Why are patients still getting and dying from acute kidney injury?

John A. Kellum

Purpose of review
Acute kidney injury is common and is associated with increased morbidity and mortality. Rates of acute kidney injury in most settings remain high and in some settings are increasing. Moreover, outcomes associated with acute kidney injury remain relatively poor. This review focuses on recent advances in understanding of acute kidney injury and discusses possible interventions based on these advances.

Recent findings
Acute kidney injury is not a disease with a single etiology and clinical course but rather a loose collection of syndromes whose unifying phenotype is an acute loss of glomerular filtration. Traditional taxonomy based on anatomic locations (pre, intra, and post) in reference to the kidney is overly simplistic and has given way to specific 'endotypes' including hepatorenal, cardiorenal, nephrotoxic, and sepsis-associated and these syndromes all have unique pathophysiologies and treatments. Our tendency to lump all of these clinical syndromes into a single disease and seek a single treatment has led to the profound lack of progress observed in terms of improving outcomes. The hope is that this is about to change.

Summary
Understanding the epidemiology, pathogenesis, and pathophysiology of acute kidney injury is critical to achieving improved outcomes for the millions of patients who develop this loose constellation of syndromes.

Keywords
acute kidney injury, classification, epidemiology, treatment

INTRODUCTION

Acute kidney injury (AKI) is now understood to be one of the most important complications seen in critical illness and a massive public health concern overall. Growing awareness for the condition has resulted in a variety of new approaches for diagnosis and treatment. Unfortunately, the traditional taxonomy based on anatomic locations (pre, intra, and post) in reference to the kidney is overly simplistic. This taxonomy has now given way to specific 'endotypes' including hepatorenal [1▪], cardiorenal [2], nephrotoxic [3], sepsis-associated AKI [4▪▪], and others and there is ever increasing evidence that these syndromes have unique pathophysiologies and treatments. Like the concept of AKI itself, care is evolving and the era of precision medicine for AKI is approaching. In this review, we will consider recent discoveries and rediscoveries that are changing the way we look at this complex disorder.

ACUTE KIDNEY INJURY IS AN EVOLVING CONCEPT

AKI is a nonspecific clinical syndrome defined by a rapid loss of glomerular filtration rate (GFR). AKI is 'nonspecific' because it can result from numerous different etiologies (Fig. 1), some of which are specific diseases that have very specific therapy. Other etiologies for AKI have distinctive epidemiology and

Center for Critical Care Nephrology, Department of Critical Care Medicine, University of Pittsburgh, Pennsylvania, USA

Correspondence to Dr John A. Kellum, MD, MCCM, Professor of Critical Care Medicine, Medicine, Clinical and Translational Science, and Bioengineering, Director, Center for Critical Care Nephrology, 604, Scaife Hall, University of Pittsburgh, 3550 Terrace Street, Pittsburgh, PA 15261, USA. Tel: +1 412 647 8110; fax: +1 412 647 2645;
e-mail: kellumja@upmc.edu

Curr Opin Crit Care 2016, 22:513–519
DOI:10.1097/MCC.0000000000000358

KEY POINTS

- AKI is not a single disease but a loose collection of clinical syndromes with differing pathogeneses and treatments.
- Older 'anatomic-based' classification systems for AKI have been displaced by etiology-specific syndromes.
- The near future will usher in an age of molecular phenotyping and precision medicine for AKI.
- Currently, best practice is to be well acquainted with individual AKI syndromes, their causes and treatments and to avoid generalizations in the care of patients with AKI.

pathogenesis but remain poorly characterized and do not yet have specific therapies.

Already in ancient times it was noted that the failure to pass urine was lethal if untreated and might be due to either 'an empty bladder' or an obstruction. Indeed, urinary catheters were used as early as 3000 BC. It was Galen who first established the kidneys as the source of urine and as organs that 'filtered the blood' [5]. Progress in the clinical assessment of renal function progressed quite slowly from the time of Galen until the 18th century when urea was discovered. However, it would be more than a century later before increases in blood urea and serum creatinine would be used to quantify azotemia ('azote' is a very old name for nitrogen). Azotemia results from reductions in GFR and together with oliguria ('small' urine) or anuria (no urine) form the cardinal features of kidney failure.

In order to support clinical diagnosis and to anchor epidemiological study, AKI is classified based on specific clinical and laboratory criteria (Table 1) [6]. However, these criteria do not define AKI, which remains a clinical diagnosis – in the same way that electrocardiographic changes and troponin do not define myocardial infarction (MI). Azotemia and oliguria are indicative not only of pathology but are also normal responses of the kidney to extracellular volume depletion or a decreased renal blood flow. Conversely, a 'normal' urine output and GFR in the face of volume depletion could only be viewed as renal dysfunction. Thus, changes in urine output and GFR are neither necessary nor sufficient for the diagnosis of renal pathology [7]. Still, they serve as the backbone for our existing diagnostic criteria [6].

Furthermore, a patient might have AKI but serum creatinine and urine output were not quantified. Alternatively, serum creatinine and urine output could be abnormal and even meet the specific criteria for AKI but mitigating conditions might make the diagnosis less likely [8▪▪]. Indeed checklists or similar tools may help in difficult cases [9▪].

Two problems further complicate the diagnosis of AKI. First, until recently most of our diagnostic tools measured only renal function, not injury *per se*. To give some sense of what that means, consider making the diagnosis of MI using only clinical signs of heart failure and echocardiography. Sure,

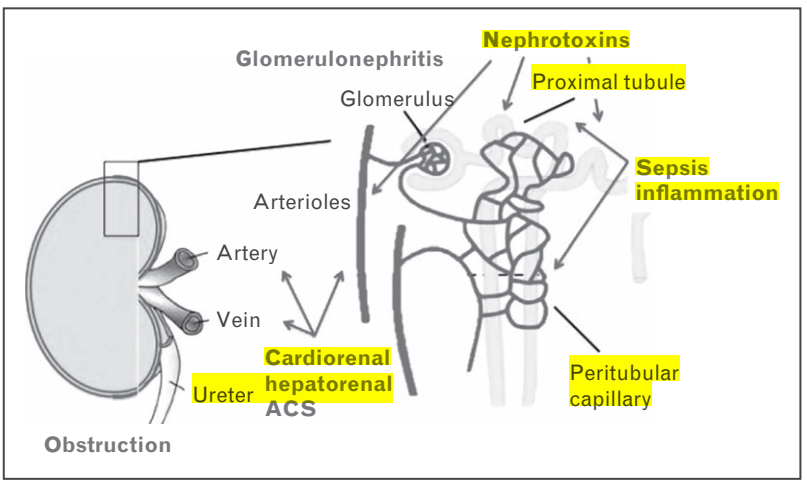

FIGURE 1. Acute kidney injury (AKI) syndromes. Although an oversimplification, the figure depicts the main AKI syndromes and their anatomic sites of injury. Therapies vary widely from discontinuation of offending nephrotoxins to diuresis/ultrafiltration ± inotropic support (cardiorenal) to vasoactive drugs (hepatorenal) to surgical decompression [abdominal compartment syndrome (ACS)] to immune modulating therapy (glomerulonephritis). Therapy for sepsis remains elusive apart from antibiotics but these agents can be nephrotoxic further complicating the phenotype.

Table 1. Acute kidney injury staging

Stage	Serum creatinine	Urine output
1	1.5–1.9 times baseline or ≥0.3 mg/dl (≥26.5 μmol/l) increase	<0.5 ml/kg/h for ≥6 but <12 h
2	2.0–2.9 times baseline	<0.5 ml/kg/h for ≥12 h
3	3.0 times baseline or increase to ≥4.0 mg/dl (≥353.6 μmol/l) or initiation of renal replacement therapy or in patients <18 years a decrease in eGFR to <35 ml/min per 1.73 m^2	<0.3 ml/kg/h for ≥24 h or anuria for ≥12 h

eGFR, estimated glomerular filtration rate. Data from: www.KDIGO.org.

sometimes we end up inferring a MI occurred from regional wall-motion abnormalities but imagine that was our only test. Surely we would miss a great many infarcts especially early on when therapy is possible and we would also confuse other causes of heart failure with ischemia and likely misapply available treatments. Serum creatinine and urine output are functional measures and do not directly measure injury. Second, because our functional measures are insensitive to injury, 'subclinical' AKI is common [10]. Paradoxically, this is less of a problem in patients with underlying chronic kidney disease because these patients have limited renal reserve – most new injuries will cause measurable changes in renal function. However, healthy individuals, particularly younger adults have substantial renal reserve [11,12▪] and can lose more than half their renal function (e.g., donating a kidney) before serum creatinine changes.

It is important to reflect on the fact these difficulties in the diagnosis of AKI are less concerning for our epidemiological understanding of the problem. A few patients may be missed and labeled as either having or not having AKI but the overall estimates will not be substantially affected – although there are important implications nonetheless as we will discuss in the next section. However, for the individual patient (or subject in a clinical trial) misdiagnosis carries grave consequences. As such, clinical judgment [6] (or in the case of trials, clinical adjudication [13▪]) is critical. At the bedside, AKI is always a clinical diagnosis.

INCIDENCE AND CLINICAL CONSEQUENCES OF ACUTE KIDNEY INJURY

The incidence of AKI in the western world is believed to be similar to that of MI or about 2.1/1000 population [14,15]. However, this is likely an underestimate due to under-diagnosis particularly outside the ICU. AKI occurs in approximately 55–60% of critically ill patients [16▪▪]. This number may seem incomprehensibly high until one realizes that the rates of respiratory and cardiovascular failure among the critically ill are similar – being critically ill usually means multiorgan dysfunction. Some estimates of AKI incidence and rates among hospitalized patients have used only serum creatinine changes but this approach fails to recognize more than a third of cases [17▪▪,18]. Among the critically ill, stage 2 or 3 AKI occurred in 18% without any changes in serum creatinine sufficient to make the diagnosis and these patients had a 8.6% hospital mortality. Conversely, only 3% had stage 2 or 3 AKI by serum creatinine without any urine output criteria and hospital mortality was only slightly higher at 11.4% [17▪▪]. Moreover, the addition of even stage 1 urine output criteria to these 'creatinine only' patients was associated with increase in mortality to 30%.

Surprisingly, similar risk-adjusted rates of AKI and mortality are seen around the world with hospital mortality increasing nearly four-fold with AKI [16▪▪]. When trying to understand the clinical consequences of AKI an interesting set of paradoxes arise. First, the early stage of AKI (i.e., stage 1) is likely the point at which AKI is most amenable to therapy and thus it is often the starting point for clinical practice guidelines [6]. However, as many as 70% of patients with stage 1 AKI resolve spontaneously and when carefully controlled for baseline severity of illness, patients who develop stage 1 without further progression are not clearly at risk for decreased survival [16▪▪].

The word 'spontaneously' might be misleading however, and what epidemiological studies cannot teach us is what effect clinical care might be having in the background. Increased awareness of AKI in recent years might be resulting in better outcomes in some types of patients particularly those wherein the AKI exposure can be modified. Let us examine three specific examples. First, AKI is commonly associated with MI [19]. Cardiorenal physiology and radiocontrast exposure both play important roles and both may be influenced by patient care decisions. Aggressive early revascularization and ventricular assist devices, both becoming increasingly prevalent,

may alter cardiac physiology and reduce AKI. Volumes and perhaps types of radiocontrast are changing as well. A recently reported, large national study found that AKI incidence in patients hospitalized with acute MI declined significantly from 2000 to 2008 despite an aging population and rising prevalence of AKI risk factors [19]. The authors suggested that these findings may reflect increased clinician awareness, better risk stratification, or greater use of AKI prevention efforts. Another population of great interest is pediatrics. Nephrotoxic AKI is a particularly prevalent condition in this population and it appears quite amenable to practice change [20]. Goldstein *et al.* at Cincinnati Children's Hospital have spearheaded efforts to reduce nephrotoxicity by identifying patients electronically – see 'Medication-induced acute kidney injury' in this issue [21]. Finally, cardiac surgery is associated with AKI and efforts such as avoiding cardiopulmonary bypass appear to reduce the risk of AKI. In a trial of nearly 3000 patients, cardiac surgery 'off-pump' reduced the risk of AKI (17.5 vs. 20.8%; relative risk, 0.83 [95% confidence interval (CI), 0.72–0.97], $P = 0.01$) compared to standard technique using cardiopulmonary bypass [22]. However, there was no significant difference between the two groups in the loss of kidney function at 1 year [17.1 vs. 15.3%, respectively; relative risk, 1.10 (95% CI, 0.95–1.29), $P = 0.23$]. Similarly, remote ischemic preconditioning appears to reduce the risk for AKI in high-risk patients [23▪▪] though larger studies in lower-risk patients have been negative [24▪,25▪] – see also 'Renal protection in the 21st century' in this issue [26]. Finally, we might also point to avoiding hydroxyethyl starch as an effective way to prevent AKI and improve survival in patients with severe sepsis [27]. Although these results were not confirmed in a larger trial [28], the exposure was less and there was still some evidence of renal toxicity even though only apparent in the rates of acute renal replacement therapy (RRT).

Another interesting paradox for AKI is that lower severity patients (though still ICU patients) seem to be more impacted by AKI compared with high severity patients [29]. Not surprisingly, stage 2–3 AKI occurred less frequently in patients admitted to ICU without respiratory or cardiovascular failure compared with those that were (25.7 vs. 51.7%). Patients developing AKI in both risk groups had higher risk of death before hospital discharge. However, the adjusted odds of hospital mortality were greater [odds ratio (OR), 2.99; 95% CI, 2.62–3.41] when AKI occurred in low-risk patients compared with those with respiratory or cardiovascular failures (OR, 1.19; 95% CI, 1.09–1.3); interaction $P < 0.001$. Thus, although survival for low-severity patients is better than for high-severity patients, the relative increase in mortality associated with AKI is actually greater for low-severity patients. In virtually all studies, AKI was associated not only with worse survival but also with substantial increases in ICU and hospital length of stay. Indeed, regardless of age group studied length of stay was approximately double when AKI complicated critical illness [30▪] and consequently costs tend to double as well [31].

WHY ARE PATIENTS STILL DYING OF ACUTE KIDNEY INJURY?

Given the numerous potential approaches to reduce AKI and its impact on survival discussed above, we might expect to be observing substantial progress in preventing and treating AKI. Sadly, this does not appear to be the case although isolated examples of progress in specific areas are clearly present [19,20] and substantial variability in AKI rates and outcomes exist across institutions even when uniform criteria are used [19,32▪]. Despite limited success so far from electronic alerting to improve clinical recognition of AKI [33▪▪] there are evolving efforts to make alerts smarter and more action-oriented [34] – see 'Computer decision support for acute kidney injury; current and future' in this series [35]. However, just what actions are needed? So far the most progress we have seen is in limiting iatrogenesis whether in the form of nephrotoxins [20], cardiopulmonary bypass [22], or certain fluids [27,36] – see also 'Fluid resuscitation for acute kidney injury – an empty promise' in this series [37]. However, we face a notable problem for many types of AKI because injury is already well established by the time patients seek medical attention. This is particularly true for syndromes such as sepsis-associated AKI in which virtually all patients who will develop AKI, manifest by serum creatinine or urine output, already have injury at the time of presentation [38▪▪]. Simply alerting clinicians to the fact a patient has already sustained AKI might be useful in so far as improving management (and facilitating recovery) but it certainly cannot prevent the condition in the first place. Alerts that inform clinicians that patients are at risk and what the specific risks are (e.g., nephrotoxic drug or combination) are likely to be much more effective. An important exception to this rule might be that automated decision support systems can help clinicians identify AKI by sorting through past laboratory data for serum creatinine values that reflect baseline renal function [39]. This can be a difficult problem particularly when patients have multiple encounters and variation in serum creatinine (which

actually might be a risk factor in itself! [40]). Determining the right baseline creatinine for a patient is no trivial matter because it affects diagnosis, staging, and assessment of recovery [8▪▪].

Another approach is to use laboratory tests which are more sensitive (or have faster kinetics) compared to serum creatinine and at the same time are more specific than urine output. Several candidates have been put forth [41,42▪] and still others are being evaluated. In the United States, only a test containing urinary insulin-like growth factor-binding protein 7 (IGFBP7) together with tissue inhibitor of metalloproteinases-2 (TIMP-2) is approved for use by the Food and Drug Administration [43] – trade name NephroCheck, Astute Medical, San Diego, California, USA. Interestingly, both molecules are inducers of G_1 cell cycle arrest, a protective mechanism – the test essentially measures the kidney's attempt to protect itself from injury [42▪]. Together these markers have demonstrated an area under the receiver operating characteristic curve (AUC) of 0.80–0.82 for prediction of AKI in the next 12 h [44,45]. [TIMP-2]·[IGFBP7] was significantly superior to all existing markers of AKI ($P < 0.002$), none of which achieved an AUC > 0.72 [44]. Furthermore, [TIMP-2]·[IGFBP7] significantly improved risk stratification when added to a nine-variable clinical model when analyzed using Cox proportional hazards model, generalized estimating equation, integrated discrimination improvement, or net reclassification improvement. [TIMP-2]·[IGFBP7] increases rapidly in response to even subinjurious stimuli [23▪▪]; it is not affected by chronic kidney disease [46▪] or by other chronic [46▪] or acute nonrenal organ failures [47▪]. The test performs equally well in medical and surgical patients [48▪] and correlates with death or dialysis at 9 months [49▪]. It has even been validated in other species [50▪]. Given these results it would seem well positioned to fill the niche of the early alarm for AKI that serum creatinine has failed to provide [42▪]. Biomarkers such as [TIMP-2]·[IGFBP7] can therefore be used to enrich the patient population that can receive additional monitoring, alternative medications and imaging techniques, and early investigation as to the cause of the renal 'stress'. Similar applications in clinical trials can dramatically reduce sample sizes and therefore costs [51].

NO MAGIC POTION: JUST GOOD MEDICINE

Early enthusiasm for novel AKI biomarkers has been tempered by the realization that there is no 'thrombolytic equivalent' for AKI. The conversation around AKI diagnostics has rapidly moved from finding AKI early to finding a treatment. The problem is that AKI is not a disease so there will almost certainly not be single treatment that works for all forms of AKI. Even diseases like cancer have dramatically different therapies depending on the cancer phenotype in question. AKI is about 50 years behind cancer! The traditional taxonomy based on anatomic locations (pre, intra, and post) in reference to the kidney is overly simplistic and has given way to specific 'endotypes' including hepatorenal [1▪], cardiorenal [2], nephrotoxic [3], sepsis-associated [4▪▪], and urinary tract obstruction and these syndromes all have unique pathophysiologies and treatments. They may also have different molecular signatures [52].

Thus, we cannot just say a patient has AKI so we need to start therapy X. Instead, we need to determine the specific AKI syndrome the patient has (Fig. 1) and prescribe a set of actions (starting as well as stopping) that matches the specific pathobiology. At times, these actions will be diametrically opposed. For example, will a patient with AKI benefit from fluid administration or diuresis or neither? The answer depends on whether the patient has cardiorenal physiology from acute decompensated heart failure where the answer will usually be diuresis or septic shock where judicious use of fluids is required (but further fluid use will not be helpful) or nephrotoxic AKI where both fluids and diuretics may be harmful. Thus, treatment X will likely be a bundle of therapies tailored to the specific AKI syndrome encountered. Even the use of RRT must be tailored as two recent trials demonstrated [53▪▪,54▪▪]. In clinical scenarios where the vast majority of patients receive RRT, early initiation results in improved survival [53▪▪], whereas in settings where only a fraction of patients ever require RRT a 'wait and see' approach may be preferred [54▪▪]. However, even here, those requiring late therapy generally do worse.

For patients with 'less severe' AKI, who are not judged as requiring RRT, outcomes are generally better. However, less severe AKI may still be in the causal pathway for morbidity and mortality in critically ill patients [55]. Effects of renal dysfunction on immune function, fluid balance, and drug clearance may result in a myriad of complications, prolonging hospitalization and increasing risk of death. Evolution in disease management from severe to 'less severe' is familiar to us all. The emergence of non-ST segment MI and 'precancerous syndromes' are both examples of evolving pathonomenclature as the epidemiology and pathobiology of diseases like coronary artery disease and cancer advance. We should expect the same as we move from acute renal failure to AKI and ultimately to acute kidney disease [56].

CONCLUSION

Understanding the epidemiology, pathogenesis, and pathophysiology of AKI is critical to achieving improved outcomes for the millions of patients who develop this loose constellation of syndromes. Specific therapies can only emerge from a better appreciation of the unique phenotypes within the broader context of AKI. Clinical and molecular characterization together with better understanding of pathogenesis are needed. Clinical trials evaluating therapies should focus on precise populations and consider biomarker enrichment strategies. At the bedside an appreciation for specific AKI syndromes rather than an all encompassing disease should advance care.

Acknowledgements

None.

Financial support and sponsorship

None.

Conflicts of interest

The author declares consulting fees and/or research funding from numerous commercial entities including Astute Medical, Alere, Baxter, Bard, BioPorto, Fresenius, NxStage, and Renal Sense.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- ■ of special interest
- ■■ of outstanding interest

1. ■ Al-Khafaji A, Nadim MK, Kellum JA. Hepatorenal disorders. Chest 2015; 148:550–558.
A recent review of hepatorenal disease include the latest diagnostic criteria and therapy.
2. Vandenberghe W, Gevaert S, Kellum JA, *et al.* Acute kidney injury in cardiorenal syndrome type 1 patients: a systematic review and meta-analysis. Cardiorenal Med 2016; 6:116–128.
3. Kane-Gill SL, LeBlanc JM, Dasta JF, *et al.* A multicenter study of the point prevalence of drug-induced hypotension in the ICU. Crit Care Med 2014; 42:2197–2203.
4. ■■ Gomez H, Ince C, De Backer D, *et al.* A unified theory of sepsis-induced acute kidney injury: inflammation, microcirculatory dysfunction, bioenergetics, and the tubular cell adaptation to injury. Shock 2014; 41:3–11.
An in depth conceptual model for sepsis-induced AKI.
5. Diamandopoulos A. Twelve centuries of nephrological writings in the Graeco-Roman world of the Eastern Mediterranean (from Hippocrates to Aetius Amidanus). Nephrol Dial Transplant 1999; 14 (Suppl 2):2–9.
6. KDIGO AKI Workgroup. Kidney Disease: Improving Global Outcomes (KDIGO) clinical practice guideline for acute kidney injury. Kidney Int Suppl 2012; 2:1–138.
7. Kellum JA. Acute kidney injury. Crit Care Med 2008; 36:S141–S145.
8. ■■ Kellum JA. Diagnostic criteria for acute kidney injury: present and future. Crit Care Clin 2015; 31:621–632.
A detailed examination of diagnostic criteria for AKI along with the discussion of clinical judgment and pitfalls in the clinical approach.
9. ■ Kellum JA, Bellomo R, Ronco C. Does this patient have acute kidney injury? An AKI checklist. Intensive Care Med 2016; 42:96–99.
A useful bedside tool for AKI.
10. Haase M, Kellum JA, Ronco C. Subclinical AKI – an emerging syndrome with important consequences. Nat Rev Nephrol 2012; 8:735–739.
11. Bellomo R, Kellum JA, Ronco C. Acute kidney injury. Lancet 2012; 380:756–766.
12. ■ Fuhrman DY, Kellum JA. Biomarkers for diagnosis, prognosis and intervention in acute kidney injury. Contrib Nephrol 2016; 187:47–54.
Introduction of the concepts of renal stress, and frailty along with a discussion of renal reserve.
13. ■ Liu KD, Vijayan A, Rosner MH, *et al.* Clinical adjudication in acute kidney injury studies: findings from the pivotal TIMP-2∗IGFBP7 biomarker study. Nephrol Dial Transplant 2016. [Epub ahead of print]
A detailed examination of clinical adjudication for AKI and relationship to biomarker results.
14. Kellum JA, Bellomo R, Ronco C. Kidney attack. JAMA 2012; 307:2265–2266.
15. Ali T, Khan I, Simpson W, *et al.* Incidence and outcomes in acute kidney injury: a comprehensive population-based study. J Am Soc Nephrol 2007; 18:1292–1298.
16. ■■ Hoste EAJ, Bagshaw SM, Bellomo R, *et al.* Epidemiology of acute kidney injury in critically ill patients: the multinational AKI-EPI study. Intensive Care Med 2015; 41:1411–1423.
The largest epidemiological study to date on AKI on the ICU.
17. ■■ Kellum JA, Sileanu FE, Murugan R, *et al.* Classifying AKI by urine output versus serum creatinine level. J Am Soc Nephrol 2015; 26:2231–2238.
Analysis of the role of urine output and serum creatinine in the classification of AKI.
18. Murugan R, Kellum JA. Acute kidney injury: what's the prognosis? Nat Rev Nephrol 2011; 7:209–217.
19. Amin AP, Salisbury AC, McCullough PA, *et al.* Trends in the incidence of acute kidney injury in patients hospitalized with acute myocardial infarction. Arch Intern Med 2012; 172:246–253.
20. Goldstein SL, Kirkendall E, Nguyen H, *et al.* Electronic health record identification of nephrotoxin exposure and associated acute kidney injury. Pediatrics 2013; 132:e756–e767.
21. Goldstein SL. Medication-induced acute kidney injury. Curr Opin Crit Care 2016.
22. Garg AX, Devereaux PJ, Yusuf S, *et al.* Kidney function after off-pump or on-pump coronary artery bypass graft surgery: a randomized clinical trial. JAMA 2014; 311:2191–2198.
23. ■■ Zarbock A, Schmidt C, Van Aken H, *et al.* Effect of remote ischemic preconditioning on kidney injury among high-risk patients undergoing cardiac surgery: a randomized clinical trial. JAMA 2015; 313:2133–2141.
Evidence for clinical effect and mechanistic insights for remote ischemic preconditioning in cardiac surgery.
24. ■ Hausenloy DJ, Candilio L, Evans R, *et al.* Remote ischemic preconditioning and outcomes of cardiac surgery. N Engl J Med 2015; 373:1408–1417.
One of two large trials of remote ischemic preconditioning for prevention of cardiac surgery associated AKI – the study was negative but was likely underpowered for this low-risk population.
25. ■ Meybohm P, Bein B, Brosteanu O, *et al.* A multicenter trial of remote ischemic preconditioning for heart surgery. N Engl J Med 2015; 373:1397–1407.
One of two large trials of remote ischemic preconditioning for prevention of cardiac surgery associated AKI – the study was negative but was likely underpowered for this low-risk population.
26. Meersch M, Zarbock A. Renal protection in the 21st century. Curr Opin Crit Care 2016.
27. Perner A, Haase N, Guttormsen AB, *et al.* Hydroxyethyl starch 130/0.42 versus Ringer's acetate in severe sepsis. N Engl J Med 2012; 367:124–134.
28. Myburgh JA, Finfer S, Bellomo R, *et al.* Hydroxyethyl starch or saline for fluid resuscitation in intensive care. N Engl J Med 2012; 367:1901–1911.
29. Sileanu FE, Murugan R, Lucko N, *et al.* AKI in low-risk versus high-risk patients in intensive care. Clin J Am Soc Nephrol 2015; 10:187–196.
30. ■ Kane-Gill SL, Sileanu FE, Murugan R, *et al.* Risk factors for acute kidney injury in older adults with critical illness: a retrospective cohort study. Am J Kidney Dis 2015; 65:860–869.
An analysis of risk factors for AKI across age groups.
31. Dasta JF, Kane-Gill SL, Durtschi AJ, *et al.* Costs and outcomes of acute kidney injury (AKI) following cardiac surgery. Nephrol Dial Transplant 2008; 23:1970–1974.
32. ■ Srisawat N, Sileanu FE, Murugan R, *et al.* Variation in risk and mortality of acute kidney injury in critically ill patients: a multicenter study. Am J Nephrol 2015; 41:81–88.
Evidence that AKI rates and outcomes vary across centers.
33. ■■ Wilson FP, Shashaty M, Testani J, *et al.* Automated, electronic alerts for acute kidney injury: a single-blind, parallel-group, randomised controlled trial. Lancet 2015; 385:1966–1974.
A well conducted study of clinical decision support for AKI. The study found that electronic alerts for AKI did not change practice nor improve outcomes. A limitation is that the alerts did not provide actionable information or specific recommendations.
34. Kellum JA, Kane-Gill SL, Handler SM. Can decision support systems work for acute kidney injury? Nephrol Dial Transplant 2015; 30:1786–1789.
35. Kashani K. Computer decision support for acute kidney injury; current and future. Curr Opin Crit Care 2016.
36. Shaw AD, Bagshaw SM, Goldstein SL, *et al.* Major complications, mortality, and resource utilization after open abdominal surgery. Ann Surg 2012; 255:821–829.
37. Watkins SC, Shaw AD. Fluid resuscitation for acute kidney injury – an empty promise. Curr Opin Crit Care 2016.

38. Kellum JA, Chawla LS, Keener C, *et al.* The effects of alternative resuscitation ■■ strategies on acute kidney injury in patients with septic shock. Am J Respir Crit Care Med 2016; 193:281–287.
An analysis of AKI in the ProCESS trial of early goal-directed therapy.
39. DeAlmeida D, Al-Jaghbeer M, Abdelhak M, Kellum JA. A study to evaluate the effectiveness of the currently utilized acute kidney injury (AKI) alert: a use case example for a learning health system. In: 48th Hawaii International Conference on System Sciences (HICSS); 2015. p. 3125–3131.
40. Palant CE, Chawla LS, Faselis C, *et al.* High serum creatinine nonlinearity: a renal vital sign? Am J Physiol Renal Physiol 2016; 311:F305–F309.
41. Murray PT, Mehta RL, Shaw A, *et al.* Potential use of biomarkers in acute kidney injury: report and summary of recommendations from the 10th Acute Dialysis Quality Initiative consensus conference. Kidney Int 2014; 85:513–521.
42. Kellum JA, Chawla LS. Cell-cycle arrest and acute kidney injury: the light and ■ the dark sides. Nephrol Dial Transplant 2015; 31:16–22.
A clinical review of novel cell-cycle arrest biomarkers.
43. FDA allows marketing of the first test to assess risk of developing acute kidney injury. FDA. http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm412910.htm [Accessed 5 September 2016].
44. Kashani K, Al-Khafaji A, Ardiles T, *et al.* Discovery and validation of cell cycle arrest biomarkers in human acute kidney injury. Crit Care 2013; 17:R25.
45. Bihorac A, Chawla LS, Shaw AD, *et al.* Validation of cell-cycle arrest biomarkers for acute kidney injury using clinical adjudication. Am J Respir Crit Care Med 2014; 189:932–939.
46. Heung M, Ortega LM, Chawla LS, *et al.* Common chronic conditions do not ■ affect performance of cell cycle arrest biomarkers for risk stratification of acute kidney injury. Nephrol Dial Transplant 2016. [Epub ahead of print]
Evidence that chronic comorbidities including chronic kidney disease do not alter the performance of cell-cycle arrest biomarkers.
47. Honore PM, Nguyen HB, Gong M, *et al.* Urinary tissue inhibitor of metallo- ■ proteinase-2 and insulin-like growth factor-binding protein 7 for risk stratification of acute kidney injury in patients with sepsis. Crit Care Med 2016. [Epub ahead of print]
Evidence that acute nonrenal organ failures in sepsis do not alter the performance of cell-cycle arrest biomarkers.
48. Gunnerson KJ, Shaw AD, Chawla LS, *et al.* TIMP2·IGFBP7 biomarker panel ■ accurately predicts acute kidney injury in high-risk surgical patients. J Trauma Acute Care Surg 2016; 80:243–249.
The performance of cell-cycle arrest biomarkers in surgical patients.
49. Koyner JL, Shaw AD, Chawla LS, *et al.* Tissue inhibitor metalloproteinase-2 ■ (TIMP-2)-IGF-binding protein-7 (IGFBP7) levels are associated with adverse long-term outcomes in patients with AKI. J Am Soc Nephrol 2015; 26:1747–1754.
The relationship of cell-cycle arrest biomarker results to long-term outcomes.
50. Peng Z-Y, Zhou F, Kellum JA. Cross-species validation of cell cycle arrest ■ markers for acute kidney injury in the rat during sepsis. Intensive Care Med Exp 2016; 4:12.
A cross-species validation (rat) of cell cycle arrest markers for AKI.
51. Kellum JA, Devarajan P. What can we expect from biomarkers for acute kidney injury? Biomark Med 2014; 8:1239–1245.
52. Huen SC, Parikh CR. Molecular phenotyping of clinical AKI with novel urinary biomarkers. Am J Physiol Renal Physiol 2015; 309:F406–F413.
53. Zarbock A, Kellum JA, Schmidt C, *et al.* Effect of early vs delayed initiation of ■■ renal replacement therapy on mortality in critically ill patients with acute kidney injury: the ELAIN randomized clinical trial. JAMA 2016; 315:2190–2199.
A moderate sized clinical trial of early versus delayed initiation of RRT for severe AKI. In this study, in which most patients received renal support, early initiation was superior.
54. Gaudry S, Hajage D, Schortgen F, *et al.* Initiation strategies for renal- ■■ replacement therapy in the intensive care unit. N Engl J Med 2016; 375:122–133.
A moderate sized clinical trial of early versus delayed initiation of RRT for severe AKI. In this study, in which fully half of all patients in the delayed arm never received renal support, early initiation was not superior. However, in those patients receiving RRT late therapy was associated with worse outcome compared to early.
55. Kellum JA, Murugan R. Effects of non-severe acute kidney injury on clinical outcomes in critically ill patients. Crit Care 2016; 20:159.
56. Kellum JA, Ronco C, Bellomo R. Acute kidney disease and the community. Lancet 2016; 387:1974–1976.