Management of Acute Kidney Injury: Core Curriculum 2018

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Acute kidney injury (AKI) is a heterogeneous disorder that is common in hospitalized patients and associated with short- and long-term morbidity and mortality. When AKI is present, prompt workup of the underlying cause should be pursued, with specific attention to reversible causes. Measures to prevent AKI include optimization of volume status and avoidance of nephrotoxic medications. Crystalloids are preferred over colloids for most patients, and hydroxyethyl starches should be avoided. Volume overload in the setting of AKI is associated with adverse outcomes, so attention should be paid to overall fluid balance. Currently there are no targeted pharmacotherapies approved for the treatment of AKI. The optimal timing of renal replacement therapy in critically ill patients with AKI is unclear, but is an area of active investigation. Recent studies suggest that AKI is not a "self-limited" process, but is strongly linked to increased risk for chronic kidney disease, subsequent AKI, and future mortality.

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Introduction

Acute kidney injury (AKI) is a common diagnosis in hospitalized patients, often occurring in patients with multiple comorbid conditions. It is associated with significant increases in both short- and long-term morbidity and mortality. Management of AKI requires an in-depth understanding of fluid and electrolyte homeostasis, as well as appropriate use of renal replacement therapy (RRT) in the acute setting. In this Core Curriculum, we review key principles regarding the diagnosis and general management of AKI for clinicians. Specific management of glomerulonephritis, thrombotic microangiopathies, and AKI in the setting of malignancy have been discussed in detail in previous Core Curriculum articles and are not addressed in depth.

Diagnosis and Evaluation of AKI

AKI is characterized by the accumulation of creatinine, urea, and other unmeasured waste products after an abrupt decrease in kidney function. More recently, injury has replaced "failure" to emphasize the disease continuum because even modest reductions in kidney function are associated with worse outcomes. AKI is common, affecting approximately 5% to 10% of hospitalized patients and up to 60% of patients admitted to the intensive care unit (ICU). AKI has a variety of causes and should not be viewed as a single disease.

Although some management strategies can be universally applied, others are disease specific. Thus, when AKI is recognized, a critical first step is the prompt evaluation for the cause of AKI, with special attention to reversible causes.

Definition

Due to significant heterogeneity in prior studies, during the past 10 years efforts have been made to develop consensus AKI definitions, in particular for use in epidemiologic studies and clinical trials. In 2012, the KDIGO (Kidney Disease: Improving Global Outcomes) group combined elements from prior definitions (Table 1). Staging is based on both urine output and serum creatinine (Scr) concentration, and if urine output and Scr concentration do not correspond to the same stage, it has been recommended that the highest stage should be considered. However, although urine output is an important kidney function parameter that identifies patients at higher risk for adverse outcomes, its pathophysiologic significance in the absence of extremes of oliguria or other surrogates of reduced glomerular filtration rate (GFR) is more controversial. It should be noted that patients who develop AKI by KDIGO urine output criteria, regardless of whether Scr criteria are present, are at risk for developing fluid overload given the typically high obligate intake of critically ill patients.

Evaluation of Kidney Function in the Acute Care Setting

> **Case:** *You are asked to see a 50-year-old African American man with diabetes and known chronic kidney disease (CKD; baseline Scr, 2.0 mg/dL) who is admitted with urosepsis. Admission Scr concentration was 2.3 mg/dL and increased to 2.6 mg/dL the following day.*
>
> **Question 1: Which statement regarding his kidney function is correct?**
> a) Using the MDRD (Modification of Diet in Renal Disease) Study equation, his estimated GFR (eGFR) is 34 mL/min/1.73 m²
> b) Use of the CKD-EPI (CKD Epidemiology Collaboration) equation is more appropriate for this patient, and his eGFR is 32 mL/min/1.73 m²
> c) Using the Cockcroft-Gault formula, his creatinine clearance is 20 to 32 mL/min
> d) His eGFR cannot be calculated because his Scr concentration is not stable
>
> *For answer, see* Appendix.

At present, GFR is the gold-standard marker for acute or chronic kidney disease, though it represents only one of many affected functions. However, GFR is almost never directly measured in the clinical setting, and surrogate markers of kidney function are typically used. Current eGFR equations (Cockcroft-Gault, MDRD Study, and CKD-EPI) cannot be used when creatinine concentration is not at steady state, as occurs during AKI. Equations have been proposed to estimate kinetic GFR when Scr concentration is actively changing, but have not been validated for widespread use. In severe AKI (eg, when the patient is oligoanuric), the assumption should be that GFR is <10 mL/min when urine output is minimal.

Furthermore, because Scr concentration lags acute changes in kidney function, the current AKI stage may not reflect current kidney function. Reductions in creatinine production during acute illness and sarcopenia (which often develops with prolonged illness), along with creatinine dilution during volume overload, further complicate the evaluation of kidney function. Cystatin C has been used for GFR estimation and is thought to be more accurate at higher GFRs and in those with reduced muscle mass. However, the same limitations regarding steady-state kinetics apply, and the impact of volume of distribution has not been studied. There is considerable interest in developing bedside tools for real-time measured GFR, but no such tools for clinical use exist at present.

Tubular injury biomarkers include neutrophil gelatinase-associated lipocalin (NGAL), kidney injury molecule 1 (KIM-1), interleukin 18 (IL-18), and liver-type fatty acid binding protein (L-FABP). Future definitions of AKI may incorporate biomarkers. There is also interest in biomarkers that reflect kidney stress, including tissue injury metalloproteinase 2 (TIMP-2) and insulin-like growth factor binding protein 7 (IGFBP-7), which have recently been approved by the US Food and Drug Administration (FDA) for the identification of patients at high risk for developing KDIGO stage 2 to 3 AKI during the next 12 to 24 hours (these biomarkers are marketed as the Nephrocheck Test [Astute Medical]). Our understanding of the clinical utility of this test is evolving rapidly; at present, this test may be useful to identify patients for implementation of care bundles (see below).

Additional Readings

▶ KIDGO AKI Workgroup. KDIGO clinical practice guideline for AKI. *Kidney Int Suppl.* 2012;2:1-138. ★ **ESSENTIAL READING**

Table 1. Comparison of Recent Consensus AKI Definitions

AKI Stage	Urine Output[a]	KDIGO	AKIN	RIFLE
1	<0.5 mL/kg/h for 6-12 h	Scr to 1.5-1.9 × baseline over 7 d or ≥0.3 mg/dL absolute increase over 48 h	Scr to 1.5-2 × baseline or ≥0.3 mg/dL absolute Scr increase within 48 h	*Risk:* Scr to ≥1.5 × increase within 7 d, sustained for ≥24 h
2	<0.5 mL/kg/h for ≥12 h	Scr to 2.0-2.9 × baseline	Scr to >2-3 × baseline	*Injury:* Scr to ≥2 × increase
3	<0.3 mL/kg/h for ≥24 h or anuria for ≥12 h	Scr to ≥3.0 × baseline, or Scr increase to ≥4.0 mg/dL or initiation of RRT	Scr to >3.0 × baseline, or Scr increase to ≥4.0 mg/dL (with increase of 0.5 mg/dL) or initiation of RRT	*Failure:* Scr to ≥3.0 × increase or Scr increase to ≥4.0 mg/dL (with increase of 0.5 mg/dL) or initiation of RRT
				Loss: Complete loss of kidney function for >4 wk
				ESKD: ESKD for >3 mo

Note: The first classification system, RIFLE, from the ADQI, incorporated 3 categories of injury and 2 outcomes that varied by severity. The outcomes (Loss, ESKD) were eliminated from the subsequent AKIN and KDIGO definitions. The AKIN definition incorporated smaller changes in Scr concentration, and the KDIGO definition added more definitive time frames to the definition. A key concept for the Scr-based definitions of AKI is the identification of baseline Scr concentration. Although the initial RIFLE criteria recommended the use of an Scr concentration that would equate to eGFR of 75 mL/min/1.73 m² by the MDRD Study equation (MDRD-75) if no baseline was available, this definition does not account for chronic kidney disease if present. It is essential to look for a prior baseline/reference Scr concentration, ideally from the 365 days before hospital admission from a clinical context in which there was not concern for AKI (eg, a stable clinic visit). This concept is discussed in detail in the KDIGO AKI clinical practice guideline.

Abbreviations: ADQI, Acute Dialysis Quality Initiative; AKI, acute kidney injury; AKIN, Acute Kidney Injury Network; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; KDIGO, Kidney Disease: Improving Global Outcomes; MDRD, Modification in Diet in Renal Disease; RIFLE, risk, injury, failure, loss of kidney function, and end-stage kidney disease; RRT, renal replacement therapy; Scr, serum creatinine.

[a]All 3 definitions (KDIGO, AKIN, RIFLE) use common urine output criteria.

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- Liu KD, Thompson BT, Ancukiewicz M, et al. AKI in patients with acute lung injury: impact of fluid accumulation on classification of AKI and associated outcomes. *Crit Care Med.* 2011;39:2665-2671.
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Cause and General Management of AKI

Evaluation of Cause of AKI

Those who meet criteria for AKI should have the cause investigated, with special attention to treatable causes (Table 2). Careful history taking, chart review, and physical examination remain the fundamental tenets of the workup. For example, after cardiopulmonary bypass surgery, AKI may be related to the bypass itself, hypovolemia, postoperative cardiogenic or (rarely early on) septic shock, or cholesterol emboli. Careful evaluation of the temporal pattern of AKI relative to the surgery and other clinical events (hypotension and iodinated contrast exposure), as well as physical examination and laboratory findings (eg,

livedo reticularis and peripheral eosinophilia suggestive of cholesterol emboli) are needed to differentiate these conditions.

All patients with AKI need careful assessment of hemodynamic and volume status using vital signs and physical examination; critically ill patients, for example, those in shock, may benefit from more invasive hemodynamic monitoring (arterial line, central venous pressure, or cardiac output monitoring). Urinary indexes (fractional excretion of sodium and urea) may be helpful in diagnosing decreased kidney perfusion (aka, prerenal azotemia) if the patient is oligoanuric. However, the utility of these indexes tends to be more limited in critically ill adults, likely as a result of coexisting pre- and intrarenal disease. Urinary microscopy for renal tubular epithelial cells and granular casts may be helpful to make the concomitant diagnosis of acute tubular necrosis (ATN), which is the most common cause of AKI occurring in the hospital. However, ATN is a misnomer because renal biopsy specimens from patients with this clinical diagnosis tend to have little frank necrosis and have evidence of significant nonlethal cell injury. Thus, ATN is used clinically to describe a specific and severe form of AKI that occurs from a variety of causes (Box 1), rather than the pathology per se.

Table 2. Causes of AKI

Type	Examples of Specific Causes
Decreased kidney perfusion ("prerenal" states)	
Hypovolemia	Increased losses (hemorrhage, burns, massive vomiting or diarrhea), poor oral intake
Reduced cardiac output	Heart failure, cardiac tamponade, massive pulmonary embolism
Renal vasomodulation/shunting	Medications (NSAID, ACEi/ARB, cyclosporine, iodinated contrast), hypercalcemia, hepatorenal syndrome, abdominal compartment syndrome
Systemic vasodilation	Sepsis, SIRS, hepatorenal syndrome
Intrarenal causes	
Vascular	Renal artery stenosis, arterial/venous cross-clamping
Microvascular	Thrombotic microangiopathies (TTP, HUS, aHUS, DIC, APS, malignant hypertension, scleroderma renal crisis, preeclampsia/HELLP syndrome, drug-induced), cholesterol emboli
Glomerular	Rapidly progressive (crescentic) GN: anti–glomerular basement membrane; immune complex diseases: IgA nephropathy, postinfectious, lupus, mixed cryoglobuminemia with MPGN; pauci-immune glomerulonephritis: ANCA-associated vasculitides: GPA, MPA, EGPA (Churg-Strauss); ANCA-negative; nephrotic-range proteinuria with associated AKI: HIV-associated nephropathy (secondary FSGS); other causes of nephrotic-range proteinuria that commonly associate with AKI: minimal change disease with ATN/AIN; membranous nephropathy + crescentic GN or renal vein thrombosis; myeloma + multiple different pathologies, but in particular light chain cast nephropathy
Tubulointerstitium	AIN: medications, infection, lymphoproliferative disease; pigment nephropathy: rhabdomyolysis (myoglobin), massive hemolysis (hemoglobin); crystal nephropathy: uric acid (tumor lysis), acyclovir, sulfonamides, protease inhibitors (indinavir, azatanavir), methotrexate, ethylene glycol, acute phosphate nephropathy, oxalate nephropathy; myeloma-associated AKI (cast nephropathy); ATN: ischemia (shock, sepsis), inflammatory (sepsis, burns), medications (see Box 1; osmotic nephrosis in setting of sucrose, mannitol and hydroxyethylstarch use)
Postrenal causes	
Bladder outlet	Benign prostatic hypertrophy, cancer, strictures, blood clots
Ureteral	Bilateral obstruction (or unilateral with one kidney): stones, malignancy, retroperitoneal fibrosis
Renal pelvis	Papillary necrosis (NSAIDs), stones

Note: Causes of AKI can be broadly divided into prerenal, intrarenal, and postrenal causes and then further subdivided as described.
Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; (a)HUS, (atypical) hemolytic uremic syndrome; AKI, acute kidney injury; ANCA, antineutrophil cytoplasmic antibody; APS, antiphospholipid syndrome; ATN/AIN, acute tubular necrosis/acute interstitial nephritis; ARB, angiotensin receptor blocker; DIC, disseminated intravascular coagulation; EGPA, eosinophilic granulomatosis with polyangiitis; FSGS, focal segmental glomerulosclerosis; GN, glomerulonephritis; GPA, granulomatosis with polyangiitis; HELLP, hemolysis, elevated liver enzymes, low platelet count) syndrome; HIV, human immunodeficiency virus; MPA, microscopic polyangiitis; MPGN, membranoproliferative glomerulonephritis; NSAID, nonsteroidal anti-inflammatory drug; SIRS, systemic inflammatory response syndrome; TTP, thrombotic thrombocytopenic purpura.

Box 1. Medications Commonly Associated With Acute Tubular Necrosis

- Aminoglycosides (tobramycin, gentamycin)
- NSAIDs (ibuprofen, naproxen, ketorolac, celecoxib)
- ACEi (captopril, lisinopril, benazepril, ramipril)
- ARB (losartan, valsartan, candesartan, irbesartan)
- Amphotericin
- Cisplatin
- Foscarnet
- Iodinated contrast
- Pentamidine
- Tenofovir
- Zolendronic acid

Note: Although not a classic cause of acute tubular necrosis, volume depletion caused by diuretics can exacerbate the effects of some of these other medications. This table does not include common causes of pigment or crystal nephropathy (which are described in Table 2) or medications associated with osmotic injury.
Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; NSAIDs, nonsteroidal anti-inflammatory drugs.

Box 2. Key Medications Requiring Dose Adjustment (or Cessation) in AKI

- Analgesics (morphine, meperidine, gabapentin, pregabalin)
- Antiepileptics (lamotrigine)
- Antivirals (acyclovir, gancyclovir, valgancyclovir)
- Antifungals (fluconazole)
- Antimicrobials (almost all antimicrobials need dose adjustment in AKI, with important exceptions of azithromycin, ceftriaxone, doxycycline, linezolid, moxifloxacin, nafcillin, rifampin)
- Diabetic agents (sulfonylureas, metformin)
- Allopurinol
- Baclofen
- Colchicine
- Digoxin
- Lithium
- Low-molecular-weight heparin
- NOACs

Note: Medications that are associated with acute tubular necrosis (Box 1) should be withheld, if possible.
Abbreviations: AKI, acute kidney injury; NOAC, novel anticoagulants.

Patients suspected of having a specific treatable intrarenal cause of AKI (such as acute interstitial nephritis [AIN], glomerulonephritis, or thrombotic microangiopathy) should have a urine sediment examination and serologic/hematologic tests, as indicated. A kidney biopsy should be considered when there is significant new proteinuria (protein excretion > 3 g/d) or hematuria, active urine sediment, or no readily identifiable cause of decreased kidney perfusion, obstruction, or ATN. A retrospective study of 68 critically ill patients who underwent kidney biopsy based on clinical suspicion found that 51% of patients had a specific cause of AKI, which led to a significant change in treatment plan in 21%. However, kidney biopsy was associated with complications in 22%, most commonly from bleeding.

AIN is likely underdiagnosed in hospitalized patients who develop AKI. The widespread use of antibiotics and proton pump inhibitors puts these patients at higher risk for AIN. When not accompanied by systemic symptoms (eg, rash and eosinophilia), AIN can be difficult to diagnose. Urinary eosinophils have been demonstrated to have poor test characteristics, and kidney biopsy is the only definitive way to establish the diagnosis. Treatment of AIN involves cessation of the culprit medication (if drug induced) and consideration of steroid therapy.

Renal ultrasonography or computed tomography of the abdomen and pelvis without iodinated contrast is indicated when obstruction is suspected. In individuals with 2 kidneys, obstruction must be bilateral to cause AKI. In those for whom there is another clear cause for AKI, routine imaging may not be warranted.

Overview of AKI Management

Patients at risk for AKI and those with AKI should have kidney function monitored closely by Scr concentration and urine output (Fig 1). Careful assessment of volume status and hemodynamics should be undertaken and treated with intravenous fluids, diuretics, or other means of hemodynamic support as indicated. These treatments, along with RRT, are discussed in subsequent sections.

Medications should be reviewed closely for nephrotoxic agents, which should be discontinued or switched to medications with less nephrotoxic potential. In a quality improvement initiative, a pharmacy-led notification for pediatric patients receiving 3 or more nephrotoxic medications or an aminoglycoside resulted in a 38% decrease in nephrotoxic medication exposure and 64% decrease in AKI incidence. In addition, medications that may accumulate with reduced GFR should be avoided or adjusted, in particular in patients with stage 2 or 3 AKI (Box 2). Although not a medication per se, in patients with AKI, exposure to gadolinium has been associated with nephrogenic systemic fibrosis, a sclerosing condition of the skin and internal organs that can result in death. Although the absolute incidence of this condition is low, the relative risks and benefits of gadolinium administration must be cautiously weighed. Newer gadolinium preparations may be associated with a lower risk of nephrogenic systemic fibrosis.

With regard to specific nephrotoxins, there is growing interest in the nephrotoxic effects of vancomycin, which in the setting of higher target trough concentrations for severe methicillin-resistant *Staphylococcus aureus* (MRSA) infections and declining kidney function can accumulate to very high levels (>50 μg/mL). Casts that contain nanospheric vancomycin have recently been described in individuals with vancomycin-associated AKI. The addition of piperacillin/tazobactam may potentiate the nephrotoxicity of vancomycin, but the mechanism is unclear. Nonsteroidal anti-inflammatory drugs and angiotensin-converting enzyme inhibitors/angiotensin receptor blockers are common classes of medications that should be discontinued. Although recent studies suggest

that the association between iodinated radiocontrast and AKI may not be as strong as previously thought, iodinated contrast should be avoided if possible in patients with or at risk for AKI.

A number of recent studies have examined bundled protocols to improve the quality and consistency of care for patients with or at risk for AKI. In one study, 276 patients undergoing cardiac surgery who had elevated TIMP-2 × IGFBP-7 concentrations were randomly assigned to routine care or a strictly implemented AKI prevention protocol (from the KDIGO guideline and consisting of items such as hemodynamic optimization and avoidance of nephrotoxins). Postoperative AKI was observed to be significantly lower in the protocol group (55% vs 72%; absolute risk reduction, 17%; P = 0.004). Notably, the biomarker strategy enriched for high-risk patients, reducing the number needed to treat. However, more work is needed to design and implement such potentially successful (and sustainable) care bundles for AKI prevention and management. Along the same lines, there has been tremendous interest in the use of electronic alert systems to identify patients with early AKI or at high risk for AKI, but the effectiveness of these alerts to change clinical practice has been variable and limited to date.

Additional Readings

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Hemodynamic Support: Fluid Management and Blood Pressure Targets

Case, continued: *Review of the patient's chart shows that he has received 4 L of 0.9% saline solution intravenously in the past 24 hours, and urine output has increased from 10 to 20 mL/h. On physical examination, vital signs include blood pressure of 95/65 mm Hg, heart rate of 72 beats/min, and oxygen saturation of 96% on 2 L/min by nasal cannula. His lungs are clear. He has peripheral edema (2+).*

Question 2: What would you recommend?
a) Continue with volume expansion because his urine output has increased significantly
b) Add norepinephrine to increase his systolic blood pressure to >105 mm Hg
c) Continue with volume expansion and add norepinephrine as well
d) Start a trial of intravenous furosemide, which could help manage his fluid overload

For answer, see *Appendix*.

Management of hemodynamics in patients with AKI, especially those in shock, is of critical importance. Although under normal conditions relatively constant renal blood flow can be maintained despite changes in blood pressures through autoregulation, these mechanisms are disrupted in AKI. Titration of fluids and vasopressors can be complex: hypotension can result in continued kidney damage in those with AKI, whereas administration of vasopressors in those without adequate intravascular volume can further reduce renal blood flow. Conversely, patients with AKI are at risk for volume overload, and intravenous fluid loading may cause harm.

Intravenous Fluid Resuscitation

Outside the setting of iodinated contrast administration, there are no randomized trials comparing intravenous fluids to placebo for AKI prevention. However, it can be assumed that those with reduced renal blood flow who can augment their cardiac output by expansion of their intravascular volume would benefit from fluid resuscitation. Early goal-directed therapy, in which septic patients received intravenous crystalloids, inotropes, and transfusions according to predefined protocols, had no effect on mortality or need for RRT in 3 subsequent large trials. Although administration of intravenous fluids in patients with sepsis and/or hypovolemia is beneficial initially, fluid overload, especially in later disease, may confer harm.

Several retrospective studies have found associations between positive fluid balance and mortality in critically ill patients. In a large multicenter cohort focused on critically ill patients, those with fluid overload (10% weight gain) at the time of dialysis therapy initiation had an odds ratio (OR) for death of 2.07 (95% confidence interval [CI], 1.27-3.37); findings were similar in those with AKI who

did not require dialysis. However, such analyses of fluid overload are likely partially confounded by severity of illness.

At present, there are numerous methods that can be used to assess fluid responsiveness, and no one method can be recommended above others. We recommend using multiple clinical assessments and repeated measures to assess fluid responsiveness. Intravenous fluids should be used judiciously in patients with AKI who are not "volume responsive." After significant volume resuscitation, even if patients remain volume responsive, vasopressor support should be considered to avoid markedly positive fluid balance. In those requiring volume resuscitation, the choice of solution is controversial. Major trials of various colloids, physiologic-balanced salt solutions, and saline solution have been completed. We next review the evidence base for fluid selection.

Colloid Versus Crystalloid

Colloids, such as albumin, hydroxyethyl starches (HESs), and gelatins, rely on oncotic gradients to selectively expand the intravascular space, while crystalloids equilibrate across intravascular and extravascular spaces. Patients with inflammatory states will have increased vascular permeability, and some of this benefit may be lost.

Albumin appears to be a relatively safe, albeit more expensive, alternative for resuscitation of critically ill patients. In the Saline Versus Albumin Fluid Evaluation (SAFE) trial, ICU patients who received 4% albumin had no renal or mortality benefit. However, less total volume was required for resuscitation in the albumin group (2.2 vs 3.1 L). Given the reduction in volume needed, albumin may have a role in special situations in which large volumes of intravenous fluids are anticipated, such as septic shock in a cirrhotic patient. There is a clear indication for albumin in the setting of large-volume paracentesis for patients with end-stage liver disease because albumin infusion is associated with lower risk for AKI. Albumin (and likely other colloids) should be avoided in patients with traumatic brain injury due to an increased risk for death.

There are a variety of HES preparations with differing molecular weights, molar substitutions, and tonicities, all of which are relatively inexpensive compared to albumin. Several trials have demonstrated renal toxicity with hyperoncotic HES administration due to proximal tubule vacuolization and swelling (osmotic nephrosis). Subsequently, trials of iso-oncotic HES preparations have tested the hypothesis that these preparations are less nephrotoxic. The Crystalloid Versus Hydroxyethyl Starch (CHEST) Study randomly assigned 7,000 ICU patients to receive saline solution or an iso-oncotic 6% HES and found an increased risk for RRT in the group that received HES (7.0% vs 5.3%; $P = 0.04$). This study demonstrates one of the potential challenges of the combined Scr concentration and urine output–based AKI criteria: although there was more AKI

defined by RIFLE (risk, injury, failure, loss of kidney function, and end-stage kidney disease) risk or injury in the saline-solution arm, this was largely driven by urine output. In contrast, the HES group, which had a lower overall rate of AKI, had higher rates of RRT and a trend toward more severe AKI. Following the publication of this study, the FDA added additional warnings to the packaging for HES.

The other synthetic colloids commonly used for volume expansion are gelatins, but there are substantially fewer data regarding the association of gelatins with AKI. In general, given the lack of clear benefit with colloid administration, routine use of these solutions is not warranted.

Finally, there is still interest in the role of colloids for the treatment of hypovolemic shock. Colloids Versus Crystalloids for the Resuscitation of the Critically Ill (CRISTAL) was a multicenter randomized open-label study of more than 2,800 ICU patients with hypovolemic shock. Patients were randomly assigned to fluid type (crystalloid or colloid), and the selection of fluid was up to the study investigator. About 45% of those in the colloid arm received HES. There was no difference in RRT requirement or mortality at 28 days (primary study end point). However, there was a significant reduction in mortality at 90 days, need for mechanical ventilation, and need for vasopressors in those who received colloids. Thus, it has been suggested that a key to the use of colloids is the optimal timing of administration. Regardless, at present, there are no data to support the routine use of colloid for volume resuscitation.

Physiologic Balanced Salt Solution Versus Normal Saline Solution

Isotonic 0.9% saline solution has a significantly higher chloride content than the extracellular space in humans (154 vs ∼110 mmol/L), and patients receiving normal saline solution are at risk for hyperchloremic metabolic acidosis. Hyperchloremia has been associated with increased renal vascular resistance, increased renin activity, and decreased GFR in animal studies. In healthy volunteers, administration of 0.9% saline solution is associated with increased extravascular volume and decreased renal cortical tissue perfusion compared to a balanced salt solution.

To explore the hypothesis that chloride-rich fluids increase the risk for AKI, Yunos et al performed an open-labeled sequential study of ICU patients at a single institution. During a 6-month period, patients were administered balanced salt solutions for resuscitation and were compared with controls from the corresponding 6 months from 1 year prior. The chloride-restricted group had a lower incidence of AKI (8.4% vs 14%) and lower rates of RRT (6.3% vs 10%). Subsequently, the SPLIT (0.9% Saline vs Plasma-Lyte 148 for ICU Fluid Therapy) trial, a multicenter randomized double-blind crossover study, did not find a significant difference in rates of AKI,

need for RRT, or mortality between the 0.9% saline solution versus Plasma-Lyte groups (Baxter). However, this study has been criticized because it was a predominantly postoperative population that received only modest resuscitation volumes (median, 2 L). Recently, data from large pragmatic trials focused on patients admitted to the emergency department or ICU at a single US institution suggests benefit with balanced salt administration with regard to the composite end point of Major Adverse Kidney Events to day 30, defined as death, need for RRT or persistently decreased kidney function at day 30/hospital discharge (ClinicalTrials.gov identifiers NCT02444988, NCT02547779, and NCT02614040).

Blood Pressure Management

There has been interest in optimal blood pressure targets in patients with shock. The SEPSISPAM (Sepsis and Mean Arterial Pressure) trial randomly assigned patients with septic shock requiring vasopressors to 2 blood pressure goals, a standard mean arterial pressure (MAP) goal (65-70 mm Hg) and a higher goal (80-85 mm Hg). There was no difference in mortality between the 2 treatment groups. However, patients with chronic hypertension in the higher MAP group had significantly lower rates of AKI and RRT. The number needed to treat to prevent 1 patient with hypertension from needing RRT was modest, at 9.5. Patients in the higher MAP group had higher rates of atrial fibrillation. Thus, blood pressure targets should likely take into account premorbid blood pressures, weighing the potential benefits of increased renal perfusion against the potentially deleterious effects of vasoconstriction resulting in hypoperfusion of other organs.

Additional Readings

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Additional Therapies for AKI: Diuretics, Nutrition, and the Future

Diuretics

Loop diuretics are commonly used in oliguric AKI despite the lack of evidence for their benefit. In addition to preventing volume overload, loop diuretics theoretically attenuate ischemic tubular injury by decreasing metabolic demand in the oxygen-poor renal medulla by inhibition of the sodium/potassium/chloride ($Na^+/K^+/2Cl^-$) cotransporter. However, clinical trials have failed to consistently show a benefit of diuretics in AKI. Thus, KDIGO recommends against the use of diuretics to treat AKI except in the setting of volume overload, when they can be used for management of volume overload itself. It has been proposed that in early AKI, urine output response to loop diuretics may have prognostic value. The hypothesis is that patients with AKI who are able to augment urine output in response to a diuretic challenge have intact tubular function and therefore may have a better renal prognosis. However, this finding has not been validated in large multicenter studies.

Nutrition and Glucose Control

AKI is a catabolic state, and patients with AKI may need enteral or parenteral nutritional support. In general, the enteral route is preferred due to the lower risk for infection (and lower volumes needed to administer equivalent calories). The nutrition prescription in AKI will vary significantly depending on the underlying cause of AKI and the form of RRT provided, if any. With regard to glycemic control, the KDIGO guideline recommends maintaining blood glucose concentrations between 110 and 149 mg/dL in critically ill patients, a range that has never been formally evaluated in randomized trials. The potential renal benefit of glucose control was demonstrated in a single-center study of surgical patients randomly assigned to a target blood glucose concentration of 80 to 110 mg/dL or 180 to 200 mg/dL, in which the incidence of severe AKI and RRT was lower in the intensive arm (4.8% vs 8.2%). A notable practice difference in this study was the provision of dextrose in the immediate

postoperative period, which may have increased the adverse consequences of hyperglycemia. Subsequently, the NICE-SUGAR (Normoglycemia in Intensive Care Evaluation–Survival Using Glucose Algorithm Regulation) Study, the largest randomized clinical trial of glycemic control in critically ill patients, highlighted the potential risks of intensive glycemic control. Participants (6,100 in total) were randomly assigned to intensive (81-108 mg/dL) or conventional (<180 mg/dL) glycemic control. There was no difference in rates of RRT between groups. However, intensive glycemic control was associated with higher mortality (OR, 1.14; 95% CI, 1.02-1.28) and a greater incidence of severe hypoglycemia (6.8% vs 0.5%). Several additional clinical trials have had similar findings. Patients with AKI may be at particularly high risk for severe hypoglycemia given the kidney's role in insulin metabolism and glucose excretion. However, severe hyperglycemia is associated with increased morbidity and mortality in a variety of clinical scenarios and should also be avoided.

Pharmacotherapies for AKI

At this time, there are no pharmacologic therapies for the prevention or treatment of AKI (Box 3). Because AKI is a heterogeneous disease, identification of a single therapy that will benefit all is challenging. Additionally, the AKI insult almost always precedes AKI detection and it is therefore difficult to intervene before the disease is established. Early identification and treatment of AKI with drugs that have pleiotropic effects on multiple pathologic pathways are most likely to be successful.

Box 3. Agents Tested in Selected Trials for Treatment of AKI

Trials ongoing
- Alkaline phosphatase (sepsis-associated AKI)
- L-Carnitine (sepsis-associated AKI)
- Remote ischemic preconditioning (post operative AKI)
- p53-targeted siRNA (post–cardiac surgery AKI)
- Extracorporeal devices (dialysis-requiring AKI)
- Vitamin D (hospitalized AKI)
- Uremic toxin absorption/pentoxifylline (hospital-acquired AKI)

No clear evidence of benefit
- α-Melanocyte-stimulating hormone
- Atrial natriuretic peptide
- Calcium channel blockers
- Diuretics[a]
- Dopamine
- Erythropoietin
- Fenoldopam
- Insulin growth factor
- N-Acetylcysteine
- Statins
- Aminophylline/theophylline[b]

Abbreviations: AKI, acute kidney injury; siRNA, short interfering RNA.
[a]Potentially useful for volume management, but not for treatment of AKI.
[b]Some interest remains for AKI prevention in neonates.

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Management of Severe AKI, Including RRT

Case, continued: *Two days later, the patient remains oliguric despite a trial of furosemide, and his Scr concentration has increased to 5.5 mg/dL. Blood pressure is 105/75 mm Hg. He has peripheral edema (3+), and oxygen saturation is 91% on 5 L/min by nasal cannula. You plan to initiate RRT.*

Question 3: Which of the following is the best statement with respect to this set of circumstances?
a) Given the role of sepsis in development of his AKI, continuous RRT (CRRT) is preferable to intermittent hemodialysis (IHD) for this patient
b) If CRRT is selected, the prescribed dose should be 35 to 40 mL/kg/h
c) CRRT and IHD have similar clinical outcomes
d) RRT can be postponed until the patient develops clear signs of uremia

For answer, see Appendix.

Patients with AKI may develop hyperkalemia, metabolic acidosis, volume overload, and/or symptoms of uremia due to reduced GFR. Hyperkalemia can be medically managed as described in Table 3. Metabolic acidosis may occur due to AKI itself (eg, inability to excrete organic acids) or conditions associated with AKI (eg, hypoperfusion leading to lactic acidosis). The kidney plays an important role, along with the liver, in lactate metabolism. Treatment of metabolic acidosis depends on its severity and must take into consideration absolute pH, rate of change of acidosis, and its underlying cause. Metabolic acidosis itself can be treated with bicarbonate or other base equivalents. Diuretics can be used to manage volume overload.

Despite these temporizing measures, some with severe AKI will require RRT. The optimal timing of RRT is an area of active investigation. Factors that may affect the timing of RRT initiation are reviewed in the Continuous Dialysis Therapies Core Curriculum. With regard to available data, retrospective studies have showed an association between early RRT and favorable outcomes. However,

Table 3. Medical Management of Hyperkalemia

Purpose of Treatment	Drug	Usual Dose	Notes
Stabilization of cardiac membrane	Calcium gluconate or calcium chloride	1 g IV over minutes, repeat as needed	Given when ECG changes[a] present; use with caution with digoxin[b]
Transcellular potassium ion shift	Insulin (regular)	10 U IV or weight based[c]	Typically administered with 25-50 g of IV glucose
	β₂-adrenergic agonist	Albuterol 5-20 mg, nebulized	Watch for tachycardia
	Sodium bicarbonate (NaHCO₃)	50 mEq/50 mL IV	Controversial outside of setting of severe metabolic acidosis; bolus dose is very hypertonic with significant sodium load
Removal from body	Loop diuretic	Furosemide 40-60 mg IV	Supplement with isotonic saline solution if euvolemic or hypovolemic; highly effective if the patient is diuretic-responsive
	Cation exchange resins	Sodium polystyrene sulfonate, 15 g orally/ rectally, 1-4×/d	Use with caution with ileus/obstruction or in patients with dehydration; associated with risk for colonic necrosis; need to ensure that the resin transits out of the GI tract; other resins are under development but are not approved for use for acute hyperkalemia

Abbreviations: AKI, acute kidney injury; ECG, electrocardiographic; GI, gastrointestinal; IV, intravenous.
[a]ECG changes include peaked T waves, prolongation of PR interval, widening of QRS, second- or third-degree heart block, and sine wave pattern (from least severe to most life-threatening).
[b]For AKI with hyperkalemia in the setting of digoxin toxicity, reversal of digoxin toxicity with digoxin antibody fragments is the treatment of choice.
[c]Weight-based insulin dosing is 0.1 U/kg of body weight, up to 10 units. It is associated with reduced risk for hypoglycemia without affecting potassium-lowering effect.

many of these studies were limited in their assessment of "early" based on serum urea nitrogen or creatinine concentration without other clinical information. Recently, 2 trials have assessed the impact of RRT timing in ICU patients. The ELAIN (Early Versus Late Initiation of Renal Replacement Therapy in Critically Ill Patients With Acute Kidney Injury) trial found that 90-day mortality was significantly lower in patients randomly assigned to earlier RRT. However, this study has been criticized as a single-center trial that included many post–cardiac surgery patients and enrolled patients with early AKI (KDIGO stage 2 AKI and elevated plasma NGAL). In contrast, the AKIKI (Artificial Kidney Initiation in Kidney Injury) Study was a multicenter trial that randomly assigned patients with more severe (KDIGO stage 3) AKI and did not find a difference in mortality between early and delayed RRT. Thus, the questions of whether early RRT is beneficial, and if so, in which patients, remain unanswered. Two large ongoing trials will help answer these questions (ClinicalTrials.gov identifiers NCT01682590 and NCT02568722). Interestingly, in the STARRT-AKI (Standard vs. Accelerated Initiation of RRT in Acute Kidney Injury) pilot and in AKIKI, a significant proportion of participants in the late initiation arm recovered kidney function before RRT. This finding suggests that in addition to patients who may benefit from the earlier provision of RRT, there are patients who may recover before the need for RRT, and our ability to identify these patients is limited at best.

RRT Prescription, Including Modality and Dose

Several aspects of the RRT prescription, including site selection for vascular access, choice of membrane and anticoagulation, and differences between convective and diffusive clearance, are discussed in detail in the Continuous Dialysis Therapies Core Curriculum. With regard to modality, the most widely used are CRRT and IHD. Prolonged intermittent RRT/sustained low-efficiency dialysis are additional options that are used less frequently. Although they appear to have similar outcomes in preliminary studies and meta-analyses comparing these modalities with other forms of RRT for AKI, there is a need for better quality evidence in these areas before their routine use can be recommended. Peritoneal dialysis can be used in the acute setting as well and can be of particular use in resource-limited settings.

There has been much interest in whether CRRT is associated with more favorable outcomes, including lower mortality and enhanced renal recovery. However, to date, small randomized clinical trials and meta-analyses have found no association between modality and outcome (mortality or renal recovery). Thus, as recommended by the KDIGO guideline, CRRT and IHD are complementary therapies; treatment considerations include the individual patient's hemodynamic status, degree of volume overload and bleeding risk, and the treating facility's availability/ experience.

An early single-center trial suggested that patients with higher CRRT intensity (35 or 45 mL/kg/h) had lower mortality when compared to lower intensity (20 mL/kg/ h). However, 2 subsequent multicenter randomized controlled trials, the VA/NIH ATN (Veterans Affairs/National Institutes of Health Acute Renal Failure Trial Network) and ANZICS RENAL (Australian and New Zealand Intensive Care Society Randomised Evaluation of Normal Versus Augmented Level of Renal Replacement Therapy in ICU) studies, found that there was no difference in mortality or renal recovery when comparing high- to low-intensity RRT. Patients in the high-intensity arm were more likely to have hypophosphatemia.
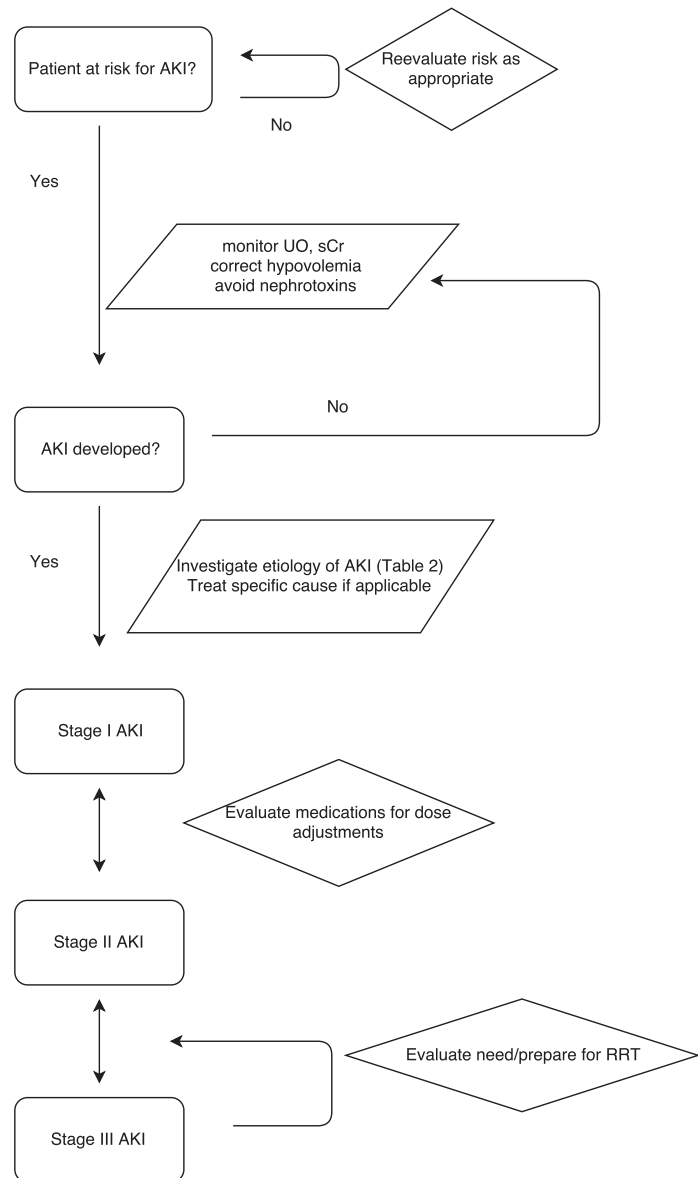
Figure 1. Conceptual model for the diagnosis and treatment of acute kidney injury (AKI). Abbreviations: UO, urine output; RRT, renal replacement therapy; sCr, serum creatinine.

Consequently, current guidelines recommend goal effluent flow rates of 20 to 25 mL/kg/h.

With regard to IHD dosing, it is important to routinely check the urea reduction ratio or Kt/V to ensure that dialysis is adequate. In the VA/NIH ATN study, median duration of an IHD session was 4 hours, with a mean blood flow rate of 360 mL/min, highlighting that in these catabolic patients, substantial time is needed to ensure an adequate dialysis dose.

Discontinuation of RRT

The decision to discontinue RRT in patients with AKI is made based on 1 of 3 clinical scenarios: intrinsic kidney function has adequately improved to meet demands, the disorder that prompted renal support has improved, or continued RRT is no longer consistent with goals of care. There is no definitive prospective evidence to guide clinicians, but urine output appears to be predictive of successful RRT discontinuation. In one study of patients on CRRT, 24-hour urine output > 400 mL/d in patients not using diuretics or >2,300 mL/d in patients using diuretics had >80% chance of successful RRT discontinuation. Other studies have suggested that quantitation of timed urinary creatinine and urea excretion (either as total excretion per 24-hour period or calculation of creatinine and urea clearance) may be helpful. Prospective studies are needed to help guide clinicians on when to attempt RRT discontinuation.

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Contrast-Induced AKI

Contrast-induced AKI (CI-AKI, also referred to as contrast-associated AKI) is a specific form of AKI that usually manifests as a transient small increase in Scr concentration within a few days of exposure to intravascular iodinated contrast. Despite its usually self-limited course, CI-AKI is associated with increased short- and long-term mortality, as well as progressive CKD. Recently, the degree to which radiocontrast affects the kidney has been debated because several studies (both meta-analyses and cohort studies) have suggested that in the aggregate population, the risk for AKI after contrast administration is perhaps overemphasized.

Nonetheless, in clinical practice, for any given study requiring iodinated contrast, the potential risks and benefits should be weighed closely. Along the same lines, patient- and procedure-level factors contribute to the risk for CI-AKI and should be assessed. The primary risk factor for CI-AKI is CKD, and the incidence of CI-AKI increases incrementally as GFR decreases or proteinuria/albuminuria increases. Diabetes further increases the risk in those with CKD. Additional patient-specific risk factors include low effective circulating blood volume and nonsteroidal anti-inflammatory drug use. Procedure-related risk factors include higher contrast volume, intra-arterial procedures, multiple contrast exposures in a short interval, and hyperosmolar contrast agents.

Management of CI-AKI aims primarily at prevention. Consideration should be given to alternative noncontrast studies if possible. Those who undergo iodinated contrast studies should have treatment with nonsteroidal anti-inflammatory drugs and other nephrotoxins discontinued, ideally at least 24 hours before the procedure. Low- or iso-osmolar radiocontrast should be used, at the lowest possible volume required. Isotonic intravenous fluid administration reduces the risk for CI-AKI and should be used in those at elevated risk. Typical regimens consist of a 1-mL/kg/h infusion 12 hours before and 12 hours after contrast exposure, or 3 mL/kg/h 1 hour before and 1.5 mL/kg/h for 4 to 6 hours postprocedure. With regard to fluid selection, although small studies suggested a benefit to the use of isotonic sodium bicarbonate solution, a large randomized clinical trial of isotonic bicarbonate versus normal saline solution (factorialized with N-acetylcysteine vs placebo) in high-risk patients undergoing angiography showed no benefit with bicarbonate or N-acetylcysteine with regard to a composite end point of death, RRT, and 50% reduction in GFR at 90 days. There have been a variety of other pharmacotherapies evaluated for CI-AKI prevention, none of which is clearly beneficial. Hemodialysis after administration of contrast is ineffective for preventing CI-AKI and may cause harm.

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Long-term Consequences of AKI

Case, continued: *Two weeks later, the patient begins to recover kidney function. He is discharged from the hospital with an Scr concentration that is stable at 2.5 mg/dL. He asks you about the long-term impact of the AKI on his health.*

Question 4: What is the best way to respond to his stated concern?
a) Because this was an acute event due to urosepsis, which is now fully treated, the AKI has no meaningful impact on the course of his underlying CKD
b) His risk for future dialysis dependency has increased significantly after this episode of AKI
c) There is no association between his recent AKI and risk for future cardiovascular disease
d) He should expect further recovery of his kidney function and return to his baseline over the next few months

For answer, see Appendix.

Although previously it was believed that most patients who developed AKI fully recovered, it is now recognized that those who experience AKI have increased risk for subsequent AKI, progressive CKD, and future mortality. Even mild stages of AKI are associated with incident CKD. In a propensity-matched cohort study of hospitalized patients who experienced renal recovery based on Scr concentration, those with AKI had an increased rate of incident CKD (relative risk [RR], 2.14; 95% CI, 1.96-2.43) and mortality (RR, 1.48; 95% CI, 1.20-1.83).

A pooled analysis of studies of long-term risk for CKD and dialysis dependence found a pooled hazard ratio of 8.8 for CKD and 3.1 for end-stage kidney disease in patients with AKI compared with those without AKI. There was a graded increase in risk by severity of AKI. Given the retrospective nature of these associations, it is controversial whether this is a causal relationship or the development of AKI is simply a marker of those at higher risk for CKD. An ongoing matched cohort study sponsored by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) is focusing on individuals who survive 3 months after a hospitalization with or without AKI and is designed to try to address some of these remaining questions.

Furthermore, identifying renal recovery based on Scr concentration may be difficult because hospitalized patients are at risk for muscle mass loss, creatinine production can by decreased by inflammation, and Scr can by diluted by iatrogenic volume overload. This was demonstrated by Prowle et al, who found that Scr concentrations were lower on discharge than on admission in ICU patients without AKI. Using a model taking into account this decrease in Scr concentration, significantly more patients with AKI would have had continued decreased kidney function compared with estimates calculated from unadjusted discharge Scr concentrations.

Apart from CKD and death, there has been considerable interest in AKI as a risk factor for cardiovascular disease events. A recent meta-analysis showed that AKI was associated with a 58% increased risk for subsequent heart failure events and 40% increased risk for acute myocardial infarction. However, because most studies were conducted in patients with pre-existing cardiovascular disease, further research is needed to elucidate potential mechanisms by which AKI contributes to CVD. One potential mechanism is through hypertension. A recent study of more than 40,000 hospitalized adult patients *without* known hypertension showed that an episode of in-hospital AKI was strongly predictive of subsequent hypertension within 2 years (adjusted OR, 1.22; 95% CI, 1.12-1.33).

It is currently recommended that all patients who experience AKI have their kidney function re-evaluated 3 months after AKI to identify those with new/worsening CKD, which should be managed accordingly. Even those who return to their baseline kidney function should be considered at elevated risk for the development of CKD. At this time it is unclear whether any intervention or increase in monitoring would reduce the risk for poor outcomes in these patients.

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APPENDIX

Answer to Question 1: (d) Because his Scr concentration is increasing, none of the standard formulas should be used to estimate his kidney function.

Answer to Question 2: He is fluid overloaded, as shown by his markedly positive fluid balance and the presence of edema. At this point, additional fluid should be administered with caution because it will likely only exacerbate fluid overload. MAP is 75 mm Hg and therefore the addition of a vasopressor is not justified. Use of furosemide may increase urine output and decrease fluid overload; however, it probably would not change the overall clinical outcome. Thus, (d) is the best answer.

Answer to Question 3: (c) There is no evidence that CRRT has a special role in patients with sepsis-associated AKI. With regard to CRRT dose, 20 to 25 mL/kg/h has similar outcomes to higher doses of therapy. The major indication for RRT is the lack of renal recovery in association with significant fluid overload and progressive hypoxemia.

Answer to Question 4: (b) AKI is a risk factor for CKD progression and end-stage kidney disease, as well as cardiovascular events (see text for full discussion). It is unknown whether he will have further improvement in kidney function over time, but it seems unlikely because his Scr concentration is now stable.