Journal of HOSPITAL MEDICINE www.journalofhospitalmedicine.com

REVIEWS

Before You Call Renal: Acute Kidney Injury for Hospitalists

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Acute kidney injury is a clinical problem of growing incidence in hospitalized patients. It increases the risk of poor outcomes, length of stay and the cost of hospitalization. Successful management of acute kidney injury requires early recognition and diagnosis through detailed medical history, careful physical exam, judicious use of laboratory and radiologic tests and timely renal consultation. Subsequent management is tailored to the likely mechanism of injury with emphasis on limiting both further injury and systemic consequences. A common sense approach to acute kidney injury is essential for hospitalists aiming to limit further injury, prevent acute complications and lessen the risk of chronic morbidity. *Journal of Hospital Medicine* 2015;10:403–408. © 2015 Society of Hospital Medicine

Acute kidney injury (AKI) is a clinical syndrome broadly defined as an abrupt decline in renal function occurring over a period of hours to days resulting in the retention of nitrogenous and metabolic waste products. Although the initial clinical manifestation of AKI may be oliguria, urine volume can remain normal or even increase. Patients may be asymptomatic, especially early in the course of AKI. The diagnosis is often made in hospitalized patients when biochemical screening reveals a recent increase in serum creatinine and/or blood urea nitrogen concentrations, or when there is a dramatic decrease in urine output.

Older studies looking at the incidence of AKI in hospitalized patients are difficult to interpret due to variable definitions of AKI. Those based on administrative databases were limited by lack of clinical context and/or variation in coding for AKI.[1]

There is no universally accepted operational definition of AKI, and more than 30 different criteria have been employed in various clinical studies. Difficulty in defining AKI lies in the lag time in the rise and fall of the serum creatinine concentration with injury and recovery, the variability of oliguria, and in the heterogeneity of patterns of renal injury. Two classification systems that attempt to capture the spectrum of AKI are the RIFLE (Risk, Injury, Failure, Loss, End Stage) criteria and the AKIN (Acute Kidney Injury Network) criteria.[2,3] The AKIN criteria parallel the risk, injury, and failure stages of the RIFLE criteria and are the most applicable to characterizing AKI in the hospital (Table 1). AKI is commonly classified by daily urine output as anuric (<50 mL/day), oliguric (<500 mL/day), or nonoliguric.

With a move toward standardized definitions, recent studies have shown a rising incidence of AKI in hospitalized patients.[4–6] According to these series, AKI develops in up to 7% of hospitalized patients and in about 30% of those admitted to intensive care units. In one study of consecutive hospital admissions, patients classified by the RIFLE criteria had a sharp rise in the rate of in-hospital mortality whether they had no change or improvement in creatinine (4.4%), or fell into a risk (15.1%), injury (29.2%), or failure (41.1%) class.[7] The in-hospital mortality of critically ill patients with AKI is higher than 50%. AKI increases length of stay and hospital costs, and affects the clinical course after discharge.[8,9] Small increases in serum creatinine during an intensive care unit stay predict increased 10-year mortality above a critical illness alone.[10]

Risk factors for AKI include advanced age, male gender, African American ethnicity, and diabetes mellitus.[11] The most important risk factor, however, is preexisting chronic kidney disease (CKD).[12] AKI and CKD are tightly linked, each increasing the risk of the other.[13–15] Preexisting renal insufficiency is a key predictor of postoperative AKI and poor surgical outcomes.[16,17]

AKI AND CLINICAL CONTEXT

The causes of AKI can be broadly divided into 3 categories: prerenal azotemia (a disorder characterized by renal hypoperfusion in which renal parenchymal tissue integrity is preserved), intrinsic kidney injury with parenchymal tissue injury, and postrenal AKI (dysfunction due to acute obstruction of the urinary tract). Table 2 lists several clinical scenarios sorted into these 3 categories.[18] The general epidemiology of AKI varies based on whether it was acquired in the community or in a hospital setting. Prerenal azotemia accounts for the bulk of community-acquired AKI, followed in lesser frequency by postrenal and intrinsic

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Additional Supporting Information may be found in the online version of this article.

Received: October 30, 2014; **Revised:** December 18, 2014; **Accepted:** December 21, 2014
 DOI 10.1002/jhm.2325
Published online in Wiley Online Library (Wileyonlinelibrary.com).

TABLE 1. Acute Kidney Injury Network Criteria

Stage	Creatinine Criteria	Urine Output Criteria
1	Increase in serum creatinine of ≥0.3 mg/dL (≥26.4 μmol/L) or increase of ≥150%–200% (1.5-fold to 2-fold) above baseline	<0.5 mL/kg/hr for >6 hours
2	Increase in serum creatinine of >200%–300% (>2-fold to 3-fold) above baseline	<0.5 mL/kg/hr for >12 hours
3	Increase in serum creatinine of >300% (3-fold) above baseline or serum creatinine ≥5.0 mg/dL (≥354 μmol/L) with an acute rise of ≥0.5 mg/dL (≥44 μmol/L)	<0.3 mL/kg/hr × 24 hours or anuria × 12 hours

TABLE 2. Causes of Acute Kidney Injury

Prerenal	Intrinsic	Postrenal
Hemorrhage	Acute tubular necrosis	Bilateral upper tract obstruction
Surgical	Ischemic	Nephrolithiasis
Gastrointestinal	Postoperative	Papillary necrosis
Retroperitoneal	Prolonged hypotension	Retroperitoneal fibrosis
Gastrointestinal losses	Sepsis	Retroperitoneal lymphadenopathy
Diarrhea	Nephrotoxins	Obstruction of solitary functioning kidney
Vomiting	Myoglobin	Lower tract obstruction
Nasogastric suction	Hemoglobin	Prostatic hypertrophy
Enteral fistula	Radiocontrast agents	Urethral stricture
Renal losses	Aminoglycosides	Bladder mass or stone
Diuretics	Intratubular obstruction	Obstructed urinary catheter
Glucosuria	Tumor lysis/uric acid	Urinary retention
Skin losses	Oxalosis/ethylene glycol ingestion	Neurogenic bladder
Excessive sweating	Phosphate nephropathy	Constipation
Burns	Light chain nephropathy	Medications
Erythroderma	Acyclovir	Anticholinergics
Third-spacing	Indinavir	Antihistamines
Hypoalbuminemia	Methotrexate	Alpha1-agonists
Pancreatitis	Acute glomerulonephritis	β-Blockers
Capillary leak	Acute interstitial nephritis	Opiates
Reduced effective arterial volume	Proton pump inhibitors	Tricyclic antidepressants
Congestive heart failure	Penicillins	
Cirrhosis	Fluoroquinolones	
Renal vasoconstriction	Atheroembolic disease	
Hypercalcemia	Acute vascular syndrome	
NSAIDs	Aortic dissection	
ACEI/ARB	Bilateral renal artery thromboembolism	
Calcineurin inhibitors	Bilateral renal vein thrombosis	
Vasopressors	Thrombotic microangiopathy	
Iodinated contrast		

NOTE: Andrew Z Fenves is the author of the book chapter from which the table was adapted. **Abbreviations**: ACEI, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; NSAIDs, nonsteroidal anti-inflammatory drugs.

etiologies. Prerenal azotemia continues to be the major cause of hospital-acquired AKI, but intrinsic kidney injury becomes more common.[5,19]

MEDICAL HISTORY

The initial goal of history taking is to establish whether the patient has AKI rather than the acute discovery of a more chronic process. A recent serum creatinine measurement can be valuable in this regard. In some cases the clinician must make a presumptive diagnosis of AKI while simultaneously reviewing past medical history and family history to assess for underlying CKD. A diagnosis of AKI is more readily established when it occurs during a hospitalization through review of urine output and serial laboratory values.

Symptoms of poor oral intake as well as salt and fluid losses from diarrhea or vomiting suggest a prerenal etiology. Subjective symptoms of lightheadedness, visual clouding, and near-syncope with standing also suggest volume depletion. Patients should be asked about recent nonsteroidal anti-inflammatory drug (NSAID) use, as these agents can exacerbate renal hypoperfusion through loss of prostaglandin-mediated afferent arteriole dilatation. Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers, especially when combined with diuretics, can generate a hypoperfusion state. Heart failure and liver disease regularly result in an expanded extracellular fluid (ECF) compartment yet a reduced effective arterial volume and predispose to renal hypoperfusion.

A history of decreased urine output or anuria suggests postrenal AKI, but its absence does not rule out urinary tract obstruction. Voiding symptoms such as urinary frequency, hesitancy, or incontinence also raise the possibility of obstructive uropathy. Flank pain and hematuria often accompany obstruction from nephrolithiasis.

Symptoms of fever, skin rash, arthralgias, sinusitis, and/or hemoptysis raise the possibility of glomerulonephritis from infection, collagen vascular disease, or vasculitis. Risk factors for viral hepatitis and human immunodeficiency virus are important to clarify as are systemic symptoms of autoimmunity (eg, dry eyes, dry mouth, eye pain/inflammation, or visual changes). The recent start of any new medication, including NSAIDs, antibiotics, or proton-pump inhibitors, raises the possibility of a drug-induced interstitial nephritis.[20] Statins are direct myotoxins, and the risk of rhabdomyolysis with renal injury increases with dose. Patients may not associate intravenous (IV) contrast or phosphate-containing bowel preparations (eg, Fleet Phospho Soda), with the development of AKI, thus the clinician must carefully review for recent exposures that could result in intrinsic renal injury.[21]

PHYSICAL EXAMINATION

Estimation of the ECF volume and effective arterial volume are central to assessing the likelihood of renal hypoperfusion. Overt hypotension is the strongest indicator of hypoperfusion, and a careful review of initial blood pressure prior to worsening of renal function can provide significant information. Normal blood pressure does not exclude renal hypoperfusion,

as acute tubular necrosis (ATN) may develop in chronically hypertensive patients whose blood pressures are acutely reduced.[22] Less-severe volume depletion is suggested by an orthostatic pulse increase of more than 30 beats/minute, measured 1 minute after standing. Orthostatic hypotension, defined as a drop in systolic pressure of more than 20 mm Hg after standing, is less helpful, as it occurs in 10% of normovolemic subjects.[23] Dry axillae and mucous membranes with a furrowed tongue are useful signs of volume depletion. Poor skin turgor and slow capillary refill have not been shown to be reliable signs of hypovolemia in adults. The neck veins are usually flat when volume contraction exists, though engorged neck veins in the setting of elevated right-sided pressures from heart failure or pulmonary hypertension may obscure this sign. Similarly, pulmonary rales, ascites, and peripheral edema may confound the exam in patients with underlying heart failure and/or cirrhosis.

Flank tenderness or a bladder palpable or percussable above the pelvic brim suggests possible urinary tract obstruction. Prostate exam should be performed on all men with AKI and a bimanual pelvic exam considered in women with changes in usual voiding pattern or with suspected gynecologic disease. Postvoid residual can be assessed at the bedside with either straight catheterization or bladder scan where available.

Signs of systemic disease associated with intrinsic AKI include fever, skin and joint findings of connective tissue disease, a new or changing heart murmur, purpura, and petechiae. Cholesterol emboli, disrupted by interarterial catheterization (eg, cardiac catheterization, angiography), cardiac or aortic surgeries, or, rarely, by systemic anticoagulation can shower throughout the vasculature, causing organ dysfunction and local inflammation. Kidney injury due to atheroemboli often has a stuttering course and may be separated in time from the vascular procedure by days to weeks. Physical exam findings of atheroembolic disease include livedo reticularis, "blue toes," purpura, painful skin nodules, and gangrene. Retinal examination may reveal atheroembolic emboli (Hollenhorst plaques).[24,25]

LABORATORY TESTING

Initial testing in AKI aims to assess the severity of injury as well as the likely mechanism of the injury. Estimation of glomerular filtration rate (GFR) gives an approximate measure of the number of functioning nephrons and hence an overall measure of renal function. Mathematical estimates of GFR, however, assume a steady state, and AKI, by definition, is not a steady state. This makes GFR estimates based on plasma creatinine unreliable. A rising serum creatinine concentration indicates that the renal injury is persistent or worsening, whereas a stable or falling creatinine concentration suggests recovery. Interventions that expand the ECF (eg, volume resuscitation with normal saline) will dilute the plasma creatinine concentration and must be considered when interpreting a falling creatinine concentration. A daily rise in the serum creatinine concentration of more than 1 mg/dL nearly always implies a GFR of <10 mL/min. Any change in serum creatinine must be interpreted with the nonlinear relationship of GFR and serum creatinine in mind (Figure 1).[26]

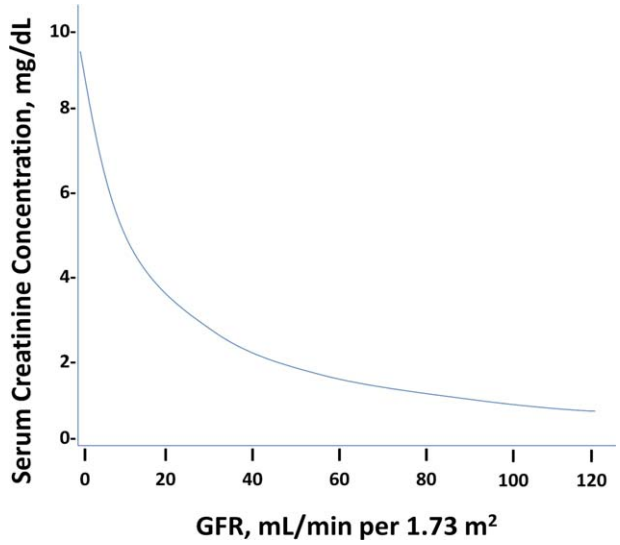

FIG. 1. Relationship of Glomerular Filtration Rate to Serum Creatinine

The fractional excretion of sodium (FENa) has been used to differentiate prerenal azotemia from intrinsic renal injury in patients with oligoanuria. Specifically, an FENa of <1% implies a prerenal cause for the oliguric AKI, whereas if it is >1%, then intrinsic renal injury is more likely. Unfortunately, there are significant limitations to this laboratory measure.[27] The FENa may be low (<1%) in any intrinsic process that causes tissue ischemia, such as vasculitis, acute glomerulonephritis, atheroembolic disease, or from intense vasoconstriction such as after IV contrast administration. Patients with severe heart failure or portal hypertension often have avid sodium retention, and can have a FENa <1% even in the setting of ATN. Alternatively, the FENa may be elevated (>1%) in prerenal patients on diuretics, with osmotic diuresis, or in the setting of aldosterone deficiency.

Examination of the urinalysis and urine sediment provides valuable information about the etiology of the AKI. Prerenal and postrenal AKI typically present with a "bland" urine, without evidence of blood, protein, or leukocyte esterase on urinalysis and few cells or hyaline casts in the sediment. The urinalysis typically has a high specific gravity in prerenal AKI, reflecting intact tubules producing a concentrated urine. An active urinary sediment suggests intrinsic renal injury that is either the mechanism of the current AKI or indicative of underlying CKD. ATN, the most common cause of intrinsic renal injury, often

produces a "dirty" urinalysis with many epithelial cells and muddy brown granular and epithelial cell casts. The urine is generally isosthenuric (ie, specific gravity of 1.010) due to loss of tubular function. A urinalysis positive for heme pigment but without red cells on microscopic analysis suggests the presence of either myoglobin from rhabdomyolysis or hemoglobin from hemolysis. Acute glomerulonephritis disrupts the usual glomerular barrier to large proteins and red cells and results in proteinuria and hematuria. Red cells that weather the journey from the glomerulus through the nephron often become dysmorphic with "Mickey Mouse ear" blebs in their membrane or are bound together by Tamm-Horsfall protein into red cell casts. Acute interstitial nephritis results in pyuria, proteinuria, and white cell casts. Urinary eosinophils are neither sensitive nor specific for interstitial nephritis and have little utility in its diagnosis.[28,29]

Given the limitations of serum creatinine as a marker of renal injury, a number of new urinary biomarkers have been recognized over the past decade.[30–32] These molecules are normal constituents of renal tubular cells that are upregulated and released into the urine in response to renal injury. Early measurement of these biomarkers might allow for detection of AKI within hours of the insult. The 2 biomarkers with the most promise include kidney injury molecule-1 (KIM-1) and neutrophil gelatinase-associated lipocalin (NGAL). KIM-1 is expressed by proximal tubular cells, and its production is sharply upregulated in response to ischemic injury. NGAL is a protein expressed primarily in immune cells, but also by renal tubular cells. Urinary NGAL levels rapidly rise in response to renal ischemia, and return to baseline following resolution of the injury. Although these urinary biomarkers are promising, they have a relatively low (70%–75%) sensitivity and specificity, and have not yet been adopted into routine clinical practice.[33]

IMAGING

Renal ultrasound is useful both in the assessment of AKI as well as in the investigation for underlying CKD. Patients with long-standing kidney disease frequently have small, echogenic kidneys consistent with fibrosis and nephron loss, or markedly distorted renal architecture in cystic diseases. Hydronephrosis and/or hydroureter suggest an acute or chronic urinary tract obstruction. However, this may not be present in the setting of early obstruction or ureteric encasement. Doppler ultrasonography of the renal vasculature can assess patency when vascular obstruction is suspected. The use of computerized tomography, magnetic resonance imaging, or angiography may be helpful in selected clinical circumstances, but their use is often limited due to the potential risk of contrast nephrotoxicity. Nuclear renal scans use less radiation than computerized tomography and are a preferred imaging modality for pediatric patients. When volume status is uncertain, echocardiography to assess both inferior vena cava volume and change in volume with respiration may be helpful.

MANAGEMENT

The general principles for management of AKI are to limit further injury and prevent systemic complications. Management of the patient with AKI greatly depends on which category of AKI is suspected, namely prerenal, intrinsic renal injury, or a postrenal (obstructive) cause. If a prerenal etiology due to true ECF volume depletion is suspected, volume resuscitation to replace baseline and ongoing losses is imperative. Careful attention to intake and output as well as serial volume assessment should dictate the strategy for resuscitation. Hyperchloremic acidosis is an expected consequence of normal saline resuscitation but is irrelevant to clinical outcomes.[34] NSAIDs, antihypertensives, especially those that affect the angiotensin/aldosterone system, and diuretics should be discontinued. Ongoing hypotension despite volume resuscitation suggests the possibility of blood loss, infection, or autonomic nervous system dysfunction. If this occurs, the patient may need to be transferred to an intensive care unit for pressor support to keep the mean arterial pressure >70 mm Hg. When prerenal AKI from reduced effective circulating volume is suspected, as in decompensated heart failure or cirrhosis, management must be tailored to the underlying pathophysiology.

If judicious volume resuscitation produces no improvement in renal function or if oliguria develops, repeat urinalysis and urine microscopy should be considered to assess for intrinsic renal injury. Aggressive volume resuscitation in the face of oliguria will not speed recovery from the intrinsic injury and may cause signs or symptoms of volume overload. This could also potentially necessitate renal replacement therapy earlier than anticipated.

In patients where an obstructive etiology for the AKI is identified, the obstruction must be relieved as soon and as safely as possible. In this regard, a timely urologic consultation may be helpful in assuring that urethral and/or ureteral conduits are placed rapidly. Interventional radiology can also assist in those patients who need percutaneous nephrostomies for the relief of the obstruction. In many patients with obstructive nephropathy, a timely intervention will avoid the need for renal replacement therapy.

The suspected mechanism of injury influences the management of intrinsic AKI. The management of ATN is primarily supportive, paying close attention to optimizing volume status, correcting electrolyte abnormalities, avoiding further nephrotoxic agents, and adjusting medication doses to the low GFR present. Over the last several decades, multiple studies have explored treatment strategies for established ATN

using various drugs and biologic agents. All have been uniformly disappointing.

When the trajectory of AKI is uncertain and the creatinine continues to rise, all medication dosing should be adjusted for GFR <10 mL/min. Antibiotics routinely will require dose reduction, but all current medications should be reviewed for risk of accumulation in renal failure. Because the half-life of oral hypoglycemic medications is unpredictable in AKI, these medications should be discontinued and replaced with insulin. Vigilance for hypoglycemia is necessary, as renal clearance of insulin is also reduced. Narcotics such as morphine and oxycodone, which are renally cleared, can produce unwanted sedation and respiratory depression if not discontinued. Fentanyl, methadone, and hydromorphone are safer choices for controlling pain in a patient with AKI.[35] Gabapentin is regularly used to treat symptoms of neuropathic pain, but can produce encephalopathy and myoclonus if not dose reduced in renal failure.[36] Clinicians should weigh the risk of overdose with underdose for each medication, namely antibiotics in critically ill patients.

TIMING OF NEPHROLOGY CONSULTATION

The optimal timing for nephrology consultation in hospital-acquired AKI is uncertain, though several studies have suggested better outcomes, including shorter length of stay and reduced mortality, with early consultation.[37–39] A renal consult is indicated when intrinsic ATN does not reverse in a timely fashion. Renal replacement therapy should be instituted to limit the systemic complications of prolonged AKI and to allow time for the renal injury to improve or resolve over time. If acute glomerulonephritis or interstitial nephritis is suspected, an urgent consultation may be required for consideration of biopsy, immunosuppression, and guidance for further management. Early consultation may help limit drug toxicities and volume overload in the setting of decreased renal clearance. Guidance on vascular access (eg, peripherally inserted central catheter placement) may prevent future complications with hemodialysis access if the patient ultimately develops end-stage renal disease (ESRD).[40]

PREVENTION OF AKI

Most studies of AKI prevention have focused on clinical scenarios where the likelihood of ATN was substantial such as in vascular or open heart surgery, or with the use of intravenous contrast agents.[41,42] This topic remains controversial, though generally supported strategies include judicious volume expansion, avoidance of hypotension, and, when using contrast, limiting the volume of contrast and using iso-osmolar formulations. As recent studies have shown uncertain benefit, the role for pretreatment with n-acetylcysteine remains uncertain. Many clinicians, however, continue to use it as a preventive strategy as there are few side effects with this medication.

TAKE HOME POINTS

- AKI is common in hospitalized patients, with prerenal azotemia being the dominant etiology in both community-acquired and hospital-acquired AKI.
- CKD is an important risk factor for AKI. AKI increases the long-term risk of developing CKD and ESRD.
- The diagnosis of AKI hinges on detailed medical history, careful physical exam, and key laboratory parameters including the urinalysis and urinary sediment.
- The management of AKI is tailored to the likely mechanism of injury. Reconsideration of the likely etiology is imperative if AKI fails to respond to initial attempts to reverse or limit injury.
- Early renal consultation for AKI is indicated when the etiology remains uncertain, AKI persists despite initial management, or acute glomerulonephritis or interstitial nephritis are suspected.

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