

Acute Kidney Injury in the Critically Ill



Robert A. Maxwell, MD*, Christopher Michael Bell, MD

KEYWORDS

- Acute kidney injury • Acute tubular necrosis • Volume overload
- Indications for dialysis • Renal replacement therapy

KEY POINTS

- Acute kidney injury (AKI) occurs in up to 50% of postsurgical intensive care unit patients with reported mortalities from 15% to 80%, with more than 50% of cases being secondary to sepsis.
- Diuretics may be used to treat volume overload in patients with AKI but should not be given to treat or reverse AKI.
- All critically ill patients and patients with AKI should be considered at risk for contrast-induced nephropathy and should receive prophylaxis with volume loading and administration of *N*-acetyl cysteine.
- Initiating renal replacement therapy (RRT) early when AKI is detected remains controversial; however, current guidelines recommend the standard indications to initiate RRT, which are volume overload, azotemia, electrolyte abnormalities, and acidosis.

INTRODUCTION AND DEFINITION

Acute kidney injury (AKI) is an often overlooked and unappreciated disease process that carries significant morbidity and mortality in up to half of critically ill patients. Mortalities range from 15% to 80% and the associated morbidity leads to a high resource and financial burden. The term AKI is a generic reference to a variety of underlying disease processes that can either result in acute tubular necrosis (ATN) caused by renal ischemia or interstitial nephritis resulting in damage to the interstitium surrounding the renal tubule caused by deposition of immune complexes that lead to decreased renal function.¹ Historically there was not a consensus on the clinical definition of AKI, but in 2012 the Kidney Disease and Improving Global Outcomes (KDIGO) work group combined the definitions for

Disclosure: The authors have nothing to disclose.

Department of Surgery, University of Tennessee College of Medicine, Chattanooga, Chattanooga, TN, USA

* Corresponding author. 979 East Third Street, Suite B401, Chattanooga, TN 37403.

E-mail address: Robert.maxwell@erlanger.org

Surg Clin N Am 97 (2017) 1399–1418

<http://dx.doi.org/10.1016/j.suc.2017.07.004>

0039-6109/17/© 2017 Elsevier Inc. All rights reserved.

surgical.theclinics.com

AKI from the Acute Kidney Injury Network (AKIN) and the Risk Injury Failure Loss End Stage (RIFLE) system²⁻⁴:

- Increase in serum creatinine level by greater than or equal to 0.3 mg/dL ($\geq 26.5 \mu\text{mol/L}$) within 48 hours
- Increase in serum creatinine level to greater than or equal to 1.5 times baseline within the previous 7 days
- Urine volume less than or equal to 0.5 mL/kg/h for 6 hours

The RIFLE system was simplified to 3 clinical stages depicting the degree of renal injury (Table 1). The rationale for the staging system has evolved from a plethora of data showing that the risk of death and need for renal replacement therapy (RRT) depend on quantitative changes in urine output and creatinine level.⁴ Throughout this article, wherever the KDIGO work group has defined level of evidence for a recommendation in its guidelines, the grade is included parenthetically based on the Grading of Recommendations Assessment, Development and Evaluation guidelines for evaluating the quality of scientific publications⁵ (Table 2).

Although creatinine level and urine output are the most readily available ways to assess renal function, several limitations need to be appreciated in clinical practice. Patients with sepsis, liver failure, or sarcopenia may have reduced creatinine production, which may result in falsely increased calculations of glomerular filtration rate (GFR).⁶⁻⁸ Major increases in protein catabolism associated with large burns, rhabdomyolysis, or major trauma can lead to increased creatinine production, which can falsely decrease GFR calculations.^{6,9} Creatinine is equally distributed throughout all fluid compartments so its concentration varies according to total body water. Therefore, using creatinine as the determinant of renal function in acute volume overload can lead to delays in the recognition of AKI until new steady states are reached.¹⁰ In an intensive care unit (ICU) population, Liu and colleagues¹¹ showed that a simple formula:

Corrected creatinine = serum creatinine $\times$ (1 + current total body water/baseline total body water)

where total body water = 60% $\times$ patient's weight could correct for changes in fluid balance and that many patients with normal serum creatinine levels met the definition of AKI when creatinine level was corrected for the volume of distribution. The patients with corrected creatinine levels who went from normal to meeting the definition for AKI after correction had significantly higher mortality than those patients who did not have significant changes in their corrected serum creatinine levels (31% mortality vs 12%, $P<.001$).¹¹

Urine output alone can be a poor predictor of AKI. Some patients maintain adequate urine output up to the point of anuria and some patients are oliguric secondary to

Table 1 Kidney Disease and Improving Global Outcomes acute kidney injury guidelines		
Stage	Serum Creatinine	Urine Output
1	1.5–1.9 times baseline or >0.3 mg/dL increase	<0.5 mL/kg/h for 6–12 h
2	2.0–2.9 times baseline	<0.5 mL/kg/h for >12 h
3	3 times baseline or >4.0 mg/dL or initiation of RRT or in patients <18 y old a decrease in eGFR <35 mL/min/1.73 m ²	<0.3 mL/kg/h for >24 h or anuria >12 h

Abbreviation: eGFR, estimated glomerular filtration rate.

Table 2
Levels of evidence

Grade	Implications	
Level 1: recommended	• Most patients should receive the recommended course of action • The recommendation can be evaluated as a candidate for developing a policy or a performance measure	
Level 2: suggested	• Different choices are appropriate for different patients. Each patient needs help to arrive at a management decision consistent with clinicians' values and preferences	
Grade	Quality of Evidence	Meaning
A	High	Further research is very unlikely to change clinicians' confidence in the estimate of effect • Several high-quality studies with consistent results • In special cases: 1 large, high-quality multicenter trial
B	Moderate	Further research is likely to have an important impact on confidence in the estimate of effect and may change the estimate • One high-quality study • Several studies with some limitations
C	Low	Further research is very likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate • One or more studies with severe limitations
D	Very low	Any estimate of effect is very uncertain • Expert opinion • No direct research evidence • One or more studies with very severe limitations

Data from Grade Working Group. Available from: <http://www.gradeworkinggroup.org/>. Accessed February 13, 2017.

hypovolemia, response to general anesthetic, and stress of trauma but do not have sustained AKI.^{12–15} Ralib and colleagues¹⁶ showed that AKI and increased mortality can be predicted by oliguria for just 6 hours and not the 12-hour period stated in the present KDIGO guidelines. Prowle and colleagues¹⁵ found that oliguria occurred frequently in critically ill patients but only 10% went on to develop AKI, whereas hemodynamic instability and increased vasopressor use was a significant risk factor. In addition, the European Renal Best Practices Work Group recommends using ideal body weight in determining weight-based urine output, thus potentially reducing the overdiagnosis of AKI and unnecessary fluid administration.¹ Diagnosis of AKI is therefore subject to the interpretation of multiple patient-specific conditions and, despite certain limitations, creatinine and urine output are the best clinical markers at this time for monitoring renal function.¹³

CAUSES AND CAUSE OF ACUTE KIDNEY INJURY

Critically ill patients with AKI may have several causative factors that should all be determined by starting with a careful review of the history, medical record, and physical examination. Sepsis, major surgery (particularly coronary artery bypass surgery), and uncompensated heart failure are the most common causes of AKI in the ICU, with sepsis accounting for more than 50% of cases. Trauma, hemorrhagic pancreatitis, and hypovolemia are other causes (Table 3).^{17,18} Another frequent contributing cause

Table 3 Causes of acute kidney injury in surgical intensive care units	
Major Causes	Contributing Factors
Sepsis	CIN
Postoperative (CABG, major vascular)	CKD
Trauma	Nephrotoxic drugs
Hemorrhage	CHF
Pancreatitis	Liver disease
Cardiorenal syndrome	Cancer
	Blood transfusion
	Volume overload
	Diabetes mellitus

Abbreviations: CABG, coronary artery bypass graft; CHF, congestive heart failure; CIN, contrast-induced nephropathy; CKD, chronic kidney disease.

is exposure to nephrotoxic drugs and intravenous contrast dye. A list of possible causes and potentiating factors should be identified and corrective actions undertaken in a timely fashion.

Drugs are the primary or associated cause of AKI in up to 25% of ICU patients and can affect the kidney in all phases of urine production.¹⁹ Twenty-two percent of the top 100 drugs used in an adult ICU at a tertiary care center were considered potentially nephrotoxic.²⁰ Intensivists should be aware of these potential risks and have a good understanding of the nephrotoxic drugs (Table 4). Current and past medication lists should be reviewed and any potentially nephrotoxic drugs should be replaced or

Table 4 Common nephrotoxic medications	
Drug Classification	Nephrotoxicity Risk
Prerenal Failure	
Diuretics	Excessive diuresis depletes extracellular volume
Antihypertensive peripheral vasodilators	Decreases systemic vascular resistance
NSAIDs, COX-2 inhibitors, anesthetics	Increased renal vascular resistance
ACE inhibitor, ARB	Decreases transcapillary pressure
Renal Failure	
Amphotericin B, iodinated contrast agents, antiretrovirals, cocaine	ATN
Antibiotics (penicillins, vancomycin, ciprofloxacin, macrolides, sulfonamides) NSAIDs, omeprazole, phenytoin, cimetidine, ranitidine, diuretics	Acute interstitial nephritis
NSAIDs, ampicillin, lithium, hydralazine, heroin	Acute glomerulonephritis
Postrenal Failure	
Acyclovir, methotrexate, sulfonamides, triamterene, ephedrine	Tubular precipitation
Anticholinergics	Bladder obstruction

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; COX-2, cyclooxygenase-2; NSAID, nonsteroidal antiinflammatory drug.

eliminated. The comorbidities that most notably increase the risk for drug-induced nephrotoxicity are chronic kidney disease (CKD), cirrhosis and liver failure, acute or chronic left heart failure, pulmonary artery hypertension with/without right heart failure, and malignancy. In addition, several major surgical procedures, such as cardiac surgery, aortic surgery, and major intra-abdominal surgery, enhance the risk of nephrotoxic drugs as well as the risk of AKI.²¹

On a microvascular level the basic underlying mechanism causing renal ischemia, cellular injury, and ATN is similar regardless of the type of precipitating event. Impaired renal blood flow secondary to hypotension, shock, and loss of autoregulation within the nephron causes imbalances in oxygen delivery, nutrient delivery, and metabolic demand, particularly within the renal tubule. The outer renal medulla maintains a low oxygen tension under normal physiologic conditions because of the countercurrent exchange mechanism that occurs as part of normal tubular resorptive function. This normally low oxygen tension in the outer renal medulla makes this area at highest risk to ischemic injury.²² Hypoxic injury leads to structural damage to tubular cells, which subsequently forms casts that obstruct tubules and cause back-leak of filtrate.^{22,23} Edema formation can further contribute to reduced blood flow and diffusion, further complicating the situation.

WORK-UP

The work-up of AKI in most patients should include serum and urine chemistries, urinalysis, and possibly renal ultrasonography. Urinalysis can be helpful in finding treatable causes such as interstitial nephritis (eosinophilia), pyelonephritis (pyuria and nitrites), and glomerulonephritis (hematuria and proteinuria).²⁴ In post-cardiac surgical patients a simple urine dipstick test positive for protein can be a predictor of postoperative AKI.²⁵ Urine microscopy can differentiate ATN from the presence of renal tubular cells or granular casts versus the presence of epithelial cells, which may indicate a normal finding.²⁶ A moderate or large number of epithelial cells could indicate infection, inflammation, or malignancy. Increased number of epithelial cells may prompt a cytologic analysis by the laboratory (Table 5).

Table 5 Urine microscopy findings and associated diagnosis	
Microscopic Finding	Significance
Epithelial cells	Small amount: normal Moderate to large amount: consider cytologic analysis
Renal tubular cells	ATN
Granular casts	ATN, significant renal disease
Dysmorphic RBCs	Glomerular disease
Nondysmorphic RBCs	Nonglomerular bleeding from anywhere in urinary tract system
Red cell casts	Glomerular disease
Leukocytes	Inflammation of urinary tract
White cell casts	Renal infection
Hyaline casts	Any renal disease
Muddy brown casts	Necrotic tubular cells indicating ATN
Bacteria	Urinary tract infection

Abbreviation: RBC, red blood cells.

Historically, evaluation of patients with AKI includes determining potential prerenal, renal, and postrenal causes. A prerenal state indicates decreased preload and that fluid resuscitation is necessary. An important distinction emerges between prerenal AKI, which implies that the creatinine level will normalize within 72 hours after appropriate hydration and stabilization compared with those patients who develop sustained evidence of renal injury, known as intrinsic AKI (creatinine level increase after 72 hours).^{27–31} Clinically, patients with fractional excretion of sodium (FE_{Na}) less than 1% have been classified as having prerenal AKI, implying that they have preserved the ability to resorb sodium from the tubule and should recover if further insult is avoided (**Table 6**).³²

However, patients with prerenal AKI do have evidence of parenchymal injury, shown by increased levels of serum biomarkers of renal injury (**Table 7**). Patients with increased creatinine levels and prerenal AKI ($FE_{Na}<1\%$) are considered part of a continuum of AKI and do not just have a hydration deficit.³³ Judicious fluid replacement in this setting is essential to improving patient outcomes. Overly aggressive fluid resuscitation leads to increased morbidity, ICU length of stay, and mortality.^{11,34} In light of concerns over the definition of prerenal and intrinsic AKI, the Acute Dialysis Quality Initiative (ADQI) work group has proposed that a new classification scheme be used to differentiate between functional AKI and kidney damage in lieu of prerenal, intrinsic, and postrenal states based on increased levels of certain renal injury biomarkers.³⁵ However, until these biomarkers become readily available laboratory tests, they have little practical clinical utility.

FE_{Na} and fractional excretion of urea (FE_{Urea}) can both be helpful in evaluating renal function. During volume contraction, normal functioning kidneys concentrate the urine, resulting in an increase of urine osmoles and decreased urine sodium and urea levels. The end result is an FE_{Na} of less than 1% or FE_{Urea} less than 35% as the body attempts to conserve water. A FE_{Na} greater than 1% or FE_{Urea} greater than 35% indicates renal tubular injury and ATN.^{36–38} When evaluating a patient who has recently received loop diuretics (eg, furosemide), the FE_{Na} may be falsely increased by more than 1%, despite the volume status. The interpretation of FE_{Na} is erroneous under these conditions because furosemide is a natriuretic, blocking resorption of sodium in the ascending loop of Henle. However, loop diuretics do not affect urea excretion in the tubule so FE_{Urea} can therefore be substituted for FE_{Na} .³⁶ FE_{Na} or FE_{Urea} is a good starting point in the differentiation of prerenal AKI from intrinsic AKI and their values can be factored into the global assessment (see **Table 6**). However, taken independently, neither has proved to be a reliable indicator of volume status or fluid responsiveness. As such, additional determinations of volume status by means other than fractional excretion, such as echocardiography or pulmonary artery catheter, are necessary in critically ill patients with AKI.^{39,40}

Table 6 Diagnostic thresholds for acute kidney injury			
	Prerenal	Intrinsic	Postrenal
FE_{Na} (%)	<1	>1	>4
U_{Na} (mmol/L)	<20	>40	>40
FE_{Urea}	<35%	>50%	N/A

Abbreviations: FE_{Urea} , fractionated excretion of urea; U_{Na} , urine sodium level.

Table 7
Comparison of the most common biomarkers of acute kidney injury diagnosis

Biomarker	Site of Injury	Disadvantage	Benefits
NGAL	Tubular Injury	Upregulated in sepsis 3 different types	Well studied
CyC	GFR/tubular Injury	No specific reference range	Not affected by age, gender, muscle mass, or diet
IL-18	Tubular injury	Upregulated in sepsis	Stronger predictor in patients with baseline eGFR <60 mL/min/1.73 m ² Better in children and adolescents
TIMP-2/IGFBP7	Cell cycle arrest		Strong negative predictive value

Abbreviations: CyC, cystatin C; IGFBP7, insulinlike growth factor binding protein 7; NGAL, neutrophil gelatinase-associated lipocalin; TIMP-2, tissue inhibitor of metalloproteinases-2.

$$FE_{Na}\% = 100 \times (\text{Serum}_{Cr} \times \text{Urine}_{Na}) / (\text{Serum}_{Na} \times \text{Urine}_{Cr})$$

$$FE_{Urea}\% = 100 \times (\text{Serum}_{Cr} \times \text{Urine}_{Urea}) / (\text{Serum}_{Urea} \times \text{Urine}_{Cr})$$

In addition, the urine osmolality can be useful if differentiating prerenal disease from ATN. In ATN the kidney loses its ability to concentrate urine, resulting in urine osmolalities less than 350 mOsmol/kg. In a prerenal disease, hypovolemia stimulates anti-diuretic hormone secretion and the resulting urine osmolality is usually more than 500 mOsmol/kg.⁴¹ However, lower values similar to those in ATN may be seen in prerenal disease and are interpreted with caution, especially in the setting of glycosuria, metabolic alkalosis, bicarbonaturia, salt-wasting disorders, or CKD.⁴²

Postrenal causes of AKI can be further evaluated with bladder ultrasonography to exclude the simple possibility of urinary retention, bladder outlet obstruction, and neurogenic bladder. A formal renal ultrasonography scan may be useful when there is ureteral obstruction from malignancy or bladder outlet abnormalities, or when the history reveals postsurgical exploration of the retroperitoneum or pelvis.⁴³ If there is no clinical suspicion of ureteral obstruction, a formal renal ultrasonography scan is likely to be a low-yield study.⁴⁴ Intensivist-performed Doppler studies may have a place in determining renal perfusion in the ICU, but until further parameters are developed the role of clinician-driven bedside ultrasonography has yet to be defined.⁴⁵

BIOMARKERS IN ACUTE KIDNEY INJURY

Translational research focusing on biomarkers of kidney injury, such as neutrophil gelatinase-associated lipocalin (NGAL), cystatin C (CyC), interleukin-18 (IL-18), tissue inhibitor of metalloproteinases-2 (TIMP-2), and insulinlike growth factor binding protein 7 (IGFBP7), have shown promise in screening for AKI before creatinine level increases, determining the degree of renal injury and the location of injury within the nephron (glomerulus vs tubule) (see [Table 7](#)). NGAL is a lipocalin protein that is covalently bound to gelatinase from neutrophils and immediately following AKI NGAL is massively upregulated in the distal part of the nephron, specifically the thick ascending limb of Henle loop, distal tubule, and collecting duct. This process leads to increased urinary and plasma NGAL levels.^{46,47} A meta-analysis conducted in 2009 by Haase and colleagues⁴⁸ showed plasma NGAL/urine NGAL and urine

NGAL alone to be predictors of the severity of AKI, need for RRT, and mortality. In cardiac surgery patients, levels of plasma NGAL and IL-18 correlated with progression of AKI.⁴⁹ IL-18 is a cytokine that induces interferon gamma and T-cell activation, and has been shown to be a reliable marker of ATN.^{50,51} In a meta-analysis, urinary IL-18 was found to be a useful biomarker of AKI in cardiac surgery patients, ICU patients, and pediatric patients.⁵² CyC is an unbound protein produced by all nucleated cells that is filtered greater than 99% by the glomeruli.⁵³ In contrast with serum creatinine, it is not affected by age, gender, diet, or muscle mass.⁵⁴ Serum CyC has been shown to be a good biomarker in the prediction of AKI, whereas urinary CyC excretion has only moderate diagnostic value. Patients with serum CyC levels less than 0.8 mg/L are less likely to develop AKI after renal insult, whereas those with levels greater than 2.04 mg/L are at increased risk of developing AKI. Patients with high CyC levels can be targeted for early intervention.⁵⁵ Urine TIMP/IGFBP7 are biomarkers expressed in the very early phase of renal tubular epithelial cell damage.⁵⁶ Meersch and colleagues⁵⁷ showed that urine TIMP/IGFBP7 levels in post-cardiac bypass surgery patients were increased 4 hours postoperatively in patients who went on to develop AKI. A significant decrease in the urinary TIMP/IGFBP7 level predicted recovery of renal function. At present AKI biomarkers are not commercially available and therefore their use in everyday clinical practice is not common. As technology improves the availability of assays, the use of biomarkers is likely to become relevant in the treatment of patients with AKI.

Chawla and colleagues⁵⁸ reported the use of a furosemide stress test (FST) as an alternative to serum biomarkers in the assessment of moderate to severe AKI. Following a dose of 1 to 1.5 mg/kg of furosemide, less than 200 mL over 2 hours indicated progression to severe AKI and need for RRT.⁵⁸ FST outperformed NGAL, IL-18, and TIMP-2/IGFBP7 in identifying patients with severe AKI and need for RRT, showing the utility of this simple test in the assessment of AKI.⁵⁹

Flechet and colleagues⁶⁰ reported on an online prognostic calculator (AKIPredictor.com) that uses demographics, comorbidities, and baseline and laboratory values 24 hours after ICU admission to compute the likelihood of AKI.⁶⁰

PREVENTION OF ACUTE KIDNEY INJURY

Early recognition and prevention of further injury are the initial goals in management of AKI by restoring renal perfusion and hemodynamic stability. Treatment of intravascular hypovolemia when present is of primary importance and selection of the most appropriate resuscitation fluid (crystalloid vs colloid)⁶¹ is critical when blood products are not indicated. Synthetic colloids (hydroxyethyl starch [HES], gelatin, and dextran) are associated with an increased incidence of AKI and should be avoided in patients at risk or who already have AKI.^{62–64} With regard to allogenic albumin, the SAFE trial found no differences in 28-day mortality, new organ dysfunction, incidence of AKI, duration of dialysis, or other secondary end points when comparing normal saline with 4% albumin in a heterogeneous ICU population.⁶⁵ However, in a subgroup analysis of patients with traumatic brain injury, albumin was associated with increased mortality, whereas in a subgroup analysis of patients with severe sepsis improved survival was shown in those receiving albumin.^{66,67} After considering these findings, KDIGO clinical practice guidelines for AKI recommend that isotonic crystalloids should be used ahead of synthetic and nonsynthetic colloids for intracellular volume expansion in patients at risk for or presenting with AKI (level 2B).⁴

Contrast-induced nephropathy (CIN), defined as a 25% increase in creatinine level within 3 days of intravascular administration of iodinated contrast media, affects

between 7% and 11% of patients undergoing intravenous contrast administration. All critically ill patients should be considered at risk for CIN and preventive measures undertaken with volume expansion (level 1A), use of iso-osmotic contrast (level 1B), and avoidance of large volumes of dye. Sodium bicarbonate's ability to prevent free radical production by alkalization of the renal tubule has not shown benefit compared with normal saline alone in multiple clinical trials but can be used for volume expansion with results equivalent to normal saline expected.^{4,67,68} Oral *N*-acetylcysteine has shown some added benefit compared with saline alone and can be added with low cost and minimal pharmacologic risk (level 2D). Data on the use of statins to prevent CIN are still too preliminary to make recommendations at present (not graded).^{4,19}

TREATMENT OF ACUTE KIDNEY INJURY

After the causes of AKI have been determined, treated, or removed, the treatment of AKI becomes largely supportive, with the intention of allowing the recovery of renal function. Oliguria and anuria are prevalent in patients with AKI, particularly after surgery and trauma, and controlling volume status becomes an important element of supportive care. In addition to decreased urine output, shock and capillary leak frequently lead to volume overload, which in turn increases morbidity, length of stay, and mortality.^{69–71} The front-line treatment of volume overload is diuretics when all sepsis has been adequately treated and patients are resuscitated and hemodynamically stable.^{4,72} (grade 2C). Loop diuretics such as furosemide or bumetanide may stimulate urine output and shift fluid balance in a favorable direction but diuretics do not reduce mortality or need for RRT.^{23,73} Several meta-analyses have shown no benefit in mortality or need for RRT when diuretics were given to patients with AKI in an attempt to convert oliguric AKI (<500 mL urine output per day) to nonoliguric (>500 mL urine output per day) AKI across multiple populations of ICU patients.^{23,28,62,63} Furthermore, diuretics have been shown to increase the incidence of AKI in patients receiving intravenous contrast dye and also increase the risk of AKI and need for RRT in cardiac surgery patients.^{23,64,65} In addition, the European Society of Critical Care Medicine and KDIGO recommend that diuretics should not be given to prevent or treat AKI or force return of renal function (level 1B).

MANAGEMENT OF ELECTROLYTE ABNORMALITIES

Hyperkalemia can occur rapidly in patients with AKI and may result in life-threatening complications. Patients with rhabdomyolysis, crush injury, and shock reperfusion syndrome are at greatest risk. Symptoms related to hyperkalemia occur when potassium levels increase to more than 7 mmol/L, which leads to cardiac and neuromuscular transmission abnormalities, but lower levels can trigger these manifestations in the acute setting. Typical signs of hyperkalemia are severe muscle weakness and peaked T waves and shortened QT interval on cardiac rhythm strips. Electrocardiogram (ECG) manifestations are more likely with rapid-onset hyperkalemia and the presence of concomitant hypocalcemia, acidemia, and hyponatremia. A review of medications should be done to identify drug causes of hyperkalemia (β -blockers, inhibitors of the renin-angiotensin-aldosterone system, potassium-sparing diuretics, heparin and its derivatives, trimethoprim, and nonsteroidal antiinflammatory drugs).^{74,75} Severe abnormalities are best treated with RRT; however, issues with timing of initiation of treatment may prompt urgent medical treatment before RRT is started. Regardless of the potassium level, treatment should be initiated on any ECG changes or neuromuscular complications. Treatment should be focused on stabilizing the cellular membranes affected by the hyperkalemia, driving extracellular potassium intracellularly

and hiding the potassium, and removing excess from the body when possible. Stabilization of the membrane is achieved with intravenous calcium gluconate or calcium chloride. To hide the potassium intracellularly, a combination of insulin and glucose are given.⁷⁶ The authors recommend a bolus of 10 units of insulin followed by 5 mL of 50% dextrose, which can reduce the potassium level by 0.5 to 1.2 mmol/L for approximately 4 to 6 hours and it can be repeated every 2 to 4 hours if awaiting RRT initiation.⁷⁷ Sodium bicarbonate works by increasing the systemic pH, triggering a release of hydrogen ions from cells and causing an influx of potassium into the cell. There are limited data on the value of sodium bicarbonate as a treatment of hyperkalemia but a few studies show that continuous infusion of sodium bicarbonate can reduce hyperkalemia in patients with a baseline metabolic acidosis in 4 to 6 hours.^{76,78}

In AKI, profound metabolic acidosis results from impaired acid secretion and reduced bicarbonate production in the renal tubule. Acidosis is further propagated by increased production of lactic acid and ketoacids in the critically ill. Severe acidemia suppresses myocardial contractility, predisposes to cardiac arrhythmias, causes venous vasoconstriction while decreasing total peripheral vascular resistance, reduces hepatic blood flow, and impairs oxygen delivery. Treatment with boluses of hypertonic (8.4%) sodium bicarbonate can worsen intracellular acidosis (deceiving clinicians through improving blood pH [paradoxic acidosis]) and lead to hyponatremia and extravasation injury if not delivered into a central vein.⁷⁹ Furthermore, in patients who are oliguric/anuric and have volume overload, the large sodium load can exacerbate the volume overload. Sodium bicarbonate treatment should be reserved for severe acidosis (pH<7.1) while awaiting dialysis in patients in whom the cause of AKI is prerenal AKI caused by volume depletion, or a postrenal obstruction. In addition, bicarbonate can be used affectively in patients with AKI caused by rhabdomyolysis in order to prevent further renal injury.⁸⁰

Monitoring of calcium levels is essential in AKI. When GFR declines phosphate excretion decreases, leading to an increase of serum phosphate level and a decline in free serum calcium level. Calcium replacement in symptomatic patients is extremely important until the underlying cause is addressed. Symptoms can include paresthesias, tetany, confusion, seizures, or QT prolongation. Treating the underlying hyperphosphatemia alleviates the hypocalcemic symptoms in many cases.^{81,82} In the critically ill this is best done with RRT.

RENAL REPLACEMENT THERAPY

If volume overload, electrolyte abnormalities, acid-base status, or azotemia complicate patient care, RRT becomes the mainstay of treatment. Approximately 13% of all ICU admissions require RRT⁸³ and this need is an independent risk factor for mortality.⁸⁴ Specific evidence-based indications for initiating RRT have not been published because of the diversity and complexity of the disease process. The KDIGO guidelines recommend following the global picture considering trends in electrolytes, azotemia, acid-base status, and degree of volume overload. The use of absolute numbers to trigger initiation of therapy is also discouraged per KDIGO guidelines.⁴

Volume overload is perhaps the most nebulous indication for RRT. Oliguria or anuria greater than 72 hours, total body weight 10% more than admission weight, and pulmonary edema causing hypoxia in the presence of AKI have been cited as indications for RRT. Azotemia with blood urea nitrogen (BUN) levels greater than 80 to 100 mg/dL begins to interfere with wound healing and causes a decrease in the level of consciousness. Potassium levels greater than 6 mmol/L and pH less than 7.15 are generally accepted thresholds for RRT.

With regard to potential benefits to early initiation of RRT, the Artificial Kidney Initiation in Kidney Injury (AKIKI) study group in 2016 evaluated initiation of early continuous RRT (CRRT) in a prospective, multicenter, open-label, randomized trial conducted in 31 intensive care units in France. The goal of the study was to see whether early initiation of RRT improved outcomes. Patients were randomized to an early group (within 6 hours of diagnosis of stage 3 AKI) or to a delayed group that met the set of standard indications for RRT listed in [Table 8](#).

There was no difference in mortality between the early and delayed groups. Almost half of the patients in the delayed group never required RRT, had a significantly lower rate of catheter-related blood stream infections (10% vs 5%; $P = .03$), and had earlier spontaneous diuresis ($P < .001$).⁸⁵ Two different meta-analyses by Wierstra and colleagues⁸⁶ and Bhatt and Das⁸⁷ found no improvement in survival for early initiation of RRT. However, in a single-center randomized control trial, Zarbock and colleagues⁸⁸ found that even earlier initiation of RRT (within 8 hours of diagnosis of stage 2) resulted in more patients with recovered renal function at 90 days versus late initiation (within 12 hours of diagnosis of stage 3; 53.6% vs 38.7%) and significantly reduced 90-day mortality (39.3% and 54.7%). The patients in the Zarbock and colleagues⁸⁸ study were started on RRT earlier than the AKIKI group with improved outcomes suggesting that very early initiation (stage 2) of RRT may be beneficial. Further research regarding timing of RRT is necessary to resolve the question about benefits of early initiation.

Intermittent hemodialysis (IHD) is the mainstay of RRT therapy in the United States in hemodynamically stable patients. IHD is performed every day or every other day depending on severity of illness and rapidly removes solutes across a semipermeable membrane using a transmembrane concentration gradient.⁸⁹ Because of rapid fluid shifts over a short course of therapy, IHD is limited by intravascular depletion and hypotension, which is detrimental to the recovery of AKI. Schiffl and colleagues⁹⁰ evaluated the outcomes of different dosing schedules of IHD in 160 ICU patients with AKI. Patients were randomized to receive daily or alternate-day IHD. Daily hemodialysis resulted in less hypotension, sepsis, gastrointestinal bleeding, and respiratory failure, and a significant decrease in mortality.⁹⁰

Hybrid modality such as slow low-efficiency dialysis (SLED) is performed over an 8-hour to 12-hour time period with lower dialysate flow rates than IHD. The benefit of SLED is the ability to use standard IHD machines, excellent solute clearance, and little impact on hemodynamic stability. A recent meta-analysis showed that renal recovery, days to renal recovery, number of treatments required for each dialysis modality, and hemodynamic instability were not significantly different between the CRRT

Table 8

Artificial Kidney Initiation in Kidney Injury study group requirements for initiation of continuous renal replacement therapy

Indications for Initiation of RRT	
Oliguria/Anuria	Sustained for >72 h
BUN Level (mg/dL)	>80–100
Potassium level (mmol/L)	>6
pH	<7.15
Volume Overload	Pulmonary edema with increased FiO_2 requirements >10% body weight

Abbreviation: FiO_2 , fraction of inspired oxygen.

and SLED treatment groups.⁹¹ The disadvantages of SLED are lack of availability of dialysis support staff for extended time on hemodialysis and lack of familiarity within the critical care community.

Hemodynamically unstable patients may not tolerate the rapid volume shifts seen with IHD. CRRT was developed for critically ill patients in shock or with otherwise tenuous hemodynamic status. CRRT is performed 24 hours a day, typically 7 days a week. Several modalities can be deployed on a CRRT machine depending on specific patient needs.

The simplest modality is slow continuous ultrafiltration (SCUF), in which blood is pumped through a semipermeable membrane causing plasma (ultrafiltrate) to be removed or ultrafiltered from the blood (Fig. 1). This modality is useful in patients who are volume overloaded with normal electrolytes and BUN, but fail to respond to diuretics.

Continuous venovenous hemofiltration (CVVH) is a CRRT modality in which a replacement fluid is added to the blood in the dialysis circuit. As this additional volume of fluid passes through the filter, solute is “pulled” with the ultrafiltrate, known as solute drag. The transportation of additional solute across the dialysis membrane by dilution of the blood with replacement fluid is known as convection (Fig. 2). The molecules removed with convection can be bigger than those removed by hemodialysis, which makes this modality potentially useful in patients with myoglobinuria or drug intoxication. Continuous venovenous hemodialysis (CVVHD) does not require a replacement fluid but uses a dialysis solution (dialysate) that is pumped countercurrent to the blood flow on the fluid side (as opposed to the blood side) of the membrane, creating a concentration gradient that allows solute exchange by diffusion (Fig. 3). CVVHD is useful in small molecule removal with solutes such as electrolytes and urea.

Another CRRT modality is continuous venovenous hemodiafiltration (CVVHDF), in which dialysate and replacement fluid are both added to their respective

SCUF

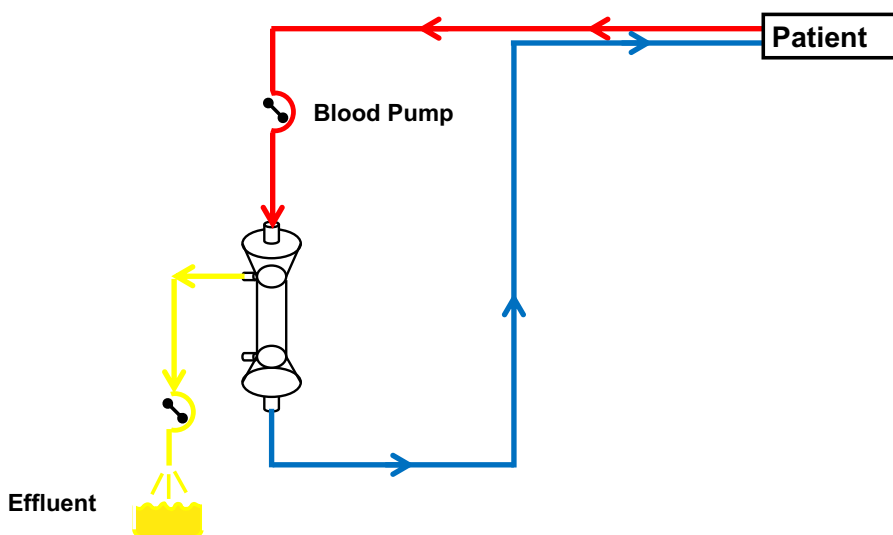


Fig. 1. SCUF, showing ultrafiltration via transmembrane pressure gradient.

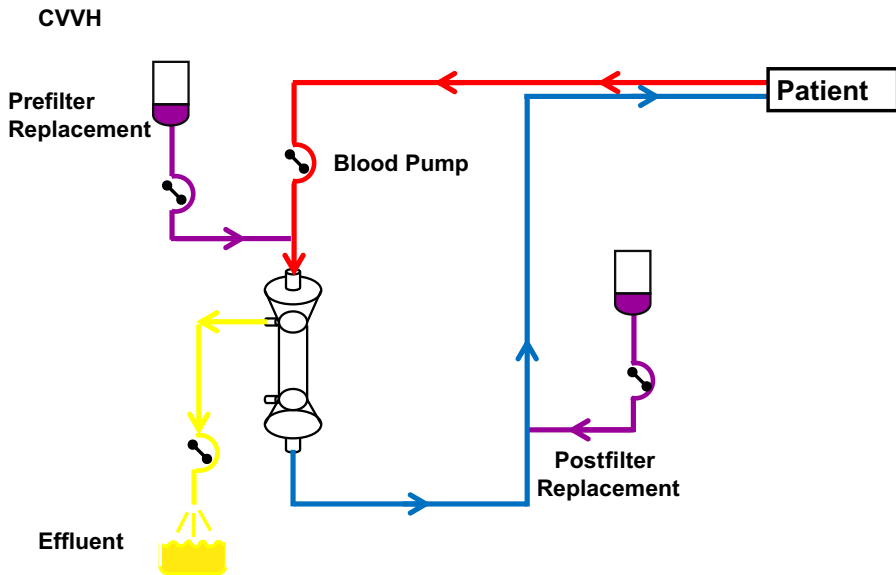


Fig. 2. CVVH using convection via replacement fluid either prefilter or postfilter.

compartments of the circuit, generating solute removal by both diffusion and convection. Fluid removal is achieved by ultrafiltration (Fig. 4).⁹² The type of modality chosen depends on the individual patient's needs. SCUF is useful in patients with volume overload and relatively normal electrolytes and BUN that do not respond well to diuretics. When patients have electrolyte abnormalities and azotemia, CVVHDF is often the most efficient CRRT modality and is frequently used in most other cases. In a

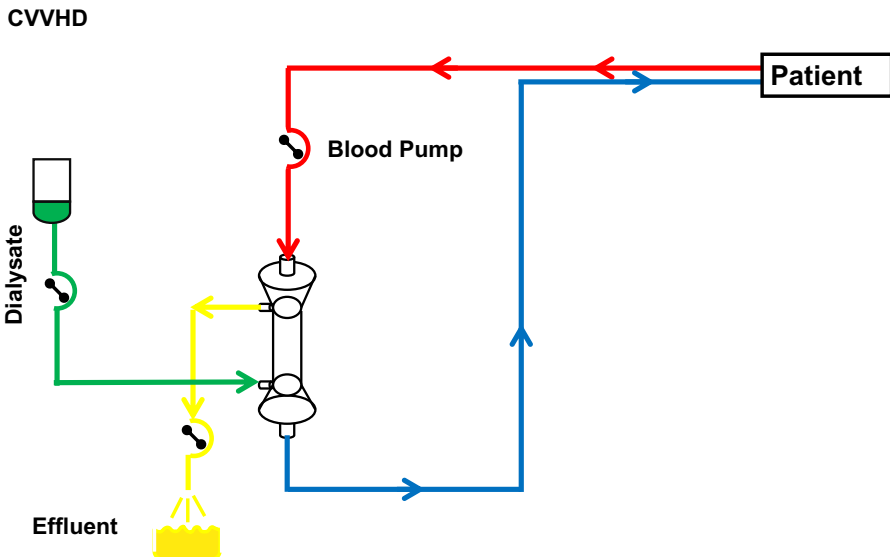


Fig. 3. CVVHD showing the diffusion of small solutes via the countercurrent of the dialysate.

CVVHDF

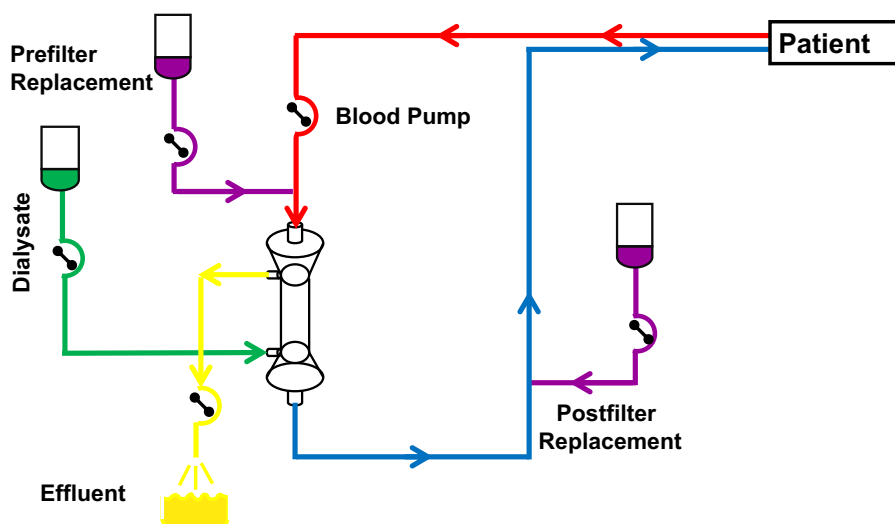


Fig. 4. CVVHDF combining components of ultrafiltration, hemodialysis, and convection.

single-center prospective randomized trial, Saudan and colleagues⁹³ compared CVVH and CVVHDF and showed decreased mortality with CVVHDF. However, no other prospective data have been reported regarding the optimal modality.⁹³

The dose of CRRT is defined as the total volume of replacement fluid and dialysate given plus ultrafiltrate removed from the patient averaged per weight in kilograms per hour. A Cochrane Review completed in 2016 included 6 large studies with 3185 patients comparing a CRRT dose of less than 35 mL/kg/h versus greater than 35 mL/kg/h. There was no difference in mortality, recovery of renal function, or ICU days. There was higher incidence of hypophosphatemia with increased dose.⁹⁴ KDIGO recommends an average 24-hour dose of effluent volume in the range of 20 to 25 mL/kg/h when considering time off modality for filter changes, operating room procedures, and radiologic procedures (grade 1A).

To prevent clot formation within the filter of circuit, 3 options with regard to anticoagulation are available: heparin, regional citrate, or no anticoagulation. Systemic heparinization is easy to monitor and prevents filter thrombosis at the risk of bleeding complications. Regional citrate works by anticoagulating the circuit with an infusion of citrate, and by placing patients on a systemic calcium infusion to replace the calcium once the filtered blood is returned to the patient, which reduces risk of bleeding. Citrate is metabolized mainly in the liver, skeletal muscle, and renal cortex, making patients with acute liver injury/failure at high risk for hypocalcemia because they may not metabolize citrate normally. When compared in a multicenter randomized control trial there was no difference in renal outcomes and mortality between citrate and heparin. However, citrate was superior in safety, efficacy, and cost⁹⁵ (grade 2B). No anticoagulation may be an option for patients with liver or bone marrow failure who may already be coagulopathic.

Because renal recovery occurs over weeks to months, timing of cessation of RRT can be a nebulous end point. Return of native urine output is generally a good sign but recovering renal tubules may lack normal function and the ability to concentrate

urine. Because of antidiuretic hormone unresponsiveness of the distal tubule and collecting system, patients recovering from AKI can develop high-output renal failure and be at risk for dehydration. Volume status needs careful monitoring and excessive urine losses may require scheduled intravenous crystalloid replacement. Uchino and colleagues,³⁴ in a post hoc analysis of a multicenter prospective observational study, found that patients with urine output greater than 400 mL/d with no diuretics and greater than 2300 mL/d with diuretics had an 80% chance of successful discontinuation of CRRT. In contrast, preadmission CKD was a strong negative predictor (odds ratio, 0.54) for unsuccessful cessation.³⁴ In a single-center retrospective study, Frohlich⁹⁶ reviewed patients who had a 2-hour creatinine clearance (2h-CrCl) drawn within 12 hours of cessation as a predictor of successful discontinuation. A 2h-CrCl of 23 mL/min had a sensitivity and specificity of 75.5% and 84.4% respectively and an overall accuracy of 78.8%. CrCl is useful because it is unaffected by use of diuretic therapy, hypotension, or oliguria.⁹⁷ In both studies a lower serum creatinine level was marginally predictive of success.

SUMMARY

AKI encompasses a wide variety of disease processes and is a common but serious problem in surgical patients. Ever-present awareness of the causes, preventive strategies, work-up, and treatment is vital to the management of critically ill surgical patients. ATN precipitated by some type of shock is the most common cause of AKI and rapid correction of the source and restoration of volume status are of paramount importance in the management of patients at risk. When AKI has led to sufficient electrolyte, acid-base, or fluid abnormalities, some form of RRT is necessary. Hemodynamically stable patients can be managed with daily IHD, whereas patients on vasopressors are likely to benefit from CRRT with care taken to provide appropriate anticoagulation and dose. Recovery from AKI may be slow, taking weeks to months, with death and end-stage renal disease being the undesired outcomes.

REFERENCES

1. Ad-hoc working group of ERBP, Fliser D, Laville M, Covic A, et al. A European Renal Best Practice (ERBP) position statement on the Kidney Disease Improving Global Outcomes (KDIGO) clinical practice guidelines on acute kidney injury: part 1: definitions, conservative management and contrast-induced nephropathy. *Nephrol Dial Transplant* 2012;27(12):4263–72.
2. Eriksson M, Brattström O, Mårtensson J, et al. Acute kidney injury following severe trauma: risk factors and long-term outcome. *J Trauma Acute Care Surg* 2015;79(3):407–12.
3. Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group. KDIGO clinical practice guideline for acute kidney injury. *Kidney Int* 2012;(Suppl(2)):1–138.
4. Khwaja A. KDIGO clinical practice guidelines for acute kidney injury. *Nephron Clin Pract* 2012;120(4):c179–84.
5. Grade Working Group. Available at: <http://www.gradeworkinggroup.org/>. Accessed February 13, 2017.
6. Doi K, Yuen PS, Eisner C, et al. Reduced production of creatinine limits its use as marker of kidney injury in sepsis. *J Am Soc Nephrol* 2009;20(6):1217–21.
7. Kim WY, Huh JW, Lim CM, et al. A comparison of acute kidney injury classifications in patients with severe sepsis and septic shock. *Am J Med Sci* 2012; 344(5):350–6.

8. Thomas ME, Blaine C, Dawney A, et al. The definition of acute kidney injury and its use in practice. *Kidney Int* 2015;87(1):62–73.
9. Star RA. Treatment of acute renal failure. *Kidney Int* 1998;54(6):1817–31.
10. Macedo E, Bouchard J, Soroko SH, et al. Fluid accumulation, recognition and staging of acute kidney injury in critically-ill patients. *Crit Care* 2010;14(3):R82.
11. Liu KD, Thompson BT, Ancukiewicz M, et al. Acute kidney injury in patients with acute lung injury: impact of fluid accumulation on classification of acute kidney injury and associated outcomes. *Crit Care Med* 2011;39(12):2665–71.
12. Guay J, Lortie L. Activation of the renin-angiotensin system contributes significantly to the pathophysiology of oliguria in patients undergoing posterior spinal fusion. *Eur J Anaesthesiol* 2004;21(10):812–8.
13. Kellum JA, Sileanu FE, Murugan R, et al. Classifying AKI by urine output versus serum creatinine level. *J Am Soc Nephrol* 2015;26(9):2231–8.
14. Lehner GF, Forni LG, Joannidis M. Oliguria and biomarkers of acute kidney injury: star struck lovers or strangers in the night? *Nephron* 2016;134(3):183–90.
15. Prowle JR, Liu YL, Licari E, et al. Oliguria as predictive biomarker of acute kidney injury in critically ill patients. *Crit Care* 2011;15(4):R172.
16. Md Ralib A, Pickering JW, Shaw GM, et al. The urine output definition of acute kidney injury is too liberal. *Crit Care* 2013;17(3):R112.
17. Pan HC, Wu PC, Wu VC, et al. A nationwide survey of clinical characteristics, management, and outcomes of acute kidney injury (AKI) - patients with and without preexisting chronic kidney disease have different prognoses. *Medicine (Baltimore)* 2016;95(39):e4987.
18. Chalkias A, Xanthos T. Acute kidney injury. *Lancet* 2012;380(9857):1904 [author reply: 1905].
19. Papadopoulos J. Drug-induced complications in the critically ill patient: a guide for recognition and treatment. Mount Prospect (IL): Society of Critical Care Medicine; 2012. p. 472.
20. Taber SS, Mueller BA. Drug-associated renal dysfunction. *Crit Care Clin* 2006;22(2):357–74, viii.
21. Perazella MA. Drug use and nephrotoxicity in the intensive care unit. *Kidney Int* 2012;81(12):1172–8.
22. Bonventre JV, Yang L. Cellular pathophysiology of ischemic acute kidney injury. *J Clin Invest* 2011;121(11):4210–21.
23. Ejaz AA, Mohandas R. Are diuretics harmful in the management of acute kidney injury? *Curr Opin Nephrol Hypertens* 2014;23(2):155–60.
24. Ostermann M, Joannidis M. Acute kidney injury 2016: diagnosis and diagnostic workup. *Crit Care* 2016;20(1):299.
25. Li SY, Chuang CL, Yang WC, et al. Proteinuria predicts postcardiotomy acute kidney injury in patients with preserved glomerular filtration rate. *J Thorac Cardiovasc Surg* 2015;149(3):894–9.
26. Becker GJ, Garigali G, Fogazzi GB. Advances in urine microscopy. *Am J Kidney Dis* 2016;67(6):954–64.
27. Klahr S, Miller SB. Acute oliguria. *N Engl J Med* 1998;338(10):671–5.
28. Macedo E, Mehta RL. Prerenal failure: from old concepts to new paradigms. *Curr Opin Crit Care* 2009;15(6):467–73.
29. Nickolas TL, O'Rourke MJ, Yang J, et al. Sensitivity and specificity of a single emergency department measurement of urinary neutrophil gelatinase-associated lipocalin for diagnosing acute kidney injury. *Ann Intern Med* 2008;148(11):810–9.

30. Pepin MN, Bouchard J, Legault L, et al. Diagnostic performance of fractional excretion of urea and fractional excretion of sodium in the evaluations of patients with acute kidney injury with or without diuretic treatment. *Am J Kidney Dis* 2007; 50(4):566–73.
31. Thadhani R, Pascual M, Bonventre JV. Acute renal failure. *N Engl J Med* 1996; 334(22):1448–60.
32. Steiner RW. Interpreting the fractional excretion of sodium. *Am J Med* 1984;77(4): 699–702.
33. Nejat M, Pickering JW, Devarajan P, et al. Some biomarkers of acute kidney injury are increased in pre-renal acute injury. *Kidney Int* 2012;81(12):1254–62.
34. Uchino S, Bellomo R, Morimatsu H, et al. Discontinuation of continuous renal replacement therapy: a post hoc analysis of a prospective multicenter observational study. *Crit Care Med* 2009;37(9):2576–82.
35. Endre ZH, Kellum JA, Di Somma S, et al. Differential diagnosis of AKI in clinical practice by functional and damage biomarkers: workgroup statements from the tenth Acute Dialysis Quality Initiative Consensus Conference. *Contrib Nephrol* 2013;182:30–44.
36. Carvounis CP, Nisar S, Guro-Razuman S. Significance of the fractional excretion of urea in the differential diagnosis of acute renal failure. *Kidney Int* 2002;62(6): 2223–9.
37. Hall IE, Coca SG, Perazella MA, et al. Risk of poor outcomes with novel and traditional biomarkers at clinical AKI diagnosis. *Clin J Am Soc Nephrol* 2011;6(12): 2740–9.
38. Pru C, Kjellstrand CM. The FENa test is of no prognostic value in acute renal failure. *Nephron* 1984;36(1):20–3.
39. Legrand M, Le Cam B, Perbet S, et al. Urine sodium concentration to predict fluid responsiveness in oliguric ICU patients: a prospective multicenter observational study. *Crit Care* 2016;20(1):165.
40. Maciel AT, Park M, Macedo E. Physicochemical analysis of blood and urine in the course of acute kidney injury in critically ill patients: a prospective, observational study. *BMC Anesthesiol* 2013;13(1):31.
41. Miller TR, Anderson RJ, Linas SL, et al. Urinary diagnostic indices in acute renal failure: a prospective study. *Ann Intern Med* 1978;89(1):47–50.
42. Benjamin IJ, Griggs RC, Wing EJ, et al. Andreoli and Carpenter's Cecil essentials of medicine. 9th edition. Philadelphia: Elsevier/Saunders; 2016. p. 1190, xxv.
43. Gamss R, Stein MW, Rispoli JM, et al. What is the appropriate use of renal sonography in an inner-city population with new-onset acute kidney injury? *J Ultrasound Med* 2015;34(9):1639–44.
44. Podoll A, Walther C, Finkel K. Clinical utility of gray scale renal ultrasound in acute kidney injury. *BMC Nephrol* 2013;14:188.
45. Schnell D, Darmon M. Bedside Doppler ultrasound for the assessment of renal perfusion in the ICU: advantages and limitations of the available techniques. *Crit Ultrasound J* 2015;7(1):24.
46. Kjeldsen L, Cowland JB, Borregaard N, et al. Isolation and primary structure of NGAL, a novel protein associated with human neutrophil gelatinase. *J Biol Chem* 1993;268(14):10425–32.
47. Singer E, Markó L, Paragas N, et al. Neutrophil gelatinase-associated lipocalin: pathophysiology and clinical applications. *Acta Physiol (Oxf)* 2013;207(4): 663–72.

48. Haase M, Bellomo R, Devarajan P, et al. Accuracy of neutrophil gelatinase-associated lipocalin (NGAL) in diagnosis and prognosis in acute kidney injury: a systematic review and meta-analysis. *Am J Kidney Dis* 2009;54(6):1012–24.
49. Koyner JL, Garg AX, Coca SG, et al. Biomarkers predict progression of acute kidney injury after cardiac surgery. *J Am Soc Nephrol* 2012;23(5):905–14.
50. Dinarello CA, Novick D, Kim S, et al. Interleukin-18 and IL-18 binding protein. *Front Immunol* 2013;4:289.
51. Parikh CR, Han G. Variation in performance of kidney injury biomarkers due to cause of acute kidney injury. *Am J Kidney Dis* 2013;62(6):1023–6.
52. Liu Y, Guo W, Zhang J, et al. Urinary interleukin 18 for detection of acute kidney injury: a meta-analysis. *Am J Kidney Dis* 2013;62(6):1058–67.
53. Grubb AO. Cystatin C—properties and use as diagnostic marker. *Adv Clin Chem* 2000;35:63–99.
54. Filler G, Bökenkamp A, Hofmann W, et al. Cystatin C as a marker of GFR—history, indications, and future research. *Clin Biochem* 2005;38(1):1–8.
55. Zhang Z, Lu B, Sheng X, et al. Cystatin C in prediction of acute kidney injury: a systemic review and meta-analysis. *Am J Kidney Dis* 2011;58(3):356–65.
56. Wang WG, Sun WX, Gao BS, et al. Cell cycle arrest as a therapeutic target of acute kidney injury. *Curr Protein Pept Sci* 2016. [Epub ahead of print].
57. Meersch M, Schmidt C, Van Aken H, et al. Urinary TIMP-2 and IGFBP7 as early biomarkers of acute kidney injury and renal recovery following cardiac surgery. *PLoS One* 2014;9(3):e93460.
58. Chawla LS, Davison DL, Brasha-Mitchell E, et al. Development and standardization of a furosemide stress test to predict the severity of acute kidney injury. *Crit Care* 2013;17(5):R207.
59. Koyner JL, Davison DL, Brasha-Mitchell E, et al. Furosemide stress test and biomarkers for the prediction of AKI severity. *J Am Soc Nephrol* 2015;26(8):2023–31.
60. Flechet M, Güiza F, Schetz M, et al. AKIpredictor, an online prognostic calculator for acute kidney injury in adult critically ill patients: development, validation and comparison to serum neutrophil gelatinase-associated lipocalin. *Intensive Care Med* 2017;43(6):764–73.
61. Yerram P, Karuparthi PR, Misra M. Fluid overload and acute kidney injury. *Hemodial Int* 2010;14(4):348–54.
62. Brunkhorst FM, Engel C, Bloos F, et al. Intensive insulin therapy and pentastarch resuscitation in severe sepsis. *N Engl J Med* 2008;358(2):125–39.
63. Rioux JP, Lessard M, De Bortoli B, et al. Pentastarch 10% (250 kDa/0.45) is an independent risk factor of acute kidney injury following cardiac surgery. *Crit Care Med* 2009;37(4):1293–8.
64. Schortgen F, Girou E, Deye N, et al. The risk associated with hyperoncotic colloids in patients with shock. *Intensive Care Med* 2008;34(12):2157–68.
65. Finfer S, Bellomo R, Boyce N, et al. A comparison of albumin and saline for fluid resuscitation in the intensive care unit. *N Engl J Med* 2004;350(22):2247–56.
66. SAFE Study Investigators, Australian and New Zealand Intensive Care Society Clinical Trials Group, Australian Red Cross Blood Service, George Institute for International Health, Myburgh J, Cooper DJ, Finfer S, et al. Saline or albumin for fluid resuscitation in patients with traumatic brain injury. *N Engl J Med* 2007;357(9):874–84.
67. Subramaniam RM, Suarez-Cuervo C, Wilson RF, et al. Effectiveness of prevention strategies for contrast-induced nephropathy: a systematic review and meta-analysis. *Ann Intern Med* 2016;164(6):406–16.

68. Brar SS, Shen AY, Jorgensen MB, et al. Sodium bicarbonate vs sodium chloride for the prevention of contrast medium-induced nephropathy in patients undergoing coronary angiography: a randomized trial. *JAMA* 2008;300(9):1038–46.
69. Bouchard J, Mehta RL. Fluid accumulation and acute kidney injury: consequence or cause. *Curr Opin Crit Care* 2009;15(6):509–13.
70. Bouchard J, Soroko SB, Chertow GM, et al. Fluid accumulation, survival and recovery of kidney function in critically ill patients with acute kidney injury. *Kidney Int* 2009;76(4):422–7.
71. RENAL Replacement Therapy Study Investigators, Bellomo R, Cass A, Cole L, et al. An observational study fluid balance and patient outcomes in the Randomized Evaluation of Normal vs. Augmented Level of Replacement Therapy trial. *Crit Care Med* 2012;40(6):1753–60.
72. Ho KM, Power BM. Benefits and risks of furosemide in acute kidney injury. *Anaesthesia* 2010;65(3):283–93.
73. Oh HJ, Kim MH, Ahn JY, et al. Can early initiation of continuous renal replacement therapy improve patient survival with septic acute kidney injury when enrolled in early goal-directed therapy? *J Crit Care* 2016;35:51–6.
74. Lee JW. Fluid and electrolyte disturbances in critically ill patients. *Electrolyte Blood Press* 2010;8(2):72–81.
75. Buckley MS, Leblanc JM, Cawley MJ. Electrolyte disturbances associated with commonly prescribed medications in the intensive care unit. *Crit Care Med* 2010;38(6 Suppl):S253–64.
76. Blumberg A, Weidmann P, Shaw S, et al. Effect of various therapeutic approaches on plasma potassium and major regulating factors in terminal renal failure. *Am J Med* 1988;85(4):507–12.
77. Lens XM, Montoliu J, Cases A, et al. Treatment of hyperkalaemia in renal failure: salbutamol v. insulin. *Nephrol Dial Transplant* 1989;4(3):228–32.
78. Blumberg A, Weidmann P, Ferrari P. Effect of prolonged bicarbonate administration on plasma potassium in terminal renal failure. *Kidney Int* 1992;41(2):369–74.
79. Kraut JA, Kurtz I. Use of base in the treatment of severe acidemic states. *Am J Kidney Dis* 2001;38(4):703–27.
80. Ron D, Taitelman U, Michaelson M, et al. Prevention of acute renal failure in traumatic rhabdomyolysis. *Arch Intern Med* 1984;144(2):277–80.
81. Reber PM, Heath H 3rd. Hypocalcemic emergencies. *Med Clin North Am* 1995;79(1):93–106.
82. Tohme JF, Bilezikian JP. Hypocalcemic emergencies. *Endocrinol Metab Clin North Am* 1993;22(2):363–75.
83. Hoste EA, Bagshaw SM, Bellomo R, et al. Epidemiology of acute kidney injury in critically ill patients: the multinational AKI-EPI study. *Intensive Care Med* 2015;41(8):1411–23.
84. Elseviers MM, Lins RL, Van der Niepen P, et al. Renal replacement therapy is an independent risk factor for mortality in critically ill patients with acute kidney injury. *Crit Care* 2010;14(6):R221.
85. Gaudry S, Hajage D, Schortgen F, et al. Initiation strategies for renal-replacement therapy in the intensive care unit. *N Engl J Med* 2016;375(2):122–33.
86. Wierstra BT, Kadri S, Alomar S, et al. The impact of “early” versus “late” initiation of renal replacement therapy in critical care patients with acute kidney injury: a systematic review and evidence synthesis. *Crit Care* 2016;20(1):122.
87. Bhatt GC, Das RR. Early versus late initiation of renal replacement therapy in patients with acute kidney injury—a systematic review & meta-analysis of randomized controlled trials. *BMC Nephrol* 2017;18(1):78.

88. Zarbock A, Kellum JA, Schmidt C, et al. Effect of early vs delayed initiation of renal replacement therapy on mortality in critically ill patients with acute kidney injury: the ELAIN Randomized Clinical Trial. *JAMA* 2016;315(20):2190–9.
89. Hemodialysis Adequacy Work Group. Clinical practice guidelines for hemodialysis adequacy, update 2006. *Am J Kidney Dis* 2006;48(Suppl 1):S2–90.
90. Schifffl H, Lang SM, Fischer R. Daily hemodialysis and the outcome of acute renal failure. *N Engl J Med* 2002;346(5):305–10.
91. Kovacs B, Sullivan KJ, Hiremath S, et al. Effect of sustained low efficient dialysis versus continuous renal replacement therapy on renal recovery after acute kidney injury in the intensive care unit: a systematic review and meta-analysis. *Nephrology (Carlton)* 2017;22(5):343–53.
92. Cerda J, Ronco C. Modalities of continuous renal replacement therapy: technical and clinical considerations. *Semin Dial* 2009;22(2):114–22.
93. Saudan P, Niederberger M, De Seigneux S, et al. Adding a dialysis dose to continuous hemofiltration increases survival in patients with acute renal failure. *Kidney Int* 2006;70(7):1312–7.
94. Fayad AI, Buamscha DG, Ciapponi A. Intensity of continuous renal replacement therapy for acute kidney injury. *Cochrane Database Syst Rev* 2016;(10):CD010613.
95. Schilder L, Nurmohamed SA, Bosch FH, et al. Citrate anticoagulation versus systemic heparinisation in continuous venovenous hemofiltration in critically ill patients with acute kidney injury: a multi-center randomized clinical trial. *Crit Care* 2014;18(4):472.
96. Frohlich S, et al. Use of 2-hour creatinine clearance to guide cessation of continuous renal replacement therapy. *J Crit Care* 2012;27(6):744.
97. Herrera-Gutierrez ME, Sellar-Pérez G, Banderas-Bravo E, et al. Replacement of 24-h creatinine clearance by 2-h creatinine clearance in intensive care unit patients: a single-center study. *Intensive Care Med* 2007;33(11):1900–6.