AKI in the ICU: definition, epidemiology, risk stratification, and outcomes

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Acute kidney injury (AKI) has emerged as a major public health problem that affects millions of patients worldwide and leads to decreased survival and increased progression of underlying chronic kidney disease (CKD). Recent consensus criteria for definition and classification of AKI have provided more consistent estimates of AKI epidemiology. Patients, in particular those in the ICU, are dying of AKI and not just simply with AKI. Even small changes in serum creatinine concentrations are associated with a substantial increase in the risk of death. AKI is not a single disease but rather a syndrome comprising multiple clinical conditions. Outcomes from AKI depend on the underlying disease, the severity and duration of renal impairment, and the patient's renal baseline condition. The development of AKI is the consequence of complex interactions between the actual insult and subsequent activation of inflammation and coagulation. Contrary to the conventional view, recent experimental and clinical data argue against renal ischemia–reperfusion as a *sine qua non* condition for the development of AKI. Loss of renal function can occur without histological signs of tubular damage or even necrosis. The detrimental effects of AKI are not limited to classical well-known symptoms such as fluid overload and electrolyte abnormalities. AKI can also lead to problems that are not readily appreciated at the bedside and can extend well beyond the ICU stay, including progression of CKD and impaired innate immunity. Experimental and small observational studies provide evidence that AKI impairs (innate) immunity and is associated with higher infection rates.

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Acute kidney injury (AKI) is now recognized as a major public health problem affecting millions of patients worldwide and leading to decreased survival, increased progression of underlying chronic kidney disease (CKD), and sometimes to new onset of CKD. Recent consensus criteria for definition and classification of AKI have allowed for more consistent estimates of epidemiology and have now led to the first clinical practice guideline for AKI.[1] However, questions remain in terms of which patients are at highest risk for AKI and for adverse outcomes. Furthermore, AKI is not a single disease but rather a syndrome comprising multiple clinical conditions. Outcomes in AKI are influenced by the underlying disease causing the condition, as well as by the severity and duration of renal impairment and by the baseline condition of the patient. In whom does AKI result in these outcomes is also the subject of active research and much speculation. This review will briefly outline the currently accepted definition and classification criteria for AKI, the epidemiology of AKI based on these criteria, and the outcomes of AKI reported in the literature. We will then examine what is known concerning the pathogenesis of AKI as relates to the clinical epidemiology and risk stratification and also explore new concepts in the pathophysiology of AKI so as to better understand how AKI results in the outcomes for which it is associated.

DEFINITION, CLASSIFICATION, AND STANDARDIZATION OF AKI

Research in acute renal failure has long been hampered by a lack of standardization in classification. At one time, more than 35 different definitions of acute renal failure were being used in the literature.[2] Depending on the definition, acute renal failure was said to affect anywhere from 1 to 25% of intensive care unit (ICU) patients and to carry a mortality rate from 15 to 60%.[3–5] Such variation limits the ability to compare studies, to standardize study protocols, or even to communicate effectively across research groups.

As a consequence of the confusion surrounding the definition of acute renal failure, demands for a consensus definition and a classification system for acute renal failure have emerged.[6,7] Following long advocacy and persistent work, such a system, the RIFLE system (Figure 1), was ultimately developed, involving a broad consensus of

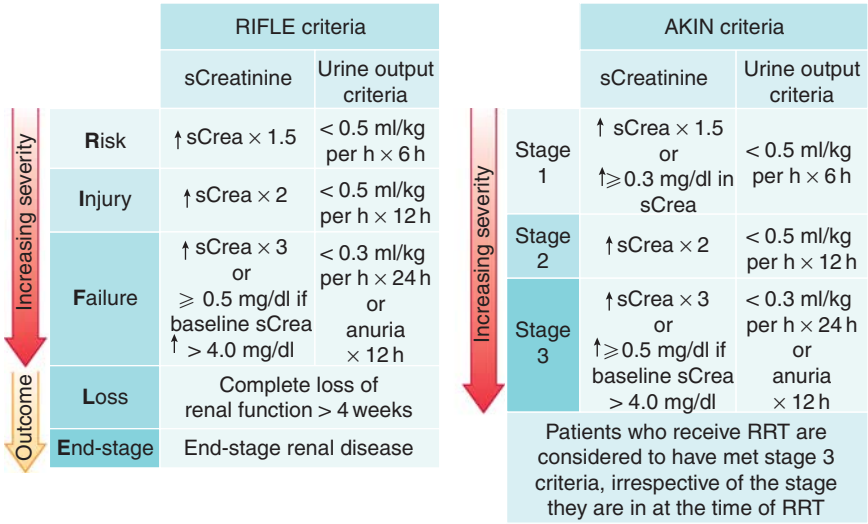

Figure 1 | Direct comparison of RIFLE (Risk of renal dysfunction, Injury to the kidney, Failure or Loss of kidney function, and End-stage kidney disease) and Acute Kidney Injury (AKI) Network criteria to classify AKI according to Bellomo *et al.*[7] and Mehta *et al.*,[8] respectively. Note that the original RIFLE criteria also listed glomerular filtration rates as reference, but these do not precisely agree with the changes in serum creatinine and were subsequently removed. For AKI Network criteria, the change in serum creatinine from baseline follows RIFLE, but there is also the option to use a 0.3 mg/dl increase if it is observed to occur within a 48-h period. RRT, renal replacement therapy.

experts.[7] The acronym RIFLE represents the increasing severity classes Risk, Injury, and Failure and the two outcome classes Loss and End-Stage Kidney Disease. The severity grades R–F are defined on the basis of changes in serum creatinine or urine output, wherein the worst of each criterion is used. The two outcome criteria, L and E, are defined by the duration of loss of kidney function.

Moreover, the term AKI is intended to encompass the entire spectrum of the syndrome, from minor impairment in renal function to the need for renal replacement therapy.[8] AKI is more than just acute renal failure; it encompasses the entire spectrum from severe to less severe conditions. Thereby, the focus is not exclusively on patients with renal failure or on those who receive dialysis, but attention is also paid to the strong association of AKI with hospital mortality even when only a minority of patients receive renal replacement therapy.[9]

The AKI Network, a somewhat larger, multidisciplinary, international group, subsequently proposed some small modifications to the RIFLE criteria (Figure 1):[8] (1) broadening of the 'Risk' category of RIFLE to include an increase in serum creatinine of at least 0.3 mg/dl, even if this does not reach the 50% threshold; (2) setting a 48-h window on the first documentation of any criteria; and (3) categorizing patients as 'Failure' if they are treated with renal replacement therapy regardless of what their serum creatinine or urine output is at the point of initiation (Figure 1). Broadening the criteria for 'Risk' (Stage 1) has led to increased sensitivity (more individuals are classified as having AKI). This difference, however, affects only 1–2% of patients. Studies validating RIFLE/AKI Network criteria have now included more than 500,000 patients.

EPIDEMIOLOGY

Using RIFLE criteria, investigators from around the world have shown that AKI is common and results in a substantial increase in hospital mortality. Uchino *et al.*[5] assessed the predictive ability of the RIFLE classification in a cohort of 20,126 patients admitted to a teaching hospital for >24 h over a 3-year period. Approximately 10% of the patients achieved a maximum RIFLE-R, 5% I and 3.5% F. The authors also found 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. R carried an odds ratio of hospital mortality of 2.5, I of 5.4, and F of 10.1.

The occurrence of AKI in the ICU was studied in 120,123 patients admitted to one of 57 intensive care units across Australia from January 2000 to December 2005.[10] Here, AKI occurred in 36.1%, with a maximum category R in 16.3%, I in 13.6%, and F in 6.3%. AKI was associated with an increase in hospital mortality (odds ratio 3.29; 95% confidence interval 3.19–3.41; $P<0.0001$). The crude hospital mortality was 17.9% for R, 27.7% for I, and 33.2% for F. After multivariable analysis, each RIFLE category was independently associated with hospital mortality (odds ratio: R 1.58, I 2.54, and F 3.22). However, this study was limited to AKI that occurred on or before the first day of ICU care and therefore primarily represents community-acquired AKI. Hoste *et al.*[9] found that AKI occurred in two-thirds of ICU patients, whereas RIFLE criteria were fulfilled at ICU admission in only 22% of patients. In multivariable analysis, AKI (hazard ratio 1.7; 95% confidence interval 1.28–2.13; $P<0.001$) and maximum RIFLE classes 'Injury' (hazard ratio 1.4; 95% confidence interval 1.02–1.88; $P=0.037$) and

'Failure' (hazard ratio 2.7; 95% confidence interval 2.03–3.55; $P<0.001$) were associated with hospital mortality after adjusting for multiple covariates.

Finally, Ali *et al.*[11] studied the incidence of AKI in the population of northern Scotland, a geographical population base of 523,390. The incidence of AKI was 2147 per million population. Sepsis was a precipitating factor in 47% of patients. RIFLE classification was useful for predicting recovery of renal function ($P<0.001$), requirement for renal replacement therapy ($P<0.001$), length of hospital stay for survivors ($P<0.001$), and in-hospital mortality ($P=0.035$). Thus, AKI is strongly associated with hospital mortality and resource use and remains so even after adjusting for baseline severity of illness, case mix, race, gender, and age.

ETIOLOGY AND RISK ASSESSMENT

Given how common AKI is and how significant its impact on survival is, one might expect more detailed information to be available on its cause. However, until recently, there have been two major obstacles to obtaining robust assessments of etiology and therefore it has been difficult to properly characterize risk for AKI. First, the lack of standard criteria for diagnosis of AKI has meant that observational studies cannot easily be compared to determine what demographic variables are associated with a general risk of AKI as against those that are specific to the underlying condition that leads to an exposure known to produce AKI. For example, risk factors for AKI in the setting of cardiac surgery tend to confound risks of AKI with risks for cardiovascular disease. A related problem comes from the observation that CKD puts patients at risk for AKI.[12,13] In most epidemiological studies it has not been possible to separate susceptibility for AKI from risk factors for CKD. In a study of 5383 critically ill patients, gender and race were not found to alter AKI susceptibility, whereas age was a consistent risk factor.[9] Interestingly, surgical admissions were at greater risk than medical and ICU admissions for cardiovascular, neurological, and respiratory disease/infection, whereas those for trauma, malignancy, and other causes were at decreased risk. Similarly, we reported recently on 1836 patients hospitalized for community-acquired pneumonia.[14] In this study, one-third (34%) of the patients developed AKI. Baseline susceptibilities for AKI in this setting included age, white race, and baseline comorbidities such as CKD, cardiac disease, and diabetes.

However, risk for disease represents the interaction between susceptibility (i.e., features intrinsic to the patient) and exposure (i.e., the causative factor or factors). Exposures known to produce AKI in susceptible populations include sepsis, ischemia, heart failure, liver disease, major surgery (especially vascular and cardiac), myonecrosis, urinary tract obstruction, and various nephrotoxins.[5] In the critically ill, sepsis is the major cause of AKI, accounting for nearly 50% of cases.[5,11,15] Several studies have reported that sepsis-induced AKI is associated with short- and long-term risk of death.[10,14]

The second obstacle to establishing accurate information on causes of AKI and therefore on risk assessment is that we continue to have an incomplete understanding of the pathogenesis of AKI in many of the circumstances in which it is seen. Although there are many reasons for this, we and others have argued that the lack of suitable animal models is a major factor.[16,17] Thus, for AKI occurring in many common settings (e.g., sepsis, cardiac surgery, radio contrast), a better understanding of pathogenesis is needed.

OUTCOMES AND PATHOPHYSIOLOGY

There is now substantial evidence from clinical studies that both short-term and long-term outcomes are adversely affected by AKI (Figure 2). As discussed above, hospital mortality increases in association with AKI stage. Furthermore, survival appears to be affected for at least 1 year and maybe longer.[14] In addition to survival, the development of sepsis appears to be common in patients with AKI and is associated with high mortality and increased hospital duration.[18]

Recovery of renal function is also a problem, with many patients failing to recover renal function. Chertow *et al.*[19] demonstrated in a cohort of critically ill patients with AKI who required renal replacement therapy that 33% of the survivors were still on renal replacement therapy after 12 months. The Acute Renal Failure Trials Network study enrolled 1124 patients with severe AKI, and nearly 25% of the survivors were dependent on renal replacement therapy on day 60.[20] However, an Australian study of 1508 patients with severe AKI found that only 5.4% of survivors still required renal replacement therapy by day 90.[21] Finally, there is emerging evidence showing that less severe AKI may be associated with important long-term outcomes including progression of CKD and cardiovascular disease.[22]

Unfortunately, very little is known about why AKI is associated with short- and long-term adverse affects. Although some manifestations of AKI are directly linked to impaired glomerular/tubular function and easily recognized at the bedside in the form of hyperkalemia, pulmonary edema, pericarditis, or encephalopathy, other effects are less obvious or might not become apparent until sometime after the patient has left the hospital. Here, the modulatory effects of AKI on the (innate) immune system and the progression from AKI to CKD have recently emerged as very critical and highly important factors.

AKI and the (innate) immune system

Current concepts about the effects of AKI on the innate immune system largely stem from experimental studies and mostly focus on interactions between the kidneys and remote organs, such as the lungs and heart. Experimental AKI has some striking effects on the heart.[23] Bilateral renal ischemia significantly increases the myocardial transcription of tumor necrosis factor-α and interleukin (IL)-1. These transcriptional changes are associated with an increase in myocardial neutrophil recruitment, as evidenced by elevated myeloperoxidase

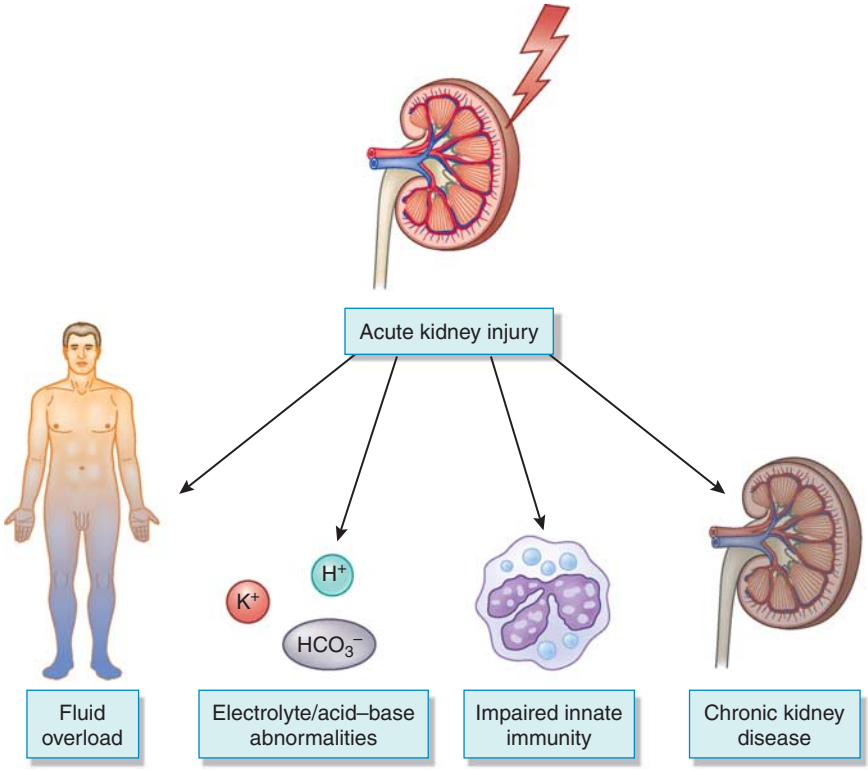

Figure 2 | Acute kidney injury (AKI) can have both immediately recognizable consequences as well as less noticeable or delayed consequences. Fluid overload and electrolyte/acid–base abnormalities represent well known, easily recognized consequences of AKI. Contrary, impaired innate immunity and chronic kidney disease do not manifest themselves immediately.

activity, and myocardial apoptosis. Blockade of tumor necrosis factor-α inhibited apoptosis. Moreover, renal ischemia–reperfusion also led to increases in left ventricular end-diastolic diameter and left ventricular end-systolic diameter, while decreasing fractional shortening.

Several studies have shown that bilateral ischemic AKI induces proinflammatory changes in the uninjured lung. In particular, post-ischemic AKI downregulates the pulmonary expression of epithelial sodium channels, Na/K–ATPase, and aquaporin-5.[24] The observed parallel increase in lung permeability is presumably a consequence of these changes, as all of these proteins have important roles in transepithelial salt and water transport and consequently in alveolar permeability.[25–27] In various experimental models, AKI also leads to altered pulmonary cytokine expression and to changes in serum cytokine concentrations. This includes changes in IL-1, IL-6, IL-12, granulocyte-macrophage colony-stimulating factor, and IL-10, as well as in some neutrophil-specific chemokines.[28] However, not all mediators are upregulated in all animal models at the same time. Different models of AKI or acute loss of renal function reveal a similar, but unique, cytokine/chemokine profile.[29] For example, only mild increases in plasma IL-6 occurred in a mouse model of folic acid-induced AKI.[30] Prophylactic administration of anti-inflammatory agents, such as IL-10 or antibodies against IL-6, can attenuate the inflammatory response and subsequent lung damage after bilateral nephrectomy or renal ischemia.[28,31]

Although the effects of AKI on the healthy lung appear to be largely pro-inflammatory, there is sound experimental evidence that AKI exerts anti-inflammatory effects on the injured lung. In a neutrophil-dependent model of HCl-induced acute lung injury, AKI impaired neutrophil recruitment into the lungs and thereby improved oxygenation.[32] The anti-inflammatory effects of AKI seemed to largely rest with neutrophils, as only circulating uremic neutrophils but not normal neutrophils circulating in uremic plasma provided protection from acute lung injury. Moreover, the anti-inflammatory effects of AKI appeared to outweigh the potential effects of impaired fluid balance, as the wet–dry ratios of HCl-injured lungs were not affected, at least early on, by AKI. These findings are supported by a recent study combining AKI with the ventilator-induced lung injury.[33] Here, the authors found that post-ischemic AKI in the context of ventilator-induced acute lung injury decreased protein concentrations and neutrophil counts in bronchoalveolar lavage fluid. Although the anti-inflammatory effects of AKI appear to be beneficial in the setting of sterile lung injury, these findings certainly raise concerns for the combined occurrence of AKI and bacterial infections, such as pneumonia. We have shown in animal studies combining two different models of AKI with *Pseudomonas aeruginosa*

pneumonia that AKI significantly impairs pulmonary recruitment of neutrophils, in particular neutrophil transmigration.[30] Consequently, oxygenation and bacterial load following inhalation of *P. aeruginosa* were worse in mice with AKI than in mice without it.

Moreover, we were able to show in another recent study that patients with septic AKI have impaired leukocyte rolling when compared with septic patients without AKI.[34] The findings that AKI affects neutrophil recruitment and subsequently causes higher bacterial load and worse outcome are further supported by clinical observations. Compared with patients without AKI, patients with AKI more frequently demonstrate bacteremia and poor outcome in various clinical settings, including peritonitis, after cardiac surgery and during hematological malignancies.[35–37]

AKI and CKD

Several recent clinical studies have provided evidence for a link between AKI, CKD, and ultimately progression to end-stage renal disease.[22,38–48] Under normal circumstances, the regeneration of the tubular epithelium after AKI occurs in a cascade-like manner, including initial de-differentiation, migration, proliferation of surviving cells, re-differentiation, and, in a last step, the full restoration of the tubular epithelium. Incomplete repair after AKI, by contrast, is characterized by persistent tubulointerstitial fibrosis and inflammation, even in the absence of prior kidney disease.[49,50] Persistent tubular interstitial fibrosis is the pathological correlate of loss of kidney function. The severity of AKI significantly determines the extent of recovery.[50,51]

It is well accepted that preexisting kidney disease increases a patient's risk of developing AKI; the risk for AKI is proportional to the respective CKD stage.[40,42,43,45] On the other hand, any episode of AKI in a patient with underlying CKD inflicts additional damage on already compromised kidneys and thereby substantially increases the rate of transition to end-stage renal disease.[39,42,43,45] Progressive kidney disease is more likely after an episode of acute-on-chronic kidney injury than after simple AKI alone.[43]

As much as inflammation is crucial for the development of AKI, it also has a crucial role in the development of interstitial fibrosis after AKI. Experimental studies have shown a delayed mononuclear cell infiltration after AKI, which is a central factor in kidney repair, regeneration, and tissue remodeling.[52,53] Although monocytes aggravate tissue injury after ischemia–reperfusion, they also contribute to fibroblast proliferation and tubular interstitial fibrosis. Capillary rarefaction represents another hallmark of tubular interstitial fibrosis.[54,55] Regeneration after AKI includes rapid and intense activation of different signaling pathways in tubular epithelial cells, giving rise to the production and secretion of growth factors, cytokines, and other mediators. Among the receptors and their respective pathways involved are Toll-like receptors, receptor tyrosine kinases, G-protein-coupled receptors, and peroxisome proliferator-activated receptor. They are thought to participate through the nuclear factor-κB-, phosphatidylinositol 3-kinase-, mitogen-activated protein kinase-, and Smad-dependent pathways.[56–64] Activation of these pathways in turn leads to enhanced production of numerous mediators that are involved in repair, regeneration, and remodeling of the kidney, such as platelet-derived growth factor, transforming growth factor, colony-stimulating factor, and epidermal growth factor.[65,66] Many of the secreted molecules have both autocrine and paracrine functions. They recruit and mobilize leukocytes and also stimulate endothelial cells and fibroblasts. All injured and regenerating tubular cells, endothelial cells, interstitial cells, and recruited inflammatory cells can produce and release these substances.[65,66]

CONCLUSION

Over the past few years, both experimental and clinical research has made important changes to the way AKI and its impact on morbidity/mortality are perceived. The development of AKI is the consequence of complex interactions between the actual insult and subsequent activation of inflammation and coagulation. Contrary to the conventional view, recent experimental and clinical data argue against renal ischemia (and reperfusion) as a *sine qua non* condition for the development of AKI. Moreover, loss of renal function can occur without histological signs of tubular damage or even necrosis.

It has become very clear that patients, especially patients in the ICU, are dying *of* AKI and not just simply *with* AKI. Even small changes in serum creatinine concentrations are associated with a substantial increase in the risk of death. Moreover, the detrimental effects of AKI are not limited to classical well-known symptoms such as fluid overload and electrolyte abnormalities. AKI can also cause problems that are not readily appreciated at the bedside and can extend well beyond ICU stay. Experimental and small observational studies provide evidence that AKI negatively affects (innate) immunity and is associated with higher rates of infection. Furthermore, AKI can also serve as a springboard for the development of CKD, in particular in patients with underlying renal insufficiency.

DISCLOSURE

The authors declared no competing interests.

REFERENCES

1. KDIGO. Acute kidney injury guideline. *Kidney Int* 2011 (in press).
2. Kellum JA, Levin N, Bouman C *et al.* Developing a consensus classification system for acute renal failure. *Curr Opin Crit Care* 2002; **8**: 509–514.
3. Liano F, Pascual J. Epidemiology of acute renal failure: a prospective, multicenter, community-based study. Madrid Acute Renal Failure Study Group. *Kidney Int* 1996; **50**: 811–818.
4. Brivet FG, Kleinknecht DJ, Loirat P *et al.* Acute renal failure in intensive care units—causes, outcome, and prognostic factors of hospital mortality; a prospective, multicenter study. French Study Group on Acute Renal Failure. *Crit Care Med* 1996; **24**: 192–198.
5. Uchino S, Kellum JA, Bellomo R *et al.* Acute renal failure in critically ill patients: a multinational, multicenter study. *JAMA* 2005; **294**: 813–818.
6. Bellomo R, Kellum J, Ronco C. Acute renal failure: time for consensus. *Intensive Care Med* 2001; **27**: 1685–1688.

7. Bellomo R, Ronco C, Kellum JA *et al.* Acute renal failure - definition, outcome measures, animal models, fluid therapy and information technology needs: the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. *Crit Care* 2004; **8**: R204–R212.
8. Mehta RL, Kellum JA, Shah SV *et al.* Acute kidney injury network: report of an initiative to improve outcomes in acute kidney injury. *Crit Care* 2007; **11**: R31.
9. Hoste EA, Kellum JA. Acute kidney injury: epidemiology and diagnostic criteria. *Curr Opin Crit Care* 2006; **12**: 531–537.
10. Bagshaw SM, George C, Bellomo R *et al.* A comparison of the RIFLE and AKIN criteria for acute kidney injury in critically ill patients. *Nephrol Dial Transplant* 2008; **23**: 1569–1574.
11. 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.
12. Hou SH, Bushinsky DA, Wish JB *et al.* Hospital-acquired renal insufficiency: a prospective study. *Am J Med* 1983; **74**: 243–248.
13. Nash K, Hafeez A, Hou S. Hospital-acquired renal insufficiency. *Am J Kidney Dis* 2002; **39**: 930–936.
14. Murugan R, Karajala-Subramanyam V, Lee M *et al.* Acute kidney injury in non-severe pneumonia is associated with an increased immune response and lower survival. *Kidney Int* 2010; **77**: 527–535.
15. Bagshaw SM, Uchino S, Bellomo R *et al.* Septic acute kidney injury in critically ill patients: clinical characteristics and outcomes. *Clin J Am Soc Nephrol* 2007; **2**: 431–439.
16. Murugan R, Kellum JA. Acute kidney injury: what's the prognosis? *Nat Rev Nephrol* 2011; **7**: 209–217.
17. Kellum impaired renal blood flow and the 'spicy food' hypothesis of acute kidney injury. *Crit Care Med* 2011; **39**: 901–903.
18. Mehta RL, Bouchard J, Soroko SB *et al.* Sepsis as a cause and consequence of acute kidney injury: program to improve care in Acute renal disease. *Intensive Care Med* 2011; **37**: 241–248.
19. Chertow GM, Christiansen CL, Cleary PD *et al.* Prognostic stratification in critically ill patients with acute renal failure requiring dialysis. *Arch Intern Med* 1995; **155**: 1505–1511.
20. Palevsky PM, Zhang JH, O'Connor TZ *et al.* Intensity of renal support in critically ill patients with acute kidney injury. *N Engl J Med* 2008; **359**: 7–20.
21. Bellomo R, Cass A, Cole L *et al.* Intensity of continuous renal-replacement therapy in critically ill patients. *N Engl J Med* 2009; **361**: 1627–1638.
22. Amdur RL, Chawla LS, Amodeo S *et al.* Outcomes following diagnosis of acute renal failure in US. veterans: focus on acute tubular necrosis. *Kidney Int* 2009; **76**: 1089–1097.
23. Kelly KJ. Distant effects of experimental renal ischemia/reperfusion injury. *J Am Soc Nephrol* 2003; **14**: 1549–1558.
24. Rabb H, Wang Z, Nemoto T *et al.* Acute renal failure leads to dysregulation of lung salt and water channels. *Kidney Int* 2003; **63**: 600–606.
25. Ma T, Fukuda N, Song Y *et al.* Lung fluid transport in aquaporin-5 knockout mice. *J Clin Invest* 2000; **105**: 93–100.
26. Hummler E, Barker P, Gatzy J *et al.* Early death due to defective neonatal lung liquid clearance in alpha-ENaC-deficient mice. *Nat Genet* 1996; **12**: 325–328.
27. Hummler E, Barker P, Beermann F *et al.* Role of the epithelial sodium channel in lung liquid clearance. *Chest* 1997; **111**: 113S.
28. Hoke TS, Douglas IS, Klein CL *et al.* Acute renal failure after bilateral nephrectomy is associated with cytokine-mediated pulmonary injury. *J Am Soc Nephrol* 2007; **18**: 155–164.
29. Hassoun HT, Grigoryev DN, Lie ML *et al.* Ischemic acute kidney injury induces a distant organ functional and genomic response distinguishable from bilateral nephrectomy. *Am J Physiol Renal Physiol* 2007; **293**: F30–40-F30-40.
30. Singbartl K, Bishop JV, Wen X *et al.* Differential effects of kidney-lung cross-talk during acute kidney injury and bacterial pneumonia. *Kidney Int* 2011; **80**: 633–640.
31. Klein CL, Hoke TS, Fang WF *et al.* Interleukin-6 mediates lung injury following ischemic acute kidney injury or bilateral nephrectomy. *Kidney Int* 2008; **74**: 901–909.
32. Zarbock A, Schmolke M, Spieker T *et al.* Acute uremia but not renal inflammation attenuates aseptic acute lung injury: A critical role for uremic neutrophils. *J Am Soc Nephrol* 2006; **17**: 3124–3131.
33. Dodd-O JM, Hristopoulos M, Scharfstein D *et al.* Interactive effects of mechanical ventilation and kidney health on lung function in an *in vivo* mouse model. *Am J Physiol Lung Cell Mol Physiol* 2009; **296**: L3–L11.
34. Rossaint J, Spelten O, Kässens N *et al.* Acute loss of renal function attenuates slow leukocyte rolling and transmigration by interfering with intracellular signaling. *Kidney Int* 2011; **80**: 493–503.
35. De Waele JJ, Hoste EA, Blot SI. Blood stream infections of abdominal origin in the intensive care unit: characteristics and determinants of death. *Surg Infect (Larchmt)* 2008; **9**: 171–177.
36. Hoste EA, Blot SI, Lameire NH *et al.* Effect of nosocomial bloodstream infection on the outcome of critically ill patients with acute renal failure treated with renal replacement therapy. *J Am Soc Nephrol* 2004; **15**: 454–462.
37. Thakar CV, Yared JP, Worley S *et al.* Renal dysfunction and serious infections after open-heart surgery. *Kidney Int* 2003; **64**: 239–246.
38. Coca SG, Yusuf B, Shlipak MG *et al.* Long-term risk of mortality and other adverse outcomes after acute kidney injury: a systematic review and meta-analysis. *Am J Kidney Dis* 2009; **53**: 961–973.
39. Hsu C-Y, Chertow GM, McCulloch CE *et al.* Nonrecovery of kidney function and death after acute on chronic renal failure. *Clin J Am Soc Nephrol* 2009; **4**: 891–898.
40. Hsu CY, Ordoñez JD, Chertow GM *et al.* The risk of acute renal failure in patients with chronic kidney disease. *Kidney Int* 2008; **74**: 101–107.
41. Chawla LS, Amdur RL, Amodeo S *et al.* The severity of acute kidney injury predicts progression to chronic kidney disease. *Kidney Int* 2011; **79**: 1361–1369.
42. Ishani A, Xue JL, Himmelfarb J *et al.* Acute kidney injury increases risk of ESRD among elderly. *J Am Soc Nephrol* 2009; **20**: 223–228.
43. Khosla N, Soroko SB, Chertow GM *et al.* Preexisting chronic kidney disease: a potential for improved outcomes from acute kidney injury. *Clin J Am Soc Nephrol* 2009; **4**: 1914.
44. Lo LJ, Go AS, Chertow GM *et al.* Dialysis-requiring acute renal failure increases the risk of progressive chronic kidney disease. *Kidney Int* 2009; **76**: 893–899.
45. Okusa MD, Chertow GM, Portilla D. The Nexus of Acute Kidney Injury, Chronic Kidney Disease, and World Kidney Day 2009. *Clin J Am Soc Nephrol* 2009; **4**: 520.
46. Thakar CV, Quate-Operacz M, Leonard AC *et al.* Outcomes of hemodialysis patients in a long-term care hospital setting: a single-center study. *Am J Kidney Dis* 2010; **55**: 300–306.
47. Waikar SS, Winkelmayer WC. Chronic on acute renal failure. *JAMA* 2009; **302**: 1227.
48. Wald R, Quinn RR, Luo J *et al.* Chronic dialysis and death among survivors of acute kidney injury requiring dialysis. *JAMA* 2009; **302**: 1179–1185.
49. Finn WF. Enhanced recovery from postischemic acute renal failure. Micropuncture studies in the rat. *Circ Res* 1980; **46**: 440–448.
50. Gueler F, Gwinner W, Schwarz A *et al.* Long-term effects of acute ischemia and reperfusion injury. *Kidney Int* 2004; **66**: 523–527.
51. Devarajan P. Update on mechanisms of ischemic acute kidney injury. *J Am Soc Nephrol* 2006; **17**: 1503–1520.
52. Ma FY, Ikezumi Y, Nikolic-Paterson DJ. Macrophage signaling pathways: a novel target in renal disease. *Semin Nephrol* 2010; **30**: 334–344.
53. Vielhauer V, Kulkarni O, Reichel CA *et al.* Targeting the recruitment of monocytes and macrophages in renal disease. *Semin Nephrol* 2010; **30**: 318–333.
54. Basile DP, Fredrich K, Chelladurai B *et al.* Renal ischemia reperfusion inhibits VEGF expression and induces ADAMTS-1, a novel VEGF inhibitor. *Am J Physiol Renal Physiol* 2008; **294**: F928–F936.
55. Basile DP, Friedrich JL, Spahic J *et al.* Impaired endothelial proliferation and mesenchymal transition contribute to vascular rarefaction following acute kidney injury. *Am J Physiol Renal Physiol* 2010; **300**: F721–F733.
56. de Borst MH, Prakash J, Sandovici M *et al.* c-Jun NH2-terminal kinase is crucially involved in renal tubulo-interstitial inflammation. *J Pharmacol Exp Ther* 2009; **331**: 896–905.
57. Geng H, Lan R, Wang G *et al.* Inhibition of autoregulated TGFbeta signaling simultaneously enhances proliferation and differentiation of kidney epithelium and promotes repair following renal ischemia. *Am J Pathol* 2009; **174**: 1291–1308.
58. Kim BS, Lim SW, Li C *et al.* Ischemia-reperfusion injury activates innate immunity in rat kidneys. *Transplantation* 2005; **79**: 1370–1377.
59. Krüger B, Krick S, Dhillon N *et al.* Donor Toll-like receptor 4 contributes to ischemia and reperfusion injury following human kidney transplantation. *Proc Natl Acad Sci USA* 2009; **106**: 3390–3395.

60. Li S, Nagothu KK, Desai V *et al.* Transgenic expression of proximal tubule peroxisome proliferator-activated receptor-alpha in mice confers protection during acute kidney injury. *Kidney Int* 2009; **76**: 1049–1062.
61. Nakagawa T, Sasahara M, Haneda M *et al.* Role of PDGF B-chain and PDGF receptors in rat tubular regeneration after acute injury. *Am J Pathol* 1999; **155**: 1689–1699.
62. Park KM, Kramers C, Vayssier-Taussat M *et al.* Prevention of kidney ischemia/reperfusion-induced functional injury, MAPK and MAPK kinase activation, and inflammation by remote transient ureteral obstruction. *J Biol Chem* 2002; **277**: 2040–2049.
63. Spurgeon KR, Donohoe DL, Basile DP. Transforming growth factor-beta in acute renal failure: receptor expression, effects on proliferation, cellularity, and vascularization after recovery from injury. *Am J Physiol Renal Physiol* 2005; **288**: F568–F577.
64. Zeng F, Singh AB, Harris RC. The role of the EGF family of ligands and receptors in renal development, physiology and pathophysiology. *Exp Cell Res* 2009; **315**: 602–610.
65. Liu KD, Brakeman PR. Renal repair and recovery. *Crit Care Med* 2008; **36**: S187–S192.
66. Sharples EJ. Acute kidney injury: stimulation of repair. *Curr Opin Crit Care* 2007; **13**: 652–655.