracy and completeness.

Refinement of Topics

The Work Group Co-Chairs prepared the first draft of the scope of work document to be considered by Work Group members. At their first 2-day meeting, members added further guideline topics until the initial working document included all topics of interest. The inclusive, combined set of questions formed the basis for the deliberation and discussion that followed. The Work Group strove to ensure that all topics deemed clinically relevant and worthy of review were identified and addressed. The four major topic areas of interest for AKI included: i) definition and classification of AKI; ii) prevention and treatment of AKI both iii) without RRT and iv) with RRT.

Populations of interest were those at risk for AKI, including those after exposure to intravascular contrast media, aminoglycosides, and amphotericin, and those with or at risk for AKI with a focus on patients with sepsis or trauma, receiving critical care, or undergoing

cardiothoracic surgery. We excluded studies on AKI from rhabdomyolysis, specific infections, and poisoning or drug overdose.

Based on the list of topics, the Work Group and ERT triaged topics to those that would be addressed by conducting a systematic review of the literature and those that would be addressed by a narrative review. For systematic review topics, the Work Group and the ERT formulated well-defined questions using a well-established system[308] that specifies population, intervention or predictor, comparator, outcome(s) of interest, and desired study design features. For some questions, we used the technique of "reverse engineering", where we reviewed a preliminary yield of RCTs and existing systematic reviews to further refine the questions of interest, the criteria for inclusion and exclusion of studies, and the boundaries of the topics.

Outcome Selection

The Work Group and the ERT made an explicit choice to limit outcomes to those deemed to be of importance for decision-making by patients and clinicians. We included categorical creatinine- or GFR-based outcomes for AKI, need for or dependence on RRT, and all-cause mortality. Continuous creatinine- or GFR-based outcomes were excluded as an outcome of interest, because, unless they are large, aggregated means of changes in continuous creatinine or GFR may be sensitive to outliers and do not show the number of patients for whom the change in kidney function crosses a prespecified, clinically meaningful threshold. For prevention, we considered avoidance of AKI to be an outcome of high importance, and, for treatment, we considered RRT and mortality to be of critical importance. For studies in patients with RRT-dependent AKI, we included catheter or filter survival, infections, bleeding, and metabolic complications as outcomes of interest. Otherwise, we excluded physiologic surrogate end-points.

Adverse effects were also of interest. However, in critically ill patients with AKI, it is often difficult to clearly distinguish nonspecific treatment-related adverse effects—for example, hemodynamic instability—from adverse outcomes of critical illness. Severe adverse effects may indirectly or directly contribute to overall morbidity and mortality. For one intervention, we consulted the package insert.

When weighting the evidence across different outcomes, we selected as the "crucial" outcome that which weighed most heavily in the assessment of the overall quality of evidence. For example, for interventions for prevention of CI-AKI, the creatinine-based AKI outcome was considered as the "crucial" outcome, as it was considered most informative for assessing the efficacy of the various interventions.

Table 19 shows the specific criteria used in the systematic review for the various topics. In general, eligibility criteria were determined based on relevance to the guideline, clinical importance, current clinical practice, estimates of the likelihood that studies of certain criteria would affect the content of the recommendations or the quality of the overall evidence, and practical issues such as available time and resources.

Most systematic reviews focused on interventions for prevention and treatment of AKI. For this, we reviewed original eligible RCTs, and existing systematic reviews of RCTs (Table

20). The review process and quality appraisal for questions of interventions is described in more detail below.

For the definition and classification of AKI, we conducted additional searches. We looked for observational studies or existing systematic reviews of observational studies examining the risk of AKI by RIFLE stages for short-term and long-term outcomes. We also looked for prediction equations to predict either risk for AKI, or risk after developing AKI, for subsequent outcomes. Pertinent studies for these topics were data-extracted directly into summary tables without quality assessment.

Judgments, Values, and Preferences

Throughout this guideline, the selection of the outcomes of interest, the assessment of the benefits and harm, appraisal of the quality of the evidence, and the choice of the strength of a recommendation, both graded and ungraded, reflect the judgments of the members of the Work Group. These are, to a large extent, affected by what the Work Group thought would be values and preferences on behalf of collective groups of patients at risk for AKI or with AKI and their providers. Judgments were discussed at Work Group meetings and teleconferences, and described in the narrative of the guideline chapters. Although within our group some range of opinion was present, overall the group agreed on the following:

A desire to be inclusive in terms of meeting criteria for AKI

Much of this guideline deals with evaluating patients at risk for AKI or determining risk profiles for patients with AKI. The proposed AKI definition is intentionally inclusive, given that even small reductions in kidney function can portend poor prognosis, even when kidney damage is unproven or even unlikely. Thus, our preference is to include all patients in the guideline, regardless of the pathological correlate for kidney injury. Many of the recommendations then focus on which patients require addition diagnostic and therapeutic management.

A progressive approach to risk and cost

In general, the Work Group put high value on avoidance of harm when evaluating preventive strategies. For treatment of AKI, as the severity increased—and, with it, the risk of death—the group put greater value on possible effectiveness of strategies, although maintained high value for avoidance of harm. Costs were not explicitly considered, but given the reality of resource restrictions in most health-care systems, the Work Group expected a greater burden of proof of consistent and meaningful efficacy with acceptable safety than mere equipoise, or promise of potential benefit with uncertain harm, before endorsing interventions currently under evaluation.

Intent to guide practice, not limit future research

The recommendations in this guideline should not be construed to imply that any particular question is settled, nor used to restrict future research. The Work Group made strong recommendations, when possible, based on current best evidence, and in view of the values and preferences cited above. Occasionally, evidence was limited and yet the relative risks and benefits of an intervention drove the Work Group to make a strong recommendation, for or against. This decision should not be misinterpreted to mean that the Work Group felt that future research should not be conducted. Indeed, even in cases where evidence is strong, an

appropriate scientific case for further research could well be made. In general, the Work Group felt that further research is needed for most of the topics covered in this guideline.

Literature Searches and Article Selection

The MEDLINE, Cochrane Central Registry for trials, and Cochrane database of systematic reviews were searched by the ERT to capture all citations relevant to the topic of AKI, including original articles and existing systematic reviews. The search was limited to publications since 1980. For CI-AKI, we limited the search to publications from 1995 onward, since prior to this date the use of high-osmolar contrast agents was common. The introduction of low-osmolar contrast agents after this date resulted in testing interventions in studies using low-osmolar contrast media. Finally, when an iso-osmolar agent became available, we examined studies of this agent against low-osmolar contrast agents.

A list of pertinent existing systematic reviews relevant to our guidelines was generated, organized by topic, and reviewed with the Work Group. If an existing systematic review adequately addressed a question of interest, and was deemed to be of sufficient quality, based on methodological rigor, this was used instead of the ERT conducting a de novo systematic review. This systematic review was then used as the starting point for building the evidence base, and was supplemented with articles from our own searches. Our searches were updated through December 16, 2010. All searches were then supplemented by articles identified by Work Group members through February 2011.

During abstract screening, journal articles reporting original data were reviewed. Editorials, letters, stand-alone abstracts, unpublished reports, and articles published in non–peer-reviewed journals were excluded. The Work Group also decided to exclude publications from journal supplements and conference proceedings, because of potential differences in the way these papers are solicited, selected, reviewed, and edited compared to peer-reviewed publications.

MEDLINE and Cochrane search results were screened by the ERT for relevance using predefined eligibility criteria, described below. For questions related to treatment, the systematic search aimed to identify RCTs with sample sizes as described in Table 19. Restrictions by sample size were based on methodological and clinical considerations. Generally, it was deemed that trials with fewer than 50 patients per arm would be unlikely to be conclusive regarding effect for patient-important clinical outcomes in AKI. However, for specific topics where only sparse data were available (e.g., the use of RRT to prevent CI-AKI), a lower sample size threshold was used to provide some information for descriptive purposes. For all treatment topics, RCTs in children were included if they met overall inclusion criteria for adults.

Literature yield for systematic review topics

Several literature searches were conducted. For questions on prevention or treatment of AKI, the ERT conducted searches that used the Mesh words for AKI and a module for RCTs (Table 21). For some interventions, we conducted focused searches. The goal of the search was to identify studies that were done in a population, which was explicitly characterized as having AKI, or which aimed to look at AKI as an outcome of interest. This search on AKI and RCTs

may not have picked up studies looking primarily at mortality or other, nonrenal outcomes, and thus may have captured only a proportion of the studies that evaluated the interventions of interest. For example, if a study on colloids for volume resuscitation in critically ill patients examined mortality but did not include information on AKI outcomes in the abstract, it would not have been identified in our search. However, the Work Group members were asked to send the ERT citations that may have been missed in the systematic searches that contained relevant information.

Specific questions or discrepancies regarding the relevance or acceptance of an article were resolved between the ERT and the Work Group members. The yield of individual studies as well as systematic reviews retained for detailed evidence review is shown in Table 20. The overall number of all citations screened was 18 385 citations. The specific numbers of abstracts identified and articles reviewed for each topic are presented in Table 22.

Data extraction

The ERT designed data-extraction forms to capture information on various aspects of the primary studies. Data fields for all topics included study setting, patient demographics, eligibility criteria, baseline kidney function (creatinine or GFR), numbers of subjects randomized, study design, study funding source, descriptions of interventions, description of outcomes, statistical methods used, results, quality of outcomes (as described below), limitations to generalizability, and free-text fields for comments and assessment of biases. Additional data fields contained information relevant to specific questions.

Summary tables

For each question of intervention, summary tables were developed to tabulate the data from studies pertinent. Each summary table contains a brief description of the baseline characteristics of the population, intervention and control treatments, concomitant therapy, outcomes, and methodological quality for each outcome. Baseline characteristics include a description of the study size, country of residence, age, baseline kidney function, and setting or procedure. The studies were listed by outcome within the table based on the hierarchy of important outcomes (Table 23). Work Group members were asked to proof and review all data and quality assessments in the summary tables on RCTs.

RR values were calculated for events. The estimates were calculated using the raw numbers when available. For those studies reporting only event rates, calculations were done using the percentages. If the study reported a RR or OR, the ERT still calculated its own estimate while including the studies' reported estimate as an annotation to the table. If there was no event in one arm, we calculated the RR by adding 0.5 to each numerator and denominator in the calculation.

Summary tables and evidence profiles are referenced in the text and published online. They are available at www.kdigo.org.

Evaluation of individual studies

Study size and duration. The study (sample) size was used as a measure of the weight of the evidence. In general, large studies provide more precise estimates. Similarly, longer-duration studies may be of better quality and more applicable, depending on other factors.

Methodological quality. Methodological quality (internal validity) refers to the design, conduct, and reporting of the outcomes of a clinical study. A three-level classification of study quality was used (Table 24). Given the potential differences in quality of a study for its primary and other outcomes, the study quality was assessed for each outcome. Variations of this system have been used in most Kidney Disease Outcomes Quality Initiative and all KDIGO guidelines, and have been recommended for the US Agency for Healthcare Research and Quality Evidence-Based Practice Center program.[309] Each study was given an overall quality grade. Each reported outcome was then evaluated and given an individual grade, depending on the quality of reporting and methodological issues specific to that outcome. However, the quality grade of an individual outcome could not exceed the quality grade for the overall study.

Results. What results were used from a study was determined by the study design, the purpose of the study, and the Work Group's question(s) of interest for which the results were used. Decisions were based on the screening criteria and outcomes of interest.

Evidence profiles

Evidence profiles were constructed by the ERT to record decisions about grades and summary effects by ERT and the Work Group members. These profiles serve to make transparent to the reader the thinking process of the Work Group in systematically combining evidence and judgments. Each Evidence Profile was reviewed by Work Group experts. Decisions were based on facts and findings from the primary studies listed in corresponding summary tables, as well as selected existing systematic reviews, and judgments of the Work Group. Judgments about the quality, consistency, and directness of evidence were often complex, as were judgments about the importance of an outcome or the summary of effects sizes. The evidence profiles provided a structured approach to grading, rather than a rigorous method of quantitatively summing up grades. For topics where several RCTs were identified, a summary table and an evidence profile were elaborated. When the body of evidence for a particular comparison of interest consisted of only one study, either a RCT or a systematic review, the summary table provides the final level of synthesis. An evidence profile was then not generated.

Grading the quality of evidence and the strength of a recommendation

A structured approach, based on GRADE[310-312] and facilitated by the use of evidence profiles, was employed in order to grade the quality of the overall evidence and the strength of recommendations. For each topic, the discussion on grading of the quality of the evidence was led by the ERT, and the discussion regarding the strength of the recommendations was led by the Work Group Chairs. The "strength of a recommendation" indicates the extent to which one can be confident that adherence to the recommendation will do more good than harm. The "quality of a body of evidence" refers to the extent to which our confidence in an estimate of effect is sufficient to support a particular recommendation.[311]

Grading the quality of evidence for each outcome. Following GRADE, the quality of a body of evidence pertaining to a particular outcome of interest was initially categorized based on study design. For questions of interventions, the initial quality grade was "High" when the body of evidence consisted of randomized controlled trials (RCTs). In theory, the initial grade would have been "Low" if the evidence consisted of observational studies or "Very Low" if it

consisted of studies of other study designs; however, the quality of bodies of evidence was formally determined only for topics where we performed systematic reviews of RCTs. The grade for the quality of evidence for each intervention/outcome pair was decreased if there were serious limitations to the methodological quality of the aggregate of studies, if there were important inconsistencies in the results across studies, if there was uncertainty about the directness of evidence including limited applicability of the findings to the population of interest, if the data were imprecise or sparse, or if there was thought to be a high likelihood of bias. The final grade for the quality of the evidence for an intervention/outcome pair could be one of the following four grades: “High”, “Moderate”, “Low”, or “Very Low” (Table 25).

Grading the overall quality of evidence. The quality of the overall body of evidence was then determined based on the quality grades for all outcomes of interest, taking into account explicit judgments about the relative importance of each outcome. The resulting four final categories for the quality of overall evidence were: “A”, “B”, “C” or “D” (Table 26). This evidence grade is indicated within each recommendation.

Assessment of net health benefit across all important clinical outcomes. The net health benefit was determined based on the estimated balance of benefits and harm across all clinically important outcomes. The assessment of net medical benefit was affected by the judgment of the Work Group and the ERT. The assessment of net health benefit is summarized in Table 27. The assessment in the table, however, was often provided in a more detailed form.

Grading the strength of the recommendations. The strength of a recommendation is graded as Level 1 or Level 2. Table 28 shows the KDIGO nomenclature for grading the strength of a recommendation and the implications of each level of patients, clinicians, and policy makers. Recommendations can be for or against doing something. Table 29 shows that the strength of a recommendation is determined not just by the quality of the evidence, but also by other, often complex judgments regarding the size of the net medical benefit, values and preferences, and costs. Formal decision analyses, including cost analysis, were not conducted.

Ungraded statements. This category was designed to allow the Work Group to issue general advice. Typically an ungraded statement meets one or more of the following criteria: it provides guidance based on common sense, it provides reminders of the obvious, it is not sufficiently specific to allow application of evidence to the issue, and therefore it is not based on systematic evidence review. Common examples include recommendations about definitions, frequency of testing, referral to specialists, and routine medical care. We strove to minimize the use of ungraded recommendations. However, many such statements exist and many are among the most important recommendations in this guideline.

This grading scheme with two levels for the strength of a recommendation together with four levels of grading the quality of the evidence, and the option of an ungraded statement for general guidance, was adopted by the KDIGO Board in December 2008. The Work Group took the primary role of writing the recommendations and rationale statements, and retained final responsibility for the content of the guideline statements and the accompanying narrative. The ERT reviewed draft recommendations and grades for consistency with the conclusions of the evidence review.

Format for recommendations

Each section contains one or more specific recommendations. Within each recommendation, the strength of recommendation is indicated as level 1 or level 2 and the quality of the supporting evidence is shown as A, B, C, or D. These are followed by a brief background with relevant definitions of terms, then the rationale which consists of a narrative summarizing the key points of the evidence base, and the judgments supporting the recommendation. In relevant sections, research recommendations suggest future research to resolve current uncertainties. Ungraded statements are designated as such by placing the terms "not graded" in parenthesis.

Limitations of Approach

Not all topics and subtopics covered by these guidelines could be thoroughly systematically reviewed. Decisions to restrict the topics or studies were made to focus systematic reviews on those topics or studies where evidence was thought to be likely to be informative when developing recommendations. The majority of the ERT and Work Group resources were devoted to review of RCTs for treatment questions, since these were deemed to be most likely to provide data to support recommendations on these topics.

For systematic review topics, the literature searches were intended to be comprehensive, but they were not exhaustive. MEDLINE and various Cochrane databases were the only databases searched. Hand searches of journals were not performed, and review articles and textbook chapters were not systematically searched. However, important studies known to the domain of experts that were missed by the electronic literature searches were added to retrieved articles and reviewed by the Work Group.

The grading of the quality of evidence for a study outcome as well as the synthesis of bodies of evidence includes many judgments. Thus, despite our efforts to be objective, consistent, and coherent, this process remains, to some degree, subjective.

Review of the Guideline Development Process

Several tools and checklists have been developed to assess the quality of the methodological process for guideline development. These include the Appraisal of Guidelines for Research and Evaluation (AGREE) criteria[313] and the Conference on Guideline Standardization (COGS) checklist.[314] Table 30 shows the COGS criteria that correspond to the AGREE checklist and how each one of them is addressed in these guidelines.

Table 19. Screening criteria for systematic review topics of nontreatment and treatment

NONTREATMENT	PICOD Criteria
Chapter 2.2: Risk Assessment	
Question: Do RIFLE stages for AKI predict short term mortality?	
Population	Patients with or without AKI
Predictor	RIFLE stage
Outcomes	Mortality up to 6 months
Study Design	Systematic review or observational cohort studies (retrospective or prospective)
Minimum No. of Subjects	No limitation on sample size.
Question: How can one predict risk for AKI?	
Population	Patients at risk for AKI including CI-AKI
Predictor	Prediction equations for AKI
Outcomes	AKI, RRT, mortality
Study Design	Prediction equations from observational cohort studies (retrospective or prospective)
Minimum No. of Subjects	No limitation on sample size.
Chapter 2.3: Evaluation and General Management of Patients with and at Risk for AKI	
Question: How does having AKI predict long term (≥6 months) mortality and CKD?	
Population	Patients with AKI
Predictor, Reference standard	Severity of AKI by RIFLE stage or other stage
Outcomes	Mortality (greater or equal to 6 months), CKD
Study Design	Systematic review or observational cohort studies (retrospective or prospective)
Minimum No. of Subjects	No limitation on sample size.
TREATMENT	
Section 3: Prevention and Treatment of AKI	
Population	Patients at risk for or with AKI, critically ill, CTS, sepsis, or trauma
Intervention	AAA (open vs. endovascular repair), Aminoglycosides, Amphotericin (conventional vs. liposomal), ANP, BNP, CCBs, Colloids, Crystalloids, Diuretics, Dopamine, EPO, Fenoldopam, Fluids, Goal-directed therapy, Glycemic control, Insulin, Insulin-like growth factor, Mannitol, NAC, Nutritional interventions, On vs. Off pump CABG, Rolofylline, Theophylline, Vasopressors
Outcomes	AKI, RRT, Mortality
Study design	Systematic review or RCT
Minimum No. of Subjects	N≥50/arm
Section 4: CI-AKI	
Population	Patients with contrast-media exposure, i.a. or i.v., elective or non elective, coronary angiogram, other angiograms or CT, with or without CKD at baseline, hypo-osmolar or iso-osmolar radio contrast media, with concurrent i.v. hydration
Intervention	Bicarbonate, IHD or HF, NAC, Theophylline, Various contrast agents (low vs. iso-osmolar)
Outcomes	CI-AKI, RRT, Mortality
Study Design	Systematic review or RCT
Minimum No. of Subjects	N≥50/arm
Chapter 5.1: Timing of RRT in AKI: Early vs. Late RRT	
Population	Patients with AKI not yet on RRT
Intervention	Early vs. late RRT
Outcomes	Recovery of kidney function, RRT dependence, Mortality
Study design	Systematic review or RCT
Minimum No. of Subjects	N≥50/arm
Chapter 5.2: Criteria for Stopping RRT in AKI	
Population	AKI requiring RRT
Intervention	Stopping RRT based on any specific criteria
Outcomes	Mortality, Need for resumption of RRT, Renal recovery
Study design	Systematic review or RCT
Minimum No. of Subjects	N≥50/arm

Chapter 5.3: Anticoagulation	
Population	AKI requiring RRT, not at increased of risk of bleeding Any dialysis modality. Exclude Liver failure and immediately postoperative
Intervention	Anticoagulation (heparin, citrate, other) vs. active, control or placebo
Outcomes	Mortality, Filter survival (Time to clotting; patency rate), Filter efficacy (dose), Bleeding; (transfusions), Adverse events
Study design	Systematic review or RCT
Minimum No. of Subjects	Circuits: N≥25/arm; Patients: N≥10/arm
Chapter 5.4: Vascular Access for RRT in AKI	
Population	Patients with AKI requiring RRT
Intervention	Tunneled vs. non-tunneled, different insertion sites, US guidance vs. landmark, Locks (saline; anticoagulant; antibiotic, antibiotic coated cap)
Outcomes	Mortality, Catheter survival (time to clotting, patency rate, Catheter blood flow rate, Bleeding (transfusions), Systemic thrombosis, Infection (local, systemic)
Study design	Systematic review or RCT
Minimum No. of Subjects	Circuits: N≥25/arm; Patients: N≥10/arm
Chapter 5.5: Dialyzer Membranes for RRT in AKI	
Population	AKI requiring RRT treated with IHD/SLED
Intervention	Biocompatible vs. bioincompatible membrane; high- vs. low-flux membrane
Outcomes	Mortality, RRT, Recovery of kidney function
Study design	Systematic review or RCT
Minimum No. of Subjects	N≥50/arm
Chapter 5.6: Modality of RRT for patients with AKI	
Chapter 5.8: Dose of RRT in AKI	
Population	Patients with AKI requiring RRT
Intervention	Different modalities, doses or intensities
Outcomes	Recovery of kidney function, RRT dependence, Mortality
Study design	Systematic review or RCT
Minimum No. of Subjects	N≥50/arm
Chapter 5.7: Buffer Solutions for RRT in Patients with AKI	
Population	AKI requiring RRT, including liver failure; sepsis; shock; lactic acidosis; hyperlactatemia
Intervention	Bicarbonate; citrate; acetate; and lactate vs. active, control or placebo
Outcomes	Mortality, RRT, Recovery of kidney function, Adverse events: acid base balance, calcium disturbance, lactate accumulation, Hemodynamic instability
Study design	Systematic review or RCT
Minimum No. of Subjects	Circuits: N≥25/arm; Patients: N≥10/arm

AAA, abdominal aortic aneurysms; AKI, acute kidney injury; ANP, atrial natriuretic peptide; BNP, brain natriuretic peptide; CABG, coronary artery bypass graft; CCB, calcium channel blocker; CI-AKI, contrast-induced acute kidney injury; CKD, chronic kidney disease; CT, computed tomography; EPO, erythropoietin; HF, hemofiltration; IHD, intermittent hemodialysis; NAC, N-acetylcysteine; RCT, randomized controlled trial; RRT, renal replacement therapy; SLED, sustained low efficiency dialysis.

Table 20. Work products for systematic review topics

Topic	Summary Table of RCTs	Existing Systematic Review	Evidence Profile
1 Definition, Evaluation and Management of AKI			
RIFLE predictor of mortality	+ (9 Observational Studies)	+ (Ricci 2008)[47]	
Long-term outcomes of AKI		+ (Coca 2009)[12]	
Prediction equations	+ (8 Observational Studies)		
2 Prevention			
CI-AKI			
Bicarbonate vs. Control	+ (10 RCTs)		+
NAC vs. Control	+ (16 RCTs)		+
Theophylline vs. Control	+ (4 RCTs)		+
IHD or HF vs. Control	+ (5 RCTs)		+
Iso vs. Low osmolar			
Intrarterial	+ (10 RCTs)		+
i.v.	+ (4 RCTs)		+
Aminoglycosides: Single vs. Multiple daily dose		+ (Summary of 6 SR)[315-320]	
Amphotericin B			
Lipid soluble formulations vs. Ampho B		+ (Johansen 2000)[321]	
Fluconazole vs. Ampho B, Echinocandins vs. Ampho B		+ (Gafter-Gvili 2008)[322]	
Rates of adverse effects of Ampho B formulations		+ (Girois 2005)(Jorgensen 2006)[323, 324]	
Frusemide vs. Control		+ (Ho 2006)[325]	
Dopamine vs. Control		+ (Friedrich 2005)[326]	
Atrial natriuretic peptide (anaritide) vs. Control	+ (2 RCTs)		+
Beta natriuretic peptide (BNP) vs. Control	+ (Mentzer 2007)[327]		
Fenoldopam vs. Control	+ (3 RCTs)		+
Insulin: Intensive insulin vs. Conventional care	+ (2 RCTs)	+ (Wiener 2008)[328]	+
NAC vs. Control in CTS	+ (5 RCTs)		+
Starch: Hydroxyethyl starch vs. Ringer's lactate	+ (Brunkhorst 2008)[329]		
Sodium nitroprusside infusion vs. Control	+ (Kaya 2007)[330]		
AAA: endovascular repair vs. Open surgical repair	+ (DREAM Study 2004)[331]		
Rolofylline vs. Control (in heart failure)	+ (Cotter 2008)[332]		
On pump vs. Off pump	+ (7 RCTs)		+
EPO vs Control	+ (Endre 2010)[281]		

3 Treatment				
Atrial natriuretic peptide (anaritide) vs. Control	+ (2 RCTs)		+	
Dopamine vs. Control	+ (Bellomo 2000)[333]	+ (Friedrich 2005)[326]		
Fenoldopam vs. Dopamine or Control	+ (2 RCTs)		+	
Frusemide vs. Control		+ (Ho 2006)[325]		
4 RRT				
Access				
Jugular vs. Femoral	+ (Parienti 2008)[334]			
Tunneled vs. Non-tunneled	+ (Klouche 2007)[335]			
Anticoagulation: Citrate vs. Heparin	+ (4 RCTs)			+
Buffer/Dialysate: Bicarbonate vs. Lactate	+ (Barenbrock 2000)[336]			
Dose				
CRRT: Various	+ (5 RCTs)			
IHD: Daily vs. Alternate day dose	+ (1 RCT)			+
CVVH vs. CVVHD	+ (1 RCT)			
Modality: Intermittent vs. Continuous		+ (Rabindranath 2007)[337]		
Timing: Early vs. Late	+ (Bouman 2002)[338]			
Membrane: Biocompatible vs. Incompatible		+ (Alonso 2005)[339]		

Table 21. AKI Search Strategies

Search for Observational Studies on AKIN or RIFLE

1. exp glomerular filtration rate/ or glomerular filtration rate.mp.
2. gfr.af.
3. exp kidney function tests/
4. cystatin C.mp.
5. urine output.mp.
6. 1 or 2 or 3 or 4 or 5
7. predict$.af.
8. formula.af.
9. equation.af.
10. exp regression analysis/ or regression analysis.mp.
11. risk.af.
12. exp Multivariate Analysis/ or univariate.mp.
13. 7 or 8 or 9 or 10 or 11 or 12
14. 6 and 13
15. exp "sensitivity and specificity"/
16. exp Predictive Value of Tests/
17. exp ROC CURVE/
18. exp Mass Screening/
19. exp diagnosis/
20. exp REPRODUCIBILITY OF RESULTS/
21. exp false negative reactions/ or false positive reactions.mp.
22. predictive value.tw.
23. (sensitivity or specificity).tw.
24. accuracy.tw.
25. roc.tw.
26. reproducibility.tw.
27. (false positive or false negative).tw.
28. likelihood ratio.tw.
29. accuracy.tw.
30. di.fs.
31. exp Case-Control Studies/
32. (case adj20 control).tw.
33. exp Longitudinal Studies/
34. longitudinal.tw.
35. exp Cohort Studies/
36. cohort.tw.
37. exp Prospective Studies/
38. exp Retrospective Studies/
39. exp Validation Studies/
40. or/15-39

41. 14 and 40
42. acute renal failure.mp. or exp Kidney Failure, Acute/
43. (acute renal failure or acute kidney failure or ARF).tw.
44. (acute renal insufficienc$ or acute kidney insufficienc$).tw.
45. anuria.mp. or exp Anuria/
46. Kidney Failure, Acute.mp.
47. exp Kidney Tubular Necrosis, Acute/ or acute kidney injury.mp.
48. acute tubular necrosis.tw.
49. acute kidney tubular necrosis.tw.
50. ATN.mp.
51. (Nephritis, Interstitial or Drug induced nephropathy).mp.
52. Renal insufficiency, Acute.mp.
53. Acute kidney failure.mp.
54. exp Uremia/ or Azotemia/ or exp Blood Urea Nitrogen/
55. (pre-renal or post-renal).tw.
56. (ur$emia or azot$emia).tw.
57. or/42-56
58. 41 and 57
59. (AKIN or RIFLE).tw.
60. 57 and 59
61. 58 or 60
62. Animals/ not humans.mp.
63. 61 not 62
64. limit 63 to (addresses or bibliography or biography or case reports or congresses or consensus development conference or consensus development conference, nih or dictionary or directory or editorial or festschrift or government publications or interview or lectures or legal cases or legislation or news or newspaper article or patient education handout or periodical index)
65. limit 63 to "review articles"
66. 63 not (64 or 65)
67. limit 66 to yr="2004 - 2008"

Search for RCTs on CI-AKI

1. exp Contrast Media/
2. (contrast media or contrast medium or contrast dye or radiographic contrast).tw.
3. (radiocontrast media or radiocontrast medium).tw.
4. contrast agent$.tw.
5. or/1-4
6. exp Nephritis/
7. (nephritis or nephropath$ or nephrotoxic$).tw.
8. ((impair$ or damag$ or reduc$) adj2 (renal or kidney)).tw.
9. renal insufficiency.tw.
10. acute renal failure.mp. or exp Kidney Failure, Acute/
11. (acute renal failure or acute kidney failure or ARF).tw.

12. (acute renal insufficienc$ or acute kidney insufficienc$).tw.
13. anuria.mp. or exp Anuria/
14. Kidney Failure, Acute.mp.
15. exp Kidney Tubular Necrosis, Acute/ or acute kidney injury.mp.
16. acute tubular necrosis.tw.
17. acute kidney tubular necrosis.tw.
18. oliguria.mp. or exp oliguria/
19. (Nephritis, Interstitial or Drug induced nephropathy).mp.
20. Renal insufficiency, Acute.mp.
21. Acute kidney failure.mp.
22. (Acute Kidney injury or AKI).mp.
23. exp Uremia/ or Azotemia/ or exp Blood Urea Nitrogen/
24. (pre-renal or post-renal).tw.
25. (ur$emia or azot$emia).tw.
26. or/6-25
27. 26 and 5
28. (contrast-induced nephr$ or contrast-associated nephr$).tw.
29. 27 or 28
30. randomized controlled trial.pt.
31. controlled clinical trial.pt.
32. randomized controlled trials/
33. Random Allocation/
34. Double-blind Method/
35. Single-Blind Method/
36. clinical trial.pt.
37. Clinical Trials.mp. or exp Clinical Trials/
38. (clinic$ adj25 trial$).tw.
39. ((singl$ or doubl$ or trebl$ or tripl$) adj (mask$ or blind$)).tw.
40. Placebos/
41. placebo$.tw.
42. random$.tw.
43. trial$.tw.
44. (latin adj square).tw.
45. exp Evaluation studies/
46. (control$ or prospectiv$ or volunteer$).tw.
47. Cross-Over Studies/
48. or/30-47
49. 29 and 48
50. Animals/ not human.mp.
51. 49 not 50
52. limit 51 to (guideline or meta analysis or practice guideline or "review")
53. 51 not 52
54. limit 53 to comment and (letter or editorial).pt.

55. limit 53 to (addresses or bibliography or biography or case reports or congresses or consensus development conference or consensus development conference, nih or dictionary or directory or editorial or festschrift or government publications or interview or lectures or legal cases or legislation or news or newspaper article or patient education handout or periodical index)
56. 53 not (54 or 55)
57. remove duplicates from 56
58. limit 57 to yr="1995 - 2008"

Studies for RCTS on Low Osmolar Contrast Agents

1. iodixanol.mp. [mp=ti, ot, ab, nm, hw, kw, sh]
2. contrast media.tw.
3. contrast medium.mp. [mp=ti, ot, ab, nm, hw, kw, sh]
4. contrast dye.mp. [mp=ti, ot, ab, nm, hw, kw, sh]
5. radiographic contrast.mp. [mp=ti, ot, ab, nm, hw, kw, sh]
6. radiographic contrast media.mp. [mp=ti, ot, ab, nm, hw, kw, sh]
7. radiographic contrast medium.mp. [mp=ti, ot, ab, nm, hw, kw, sh]
8. contrast agent.mp. [mp=ti, ot, ab, nm, hw, kw, sh]
9. dimer.mp. [mp=ti, ot, ab, nm, hw, kw, sh]
10. dimeric.mp. [mp=ti, ot, ab, nm, hw, kw, sh]
11. iso-osmola$.tw.
12. isoosmola$.tw.
13. Visipaque.mp. [mp=ti, ot, ab, nm, hw, kw, sh]
14. or/1-13
15. nephrotoxicity.mp. [mp=ti, ot, ab, nm, hw, kw, sh]
16. nephritis.mp. [mp=ti, ot, ab, nm, hw, kw, sh]
17. nephrotoxic$.tw.
18. kidney.mp. [mp=ti, ot, ab, nm, hw, kw, sh]
19. Renal.mp. [mp=ti, ot, ab, nm, hw, kw, sh]
20. creatinine.mp. [mp=ti, ot, ab, nm, hw, kw, sh]
21. adverse effect.mp. [mp=ti, ot, ab, nm, hw, kw, sh]
22. adverse event.mp. [mp=ti, ot, ab, nm, hw, kw, sh]
23. side effect.mp. [mp=ti, ot, ab, nm, hw, kw, sh]
24. or/15-23
25. 14 and 24
26. randomized controlled trial.pt.
27. controlled clinical trial.pt.
28. randomized controlled trials/
29. Random Allocation/
30. Double-blind Method/
31. Single-Blind Method/
32. clinical trial.pt.
33. Clinical Trials.mp. or exp Clinical Trials/
34. (clinic$ adj25 trial$).tw.

35. ((singl$ or doubl$ or trebl$ or tripl$) adj (mask$ or blind$)).tw.
36. Placebos/
37. placebo$.tw.
38. random$.tw.
39. trial$.tw.
40. (latin adj square).tw.
41. (control$ or prospectiv$ or volunteer$).tw.
42. Cross-Over Studies/
43. or/26-42
44. 25 and 43
45. remove duplicates from 44
46. Animals/ not humans.mp. [mp=ti, ot, ab, nm, hw, kw, sh]
47. 45 not 46

Search for RCTs on Prevention and Treatment of AKI

1. acute renal failure.mp. or exp Kidney Failure, Acute/
2. (acute renal failure or acute kidney failure or ARF).tw.
3. (acute renal insufficienc$ or acute kidney insufficienc$).tw.
4. anuria.mp. or exp Anuria/
5. Kidney Failure, Acute.mp.
6. exp Kidney Tubular Necrosis, Acute/ or acute kidney injury.mp.
7. acute tubular necrosis.tw.
8. acute kidney tubular necrosis.tw.
9. oliguria.mp. or exp oliguria/
10. (Nephritis, Interstitial or Drug induced nephropathy).mp.
11. Renal insufficiency, Acute.mp.
12. Acute kidney failure.mp.
13. (Acute Kidney injury or AKI).mp.
14. exp Uremia/ or Azotemia/ or exp Blood Urea Nitrogen/
15. (pre-renal or post-renal).tw.
16. (ur$emia or azot$emia).tw.
17. or/1-16
18. randomized controlled trial.pt.
19. controlled clinical trial.pt.
20. randomized controlled trials/
21. Random Allocation/
22. Double-blind Method/
23. Single-Blind Method/
24. clinical trial.pt.
25. Clinical Trials.mp. or exp Clinical Trials/
26. (clinic$ adj25 trial$).tw.
27. ((singl$ or doubl$ or trebl$ or tripl$) adj (mask$ or blind$)).tw.
28. Placebos/

29. placebo$.tw.
30. random$.tw.
31. trial$.tw.
32. (latin adj square).tw.
33. Comparative Study.tw.
34. exp Evaluation studies/
35. Follow-Up Studies/
36. Prospective Studies/
37. (control$ or prospectiv$ or volunteer$).tw.
38. Cross-Over Studies/
39. or/18-38
40. 17 and 39
41. Animals/ not human.mp.
42. 40 not 41
43. limit 42 to (guideline or meta analysis or practice guideline or "review")
44. 42 not 43
45. limit 44 to comment and (letter or editorial).pt.
46. limit 44 to (addresses or bibliography or biography or case reports or congresses or consensus development conference or consensus development conference, nih or dictionary or directory or editorial or festschrift or government publications or interview or lectures or legal cases or legislation or news or newspaper article or patient education handout or periodical index)
47. 44 not (45 or 46)
48. limit 47 to yr="1980 - 2008"
49. limit 48 to yr="1980 - 1995"
50. limit 48 to yr="1996-2008"
51. remove duplicates from 49
52. remove duplicates from 50
53. 51 or 52

Search for RCTs on On vs. Off-pump CABG

1. coronary artery bypass, off-pump/
2. (coronary artery bypass and (off adj2 pump)).mp. [mp=ti, ot, ab, nm, hw, sh, kw]
3. *Coronary Artery Bypass, Off-Pump/
4. 1 or 3 or 2
5. randomized controlled trial.pt.
6. controlled clinical trial.pt.
7. randomized controlled trials/
8. Random Allocation/
9. Double-blind Method/
10. Single-Blind Method/
11. clinical trial.pt.
12. Clinical Trials.mp. or exp Clinical Trials/
13. (clinic$ adj25 trial$).tw.

14. ((singl$ or doubl$ or trebl$ or tripl$) adj (mask$ or blind$)).tw.
15. Placebos/
16. placebo$.tw.
17. random$.tw.
18. trial$.tw.
19. (latin adj square).tw.
20. Comparative Study.tw.
21. exp Evaluation studies/
22. Follow-Up Studies/
23. Prospective Studies/
24. (control$ or prospectiv$ or volunteer$).tw.
25. Cross-Over Studies/
26. or/5-25
27. 4 and 26
28. limit 27 to (guideline or meta analysis or practice guideline or "review")
29. 27 not 28
30. Animals/ not humans.mp. [mp=ti, ot, ab, nm, hw, kw, sh]
31. 29 not 30
32. remove duplicates from 31

Search for RCTs on Questions Regarding Dialysis

1. Renal replacement therapy.mp.
2. exp Renal Dialysis/
3. hemodialysis.mp.
4. haemodialysis.mp.
5. "Kidney, Artificial"/
6. exp peritoneal dialysis/ and peritoneal dialysis.mp.
7. exp ultrafiltration/ and ultrafiltration.mp.
8. Hemofiltration.mp. [mp=ti, ot, ab, sh, hw, kw, nm]
9. haemofiltration.mp. [mp=ti, ot, ab, sh, hw, kw, nm]
10. hemofilt$.mp. [mp=ti, ot, ab, sh, hw, kw, nm]
11. haemofilt$.mp. [mp=ti, ot, ab, sh, hw, kw, nm]
12. haemodialfiltration.mp. [mp=ti, ot, ab, sh, hw, kw, nm]
13. haemodiafilt$.tw.
14. hemodiafilt$.tw.
15. (CVVH or continuous veno-venous hemofiltration).tw.
16. (CAVH or continuous arterio-venous hemodiafiltration).tw.
17. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16
18. acute renal failure.mp. or exp Kidney Failure, Acute/
19. (acute renal failure or acute kidney failure or ARF).tw.
20. (acute renal insufficienc$ or acute kidney insufficienc$).tw.
21. anuria.mp. or exp Anuria/
22. Kidney Failure, Acute.mp.

23. exp Kidney Tubular Necrosis, Acute/ or acute kidney injury.mp.
24. acute tubular necrosis.tw.
25. acute kidney tubular necrosis.tw.
26. oliguria.mp. or oliguria.tw.
27. (Nephritis, Interstitial or Drug induced nephropathy).mp.
28. Renal insufficiency, Acute.mp.
29. (Acute Kidney injury or AKI).mp.
30. Acute kidney failure.mp.
31. exp Uremia/ or Azotemia/ or exp Blood Urea Nitrogen/
32. (pre-renal or post-renal).tw.
33. (ur$emia or azot$emia).tw.
34. or/18-33
35. 17 and 34
36. randomized controlled trial.pt.
37. controlled clinical trial.pt.
38. randomized controlled trials/
39. Random Allocation/
40. Double-blind Method/
41. Single-Blind Method/
42. clinical trial.pt.
43. Clinical Trials.mp. or exp Clinical Trials/
44. (clinic$ adj25 trial$).tw.
45. ((singl$ or doubl$ or trebl$ or tripl$) adj (mask$ or blind$)).tw.
46. Placebos/
47. placebo$.tw.
48. random$.tw.
49. trial$.tw.
50. exp Evaluation studies/
51. Cross-Over Studies/
52. or/36-51
53. 52 and 35
54. Animals/ not human.mp.
55. 53 not 54
56. limit 55 to (guideline or meta analysis or practice guideline or "review")
57. 55 not 56
58. limit 57 to yr="1980 - 2008"
59. remove duplicates from 58

Search for Systematic Reviews on AKI

1. acute renal failure.mp. or exp Kidney Failure, Acute/
2. (acute renal failure or acute kidney failure or ARF).tw.
3. (acute renal insufficienc$ or acute kidney insufficienc$).tw.
4. anuria.mp. or exp Anuria/

5. Kidney Failure, Acute.mp.
6. exp Kidney Tubular Necrosis, Acute/ or acute kidney injury.mp.
7. acute tubular necrosis.tw.
8. acute kidney tubular necrosis.tw.
9. ATN.mp.
10. (Nephritis, Interstitial or Drug induced nephropathy).mp.
11. Renal insufficiency, Acute.mp.
12. Acute kidney failure.mp.
13. exp Uremia/ or Azotemia/ or exp Blood Urea Nitrogen/
14. (pre-renal or post-renal).tw.
15. (ur$emia or azot$emia).tw.
16. or/1-15
17. meta analysis.mp. or exp Meta-Analysis/
18. (meta-analysis or metaanalysis).ti.
19. systematic review.mp.
20. systematic literature.mp.
21. systematic review.ti.
22. systematic review$.tw.
23. (guideline or practice guideline).mp.
24. (evidence review or evidence based).mp. [mp=ti, ab, tx, kw, ct, ot, nm, hw]
25. 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24
26. 16 and 25
27. remove duplicates from 26
28. Animals/ not human.mp. [mp=ti, ab, tx, kw, ct, ot, nm, hw]
29. 27 not 28

Search for Systematic Reviews on Amphotericin B, Triazoles, and Echinocandins

1. exp Nephritis/
2. (nephritis or nephropath$ or nephrotoxic$).tw.
3. ((impair$ or damag$ or reduc$) adj2 (renal or kidney)).tw.
4. renal insufficiency.tw.
5. acute renal failure.mp. or exp Kidney Failure, Acute/
6. (acute renal failure or acute kidney failure or ARF).tw.
7. (acute renal insufficienc$ or acute kidney insufficienc$).tw.
8. anuria.mp. or exp Anuria/
9. Kidney Failure, Acute.mp.
10. exp Kidney Tubular Necrosis, Acute/ or acute kidney injury.mp.
11. acute tubular necrosis.tw.
12. acute kidney tubular necrosis.tw.
13. oliguria.mp. or exp oliguria/
14. (Nephritis, Interstitial or Drug induced nephropathy).mp.
15. Renal insufficiency, Acute.mp.
16. Acute kidney failure.mp.

17. (Acute Kidney injury or AKI).mp.
18. exp Uremia/ or Azotemia/ or exp Blood Urea Nitrogen/
19. (pre-renal or post-renal).tw.
20. (ur$emia or azot$emia).tw.
21. nephrotoxicity.mp. [mp=ti, ab, tx, kw, ct, ot, nm, hw]
22. nephrotoxic$.tw.
23. kidney.mp. [mp=ti, ab, tx, kw, ct, ot, nm, hw]
24. Renal.mp. [mp=ti, ab, tx, kw, ct, ot, nm, hw]
25. creatinine.mp. [mp=ti, ab, tx, kw, ct, ot, nm, hw]
26. adverse effect.mp. [mp=ti, ab, tx, kw, ct, ot, nm, hw]
27. adverse event.mp. [mp=ti, ab, tx, kw, ct, ot, nm, hw]
28. side effect.mp. [mp=ti, ab, tx, kw, ct, ot, nm, hw]
29. or/1-28
30. meta analysis.mp. or exp Meta-Analysis/
31. (meta-analysis or metaanalysis).ti.
32. systematic review.mp.
33. systematic literature.mp.
34. systematic review.ti.
35. systematic review$.tw.
36. (guideline or practice guideline).mp.
37. (evidence review or evidence based).mp. [mp=ti, ab, tx, kw, ct, ot, nm, hw]
38. or/30-37
39. antifungal agents/
40. exp amphotericin B/
41. fungizon$.tw.
42. anfo$.tw.
43. ampho$.tw.
44. Amphotericin B.tw.
45. candipres$.tw.
46. (amphotericin B colloidal dispersion or ABCD).tw.
47. Amphotericin B lipid complex.mp.
48. (Amphotericin B lipid complex or ABLC).tw.
49. (liposomal amphotericin B or L-AmB).tw.
50. abelcet$.tw.
51. ambisome$.tw.
52. lipid formulation amph$.tw.
53. (amphoterin B colloidal dispersion or ABCD).tw.
54. exp triazoles/
55. triazoles$.tw.
56. exp fluconazole/
57. flucon$.tw.
58. exp itraconazole/
59. diflucan$.tw.

60. itraconazole.tw.
61. itracon$.tw.
62. sporanox$.tw.
63. voriconazole.tw.
64. vfend$.tw.
65. posaconazol$.tw.
66. posafilin$.tw.
67. posanin$.tw.
68. varuconazol$.tw.
69. exp echinocandins/
70. echinocandin$.tw.
71. caspofungin$.tw.
72. micafungin$.tw.
73. anidulofungin$.tw.
74. cancidas$.tw.
75. funguard$.tw.
76. mycamin$.tw.
77. anidrasona$.tw.
78. anidrosan$.tw.
79. or/39-78
80. Animals/ not human.mp. [mp=ti, ab, tx, kw, ct, ot, nm, hw]

Search for Systematic Reviews on Aminoglycosides

1. exp Nephritis/
2. (nephritis or nephropath$ or nephrotoxic$).tw.
3. ((impair$ or damag$ or reduc$) adj2 (renal or kidney)).tw.
4. renal insufficiency.tw.
5. acute renal failure.mp. or exp Kidney Failure, Acute/
6. (acute renal failure or acute kidney failure or ARF).tw.
7. (acute renal insufficienc$ or acute kidney insufficienc$).tw.
8. anuria.mp. or exp Anuria/
9. Kidney Failure, Acute.mp.
10. exp Kidney Tubular Necrosis, Acute/ or acute kidney injury.mp.
11. acute tubular necrosis.tw.
12. acute kidney tubular necrosis.tw.
13. oliguria.mp. or exp oliguria/
14. (Nephritis, Interstitial or Drug induced nephropathy).mp.
15. Renal insufficiency, Acute.mp.
16. Acute kidney failure.mp.
17. (Acute Kidney injury or AKI).mp.
18. exp Uremia/ or Azotemia/ or exp Blood Urea Nitrogen/
19. (pre-renal or post-renal).tw.
20. (ur$emia or azot$emia).tw.

21. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20
22. meta analysis.mp. or exp Meta-Analysis/
23. (meta-analysis or metaanalysis).ti.
24. systematic review.mp.
25. systematic literature.mp.
26. systematic review.ti.
27. systematic review$.tw.
28. (guideline or practice guideline).mp.
29. (evidence review or evidence based).mp. [mp=ti, ab, tx, kw, ct, ot, nm, hw]
30. 27 or 25 or 22 or 28 or 24 or 26 or 23 or 29
31. 21 and 30
32. remove duplicates from 31
33. aminogycosides.tw.
34. gentamicin.tw.
35. tobramycin.tw.
36. amikacin.tw.
37. streptomycin.tw.
38. neomycin.tw.
39. kanamycin.tw.
40. paromomycin.tw.
41. netilmicin.tw.
42. spectinomycin.tw.
43. 35 or 33 or 39 or 40 or 36 or 41 or 38 or 34 or 37
44. 43 and 31
45. remove duplicates from 44
46. Animals/ not human.mp. [mp=ti, ab, tx, kw, ct, ot, nm, hw]
47. 45 not 46
48. remove duplicates from 47

Table 22. Literature search yield of primary articles for systematic review topics

Topic	Abstracts screened	Number of systematic reviews identified	Number of existing systematic reviews included	Original articles included in summary tables *
Definition	18 385	4	2	17
Prevention and Treatment		40	15	25
CI-AKI		22	0	51
Dialysis		24	2	15

*Available at www.kdigo.org
CI-AKI, contrast-induced acute kidney injury.

Table 23. Hierarchy of importance of outcomes

Hierarchy[a]	Outcomes[b]
Critical importance	Mortality, RRT
High importance (often noted to be the "Crucial" outcome)	AKI, CI-AKI

a. Outcomes of lesser importance are excluded from review.
b. This categorization was the consensus of the Work Group for the purposes of these guidelines only. The lists are not meant to reflect outcome ranking for other areas of management. The Work Group acknowledges that not all clinicians, patients or families, or societies would rank all outcomes the same. Since this guideline focused on AKI, other outcomes of importance to critically ill patients were not included.

AKI, acute kidney injury; CI-AKI, contrast-induced acute kidney injury; RRT, renal replacement therapy.

Table 24. Classification of study quality

Good quality:	Low risk of bias and no obvious reporting errors, complete reporting of data.
Fair quality:	Moderate risk of bias, but problems with study are unlikely to cause major bias.
Poor quality:	High risk of bias or cannot exclude possible significant biases. Poor methods, incomplete data, reporting errors.

Table 25. GRADE system for grading quality of evidence

Step 1: Starting grade for quality of evidence based on study design	Step 2: Reduce grade	Step 3: Raise grade	Final grade for quality of evidence and definition
Randomized trials = High	*Study quality* -1 level if serious limitations -2 levels if very serious limitations *Consistency* -1 level if important inconsistency *Directness* -1 level if some uncertainty -2 levels if major uncertainty *Other:* -1 level if sparse or imprecise data -1 level if high probability of reporting bias	*Strength of association* +1 level is strong[a], no plausible confounders +2 levels if very strong[b], no major threats to validity *Other* +1 level if evidence of a dose response gradient +1 level if all residual plausible confounders would have reduced the observed effect	High = Further research is unlikely to change confidence in the estimate of the effect
Observational study = Low			Moderate = Further research is likely to have an important impact on confidence in the estimate of effect and may change the estimate Low = Further research is very likely to have an important impact on confidence in the estimate and may change the estimate
Any other evidence = Very low			Very low = Any estimate of effect is very uncertain

a. Strong evidence of association is defined as 'significant relative risk of >2 (<0.5)' based on consistent evidence from two or more observational studies, with no plausible confounders.
b. Very strong evidence of association is defined as 'significant relative risk of >5 (<0.2)' based on direct evidence with no major threats to validity.

Reprinted by permission from Macmillan Publishers Ltd: Kidney International. Uhlig K, Macleod A, Craig J, et al. Grading evidence and recommendations for clinical practice guidelines in nephrology. A position statement from Kidney Disease: Improving Global Outcomes (KDIGO). Kidney Int 70: 2058-2065, 2006 [312]; Accessed: http://www.nature.com/ki/journal/v70/n12/full/5001875a.html

Table 26. Final grade for overall quality of evidence

Grade	Quality of evidence	Meaning
A	High	We are confident that the true effect lies close to that of the estimate of the effect.
B	Moderate	The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
C	Low	The true effect may be substantially different from the estimate of the effect.
D	Very low	The estimate of effect is very uncertain, and often will be far from the truth.

Table 27. Balance of benefits and harm

When there was evidence to determine the balance of medical benefits and harm of an intervention to a patient, conclusions were categorized as follows:

- Net benefits = the intervention clearly does more good than harm.
- Trade-offs = there are important trade-offs between the benefits and harm.
- Uncertain trade-offs = it is not clear whether the intervention does more good than harm.
- No net benefits = the intervention clearly does not do more good than harm.

Table 28. Implications of the strength of a recommendation

Grade*	Implications		
	Patients	Clinicians	Policy
Level 1 "We recommend"	Most people in your situation would want the recommended course of action and only a small proportion would not.	Most patients should receive the recommended course of action.	The recommendation can be evaluated as a candidate for developing a policy or a performance measure.
Level 2 "We suggest"	The majority of people in your situation would want the recommended course of action, but many would not.	Different choices will be appropriate for different patients. Each patient needs help to arrive at a management decision consistent with her or his values and preferences.	The recommendation is likely to require substantial debate and involvement of stakeholders before policy can be determined.

Table 29. Determinants of strength of recommendation

Factor	Comment
Balance between desirable and undesirable effects	The larger the difference between the desirable and undesirable effects, the more likely a strong recommendation is warranted. The narrower the gradient, the more likely a weak recommendation is warranted.
Quality of the evidence	The higher the quality of evidence, the more likely a strong recommendation is warranted.
Values and preferences	The more variability in values and preferences, or more uncertainty in values and preferences, the more likely a weak recommendation is warranted.
Costs (resource allocation)	The higher the costs of an intervention—that is, the more resources consumed—the less likely a strong recommendation is warranted.

Table 30. The Conference on Guideline Standardization (COGS) checklist for reporting clinical practice guidelines

Topic	Description	Discussed in KDIGO AKI Guidelines
1. Overview material	Provide a structured abstract that includes the guideline's release date, status (original, revised, updated), and print and electronic sources.	Appendix A: Background
2. Focus	Describe the primary disease/condition and intervention/service/technology that the guideline addresses. Indicate any alternative preventative, diagnostic or therapeutic interventions that were considered during development.	Chapter 1.1: Introduction Appendix A: Background Section 2: AKI Definition Guideline addresses prevention and treatment of AKI including radiocontrast-induced AKI.
3. Goal	Describe the goal that following the guideline is expected to achieve, including the rationale for development of a guideline on this topic.	This clinical practice guideline is intended to assist the practitioner caring for patients at risk for or with AKI in evaluation and in selecting treatments (among the different options) to improve patient survival and preserve.or recover kidney function.
4. User/setting	Describe the intended users of the guideline (e.g. provider types, patients) and the settings in which the guideline is intended to be used.	Providers: Nephrologists (adult and pediatric), Critical care specialists, Dialysis providers (including nurses), Radiologists, Cardiologists, Internists, Infectious disease specialists, Epidemiologists and Pediatricians Patients: Adult and pediatric individuals at risk for or with AKI and their relatives and friends Policy Makers: Those in related health fields
5. Target population	Describe the patient population eligible for guideline recommendations and list any exclusion criteria.	Individuals at risk for or with AKI, adult and pediatric.
6. Developer	Identify the organization(s) responsible for guideline development and the names/credentials/potential conflicts of interest of individuals involved in the guideline's development.	Organization: KDIGO
7. Funding source/sponsor	Identify the funding source/sponsor and describe its role in developing and/or reporting the guideline. Disclose potential conflict of interest.	KDIGO is supported by the following consortium of sponsors: Abbott, Amgen, Belo Foundation, Coca-Cola Company, Dole Food Company, Genzyme, Hoffmann-LaRoche, JC Penney, NATCO—The Organization for Transplant Professionals, National Kidney Foundation—Board of Directors, Novartis, Robert and Jane Cizik Foundation, Shire, Transwestern Commercial Services, and Wyeth. No funding is accepted for the development or reporting of specific guidelines. All stakeholders could participate in open review. Refer to Biographic and Disclosure Information section.

Topic	Description	Discussed in KDIGO AKI Guidelines
8. Evidence collection	Describe the methods used to search the scientific literature, including the range of dates and databases searched, and criteria applied to filter the retrieved evidence.	MEDLINE search for relevant terms including kidney, kidney disease, renal replacement therapy, AKI, CI-AKI and specific treatments. The search was no limited to English language. Publication dates were limited since 1995 for CI-AKI and since 1980 for all other topics (See Table 21: AKI Search Strategies). The search was updated through December 16, 2010 and supplemented by articles identified by Work Group members through February 2011.
9. Recommendation grading criteria	Describe the criteria used to rate the quality of evidence that supports the recommendations and the system for describing the strength of the recommendations. Recommendation strength communicates the importance if adherence to a recommendation and is based on both the quality of the evidence and the magnitude of anticipated benefits and harms.	Quality of individual studies was graded in a three-tiered grading system (see Table 24). Quality of evidence (Table 25) was graded following the GRADE approach Strength of the recommendation was graded in a two-level grading system which was adapted from GRADE for KDIGO with the quality of overall evidence graded on a four-tiered system (Table 26 and Table 28).
10. Method for synthesizing evidence	Describe how evidence was used to create recommendations, e.g., evidence tables, meta-analysis, decision analysis.	1) Topics were triaged either to a) systematic review, b) narrative summary alone. For systematic review topics, summary tables and evidence profiles were generated. 2) The steps outlined by GRADE for guideline development of treatment interventions were followed.
11. Prerelease review	Describe how the guideline developer reviewed and/or tested the guidelines prior to release.	Guidelines underwent internal review by the KDIGO Board of Directors and external public review administered by KDIGO yielded 124 responses. Public review comments were compiled and fed back to the Work Group, which considered comments in its revision of the guideline.
12. Update plan	State whether or not there is a plan to update the guideline and, if applicable, expiration date for this version of the guideline.	There is no specific date set yet for updating of this guideline. Generally KDIGO attempts to update its guideline every 5 years. Information on registered ongoing studies and new publications will be reviewed periodically to evaluate their potential to impact on the recommendations in this guideline. Interim updates may be conducted if new evidence becomes available that would substantively change the content or strength of recommendations.
13. Definitions	Define unfamiliar terms and those critical to correct application of the guideline that might be subject to misinterpretation.	Chapter 1.1: Introduction Appendix A: Background Section 2: AKI Definition

Topic	Description	Discussed in KDIGO AKI Guidelines
14. Recommendations and rationale	State the recommended action precisely and the specific circumstances under which to perform it. Justify each recommendation by describing the linkage between the recommendation and its supporting evidence. Indicate the quality of evidence and the recommendation strength, based on the criteria described in 9.	Recommendations are provided in Sections 2-5 Each recommendations builds on a supporting rationale with evidence tables if available. The strength of the recommendation and quality of supporting evidence are provided in parenthesis after each recommendation, following the GRADE approach..
15. Potential benefits and harm	Describe anticipated benefits and potential risks associated with implementation of guideline recommendations.	This depends on the recommendation. Summary of the benefits and harm for each intervention is provided in Sections 3-5, in summary tables and evidence profiles, and discussed in the rationale for each guideline statement.
16. Patient preferences	Describe the role of patient preferences when a recommendation involves a substantial element of personal choice or values.	Level 2 (or weak or discretionary) recommendations inherently indicate a greater need to help each patient arrive at a management decision consistent with her or his values and preferences.
17. Algorithm	Provide (when appropriate) a graphical description of the stages and decisions in clinical care described by the guideline.	Appendix A: Background Section 2: AKI Definition
18. Implementation considerations	Describe anticipated barriers to application of the recommendations. Provide reference to any auxiliary documents for providers or patients that are intended to facilitate implementation. Suggest review criteria for measuring changes in care when the guideline is implemented.	Given the limitations of the evidence base, recommendations could not be very specific. Suggestions were provided for future research in the field of AKI.

AKI, acute kidney disease; CI-AKI, contrast-induced acute kidney disease; KDIGO, Kidney Disease: Improving Global Outcomes; KDOQI, Kidney Disease Outcomes Quality Initiative. Adapted with permission.[314]

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