CHAPTER 107

Immunologic and Infectious Complications of Acute Kidney Injury

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OBJECTIVES

This chapter will:

1. Provide an overview of the epidemiology of infection in patients with acute kidney injury.
2. Describe the diverse pathophysiologic mechanisms that may explain increased risk for infection in patients with acute kidney injury.

EPIDEMIOLOGY OF INFECTION IN PATIENTS WITH ACUTE KIDNEY INJURY

Infection is among the most important causes of morbidity, hospitalization, costs, and mortality in patients with end-stage renal disease. After cardiovascular disease, infection is the second most frequent cause of hospitalization among chronic hemodialysis patients.[1–3] Furthermore, for the United States, it has been estimated that there are about 450,000 cases of sepsis on a yearly basis, responsible for more than 100,000 deaths. Consequently, sepsis is, after acute myocardial infarction, the most frequent cause of mortality.[2] The Centers for Disease Control and Infection Prevention warned that its incidence is still increasing.[2,4] Furthermore, the subgroup of patients diagnosed with end-stage renal disease and treated with renal replacement therapy (RRT) even has an approximate annual sepsis-attributed mortality rate of up to 45 times higher as compared with the general population.[5] With regard to infectious complications in patients with acute kidney injury (AKI), there are considerably less data available. Several studies demonstrated that infection and sepsis are the most important cause in the development of severe AKI.[6–9] In the Beginning and Ending

of Supportive Therapy (B.E.S.T.) Kidney trial, including almost 30,000 critically ill patients from 54 centers of 23 different countries from all over the world, septic shock was present in about half of the patients found and thereby the main contributing factor in the development of severe AKI.[7] As compared with patients hospitalized on a general ward, there is increasing evidence that AKI patients are more susceptible for infection, similarly to patients with chronic kidney disease. In our institution we observed that of all AKI patients undergoing RRT, 87% experienced an episode of infection during their intensive care unit (ICU) course. Of these, 41% developed infection during, and 59% developed infection before or after RRT.[10] In another study of our group, we found that critically ill AKI patients treated with RRT had a twofold higher odds for developing nosocomial bloodstream infection than those without.[11] In addition, in two thirds of patients, bloodstream infection was caused by an antimicrobial-resistant microorganism.[12,13] In a single-center study, performed in The Cleveland Clinic Foundation, Thakar et al. found that the postoperative course of patients who had undergone open-heart surgery and developed AKI treated with RRT was complicated with infection in 58.5%, compared with 23.7% and 1.6% in AKI patients not treated with RRT, and patients without AKI, respectively (both, $p < .001$).[14] Finally, in the multicenter prospective observational trial on the epidemiology of AKI conducted in Madrid during 1991 and 1992, infection was identified as the cause of death in 40% of ICU patients with severe AKI.[15]

BOX 107.1

Factors That Contribute to the Increased Risk for Infection in Patients With Acute Kidney Injury

Factors associated with AKI:
- Inflammation
- Acidosis
- Uremia
- Volume overload
- Malnutrition
- Decreased immunity
- RRT
- Inadequate antimicrobial therapy

RRT procedure-related factors:
- Intravascular catheter
- Loss of micronutrients – malnutrition

AKI, Acute kidney injury; *RRT,* renal replacement therapy.

PATHOGENESIS OF INFECTION IN PATIENTS WITH ACUTE KIDNEY INJURY

As mentioned above, infection is a dreaded complication in chronic as well as in AKI patients because of its associated worse outcome. In chronic dialysis patients several pathophysiologic factors have been proposed that enhance the risk for infection.[16] There are less data in medical literature on this in AKI patients. However, many of the factors that may contribute to the development of infection in patients with chronic kidney disease are also present in patients with AKI. Contributing factors for infection in AKI involve pathophysiologic mechanisms (increased inflammation, volume overload, and electrolyte disturbances), treatment-related factors (dialysis catheter-related infection), and effects on distant organs involved in defense against pathogens. These factors are highlighted and discussed in detail (Box 107.1 and Fig. 107.1).

Increased Inflammation

There is increasing evidence that AKI is caused, at least partly, by an inflammatory cascade resulting in a deterioration of organ function.[17–23] This response occurs as the release of cytokines and other inflammatory mediators and seldom will be localized to one single-organ system but also will affect negatively other organs as well.[24] As such, it is likely that this systemic inflammatory response also will cause generalized inflammation and organ dysfunction.

Inflammation is a natural defense mechanism against pathogens; however, excess or unresolved inflammation can cause tissue damage.[25] Inflammation during ischemia-reperfusion has many similarities with inflammation caused by microbial pathogen and is pathophysiologic, divided into an early and late phase.[26] The early phase is triggered by cell damage or death, causing a release of cytokines and recruitment of neutrophils and macrophages to the site of injury. Necrotic cells release damage-associated molecular patterns (DAMPs), which activate pattern recognition receptors, such as Toll-like receptors (TLRs).[27–29] Activated renal parenchyma cells also secrete chemokines, promoting neutrophil, macrophage, and monocyte inflammatory responses. The early phase lasts minutes to hours.[27,30,31] Overlapping with the first phase, a second phase occurs, mediated primarily by immune cells. Proinflammatory mediators are produced in the kidney by phagocytic cells as well as in the bloodstream by activated neutrophils and monocytes.[32–36] The inflammatory response eventually initiates a range of antiinflammatory cytokines, induced by T cells, to repair renal damage.[37] Ideally, pro- and antiinflammatory mechanisms should be in balance; however, prolonged hypoxia leads to an abnormal repair, renal fibrosis, and chronic loss of kidney function.[27,28]

Understanding of the cellular and molecular mechanisms underlying the inflammatory response is important for future strategies in prevention and treatment of AKI.[38] Especially, blockade of innate immune receptors, influencing parenchymal cells involved in inflammation, and molecules generated within injured cells are targets for investigation.[39–41] An important discovery is that many of the triggers and cellular mediators responsible for initial organ damage are also important in the repair phase.[27,42,43] For example, macrophages play a different role depending on the inflammatory phase; M1 leads to inflammation, whereas M2 has an antiinflammatory function.[44] This means that interventions targeting early phase mediators can influence unintentionally negatively proinflammatory and repair mechanisms.[43] Future targets for investigation are the parenchymal cells, because of their early role in inflammation, soluble mediators of cellular injury, cytokines, and the interaction with immune cells.[38]

Finally, evidence is growing for what is called "organ cross-talk"; that is, infection may lead to AKI, and AKI in its turn may lead to decreased functioning of other organs, as has been demonstrated clearly for the lungs. After ischemia/reperfusion injury of the kidneys, deregulation of the salt and water channels develops, resulting in increased vascular permeability in the lungs, secondary leading to interstitial edema.[45,46] In contrast to sepsis-induced acute respiratory distress syndrome (ARDS), AKI-induced

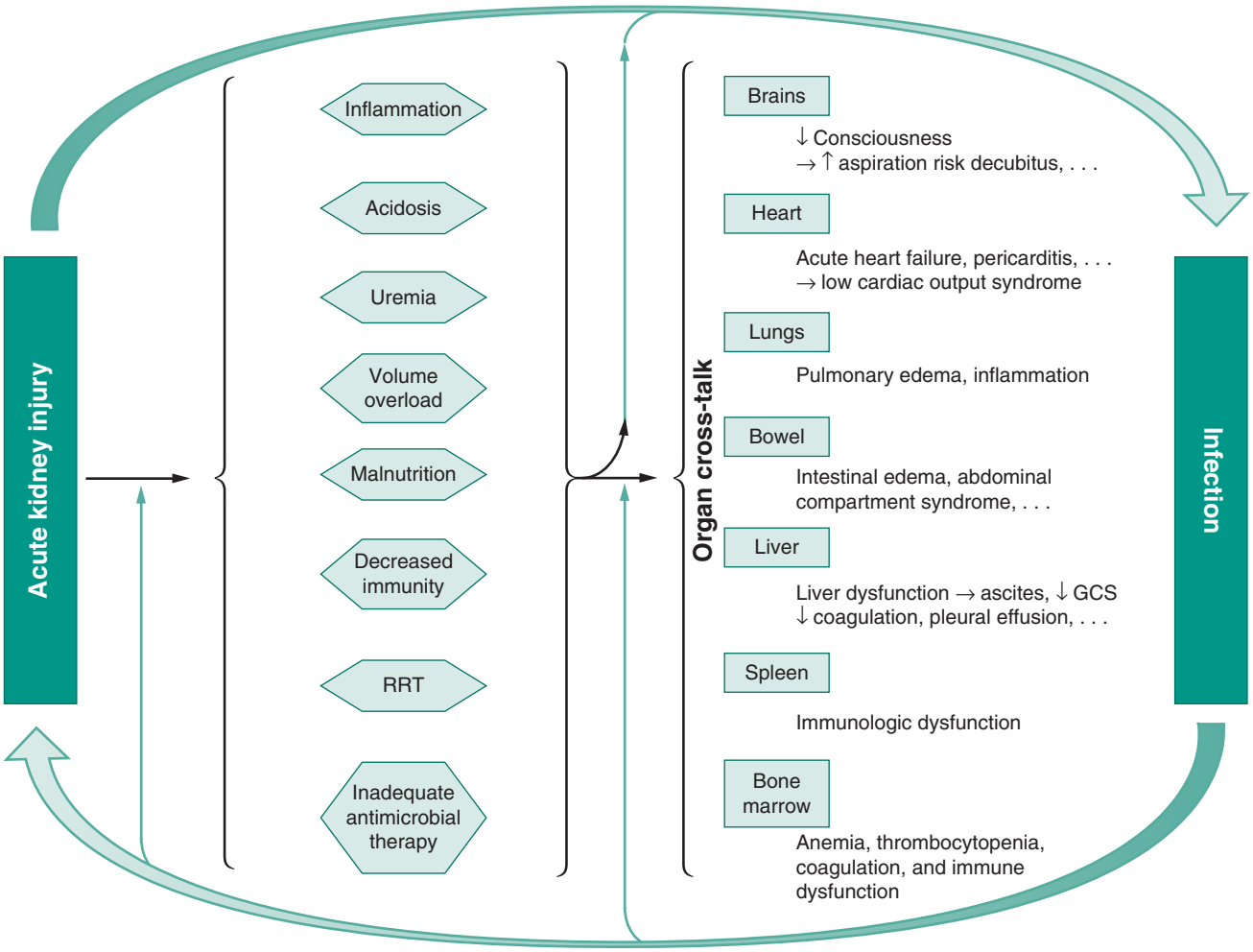

FIGURE 107.1 Interactions between various pathogenetic factors that contribute to increased risk for infection. All pathogenetic factors between braces will influence each other. *GCS,* Glasgow Coma Scale; *RRT,* renal replacement therapy.

ARDS generally is characterized by an induction of cytokine-induced neutrophil chemoattractant 2, a distinct expression of various heat shock proteins, and a low level of cellular infiltration.[47]

The underlying cause for this deregulated inflammatory response is not entirely clear. Deregulation of the lung salt and water channels is related to the severity of AKI, suggesting that uremia may be responsible.[45] Increased cytokine levels and oxidative stress in patients with end-stage renal disease additionally suggest that uremia may play a crucial role in the development of a deregulated inflammation state.[48–50] Next, acidosis also may contribute to the degree of the inflammatory status in AKI patients. The effects on inflammation appear to vary according to the type of acidosis, that is, respiratory versus metabolic, and hyperchloremic versus lactic acidosis, respectively. Hyperchloremic acidosis is more proinflammatory compared with lactic acidosis. In vitro experiments demonstrated that hyperchloremic acidosis increased the IL-6/IL-10 ratio, and NF-κB DNA binding.[51] In vivo experiments, on the other hand, demonstrated that acidosis led to increased nitric oxide levels, lower blood pressure, or even shock.[52] Also, acidosis has been shown to worsen lung and intestinal injury and to decrease the gut barrier function, thereby facilitating systemic breakthrough of microorganisms.[53–56]

Decreased Immunity

There is salient evidence for an immune-depressed state in uremic patients, especially in those with chronic renal failure treated with RRT. Several uremic retention compounds, such as leptin,[57] advanced glycation end-products (AGEs),[58] guanidines,[59] and P-cresol,[60–62] interfere with normal white blood cell function, phagocytosis, or endothelial function, and thus negatively affect immunity competence. Other factors that are believed to contribute to these effects in chronic uremia are (1) malnutrition, (2) iron overload, (3) anemia, and (4) bioincompatibility of dialyzer membranes. Finally, acidosis also may impair immune function by depressant effects on polymorphonuclear and lymphocyte function.[63,64] Because uremia and many of the above-mentioned factors are also present in AKI patients, immune suppression seems plausible in these patients.[16,50]

Loss of Protective Barriers Against Invading Microorganisms

Given the acute setting, RRT in the majority of AKI patients usually is performed by the use of an indwelling intravascular catheter with a large diameter and not by means of

surgically constructed arteriovenous fistula or by peritoneal dialysis. Several studies address the optimal vascular access site for temporal dialysis catheter placement. Dialysis catheters inserted in the internal jugular and femoral vein have similar risk for bacterial colonization and catheter dysfunction, except when BMI is greater than 28 kg/m^2.[65–70] An important factor in the choice of site is mobilization of the patient. Getting the patient out of the ICU bed is less practical and comfortable if the catheter is placed in the femoral vein.

Because of all the specific issues related to hemodialysis treatment (e.g., temporary use of a dialysis catheter, frequent manipulation of the catheter, use of an extracorporeal circuit, multiple infusions), whereby various protective barriers are affected, infection heralds a major problem in dialyzed patients.

Volume Overload and Altered Permeability of Tissue Membranes

Oliguria leads to volume overload in AKI patients. Especially in critically ill AKI patients with severe systemic infection, large amounts of fluids are administered during resuscitation. Fluid retention is associated with a whole list of complications. Increased volume of distribution affects the absorption of many drugs.[71] Tissue edema and compromised tissue perfusion may lead to pressure ulcers and negatively influence wound healing.[72] Respiratory insufficiency may occur as a complication of pulmonary edema and pleural effusion. Volume overload also is associated with intraabdominal hypertension and secondary abdominal compartment syndrome, which, in turn, promotes bacterial translocation through the intestinal mucosa.[73,74] This subsequently leads to increasing length of hospital stay and use of healthcare resources.

Pulmonary Function

Volume overload may cause pulmonary vascular congestion, pleural effusions, and/or intra-abdominal hypertension, leading to decreased gas exchange between the alveolar and capillary membranes. Compared with the general population, AKI patients more often experience interstitial edema by deregulation of the inflammatory cascade and increased vascular permeability.[45,46,54] As noted earlier, AKI may affect the lung via increased renal production or impaired clearance of mediators of lung injury, such as proinflammatory cytokines.[75] Decreased immune function, in combination with all of the previously mentioned factors, and paralleled by an increase in baseline activity, may lead to inflammation, infection, or pneumonia. As well, loss of muscle mass as a result of being confined to the bed for a long period or to decreased mobility, and oversedation resulting from retention of sedative and anesthetic drugs may prolong the duration of mechanical ventilation, and therefore the time at risk for infection or other life-threatening complications.

Cardiac Function

AKI can lead to cardiac malfunction, or cardiorenal syndrome type 3, through several mechanisms.[76] Volume overload may lead to acute decompensated heart failure and cardiomyopathy. Inflammation can trigger acute cardiac disorders, such as pericarditis through release of neutrophils and inflammatory cytokines.[77] Impaired cardiac function, in turn, leads to decreased perfusion of all organs, including the kidneys with further deterioration of function.[78,79] The bidirectional interaction of kidneys and the heart previously has been described as the cardiorenal syndrome.[76] Decreased perfusion of lungs, liver, bowels, and the spleen increases risk of infection.[80,81]

Hematologic: Spleen and Bone Marrow

The spleen is an organ with an important host defense function and plays an important role in the inflammatory response in the kidney after ischemia. Experiments in mice showed that exposure of the spleen to ultrasound waves stimulated the cholinergic system and blunted the inflammatory reaction with reduced accumulation of neutrophils and myeloid cells in the kidney tissue.[82] Splenectomy during AKI resulted in a significant exacerbation of lung injury, suggesting potential protective effects of the spleen on kidney pulmonary cross-talk in AKI.[83] When AKI results in hypoperfusion of the spleen, this may lead to decreased immunologic protection and higher risk of infection. Finally, AKI also depresses bone marrow function resulting in anemia, thrombocytopenia, coagulation disorders, and immune dysfunction.[84]

Gastrointestinal and Liver Function

In AKI, hypervolemia and inflammation possibly leads to bowel edema and a change in gut flora, which in turn may facilitate translocation of intestinal microorganisms and infection.[85,86] The influence of liver dysfunction on kidney function is well known and described as the hepatorenal syndrome in liver failure. Conversely, AKI can cause subtle changes in liver function, including alterations in protein and lipid metabolism, immunity and inflammation, and drug metabolism.[87,88] In analogy with the interaction between kidneys and lungs and the heart, vascular congestion and permeability are observed and possible explanations for liver dysfunction in AKI.[89,90] Liver dysfunction may contribute to increased risk for infection by several factors such as translocation of microbes from the gut, impaired hepatic clearance, and peripheral immune paralysis.[91] In addition, complications of severe liver dysfunction such as portal hypertension with volume retention, ascites and hepatorenal syndrome, neurologic impairment, hypotension, and hypoperfusion of all organs contribute to increased risk of infection.

Neuromuscular Function

AKI also affects neurologic function through release of inflammatory mediators and retention of uremic toxins. This contributes to the neuropathy and myopathy of severely ill ICU patients.[77] Also, increase in cerebral vascular permeability and electrolyte disturbances may lead to altered consciousness and even death.[81] Reduced consciousness and neuromuscular weakness can lead to aspiration and decubitus wounds.[77]

Malnutrition

Malnutrition is an important problem in hospitalized patients and in severely ill ICU patients. AKI patients are

particularly at risk for malnutrition. Fiaccadori et al. found that about 42% of patients who were referred to the renal intermediate care unit were severely malnourished.[92] Malnourished patients had impaired immunologic function, as illustrated by lower total lymphocyte count, and lower levels of IgG, IgA, and IgM. In addition, severely malnourished patients with accompanying AKI had increased odds for developing severe sepsis as compared with patients without AKI. AKI patients are at greater risk for malnourishment on admission to the ICU but probably are also at greater risk for malnourishment or suboptimal feeding during their ICU stay. The same Italian group found that AKI patients are at greater risk for gastroparesis and withdrawal of enteral nutrition.[93] Finally, AKI patients on RRT may lose important amounts of micronutrients such as vitamin C, folate, magnesium, calcium, selenium, and thiamin, which therefore should be substituted.[94]

Glucose Metabolism

An altered glucose metabolism also may contribute to the increased risk for infection in AKI patients. Systemic infection provokes a stress-induced hypermetabolic response through the activation of the hypothalamic-adrenal axis, which in turn increases hepatic glucose production and inhibits insulin-mediated glucose uptake into skeletal muscles.[95] Acidosis has untoward effects on the glucose metabolism, causing induction of insulin resistance and inhibition of anaerobic glycolysis.[96] Hyperglycemia secondary to this altered glucose metabolism has been associated with immune dysfunction and increased susceptibility to infection,[97] probably by proinflammatory effects and decreased phagocytosis.[98] On the other hand, the release of inflammatory mediators is, in turn, associated with pronounced insulin resistance in these patients.[99] In addition, limited data suggest that perioperative glucose control and glucose control in the critically ill are associated with a lower incidence of AKI.[100–107]

Pharmacokinetics of Antimicrobial Agents

Suboptimal dosing of antibiotic agents is an important cause of failure to eradicate microorganisms. Most antimicrobial agents are eliminated through the kidneys, and the dose and/or dosing interval should be adjusted to kidney function. However, kidney function is seldom a steady state in AKI patients.[108] Adjustments of antimicrobial dose or interval to kidney function therefore frequently are based on incorrect or less accurate assessments of kidney function. Also, distribution volumes may increase considerably in severely ill AKI patients, which may, in turn, result in decreased, possibly nontherapeutic, levels of antimicrobial agents. Finally, correct dosing of antimicrobial agents in AKI patients on RRT is a challenge. Although recommendations concerning dosing and interval frequencies are available for most antibiotic agents, these may not necessarily be correct in a specific situation. For instance, dosage adjustment recommendations for antibiotics may be based on observations in chronic dialysis patients. Large variation between different RRT treatment strategies used in clinical practice is characteristic. For instance, Continuous veno-venous hemofiltration (CVVH) may differ in many aspects: substitution fluid may be administered in predilution or postdilution mode, or the "dose" of CVVH or ultrafiltration volume may vary considerably, some units use 20 mL/kg/hr, whereas others use 35, or even 50, mL/kg/hr.[109] All these factors may lead to inadequate antimicrobial therapy and therapeutic failure in AKI patients with infection and increase the risk for antimicrobial resistance.

CONCLUSION

Infection remains a frequent and major problem in AKI patients treated with RRT. Data about the effect of immunologic changes on the increased susceptibility for infection in this specific cohort of patients are limited. However, to treat AKI patients more effectively, there is a strong need to improve our knowledge regarding the underlying immunologic changes in these patients. Also, better insights in the epidemiology of infection in these patients are warranted. Future studies should be conducted in well-defined populations with special emphasis not only on the immunologic but also on the infectious factors.

Key Points

1. Infection is an important cause of acute kidney injury (AKI), and in turn, patients with AKI are at increased risk for infection.
2. AKI patients have increased inflammation, which in turn may decrease immune response.
3. Volume overload may through diverse mechanisms contribute to the pathogenesis of infection.
4. Malnutrition is probably a frequent, and less well appreciated, occurring complication. This also contributes to decreased immune state and increased risk for infection.
5. Dosing of antimicrobial agents may be less optimal, leading to inadequate eradication of microorganisms.

Key References

10. Reynvoet E, Vandijck DM, Blot S, et al. Epidemiology of infection in critically ill patients with acute renal failure. *Crit Care Med*. 2009;37:2203-2209.
21. 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.
38. Rabb H, Griffin MD, McKay DB, et al. Inflammation in AKI: current understanding, key questions, and knowledge gaps. *J Am Soc Nephrol*. 2016;27:371-379.
77. Shiao CC, Wu PC, Huang TM, et al. Long-term remote organ consequences following acute kidney injury. *Crit Care*. 2015;19:438.
80. Doi K, Rabb H. Impact of acute kidney injury on distant organ function: recent findings and potential therapeutic targets. *Kidney Int*. 2016;89:555-564.

A complete reference list can be found online at ExpertConsult.com.

References

1. Rayner HC, Pisoni RL, Bommer J, et al. Mortality and hospitalization in haemodialysis patients in five European countries: results from the Dialysis Outcomes and Practice Patterns Study (DOPPS). *Nephrol Dial Transplant*. 2004;19:108-120.
2. United States Renal Data System. USRDS 2006 Annual Data Report. 2006.
3. Liu JW, Su YK, Liu CF, et al. Nosocomial blood-stream infection in patients with end-stage renal disease: excess length of hospital stay, extra cost and attributable mortality. *J Hosp Infect*. 2002;50:224-227.
4. Angus DC, Linde-Zwirble WT, Lidicker J, et al. Epidemiology of severe sepsis in the United States: analysis of incidence, outcome, and associated costs of care. *Crit Care Med*. 2001;29:1303-1310.
5. Sarnak MJ, Jaber BL. Mortality caused by sepsis in patients with end-stage renal disease compared with the general population. *Kidney Int*. 2000;58:1758-1764.
6. 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.
7. Uchino S, Kellum JA, Bellomo R, et al. Acute renal failure in critically ill patients: a multinational, multicenter study. *JAMA*. 2005;294:813-818.
8. Waikar SS, Curhan GC, Wald R, et al. Declining mortality in patients with acute renal failure, 1988 to 2002. *J Am Soc Nephrol*. 2006;17:1143-1150.
9. Xue JL, Daniels F, Star RA, et al. Incidence and mortality of acute renal failure in Medicare beneficiaries, 1992 to 2001. *J Am Soc Nephrol*. 2006;17:1135-1142.
10. Reynvoet E, Vandijck DM, Blot S, et al. Epidemiology of infection in critically ill patients with acute renal failure. *Crit Care Med*. 2009;37:2203-2209.
11. 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.
12. Hoste EA, Vandijck DM, Vanholder RC, et al. Health implications of antimicrobial resistance for patients with acute kidney injury and bloodstream infection. *Infect Control Hosp Epidemiol*. 2007;28:1107-1110.
13. Vandijck DM, Blot SI, Decruyenaere JM, et al. Costs and length of stay associated with antimicrobial resistance in acute kidney injury patients with bloodstream infection. *Acta Clin Belg*. 2008;63:31-38.
14. Thakar CV, Yared JP, Worley S, et al. Renal dysfunction and serious infections after open-heart surgery. *Kidney Int*. 2003;64:239-246.
15. Liaño F, Junco E, Pascual J, et al. The spectrum of acute renal failure in the intensive care unit compared to that seen in other settings. *Kidney Int*. 1998;53(suppl 66):S16-S24.
16. Vanholder R, Van Biesen W. Incidence of infectious morbidity and mortality in dialysis patients. *Blood Purif*. 2002;20:477-480.
17. Bonventre JV, Zuk A. Ischemic acute renal failure: an inflammatory disease? *Kidney Int*. 2004;66:480-485.
18. Donnahoo KK, Meldrum DR, Shenkar R, et al. Early renal ischemia, with or without reperfusion, activates NFkappaB and increases TNF-alpha bioactivity in the kidney. *J Urol*. 2000;163:1328-1332.
19. Donnahoo KK, Meng X, Ayala A, et al. Early kidney TNF-alpha expression mediates neutrophil infiltration and injury after renal ischemia-reperfusion. *Am J Physiol*. 1999;277:R922-R929.
20. Donnahoo KK, Shames BD, Harken AH, et al. Review article: the role of tumor necrosis factor in renal ischemia-reperfusion injury. *J Urol*. 1999;162:196-203.
21. 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.
22. Gomez H, Kellum JA. Sepsis-induced acute kidney injury. *Curr Opin Crit Care*. 2016.
23. Ramesh G, Reeves WB. Inflammatory cytokines in acute renal failure. *Kidney Int Suppl*. 2004;S56-S61.
24. Vandijck DM, Reynvoet E, Blot SI, et al. Severe infection, sepsis and acute kidney injury. *Acta Clin Belg*. 2007;332-336.
25. Medzhitov R. Inflammation 2010: new adventures of an old flame. *Cell*. 2010;140:771-776.
26. Chen GY, Nunez G. Sterile inflammation: sensing and reacting to damage. *Nat Rev Immunol*. 2010;10:826-837.
27. Anders HJ, Schaefer L. Beyond tissue injury-damage-associated molecular patterns, toll-like receptors, and inflammasomes also drive regeneration and fibrosis. *J Am Soc Nephrol*. 2014;25:1387-1400.
28. Kurts C, Panzer U, Anders HJ, et al. The immune system and kidney disease: basic concepts and clinical implications. *Nat Rev Immunol*. 2013;13:738-753.
29. Valles PG, Lorenzo AG, Bocanegra V, et al. Acute kidney injury: what part do toll-like receptors play? *Int J Nephrol Renovasc Dis*. 2014;7:241-251.
30. Linkermann A, Chen G, Dong G, et al. Regulated cell death in AKI. *J Am Soc Nephrol*. 2014;25:2689-2701.
31. Ratliff BB, Rabadi MM, Vasko R, et al. Messengers without borders: mediators of systemic inflammatory response in AKI. *J Am Soc Nephrol*. 2013;24:529-536.
32. Awad AS, Rouse M, Huang L, et al. Compartmentalization of neutrophils in the kidney and lung following acute ischemic kidney injury. *Kidney Int*. 2009;75:689-698.
33. Carlin LM, Stamatiades EG, Auffray C, et al. Nr4a1-dependent Ly6C(low) monocytes monitor endothelial cells and orchestrate their disposal. *Cell*. 2013;153:362-375.
34. Li L, Huang L, Sung SS, et al. NKT cell activation mediates neutrophil IFN-gamma production and renal ischemia-reperfusion injury. *J Immunol*. 2007;178:5899-5911.
35. Renner B, Strassheim D, Amura CR, et al. B cell subsets contribute to renal injury and renal protection after ischemia/reperfusion. *J Immunol*. 2010;185:4393-4400.
36. Zhang ZX, Wang S, Huang X, et al. NK cells induce apoptosis in tubular epithelial cells and contribute to renal ischemia-reperfusion injury. *J Immunol*. 2008;181:7489-7498.
37. Gandolfo MT, Jang HR, Bagnasco SM, et al. Foxp3+ regulatory T cells participate in repair of ischemic acute kidney injury. *Kidney Int*. 2009;76:717-729.
38. Rabb H, Griffin MD, McKay DB, et al. Inflammation in AKI: current understanding, key questions, and knowledge gaps. *J Am Soc Nephrol*. 2016;27:371-379.
39. Lee CG, Kim JG, Kim HJ, et al. Discovery of an integrative network of microRNAs and transcriptomics changes for acute kidney injury. *Kidney Int*. 2014;86:943-953.
40. Molitoris BA. Therapeutic translation in acute kidney injury: the epithelial/endothelial axis. *J Clin Invest*. 2014;124:2355-2363.
41. Reilly M, Miller RM, Thomson MH, et al. Randomized, double-blind, placebo-controlled, dose-escalating phase I, healthy subjects study of intravenous OPN-305, a humanized anti-TLR2 antibody. *Clin Pharmacol Ther*. 2013;94:593-600.
42. Kulkarni OP, Hartter I, Mulay SR, et al. Toll-like receptor 4-induced IL-22 accelerates kidney regeneration. *J Am Soc Nephrol*. 2014;25:978-989.
43. Zhang MZ, Yao B, Yang S, et al. CSF-1 signaling mediates recovery from acute kidney injury. *J Clin Invest*. 2012;122:4519-4532.
44. Jang HR, Rabb H. Immune cells in experimental acute kidney injury. *Nat Rev Nephrol*. 2015;11:88-101.
45. 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.
46. Kramer AA, Postler G, Salhab KF, et al. Renal ischemia/reperfusion leads to macrophage-mediated increase in pulmonary vascular permeability. *Kidney Int*. 1999;55:2362-2367.
47. Kim DJ, Park SH, Sheen MR, et al. Comparison of Experimental Lung Injury from Acute Renal Failure with Injury due to Sepsis. *Respiration*. 2006;73:815-824.
48. Vaziri ND. Oxidative stress in uremia: nature, mechanisms, and potential consequences. *Semin Nephrol*. 2004;24:469-473.
49. Glorieux G, Vanholder R, Lameire N. Uraemic retention and apoptosis: what is the balance for the inflammatory status in uraemia? *Eur J Clin Invest*. 2003;33:631-634.
50. Vanholder R, De Smet R. Pathophysiologic effects of uremic retention solutes. *J Am Soc Nephrol*. 1999;10:1815-1823.
51. Kellum JA, Song M, Li J. Lactic and hydrochloric acids induce different patterns of inflammatory response in LPS-stimulated RAW 264.7 cells. *Am J Physiol Regul Integr Comp Physiol*. 2004;286:R686-R692.

52. Kellum JA, Song M, Venkataraman R. Effects of hyperchloremic acidosis on arterial pressure and circulating inflammatory molecules in experimental sepsis. *Chest*. 2004;125:243-248.
53. Pedoto A, Nandi J, Oler A, et al. Role of nitric oxide in acidosis-induced intestinal injury in anesthetized rats. *J Lab Clin Med*. 2001;138:270-276.
54. Pedoto A, Caruso JE, Nandi J, et al. Acidosis stimulates nitric oxide production and lung damage in rats. *Am J Respir Crit Care Med*. 1999;159:397-402.
55. Salzman AL, Wang H, Wollert PS, et al. Endotoxin-induced ileal mucosal hyperpermeability in pigs: role of tissue acidosis. *Am J Physiol*. 1994;266:G633-G646.
56. Unno N, Hodin RA, Fink MP. Acidic conditions exacerbate interferon-gamma-induced intestinal epithelial hyperpermeability: role of peroxynitrous acid. *Crit Care Med*. 1999;27:1429-1436.
57. Ottonello L, Gnerre P, Bertolotto M, et al. Leptin as a uremic toxin interferes with neutrophil chemotaxis. *J Am Soc Nephrol*. 2004;15:2366-2372.
58. Glorieux G, Helling R, Henle T, et al. In vitro evidence for immune activating effect of specific AGE structures retained in uremia. *Kidney Int*. 2004;66:1873-1880.
59. Glorieux GL, Dhondt AW, Jacobs P, et al. In vitro study of the potential role of guanidines in leukocyte functions related to atherogenesis and infection. *Kidney Int*. 2004;65:2184-2192.
60. Cerini C, Dou L, Anfosso F, et al. P-cresol, a uremic retention solute, alters the endothelial barrier function in vitro. *Thromb Haemost*. 2004;92:140-150.
61. Dou L, Cerini C, Brunet P, et al. P-cresol, a uremic toxin, decreases endothelial cell response to inflammatory cytokines. *Kidney Int*. 2002;62:1999-2009.
62. Vanholder R, De Smet R, Waterloos MA, et al. Mechanisms of uremic inhibition of phagocyte reactive species production: characterization of the role of p-cresol. *Kidney Int*. 1995;47:510-517.
63. Lardner A. The effects of extracellular pH on immune function. *J Leukoc Biol*. 2001;69:522-530.
64. Kellum JA, Song M, Li J. Science review: extracellular acidosis and the immune response: clinical and physiologic implications. *Crit Care*. 2004;8:331-336.
65. Dugue AE, Levesque SP, Fischer MO, et al. Vascular access sites for acute renal replacement in intensive care units. *Clin J Am Soc Nephrol*. 2012;7:70-77.
66. Parienti JJ, Dugue AE, Daurel C, et al. Continuous renal replacement therapy may increase the risk of catheter infection. *Clin J Am Soc Nephrol*. 2010;5:1489-1496.
67. Parienti JJ, Mongardon N, Megarbane B, et al. Intravascular Complications of Central Venous Catheterization by Insertion Site. *N Engl J Med*. 2015;373:1220-1229.
68. Parienti JJ, Thirion M, Megarbane B, et al. Femoral vs jugular venous catheterization and risk of nosocomial events in adults requiring acute renal replacement therapy: a randomized controlled trial. *JAMA*. 2008;299:2413-2422.
69. Timsit JF, Bouadma L, Mimoz O, et al. Jugular versus femoral short-term catheterization and risk of infection in intensive care unit patients. Causal analysis of two randomized trials. *Am J Respir Crit Care Med*. 2013;188:1232-1239.
70. Mrozek N, Lautrette A, Timsit JF, et al. How to deal with dialysis catheters in the ICU setting. *Ann Intensive Care*. 2012;2:48.
71. Power BM, Forbes AM, van Heerden PV, et al. Pharmacokinetics of drugs used in critically ill adults. *Clin Pharmacokinet*. 1998;34:25-56.
72. Brandstrup B, Tonnesen H, Beier-Holgersen R, et al. Effects of intravenous fluid restriction on postoperative complications: comparison of two perioperative fluid regimens: a randomized assessor-blinded multicenter trial. *Ann Surg*. 2003;238:641-648.
73. Kirkpatrick AW, De Waele JJ, Ball CG, et al. The secondary and recurrent abdominal compartment syndrome. *Acta Clin Belg*. 2007;60-65.
74. Cheatham ML, Malbrain ML, Kirkpatrick A, et al. Results from the International Conference of Experts on Intra-abdominal Hypertension and Abdominal Compartment Syndrome. II. Recommendations. *Intensive Care Med*. 2007;33:951-962.
75. Hoke TS, Douglas IS, Klein CL, et al. Acute Renal Failure after Bilateral Nephrectomy Is Associated with Cytokine-Mediated Pulmonary Injury. 2007. p. 155-164.
76. Ronco C, Haapio M, House AA, et al. Cardiorenal syndrome. *J Am Coll Cardiol*. 2008;52:1527-1539.
77. Shiao CC, Wu PC, Huang TM, et al. Long-term remote organ consequences following acute kidney injury. *Crit Care*. 2015;19:438.
78. Aronson D, Abassi Z, Allon E, et al. Fluid loss, venous congestion, and worsening renal function in acute decompensated heart failure. *Eur J Heart Fail*. 2013;15:637-643.
79. Kajimoto K, Sato N, Keida T, et al. Associations of anemia and renal dysfunction with outcomes among patients hospitalized for acute decompensated heart failure with preserved or reduced ejection fraction. *Clin J Am Soc Nephrol*. 2014;9:1912-1921.
80. Doi K, Rabb H. Impact of acute kidney injury on distant organ function: recent findings and potential therapeutic targets. *Kidney Int*. 2016;89:555-564.
81. Grams ME, Rabb H. The distant organ effects of acute kidney injury. *Kidney Int*. 2012;81:942-948.
82. Gigliotti JC, Huang L, Ye H, et al. Ultrasound prevents renal ischemia-reperfusion injury by stimulating the splenic cholinergic anti-inflammatory pathway. *J Am Soc Nephrol*. 2013;24:1451-1460.
83. Andres-Hernando A, Altmann C, Ahuja N, et al. Splenectomy exacerbates lung injury after ischemic acute kidney injury in mice. *Am J Physiol Renal Physiol*. 2011;301:F907-F916.
84. Scheel PJ, Liu M, Rabb H. Uremic lung: new insights into a forgotten condition. *Kidney Int*. 2008;74:849-851.
85. Khoury T, Tzukert K, Abel R, et al. The gut-kidney axis in chronic renal failure: a new potential target for therapy. *Hemodial Int*. 2016.
86. Ramezani A, Massy ZA, Meijers B, et al. Role of the gut microbiome in uremia: a potential therapeutic target. *Am J Kidney Dis*. 2016;67:483-498.
87. Dixon J, Lane K, Macphee I, et al. Xenobiotic metabolism: the effect of acute kidney injury on non-renal drug clearance and hepatic drug metabolism. *Int J Mol Sci*. 2014;15:2538-2553.
88. Lane K, Dixon JJ, MacPhee IA, et al. Renohepatic crosstalk: does acute kidney injury cause liver dysfunction? *Nephrol Dial Transplant*. 2013;28:1634-1647.
89. Golab F, Kadkhodaee M, Zahmatkesh M, et al. Ischemic and non-ischemic acute kidney injury cause hepatic damage. *Kidney Int*. 2009;75:783-792.
90. Park SW, Chen SW, Kim M, et al. Cytokines induce small intestine and liver injury after renal ischemia or nephrectomy. *Lab Invest*. 2011;91:63-84.
91. Selvapatt N, Singanayagam A, Wendon J, et al. Understanding infection susceptibility in patients with acute-on-chronic liver failure. *Intensive Care Med*. 2014;40:1363-1366.
92. Fiaccadori E, Lombardi M, Leonardi S, et al. Prevalence and clinical outcome associated with preexisting malnutrition in acute renal failure: a prospective cohort study. *J Am Soc Nephrol*. 1999;10:581-593.
93. Fiaccadori E, Maggiore U, Giacosa R, et al. Enteral nutrition in patients with acute renal failure. *Kidney Int*. 2004;65:999-1008.
94. Cano N, Fiaccadori E, Tesinsky P, et al. ESPEN guidelines on enteral nutrition: adult renal failure. *Clin Nutr*. 2006;25:295-310.
95. Mizock BA. Alterations in fuel metabolism in critical illness: hyperglycaemia. *Best Pract Res Clin Endocrinol Metab*. 2001;15:533-551.
96. DeFronzo RA, Beckles AD. Glucose intolerance following chronic metabolic acidosis in man. *Am J Physiol*. 1979;236:E328-E334.
97. Zerr KJ, Furnary AP, Grunkemeier GL, et al. Glucose control lowers the risk of wound infection in diabetics after open heart operations. *Ann Thorac Surg*. 1997;63:356-361.
98. Weekers F, Giulietti AP, Michalaki M, et al. Metabolic, endocrine, and immune effects of stress hyperglycemia in a rabbit model of prolonged critical illness. *Endocrinology*. 2003;144:5329-5338.
99. Vanholder R, Van Landschoot N, Waterloos MA, et al. Phagocyte metabolic activity during hemodialysis with different

dialyzers not affecting the number of circulating phagocytes. *Int J Artif Organs*. 1992;15:89-92.
100. Finney SJ, Zekveld C, Elia A, et al. Glucose control and mortality in critically ill patients. *JAMA*. 2003;290:2041-2047.
101. Giannini F, Latib A, Jabbour RJ, et al. Impact of post-procedural hyperglycemia on acute kidney injury after transcatheter aortic valve implantation. *Int J Cardiol*. 2016;221:892-897.
102. Kim WH, Park MH, Kim HJ, et al. Potentially modifiable risk factors for acute kidney injury after surgery on the thoracic aorta: a propensity score matched case-control study. *Medicine (Baltimore)*. 2015;94:e273.
103. Mita N, Kawahito S, Soga T, et al. Strict blood glucose control by an artificial endocrine pancreas during hepatectomy may prevent postoperative acute kidney injury. *J Artif Organs*. 2016.
104. Pittas AG, Siegel RD, Lau J. Insulin therapy for critically ill hospitalized patients: a meta-analysis of randomized controlled trials. *Arch Intern Med*. 2004;164:2005-2011.
105. Schetz M, Vanhorebeek I, Wouters PJ, et al. Tight blood glucose control is renoprotective in critically ill patients. *J Am Soc Nephrol*. 2008;19:571-578.
106. Song JW, Shim JK, Yoo KJ, et al. Impact of intraoperative hyperglycaemia on renal dysfunction after off-pump coronary artery bypass. *Interact Cardiovasc Thorac Surg*. 2013;17:473-478.
107. van den Berghe G, Wouters P, Weekers F, et al. Intensive insulin therapy in critically ill patients. *N Engl J Med*. 2001;345:1359-1367.
108. Lameire N, Hoste E. Reflections on the definition, classification, and diagnostic evaluation of acute renal failure. *Curr Opin Crit Care*. 2004;10:468-475.
109. Ricci Z, Ronco C, D'Amico G, et al. Practice patterns in the management of acute renal failure in the critically ill patient: an international survey. *Nephrol Dial Transplant*. 2006;21:690-696.