Drug Induced Acute Kidney Injury

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KEYWORDS

• Acute kidney injury • Drugs • Nephrotoxicity • Interstitial nephritis

HOSPITAL MEDICINE CLINICS CHECKLIST

1. Many cases of acute kidney injury (AKI) in hospitalized patients are multifactorial, with epidemiologic studies estimating that nephrotoxic drugs contribute to 19% to 25% of cases in critically ill patients.
2. Risk factors for drug-induced AKI may be patient, disease, or medication specific. Established risk factors include age greater than 60 years, diabetes mellitus, chronic kidney disease, heart or liver failure, dehydration, sepsis, concomitant nephrotoxin exposures, cardiac surgery, and nonrenal solid organ transplantation.
3. The four most common mechanisms of drug-induced nephrotoxicity include vasoconstriction, altered intraglomerular hemodynamics, direct tubular toxicity, and acute interstitial nephritis.
4. Antibiotics, nonsteroidal anti-inflammatory drugs, and proton pump inhibitors are common causes of acute interstitial nephritis, although many medications including anticonvulsants, antivirals, and histamine-2 receptor blockers, are potential causes.
5. Although the physical examination and basic laboratory studies may help evaluate the severity of AKI and occasionally provide clues to the mechanism of drug-induced nephrotoxicity, a thorough history and review of medication exposure is paramount for determining the cause of AKI. Renal biopsy is reserved for cases of prolonged renal injury without apparent cause or with suspected glomerular disease.
6. The classic triad of eosinophilia, rash, and fever is encountered in less than 10% of cases of acute interstitial nephritis.

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7. Aside from discontinuation of potentially causative medications, treatment of drug-induced nephrotoxicity is largely supportive. A short steroid course may be helpful in cases of suspected acute interstitial nephritis when AKI does not improve rapidly with medication withdrawal.
8. AKI is an independent risk factor for mortality in the hospitalized patient. For survivors of AKI, recovery to baseline renal function varies depending on the stage of AKI.
9. Preventative strategies that may reduce the risk of drug-induced AKI include minimizing use of nephrotoxic agents, optimizing patient-related risk factors, and early detection of AKI with appropriate dosage adjustments for glomerular filtration rate variation. Computerized provider order entry with clinical decision support and greater incorporation of pharmacists into health care team rounds are system-based prevention strategies that may reduce the risks and costs of medication-induced AKI in hospitalized patients.

DEFINITIONS

What is the definition of acute kidney injury?

The definition of acute kidney injury (AKI) continues to evolve, and most clinicians use the Acute Kidney Injury Network (AKIN) definition or the risk, injury, failure, loss, end-stage kidney disease (RIFLE) criteria. The AKIN and RIFLE classifications are compared below (**Table 1**).[1,2] In 2012, the Kidney Disease: Improving Global Outcomes (KDIGO) group published clinical practice guidelines defining AKI as an increase in serum creatinine by 50% within 7 days, or an increase in serum creatinine by 0.3 mg/dL within 2 days, or oliguria, defined as a urine volume of less than 0.5 mL/kg/h for 6 hours.[3]

Table 1
Comparison of AKIN and RIFLE definitions of acute kidney injury

AKIN Stage	Serum Creatinine Criteria	Urine Output Criteria
1	Increase by ≥0.3 mg/dL or ≥1.5 – <2.0 times baseline	<0.5 mL/kg per h for >6 h
2	Increase by ≥2 to <3 times baseline	<0.5 mL/kg per h for >12 h
3	Increase by ≥3 times baseline, or ≥4 mg/dL with acute increase of ≥0.5 mg/dL, or need for RRT	<0.3 mL/kg per h for 24 h or anuria for 12 h

RIFLE Level	Serum Creatinine Criteria	GFR Criteria	Urine Output Criteria
Risk	1.5-fold increase	Decrease by 25%	<0.5 mL/kg per h for 12 h
Injury	2-fold increase	Decrease by 50%	<0.5 mL/kg per h for 12 h
Failure	3-fold increase	Decrease by 75%	<0.3 mL/kg per h for 24 h or anuria for 12 h

Abbreviation: RRT, renal replacement therapy.

EPIDEMIOLOGY

What is the prevalence of drug-induced AKI in hospitalized patients?

AKI is common in the hospitalized patient, with recent epidemiologic studies using the AKIN definition finding rates of 3.19% to 22.7%.[1–5] The prevalence can vary by population as well, with rates as high as 60% in elderly and critically ill patients.[5] The incidence of hospital-acquired AKI is about 5 to 10 times higher than that of community-acquired cases, and the incidence seems to have increased over the past decade.[5,6]

Approximately 20% of community-acquired and hospital-acquired episodes of AKI are attributed to drug toxicity based on clinical parameters. However, one Chinese study, using renal biopsy to elucidate the cause of acute on chronic renal failure in 104 patients, found that 35% of renal injury was drug related.[7] Although many cases of AKI in hospitalized patients are multifactorial, epidemiologic studies estimate that nephrotoxic drugs contribute to 19% to 25% of cases in critically ill patients.[5,8]

What are the patient-related risk factors for drug-induced AKI?

Patient-specific risk factors include age greater than 60 years and baseline diagnoses of diabetes mellitus, chronic kidney disease (CKD), heart failure, liver failure, arterial vascular disease, multiple myeloma, and hypoalbuminemia. The association between gender, race, and/or genetic variation as independent risk factors of AKI has been less well established.[5,9–12]

There are several acute clinical conditions that have been associated with increased risk of AKI, including intravascular volume depletion, sepsis, hypotension/shock, rhabdomyolysis, need for mechanical ventilation, exposure to multiple nephrotoxins, acid-base disturbances, and abdominal compartment syndrome. In addition, cardiac surgery for myocardial reperfusion or valve replacement and nonrenal solid organ transplantation increase the risk of AKI.[5,9–13]

Regardless of the acute or chronic nature of the risk factors, the more comorbidities an individual patient has, the higher the risk of AKI.

What are the drug-related risk factors for drug-induced AKI?

Some medications are inherently nephrotoxic regardless of dosage, duration of use, or comorbid conditions, with mechanisms of toxicity discussed later. Other medications cause renal injury with less consistency or in an idiosyncratic pattern. Toxicity in these situations may depend on peak drug concentrations; duration of use; frequency of dosing; route, rate, and timing of administration; or concomitant use of other nephrotoxins.[5]

PATHOPHYSIOLOGY

How do medications injure the kidney?

Despite the large number of nephrotoxic medications, there is a finite number of pathways leading to kidney injury. The medications most frequently implicated in AKI exert their deleterious effects via one of four mechanisms:

1. Vasoconstriction
2. Altered intraglomerular hemodynamics

3. Direct tubular toxicity, including medication-induced rhabdomyolysis
4. Acute interstitial nephritis

Less common mechanisms include thrombotic microangiopathy (TMA), crystal deposition, osmotic injury, retroperitoneal fibrosis, or the induction of de novo glomerular disease and vasculitides.[5,14,15] In addition, a medication may cause AKI through more than one mechanism. Refer to **Table 2** for a brief synopsis of the medications most commonly associated with nephrotoxicity, all of which will be discussed in greater detail in the text below.

Any medication causing volume depletion, such as diuretics and cathartics, can also adversely affect kidney function. Because these medications do not cause direct injury to the kidneys, they are not considered further in this article.

Which medications cause kidney injury via vasoconstriction?

The calcineurin inhibitors (CNIs) cyclosporine and tacrolimus, immunosuppressants used in organ transplantation, are the prototypical medications leading to vasoconstriction-induced AKI. Vasoconstriction is dose dependent, and is mediated via a mismatch of intrarenal vasoconstrictors and vasodilators.[16] The injury is typically reversible on cessation of the CNI, although it is important to continue to monitor levels to ensure effective immunosuppression, and restart as the levels wane.

In addition to higher dose, other risk factors for CNI nephrotoxicity include older age of the transplanted kidney, volume depletion/diuretic use, use of other nephrotoxins, and use of agents that interfere with metabolism of the CNIs resulting in increased levels, including azole antifungals. Nondihydropyridine calcium channel blockers (CCBs) such as diltiazem and verapamil may also increase CNI levels, but dihydropyridines may protect against the development of vasoconstrictive injury.[17] CNIs may also cause kidney injury by direct tubular toxicity, and rarely via a thrombotic microangiopathy.[17]

Several of the agents that cause tubular toxicity (discussed later), may also induce kidney injury via vasoconstriction. Vasoconstrictor agents used for hemodynamic support in the intensive care unit and radiocontrast agents may also injure the kidney through this mechanism.[18,19]

Which medications alter intraglomerular hemodynamics?

The glomerular filtration rate (GFR) is a function of renal blood flow and the resistances of the afferent arterioles, which supply blood to the glomerular capillaries, and the efferent arterioles, which transport blood not destined for ultrafiltration. The optimal configuration for enhanced glomerular filtration would be a widely dilated afferent arteriole, permitting a large influx of blood, accompanied by efferent vasoconstriction such that more of the delivered blood is shunted across the glomerular capillaries.

Nonsteroidal Antiinflammatory Drugs

Renal prostaglandins promote afferent vasodilation.[20] They are particularly important in volume depletion or other states associated with decreased renal perfusion, such as congestive heart failure, cirrhosis, and nephrotic disorders, in which afferent vasodilation is needed to maintain GFR.[21] Nonsteroidal antiinflammatory drugs (NSAIDs) inhibit prostaglandin formation via inhibition of either one or both isoforms of cyclooxygenase (COX-1 and COX-2). Although the rate of renal complications is low, the volume of NSAIDs in use makes this an important consideration in cases of AKI.

Table 2
Risk factors and mechanisms for nephrotoxicity by medication class

Drug Name/Class	Risk Factors for Nephrotoxicity	Mechanism of Nephrotoxicity
ACE inhibitors/ angiotensin receptor blockers	Concomitant NSAID use Volume depletion/diuretic use Congestive heart failure Bilateral renal artery stenosis	Altered intraglomerular hemodynamics
Amphotericin	High dosage Preexisting CKD Concomitant nephrotoxins	Direct tubular toxicity
Calcineurin inhibitors	Old age of transplanted kidney Volume depletion/diuretic use Concomitant nephrotoxins Use of agents that interfere with CNI metabolism (azoles, dihydropyridine CCBs)	Intrarenal vasoconstriction (primary), direct tubular toxicity, TMA (rarely)
Cisplatin	Old age Volume depletion Female sex CKD Chronic liver disease	Direct tubular toxicity, intrarenal vasoconstriction
AGs	Old age Preexisting CKD Volume depletion High dosage Prolonged duration of therapy Concomitant nephrotoxins	Direct tubular toxicity (primary), intrarenal vasoconstriction
NSAIDs	High NSAIDs dose Age >65 y Concomitant nephrotoxins Congestive heart failure	Altered intraglomerular hemodynamics, AIN, papillary necrosis (rare)
PPIs	Variable duration of use, occurs on average after 2–3 mo of use	AIN
Statins	Old age Female gender Asian descent Low body mass index Drug abuse Concomitant untreated hypothyroidism Liver disease CKD Family/personal history of statin-induced myopathy	Rhabdomyolysis with resultant myoglobin-induced tubular toxicity
Vancomycin	High average serum trough levels ($\geq$15 mg/L) Prolonged duration of therapy (>7 d) Baseline CKD (Cr >1.7 mg/dL) Concomitant nephrotoxins Sepsis Vasopressor use	Direct tubular toxicity

Several population-based studies have defined the risk of NSAID-induced AKI. In one case-controlled study, NSAID use was associated with a 4-fold increased risk of renal failure, a risk that increases with higher NSAID dose, age greater than 65 years, and concomitant use of other nephrotoxic drugs.[22] A more recent case-controlled study found a 3-fold higher risk of kidney failure in NSAID users versus nonusers, and also identified a dose-dependent relationship.[23] This study also showed that the combination of heart failure and NSAID use conferred more than a 7-fold risk of acute renal failure compared with a 2.8-fold risk for heart failure alone.[23] Although it was hoped that COX-2 inhibitors would confer some protection against nephrotoxicity, their rate of kidney failure is similar to that of nonselective NSAIDs.[24]

In addition to hemodynamically-induced AKI, NSAIDs may rarely lead to acute interstitial nephritis (discussed later).[20] Renal papillary necrosis is an even rarer form of NSAID-induced renal injury, typically occurring after a massive overdose of NSAIDs in a dehydrated patient with previously normal kidney function.[21]

Renin-Angiotensin System Inhibitors

Similar to prostaglandins, angiotensin II is an important determinant of intraglomerular pressure, particularly in periods of decreased afferent arteriolar flow.[25] Angiotensin II causes a preferential efferent arteriolar vasoconstriction, such that a higher proportion of blood is filtered through the lower pressure glomerular capillary system.

Renin-angiotensin system (RAS) inhibitors, which include angiotension-converting enzyme inhibitors (ACE-I) and angiotensin receptor blockers are commonly used for their beneficial effects in hypertension, proteinuric renal disease, congestive heart failure, and coronary artery disease.[26,27] They may lead to a decrease in GFR by preventing efferent arteriolar vasoconstriction, particularly in patients with decreased effective arterial volume, such as those with congestive heart failure, especially if on diuretics.[25] Bakris and Weir[25] found that antihypertensive therapy with an ACE-I in patients with preexisting CKD typically causes a small decrease in kidney function, manifested as a creatinine increase of less than or equal to 30%. This decrease occurs in the first 2 weeks, and rarely leads to progressive AKI unless ACE-I use is superimposed on NSAID use or concomitant volume depletion, either because of diuretics or other causes.[25] Patients with heart failure, in whom RAS inhibitors and diuretics are often prescribed simultaneously, are at increased risk for kidney failure. One study showed that patients with heart failure treated with an ACE-I have a 25% incidence of AKI, and that the risk increases with worsening heart failure.[28]

There are no randomized controlled trials addressing what level of creatinine increase should prompt discontinuation of ACE-I and angiotensin receptor blockers. Expert opinion suggests that RAS inhibitors should be discontinued or the dose reduced if the creatinine increase is greater than 30%.[27] Although rare, particular care is needed in patients with bilateral renal artery stenosis, or unilateral stenosis in a solitary kidney. Because of fixed obstruction proximally, afferent vasodilation is unable to augment glomerular blood flow, rendering these patients exquisitely sensitive to changes in efferent vascular tone. Efferent vasodilation, as occurs with RAS inhibitors, may lead to a precipitous decline in GFR.

Which medications commonly cause kidney injury via damage to the renal tubules?

Acute tubular injury (commonly known as acute tubular necrosis) is the most common mechanism of drug-induced nephrotoxicity in the hospitalized patient.[29] Common tubulotoxins include aminoglycosides (AGs), amphotericin B (AmB), platinum-containing

chemotherapeutic agents and vancomycin. Although not a medication per se, radiocontrast agents commonly lead to tubulotoxicity (in addition to the vasoconstrictive injury mentioned earlier).[19]

Aminoglycosides

AGs lead to nephrotoxicity in 10% to 25% of cases, depending on the population studied.[30] Risk factors for AG toxicity may be related to the patient, such as older age; preexisting CKD and volume depletion; the dosage and duration of the treatment regimen; or the concurrent administration of other nephrotoxic agents.[30] The nephrotoxicity of AGs is related to their accumulation in tubular cells, particularly in the proximal tubule, where they activate apoptotic pathways, interrupt the respiratory chain, and induce oxidative damage via the production of free radicals.[30] In addition to their tubular effects, AGs may also promote injury via vasoconstriction.[30] The nephrotoxicity of AGs is not completely preventable, but frequent monitoring of AG levels may decrease the risk. In one study, patients with frequently monitored levels (ie, daily) had less nephrotoxicity compared with a strategy of monitoring every 2 to 3 days.[31] Other potential strategies for the prevention of AG toxicity include inhibition of tubular cell AG accumulation and cotreatment with renoprotective drugs, particularly antioxidants.[30] Although early work seems promising, neither has shown clinical benefit at this time.

Amphotericin B

AmB is a potent antifungal, although its use is complicated by kidney dysfunction, characterized by a decrease in GFR, often accompanied by hypokalemia, hypomagnesemia, a renal tubular acidosis, and, less frequently, nephrogenic diabetes insipidus.[32] Two cohort studies show that a dose-dependent AKI occurs in approximately one-quarter of patients receiving conventional AmB.[32,33] Other factors predisposing to amphotericin nephrotoxicity include the presence of CKD and concomitant use of additional nephrotoxic agents, particularly cyclosporine.[32,33] AmB-induced AKI may not completely resolve: 70% of patients had a serum creatinine greater than or equal to 0.5 mg/dL more than baseline on discharge or death.[33] Sodium loading has been shown to ameliorate conventional AmB nephrotoxicity.[34]

Concerns about kidney toxicity led to the development of several different lipid preparations of AmB. A recent meta-analysis comparing rates of nephrotoxicity between conventional and lipid-associated AmB found that lipid preparations of AmB (irrespective of specific type) led to a 50% to 60% relative risk reduction in the development of nephrotoxicity, albeit at increased cost.[35] With respect to specific lipid preparations, lipid complex AmB and liposomal AmB had similar rates of nephrotoxicity.[36]

Cisplatin

Cisplatin and other platinum-based therapies are commonly used to treat many types of solid tumors,[37] but side effects limit their use. Cisplatin nephrotoxicity is common, occurring in approximately one-third of patients in a dose-dependent manner.[37,38] After entering the renal tubular cells, cisplatin exerts its deleterious effects via several mechanisms, including oxidative injury, inflammation, and apoptosis.[38] Cisplatin may also cause injury via vasoconstriction.[37] In addition to AKI, cisplatin may induce a Fanconi syndrome characterized by urinary loss of phosphorus, uric acid, and glucose, and a type 2 renal tubular acidosis caused by bicarbonate wasting. Hypokalemia and hypomagnesemia are common.[38] Other platinum agents are less nephrotoxic than cisplatin, but still must be used with caution, because the risk is not negligible. Ifosfamide may also cause a nephrotoxic syndrome similar to cisplatin with AKI and Fanconi syndrome.[38]

Similar to other medications, several factors increase the risk of nephrotoxicity. Some are immutable, including older age, female sex, and the presence of chronic liver or kidney disease.[38] Others, such the presence of volume depletion, may be addressed before administration of the medications.

Vancomycin

Vancomycin is a glycopeptide antibiotic that has been used to treat multidrug-resistant gram-positive infections for more than 60 years.[39] Nephrotoxicity has long been associated with its use, first reported caused by impurities from the manufacturing process and later as a bona fide association with the drug itself.[40] The prevalence of kidney injury caused by vancomycin varies widely from study to study, depending on characteristics of the patient population, dose and duration of therapy, definition of AKI, and concomitant use of other nephrotoxins,[39] making it difficult to determine an exact rate. Most studies show that vancomycin-induced nephrotoxicity in patients without predisposing factors is an unusual, and typically reversible, event, occurring in less than or equal to 5% of patients, and often at rates no higher than alternative antibiotics.[40]

Several factors seem to increase the nephrotoxic potential of vancomycin. Risk factors include baseline CKD (serum creatinine >1.7 mg/dL), sepsis, and the need for vasopressors.[41,42] Concomitant administration of nephrotoxins, including CNIs, AGs, AmB, loop diuretics, tenofovir, cephalosporins, and radiocontrast agents, increase the risk of vancomycin-associated AKI.[39,40,43] Hidayat and colleagues[43] found that coadministration of another nephrotoxin increased the rate of vancomycin-induced AKI from 5% to 22%.

Aggressive dosing strategies also predispose to nephrotoxicity. Observational studies suggest that doses greater than or equal to 4 g per day triple the risk.[44] Higher serum trough levels of vancomycin are also associated with more nephrotoxicity. A recent prospective trial showed that trough concentrations greater than or equal to 15 mg/L were associated with greater than a 3-fold increased risk of kidney injury compared with those less than 15 mg/L (29.6% vs 8.9% respectively).[45] Risk also increases as the duration of treatment lengthens. Patients on vancomycin for longer than 2 weeks are 5 times more likely to develop nephrotoxicity compared with those treated for less than 1 week.[39]

Others

Other medications causing tubular damage include methotrexate; the antivirals foscarnet, cidofovir, and tenofovir; pentamidine; and the bisphosphonate zolendronic acid.[5,46,47]

Which medications cause kidney injury via rhabdomyolysis?

In addition to direct tubular toxicity, some medications exert deleterious effects via muscle injury or rhabdomyolysis, with statins being the most common.[48] Observational studies show a 5% to 20% incidence of statin-induced myopathy, although most cases are mild and not associated with AKI.[49] Patients with rhabdomyolysis typically present with diffuse myalgias, a flulike syndrome, and dark, pigment-stained urine, with hematuria on urine dipstick (caused by myoglobin) but no red blood cells on microscopy. In the setting of suggestive clinical signs and symptoms, rhabdomyolysis is diagnosed by showing a creatinine kinase level greater than 10 times the upper limit of normal.

The incidence has been estimated in 3.4 cases per 100,000 patient-years for all patients, but may be higher in select populations or with select statins.[49] Older age, female gender, Asian descent, low body mass index, drug abuse, concomitant untreated hypothyroidism, liver disease or kidney disease, and a family history or previous personal history of statin-induced myopathy imparts a higher risk of statin-induced rhabdomyolysis.[49] One meta-analysis of statin-induced adverse events found that atorvostatin had the highest incidence of rhabdomyolysis and fluvastatin the lowest, although rosuvastatin was not included in this analysis.[50] The development of rhabdomyolysis is dose dependent, and medications that increase the plasma concentrations of statins (such as CNIs, macrolides, amiodarone, azoles, nondihydropyridine CCBs, protease inhibitors, and gemfibrozil) are associated with highest risk.[49]

Which medications injure the kidney via interstitial nephritis?

Acute interstitial nephritis (AIN) is a condition in which kidney dysfunction is accompanied by interstitial inflammation and edema. It is difficult to determine the exact prevalence of AIN, because many cases are not confirmed by biopsy. A recent study documented that 2.7% of all kidney biopsies showed AIN. When limited to biopsies done for AKI, 13% showed AIN.[51] The prevalence of AIN on biopsy has increased from 1.5% between 1994 and 1997 to 4.2% between 2006 and 2009, much of this in the elderly.[51] Whether this increase represents an increase of the number of cases or simply better detection is a matter of debate.

Medications are the most common cause of AIN, with 71% of cases being drug related.[52] Antibiotics, NSAIDs, and protein pump inhibitors (PPIs) are classically implicated in AIN, although many medications, including anticonvulsants, antivirals, and histamine-2 receptor blockers are potential offenders.[53]

Antibiotics, particularly penicillins and β-lactams, are the most common cause of AIN.[54] Most patients (>75%) present with the classic findings of fever, rash, or eosinophilia, several days to 2 weeks after starting the offending agent.[53] Non–β-lactams causing AIN include rifampin,[55] sulfonamides (especially in patients with human immunodeficiency virus and transplants),[56,57] and fluoroquinolones.[58]

NSAID-associated AIN is estimated to occur in 1 out of 5000 to 10,000 patients.[59] NSAID-induced AIN differs from that of antibiotics in several important ways. The duration of time between drug exposure and AIN is longer with NSAIDs (typically 6–18 months) compared with β-lactams, and findings such as eosinophiluria, rash, and fever are less common, occurring in less than 10% of cases.[53] AIN is seen with both nonselective NSAIDs and COX-2 inhibitors.[60]

PPI-induced AIN is also distinct from the β-lactam–induced AIN. The mean duration between exposure to a PPI and the development of AIN is between that of β-lactams and NSAIDs (mean 13 weeks).[61] Similar to NSAIDs, PPI-related disease is less likely to display manifestations of hypersensitivity, such as a fever or a rash. Although many PPIs cause AIN, omeprazole is most often implicated.[61]

The presentation of AIN is variable, and a high degree of suspicion is required for its diagnosis. Symptoms are either absent or nonspecific.[53] As noted earlier, the traditionally recognized signs of fever and rash may be absent depending on the medication involved.

The preceding is not a comprehensive list. Many other medications have been implicated in causing kidney dysfunction by one or a combination of the methods listed earlier.[5,14,18] Readers are encouraged to consult package inserts or the medical literature for particular drugs of interest. **Table 2** provides a summary of the most common nephrotoxic medications.

HISTORY AND EXAMINATION

What aspects of the history and physical examination may be helpful in identifying the cause of AKI in hospitalized patients?

A thorough history is paramount in determining the cause of AKI in a hospitalized patient. AKI may be associated with edema, shortness of breath, weight gain, nausea, vomiting, and confusion, but these findings lack sensitivity and specificity. AKI is often, but not universally, associated with change in urine output. Less common is change in urine color, although dark urine may indicate the presence of glomerular disease or rhabdomyolysis-induced myoglobinuria. Before attributing AKI to a specific medication, it is important to rule out other causes of kidney injury, such as volume depletion, obstruction, and so forth. A careful review of medications, including over-the-counter medications, herbal remedies, and recreational drug use, should be performed, with special attention to the start date, dosage, frequency of use, and, if applicable, prior drug levels. Clinicians should ask about traditional AIN symptoms including arthralgias (seen in 45% of AIN cases), fever (30%), rash, or loin pain (each 21%),[62] recognizing that these too may be nonspecific, and vary depending on the medication involved.[53]

The physical examination should focus on evaluation for systemic signs that suggest a cause for renal failure including fever, rash, purpura, as well as signs that suggest the need for urgent dialysis, such as hypertension, hypoxia, respiratory distress, crackles on lung examination, increased jugular venous pressure, ascites, leg edema, and anasarca.

DIAGNOSIS

What diagnostic testing may help in the evaluation of suspected drug-induced AKI?

As with most cases of AKI, regardless of cause, diagnostic evaluation should include a basic metabolic panel and urinalysis with microscopy. Depending on the suspected cause of the drug-induced AKI, additional testing including urine electrolytes, creatinine kinase, complete blood count with differential, and/or peripheral blood smear may be considered. The usefulness of drug levels (ie, vancomycin or gentamicin levels) once AKI has developed is unclear, because an increased level at that point may reflect the result, rather than the cause, of the AKI.

Radiographic tests lack sensitivity and specificity for drug-induced AKI, including AIN. Although they may be considered if the cause of AKI is unclear, they have limited usefulness in confirming or excluding drug-induced nephrotoxicity.

A renal biopsy is typically unnecessary, but may be considered in cases of prolonged renal injury, particularly when the cause is not apparent, or with suspected glomerular disease. In many cases of drug-induced AKI, withdrawal of the suspected culprit medication with close monitoring for clinical improvement can be a helpful diagnostic tool.

How useful are eosinophilia and eosinophiluria in making a diagnosis of AIN?

The most common laboratory finding in patients with AIN is an increase in blood urea nitrogen and creatinine. Patients may also have hematuria and mild proteinuria, although these are less consistently seen.[53] Eosinophilia and eosinophiluria are often used clinically to confirm an AIN diagnosis, but a critical appraisal of the data shows that these variables are too insensitive and nonspecific for this use.

Eosinophilia is seen in approximately 35% of AIN cases.[54,62] The classic triad of eosinophilia, rash, and fever is encountered in less than 10% of cases.[53]

Eosinophiluria has a sensitivity of 67% and a specificity of 87% for the diagnosis of AIN.[53] Other conditions that may present with eosinophiluria include urinary tract infections (cystitis, prostatitis, and pyelonephritis), atheroembolic disease, acute tubular necrosis, and rapidly progressive glomerulonephritis.

A kidney biopsy is needed for the definitive diagnosis of AIN. Pathology typically shows interstitial inflammation, often, but not invariably, containing eosinophils. Immunofluorescence and electron microscopy are not particularly useful in the diagnosis of AIN, except when they show an alternative disease process.[53] In practice, if AIN is suspected based on the clinical presentation, biopsy may be deferred in the short term while the patient is monitored for renal recovery after withdrawal of the suspected offending agent.

MANAGEMENT

What interventions are most helpful in the treatment of suspected medication-induced AKI?

In general, if a medication is suspected to be playing a role in the development of AKI, all potential nephrotoxic medications should be discontinued and replaced with an equally effective, less nephrotoxic, alternative agent if possible. Doses of remaining medications should be adjusted based on the patient's current GFR.[5,14,63] Unless the patient has clinical evidence of symptomatic volume overload, discontinuation of any prescribed diuretics and a trial of intravenous hydration should be strongly considered.

In most cases of medication-induced AKI, subsequent management is supportive, focusing on stabilization of electrolyte and acid-base abnormalities, stabilizing blood pressure, and close monitoring of volume status and urine output. Consultation with a nephrologist should be considered for patients with AKIN stage 2 to 3 renal injury to help determine the need for renal replacement therapy.

What is the role of systemic steroids in the management of medication-induced AIN?

Treatment of AIN primarily consists of removing the causative agent.[53,64] Often, patients are on multiple potential offending medications, and determining which medication to stop is difficult. In this case, the clinician should be guided by the temporal relationship between the introduction of the medication and the development of AIN.

The role of systemic steroids for the management of AIN remains controversial. Although AIN has long been considered self-limiting and fully reversible once the offending medication is discontinued, renal recovery may takes weeks to months, and some observational studies have found that serum creatinine concentrations remain chronically elevated above baseline in up to 40% of patients.[52,64] To date, there have been no randomized controlled trials to assess the efficacy of systemic steroid use for AIN. Retrospective observational studies have had conflicting results, some showing significant benefit in terms of improvement or normalization of serum creatinine and/or decreased requirement of dialysis,[65] whereas other studies failed to show a significant difference in renal function, particularly in patients with NSAID-induced AIN.[62,66] Based on the available evidence, expert opinion suggests consideration of a short course of moderate-dose to high-dose steroids (prednisone 40–60 mg/d) for 1 week followed by a rapid taper in patients without a clear contraindication and in

cases in which spontaneous recovery is not seen within 1 to 2 weeks of withdrawal of the inciting drug.[53,64,67,68]

PROGNOSIS

What is the prognosis for medication-induced AKI in hospitalized patients?

Based on multiple epidemiologic studies, the mortality for AKI in hospitalized patients is estimated at 10.8% to 32.3%, with rates exceeding 50% in critically ill patients admitted to the intensive care unit (ICU).[1–3,69,70] In their 1-year observational study of hospital-acquired AKI in a single academic tertiary care center, Wang and colleagues[3] found that after adjustment for age, sex, race, serum creatinine concentration on admission, and the severity of illness index, AKI was independently associated with in-hospital mortality with an adjusted odds ratio of 4.43 (95% confidence interval 3.68–5.35). Many of the same factors that are associated with increased risk of developing AKI also predict a worse prognosis once AKI has developed. These risk factors include ICU admission, length of stay in ICU, advanced age, multisystem organ failure ($\geq$4), more severe AKI (AKIN stages 2–3), need for renal replacement therapy, mechanical ventilation, sepsis, severe acute pancreatitis, malignancy, and baseline CKD.

For AKI survivors, full recovery of renal function to preadmission baseline value varies depending on the stage of AKI, with rates of recovery ranging from 71% to 80% in stage 1 AKI to 21% to 58.8% in stage 3 AKI.[3,69,70] The time to achieve full recovery is also more prolonged the higher the stage of AKI. AKI is also a risk factor for progressive CKD after discharge.[71,72,73]

As expected, studies have also found that development of AKI in hospitalized patients significantly increases length of stay and cost, again with higher AKI stage associated with the greatest increase.

PREVENTION

What interventions can be used for all hospitalized patients to decrease their risk of drug-induced AKI?

Risk factor assessment and general preventive measures for avoiding AKI should be considered in all hospitalized patients. General prevention strategies include substituting equally effective, less nephrotoxic medications; avoiding the use of 2 or more nephrotoxic medications concurrently whenever possible; assessing baseline renal function before starting therapy; and close monitoring of renal function throughout therapy, with dose adjustments as needed for fluctuations in GFR. In addition, if modifiable patient risk factors are identified, such as volume depletion, these should be corrected as early as possible.[5,14,63]

In recent years, significant research has focused on earlier detection of AKI, particularly in critically ill patients. Serum creatinine is an insensitive marker, because it is subject to both glomerular filtration and tubular secretion, and its speed of increase from baseline depends on the extent of the acute injury and baseline kidney functional reserve. With the variability in an individual's baseline serum concentration, interpreting single time-point values is difficult, and AKI may not manifest as a detectable increase in creatinine concentrations until 24 to 48 hours following the initial damage.[74] Based on animal and limited human trials to date, novel urinary protein biomarkers seem capable of providing a more sensitive means of detecting AKI, some

with the ability to distinguish between the various mechanisms and anatomic sites of acute injury. Further prospective clinical studies are required to examine the validity of biomarkers after acute drug or toxin exposure, and to determine whether they improve clinical outcomes in routine practice.[74,75]

PERFORMANCE IMPROVEMENT

Two approaches to minimizing the health care risk and cost associated with medication-induced AKI in the hospital setting include the use of electronic health records and computerized physician order entry (CPOE) systems with integrated clinical decision support and greater inclusion of pharmacists as part of the multidisciplinary health care team.

CPOE with decision support may help identify patients with risk factors for drug-induced AKI, as well as those with developing AKI or chronic renal insufficiency. They may also assist with drug dosing based on GFR changes. Although studies of CPOE with or without clinical decision support have shown increased identification of incorrect dosing, improvements in appropriate renal-based dosing, decreased costs, and shorter lengths of hospital stay, studies have also revealed how individual system variations and a lack of optimal provider compliance with system warnings and recommendations can hamper their efficacy.[75–79]

The benefit of pharmacist participation in clinical rounding was highlighted by Leape and colleagues[80] in their 1999 study of critical care pharmacists. Pharmacists' recommendations to prescribers during ICU rounds were reported to reduce the incidence of preventable adverse drug events (ADEs) by 72% and led to a projected annual cost saving of $270,000 (US dollars) for the study's single ICU.[80] Similar results have been seen in studies of pharmacists rounding on general medicine unit teams.[81–84] One single-blinded case-controlled study showed that inclusion of a pharmacist on the general medicine team rounds decreased preventable ADEs by 78%.[83] Another prospective cohort study showed a 51% reduction in preventable medication errors, a significant decrease in the number of patients who experienced an error, and a shorter duration in continuation of an error once it had occurred.[84]

In the aforementioned studies, as well as others, pharmacist interventions included clarification of drug orders, identification of potential problems with continuing therapy after discharge, and recommendations for therapeutic drug monitoring, dosage and frequency adjustments in patients with and without renal impairment, discontinuation of therapy after an appropriate duration, and appropriate use of drugs such as sedatives, analgesics, and antibiotics.[80,81,83]

CLINICAL GUIDELINES

1. The Kidney Disease Improving Global Outcomes (KDIGO) Working Group. KDIGO clinical practice guideline for acute kidney injury. Kidney Int 2012;2(Suppl 1):1–141.
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