Drug-induced acute kidney injury in the critically ill adult: Recognition and prevention strategies

Michael L. Bentley, PharmD, FCCM; Howard L. Corwin, MD, FCCM; Joseph Dasta, MSc, FCCP, FCCM

Acute kidney injury is common in critically ill patients, with an incidence of 20% to 30%. It has been associated with increased mortality, hospital length of stay, and total cost. A number of strategies may be beneficial in identifying at-risk patients. In addition, using preventive measures and avoiding nephrotoxic medications are paramount in reducing the overall incidence. Although multifactorial, drug-induced acute kidney injury may account for up to 25% of all cases of acute kidney injury in this population. This review focuses on the mechanisms of drug-induced acute kidney injury in critically ill adults and offers preventive strategies when appropriate. (Crit Care Med 2010; 38[Suppl.]:S169–S174)

KEY WORDS: acute kidney injury; acute kidney failure; drug-induced

Acute kidney injury (AKI) is common in hospitalized patients, ranging between 4.9% and 7% (1, 2), depending on the patient population and definition used. In the elderly, it may be as high as 60% (3). AKI is also common in patients who are critically ill, having a reported incidence of 20% to 30%, with approximately 6% of those requiring renal replacement therapy (4). The development of AKI has been associated with increased mortality, length of stay, and hospital cost (5). In one study of AKI developing in patients after cardiac bypass surgery, total postoperative costs doubled compared with those in a group of matched controls. Even patients with a small increase in serum creatinine (peak 1.5 times baseline) had total postoperative costs $11,234 higher than controls (6). The epidemiology of AKI in the critically ill is often multifactorial; however, medications have been associated with 15% to 25% of all cases of AKI (7–9).

The medications implicated in causing drug-induced AKI can be classified based on their mechanism of renal injury (Table 1), such as prerenal, intrinsic renal, and postrenal (obstructive), as well as their histopathologic findings (i.e., osmotic nephrosis) (10–13). The mechanisms of toxicity are complex and, in many cases, affect more than one aspect of kidney function. This review focuses on the major types of drug-induced kidney injury seen in the critically ill patient.

Prerenal (alterations in intraglomerular hemodynamics)

Nonsteroidal anti-inflammatory drugs, including the cyclooxygenase inhibitors

Blood flow through the kidney is primarily mediated by vasodilation and vasoconstriction of the afferent and efferent arterioles. The purpose of this autoregulated process is to maintain an adequate intraglomerular pressure, preserving both glomerular filtration and urine output. When blood flow to the kidney is decreased, the normal physiologic response is increased prostaglandin synthesis by the kidney. The enzyme responsible for converting arachidonic acid to the vasodilatory, and proinflammatory, prostaglandin is cyclooxygenase (COX). Under normal circumstances the increased production results in vasodilation of the afferent arterioles leading to greater blood flow through the glomerulus. However, in patients with diseases known to decrease renal perfusion (preexisting renal disease, sepsis, etc.), this response may not be adequate to maintain blood flow through the kidney. Furthermore, this response is blunted by drugs inhibiting prostaglandin synthesis or by those affecting the compensatory vasoconstriction of the efferent arterioles, e.g., angiotensin-converting enzyme inhibitors and angiotensin receptor blockers (14–16).

Nonsteroidal anti-inflammatory drugs (NSAIDs) are used to treat a wide range of acute and chronic medical conditions. Their association with AKI is well documented, and it appears that their greatest potential to cause harm is related to their dose and duration of therapy (14). However, AKI may occur rapidly in patients with preexisting renal disease, in disease states known to decrease renal perfusion, and when administered in combination with known nephrotoxic drugs. All NSAIDs have been associated with AKI, and consideration should be given to either avoid their use or, when indicated, use with extreme caution.

The introduction of COX-2 inhibitors into the market was an attempt to eliminate or greatly reduce the unwanted effects of the nonselective NSAIDs. These agents selectively inhibit the proinflammatory action of the COX-2 enzyme, sparing the favored vasodilatory activity of COX-1. Despite this well-intended approach, renal failure has been associated with COX-2 inhibitors in at-risk patients (17, 18).

Patients most likely to develop AKI that appears to be attributable to intra-

From Department of Pharmacy Services (MLB), Carilion Clinic, Roanoke Memorial Hospital, Roanoke, VA; Section of Critical Care Medicine (HLC), Department of Anesthesiology, Dartmouth-Hitchcock Medical Center, Lebanon, NH; College of Pharmacy (JD), The Ohio State University, Columbus, OH; College of Pharmacy (JD), University of Texas, Austin, TX.

Dr. Dasta is a consultant for Cadence Pharmaceuticals, Eisai Pharmaceuticals, Edge Therapeutics, Inc., Hospira, Myriad Pharmaceuticals, Otsuka, and The Medicines Company; and is on the speaker's bureau for the France Foundation (sponsored by Hospira) and The Medicines Company. The remaining authors have not disclosed any potential conflicts of interest.

For information regarding this article, E-mail: mlbentley@carilionclinic.org

DOI: 10.1097/CCM.0b013e3181de0c60

Table 1. Classification of drug-induced acute kidney injury

Etiology	Agents
Prerenal	NSAIDs, cyclooxygenase inhibitor-2, angiotensin-converting enzyme inhibitors, angiotensin receptor-blocking agents, cyclosporine, tacrolimus, radiocontrast agents, interleukin-2, diuretics
Intrinsic	
Acute tubular necrosis	Aminoglycosides, amphotericin B, radiocontrast agents, antiretrovirals (adefovir, cidofovir, tenofovir, and foscarnet), cisplatin, zoledronate, cisplatin, cocaine
Acute allergic interstitial nephritis	Antimicrobials (penicillins, cephalosporins, sulfonamides, ciprofloxacin, vancomycin, macrolides, tetracyclines and rifampin), NSAIDs, cyclooxygenase inhibitor-2 inhibitors, proton pump inhibitors (omeprazole and lansoprazole), anticonvulsants (phenytoin and valproic acid), cimetidine and ranitidine, diuretics, cocaine
Glomerulonephritis	NSAIDs, ampicillin, rifampin, lithium, penicillamine, hydralazine, gold, mercury, heroin
Postrenal	Acyclovir, methotrexate, sulfadiazine, foscarnet, indinavir, tenofovir, sulfonamides, triamterene, large-dose vitamin C (because of oxalate crystals), guaifenesin, and ephedrine (nephrolithiasis)
Other	
Osmotic nephrosis[a]	Intravenous immunoglobulins, starches, mannitol, radiocontrast agents (in addition to acute tubular necrosis)

NSAIDs, nonsteroidal anti-inflammatory drugs.
[a]Classified based on histopathology.
Adapted from references 10–13.

glomerular hemodynamic alterations after NSAID use are those with preexisting renal disease or prerenal states (heart failure, volume depletion), or who use concomitant nephrotoxins (18). NSAID-induced AKI is usually reversible once the offending agent is discontinued.

Besides the effects NSAIDs have on the intraglomerular hemodynamics of the kidney, they have been associated with AKI through other mechanisms. NSAID-associated AKI may occur as a result of interstitial nephritis, nephrotic syndrome, or papillary necrosis (10).

Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers

The efferent arterioles also play an important role in maintaining adequate intraglomerular hemodynamics. Vasoconstriction of these arterioles is primarily mediated by angiotensin II. When renal perfusion decreases, in addition to the effects of the vasodilatory prostaglandins on the afferent arterioles, vasoconstriction of the efferent vessels occurs in an attempt to maintain adequate intraglomerular pressure.

Drugs such as the angiotensin-converting enzyme inhibitors and angiotensin receptor blockers reduce angiotensin II synthesis, or its activity, resulting in efferent arteriole vasodilatation. As a result, the transglomerular pressure decreases, leading to a reduction in glomerular filtration rate and a decline in urine production. Patients at most risk for AKI are those with decreased renal perfusion (heart failure, volume depletion) (19). Patients with bilateral renal artery stenosis are also at increased risk (20, 21).

Injury that occurs from angiotensin-converting enzyme inhibitors and angiotensin receptor blockers is usually reversible. However, mild elevations in serum creatinine may be tolerated to maximize the morbidity and mortality benefits of these agents. In patients with creatinine values of >1.4 mg/dL, increases of up to 30% (that stabilize within the first 2 mos of therapy) have been associated with improved long-term renal function. Angiotensin-converting enzyme inhibitors should be continued unless serum creatinine exceeds 30% from baseline or if hyperkalemia develops (22).

Calcineurin inhibitors

Since their release, calcineurin inhibitors (CNI), e.g., cyclosporine and tacrolimus, have dramatically improved graft and patient survival. Nephrotoxicity associated with these agents is common and occurs either acutely (hemodynamically mediated) or after chronic use (interstitial damage). Acute injury is believed to be dose- and concentration-dependent; however, it may be seen in patients with therapeutic blood concentrations. AKI is reversible after dose reduction. In contrast, CNI-induced chronic renal failure is associated with interstitial nephritis and is usually irreversible (23, 24). Generally, it is not associated with dose or concentration of causative agent. Achieving the goals of reduced nephrotoxicity and preventing graft rejection may require newer strategies (25, 26); however, cyclosporine and tacrolimus continues to be first-line therapy for many patients.

Although not totally understood, CNI-induced AKI is believed to result primarily from afferent vasoconstriction, although efferent vasoconstriction probably occurs as well. This, at least in part, may be attributable to increased production of vasoconstrictive factors, such as thromboxane A_2 and endothelin, and a reduction in renal vasodilatory prostaglandins and inhibition of nitric oxide (23, 24, 27–29). As a result, renal plasma flow is decreased, leading to a reduction in glomerular filtration rate.

CNI-associated AKI may develop early in therapy. It can occur within a few days to several weeks after the initiation of either cyclosporine or tacrolimus. Clinical and laboratory findings may include hypertension, reduced glomerular filtration rate, increased serum creatinine, hyperkalemia, and renal tubular acidosis (30).

In addition to therapeutic drug monitoring, the avoidance of other potentially nephrotoxic agents (particularly NSAIDs) and the maintenance of adequate renal blood flow are important preventive strategies. CNI-induced AKI generally improves once the dose of cyclosporine or tacrolimus is reduced or the drug is discontinued.

Intrinsic AKI

Drug-induced intrinsic AKI includes acute tubular necrosis, acute interstitial nephritis (AIN), glomerulonephritis, and thrombotic microangiopathy. Acute tubular necrosis and AIN are discussed in detail.

Acute tubular necrosis

Acute tubular necrosis has been associated with several medications com-

monly used in the intensive care setting (e.g., aminoglycosides and amphotericin B). AKI associated with contrast dye is also commonly seen in the intensive care unit and is discussed later. A number of medications less commonly used in the intensive care setting can cause acute tubular necrosis and lead to AKI. Although not discussed in this review, they include, but are not limited to, many of the antiretrovirals (adefovir, cidofovir, tenofovir, and foscarnet), cisplatin, and zoledronate, a bisphosphonate (31, 32).

Aminoglycosides

Aminoglycoside (AG) antibiotics have been available to treat Gram-negative infections for many years and their renal toxicity is well-documented. Toxicity can occur early or late in therapy but can be minimized with therapeutic drug monitoring. AG-associated nephrotoxicity can range from mild and rapidly reversible to severe requiring a prolonged recovery time. In the latter, renal replacement therapy is often required. AGs are nonprotein-bound and readily undergo glomerular filtration. As a result, intratubular concentration can easily become toxic when trough serum concentrations remain high for extended periods.

The mechanism for toxicity centers on the cationic charge of these drugs. AGs bind to the negatively charged acidic phospholipids of the brush border membrane in the proximal tubule, where they undergo rapid transport into lysosomes. Once inside the lysosome, they interfere with cellular function affecting protein synthesis and interrupting normal function of the mitochondria and the sodium-potassium-adenosine triphosphatase pump (33–35). The number of cationic groups on an AG molecule, at least in part, may determine the degree of toxicity associated with each drug (36–38). The most nephrotoxic AG appears to be neomycin, whereas streptomycin may be least toxic. Gentamicin, tobramycin, and amikacin are in the intermediate category (38–40).

Laboratory and clinical manifestations of AG-induced acute tubular necrosis generally appears 5 to 10 days after a toxic insult and at times may be seen after discontinuation of AG therapy. Both an increase in serum creatinine and blood urea nitrogen may be seen, as well as hypomagnesemia, hypocalcemia, and hypokalemia. In general, AG-induced AKI results in nonoliguric renal failure (10, 41).

The risk of toxicity is most likely multifactorial and includes prerenal states (i.e., volume depletion), preexisting renal or liver disease, concomitant nephrotoxic drug administration, advanced age, more frequent use of iodinated contrast agents, and diabetes (42). Cumulative dose (especially when associated with persistent elevated trough concentrations) may also be associated with an increased risk of toxicity. In addition, and as discussed, the type of AG may also play a role.

Strategies to minimize toxicity include adequate hydration, avoidance of concomitant nephrotoxic medications, serial monitoring of renal function, therapeutic drug monitoring, and, potentially, extended interval AG dosing (i.e., once daily). This dosing technique relies primarily on two pharmacodynamic properties exhibited by AGs. First, their bactericidal activity is concentration-dependent. For traditional dosing, and in patients with normal renal function, 1 to 2 mg/kg (gentamicin or tobramycin) is administered every 8 hrs. In patients receiving extended-interval therapy, the dose is administered at either 5 or 7 mg/kg (gentamicin or tobramycin), once daily. The resultant concentration exceeds the minimal inhibitory concentration of most Gram-negative organisms by at least 10 times. This maximizes the area under the curve to minimal inhibitory concentration and the peak-to-minimal inhibitory concentration ratios. The second pharmacodynamic property relies on the postantibiotic effect, i.e., continued killing of the organism once the drug concentration falls below the minimal inhibitory concentration (43, 44). Favorable pharmacodynamic properties and the potential of less nephrotoxicity (lower trough concentrations) have made this dosing strategy common in clinical practice. Extended-interval amikacin (15–20 mg/kg) dosing is also used clinically, and the same pharmacodynamic principles apply.

Amphotericin B

Although used less commonly today because of the availability of newer antifungal agents (e.g., itraconazole, voriconazole, miconazole, and caspofungin), amphotericin B is still used by many clinicians to treat life-threatening fungal infection. The incidence of amphotericin B-associated AKI has been reported to be as high as 80% and appears to be associated with the cumulative amphotericin B dose.

The mechanism of nephrotoxicity is most likely associated with several factors. The first is by activating vasoconstrictive prostaglandins that affect the afferent arterioles. Vasoconstriction results in decreased blood flow, i.e., decreased oxygen delivery, followed by cell necrosis and death. Second, amphotericin B binds to epithelial cells in the proximal and distal tubule-collecting ducts. This injury results in increased sodium and potassium permeability and, ultimately, increased oxygen requirements (44–47).

Numerous risk factors are associated with amphotericin B nephrotoxicity and include volume depletion, preexisting renal insufficiency, the use of concomitant nephrotoxins, and single and cumulative dose (46). Laboratory and clinical signs of toxicity are increased serum creatinine and blood urea nitrogen, and oliguria may be seen. Electrolyte wasting (sodium, potassium, and magnesium) may be seen in patients with or without nephrotoxicity.

Several strategies to minimize toxicity have been suggested. Sodium loading before each dose of amphotericin B followed by adequate volume replacement may be beneficial (46). Lipid-based formulations have also been developed to lessen the likelihood of toxicity. Although beneficial, in most clinical settings they are reserved for patients with preexisting renal dysfunction (48).

Radiocontrast media

The use of intravenous contrast dye as a diagnostic tool is common, and its associated nephrotoxicity is well-known. Like many drugs or disease processes resulting in AKI, the incidence of contrast-induced nephropathy (CIN) varies depending on the definition used or on the procedure requiring contrast administration, and is influenced by underlying risk factors (in particular, chronic renal failure). The incidence of AKI ranges from 0% to 34% (49), with the overall incidence today decreasing because of greater awareness, preventive strategies, and availability of less toxic agents. However, as the mean age of the population increases, along with associated comorbid conditions, the true incidence of CIN will continue to vary. If AKI occurs, then it is usually seen within 3 days after administration of the contrast agent. An increase in serum creatinine generally occurs within 24 hrs and typically peaks in 5 days.

The etiology of CIN is multifactorial. Vasoconstriction is caused by the release of adenosine, endothelin, and other renal vasoconstrictors. In addition and because iodinated contrast is water-soluble, it concentrates in the renal tubules and collecting ducts, where it causes direct cellular injury and death (50). In addition, dyes that are hyperosmolar may further compromise renal perfusion by causing an osmotic diuresis (osmotic nephrosis is discussed in a later section) and impaired blood flow. Decreased flow is a direct result of the increased viscosity from some of these agents (51). A detailed review of CIN pathophysiology is outside the scope of this report, and the reader is referred to recent reviews (52, 53).

A number of strategies to reduce the incidence of CIN have been described. Identifying at-risk patients (53–55) is important (patients with preexisting renal disease, hypertension, diabetes mellitus, advanced age, or concomitant nephrotoxic drugs) so appropriate measures can be undertaken to limit the toxic effects associated with the contrast agent. Contrast agents having a higher osmolality may be more likely to cause CIN (56, 57), but data are conflicting (58). However, the volume of contrast administered is likely an independent predictor of CIN, i.e., the more contrast given, the greater the chance of toxicity. An important area of interest has been protection from CIN using hydration with crystalloid solutions and/or the use of N-acetylcysteine. Both normal saline and sodium bicarbonate infusions have shown promise and are used widely. However, studies have not demonstrated a clear advantage with either approach (59). N-acetylcysteine, although initially promising, in fact may not provide adequate protection particularly if used alone (60).

If contrast is indicated, then it is advisable to choose a low-osmolar agent using the minimal amount necessary for the diagnostic procedure. In addition, adequate hydration using a saline solution, with either sodium chloride or sodium bicarbonate (infused at 3 mL/kg/hr for 1 hr, followed by 1 mL/kg/hr for the subsequent 6 hrs), should be used to furthur decrease the likelihood of AKI.

AIN

Drug-induced AIN accounts for 3% to 15% of all drug-induced AKI (41, 61). It is a hypersensitivity reaction that affects both renal tubules and the interstitium. Many drugs are associated with AIN, including antibiotics (penicillins, cephalosporins, sulfonamides, ciprofloxacin, vancomycin, and rifampin), NSAIDs and selective COX-2 inhibitors, proton pump inhibitors (omeprazole and lansoprazole), and allopurinol, to name a few (10, 41). AKI seen with the chronic administration of calcineurin inhibitors, cyclosporine and tacrolimus, also has been associated with AIN.

Symptoms include fever, rash, and eosinophilia, which may not be seen for several weeks after a first exposure. However, with a second exposure, these symptoms may be seen within 3 to 5 days. Eosinophiluria and sterile pyuria are common renal manifestations (11, 41).

In patients presenting with AKI and receiving medications known to cause AIN, AIN should be ruled out by clinical signs, examination of the urine, and, if necessary, renal biopsy. In general, AIN is self-limiting once the offending medication is discontinued. Recovery may take weeks to a few months but is usually reversible. AKI associated with the chronic use of CNI is an exception to this rule. In this case, AIN is often irreversible.

Osmotic nephrosis

Osmotic nephrosis is often seen with hyperosmolar agents. The most notable agents are high-osmolar radiocontrast agents, intravenous immune globulins, and intravenous starches (62). In addition, mannitol has also been associated with osmotic nephrosis (63). AKI associated with the use of intravenous immune globulins is believed to be secondary to the stabilizing agent, sucrose. On biopsy, the renal proximal tubular cells are swollen with cytoplasmic vacuolization and edema results in narrowing of the lumen whereas the glomeruli are spared (62).

Nephrotoxicity is most commonly seen in patients who have preexisting risk factors, such as administration of concomitant nephrotoxins, the elderly, and those with underlying renal insufficiency. After the administration of intravenous immune globulins, the onset of renal failure is usually seen within 2 to 4 days. In general, renal failure is reversible after supportive care and, in some cases, renal replacement therapy is needed.

Although controversial, AKI associated with the use of the hydroxyethyl starches resembles AKI seen with other drugs known to cause osmotic nephrosis. Volume expansion using these agents should be undertaken with caution in patients known to have underlying risk factors for AKI. In addition, lower molecular substitution and lower-molecular-weight starches (e.g., pentastarch) may reduce the risk of AKI. However, studies confirming these findings are conflicting.

Tubular obstruction

A number of medications are known to cause tubular obstruction. Examples include acyclovir, methotrexate (MTX), sulfadiazine, foscarnet, indinavir, tenofovir, and triamterene (also associated with hemodynamically mediated AKI). Obstruction from the active drug and/or its metabolites can occur in the renal tubules or lower urinary tract, or can result in nephrolithiasis. Risk factors may be specific to the offending agent; however, preexisting renal dysfunction and poor hydration are common. Of these agents, acyclovir and MTX are discussed in further detail.

Acyclovir is cleared by the kidney through glomerular filtration and tubular secretion. Approximately 62% to 91% of the drug is eliminated unchanged (64, 65). In low-flow states (hypoprofession secondary volume depletion) acyclovir, primarily an insoluble drug, may precipitate in the renal tubal resulting in obstruction. Urinalysis typically shows crystalluria, hematuria, and pyuria (64–66).

AKI after acyclovir administration is most often associated with high-dose intravenous therapy and develops 24 to 48 hrs after the insult. Typically, it is reversible after discontinuation and adequate hydration. However, in some cases, short-term hemodialysis may be necessary. Strategies to reduce the likelihood of acyclovir-induced AKI include adequate hydration, dose reduction in patients with preexisting renal insufficiency, avoidance of rapid infusions, and avoidance of other nephrotoxic medications.

Like acyclovir, MTX-induced AKI is more commonly associated with high-dose therapy and preexisting renal dysfunction. Renal clearance is >90%, and precipitation in the tubules occurs after low-flow states. However, unlike acyclovir, the urine solubility of MTX is pH-dependent and is most soluble in alkaline urine (67).

Strategies to reduce MTX-induced AKI (especially with high-dose therapies) include adequate hydration and urine alkalinization. Leucovorin is commonly administered as "rescue" therapy after high-

dose MTX administration. It does not treat or prevent AKI, but rather it is used to prevent cell destruction from the toxic effects of MTX that may have accumulated (68).

Computerized prescriber order entry and clinical decision support as a means to improve prescribing and preventing drug-induced nephrotoxicity

Interest in systems and processes to improve patient safety has steadily gained acceptance in the healthcare community. Much of this has been driven by the Institute of Medicine's report, "To Err Is Human: Building a Safer Health Care System" (69). Although many types of medical errors are possible, preventable adverse drug events appear to be the most common medication-related error (70–72). Systems could be developed to alert prescribers when patients have risk factors for nephrotoxicity relating to the drugs being prescribed. In addition, patients with renal impairment may be at greater risk because many drugs are cleared by the kidneys and, if not dose-adjusted, can accumulate, leading to unwanted effects, i.e., preventable adverse drug events.

Computerized prescriber order entry with or without clinical decision support (CDS) can assist in reducing many medication errors. Chertow et al (73) used a real-time computerized decision support system to assist clinicians when prescribing medications to hospitalized patients. The system was able to determine whether a patient had renal insufficiency (defined as an estimated creatinine clearance of <80 mL/min by the Cockroft-Gault equation) and, in real time, modify the prescribed dose and frequency. Despite an overall improvement in the "appropriateness of dosing," 49% of orders were still considered inappropriate in the intervention group. They speculated that some physicians may have been reluctant to reduce the dose, particularly among more critically ill patients, whereas others may have disregarded the advice altogether in favor of their own practice.

Nash et al (74) investigated a slightly different approach. Their computerized order entry system provided the prescriber with medication dose and route of administration; however, it did not provide CDS. Their strategy was to develop a medication safety reporting system to detect inappropriate medications or doses. Each morning the medication safety reporting system generated a printed report of "violations." Data were collected during three time periods (baseline, intervention by a quality-improvement nurse, and intervention by a pharmacist) and the "excessive dose" was compared. The rates of excessive dosage were 23.2% at baseline, 17.3% in the quality-improvement nurse intervention group, and 16.8% in the pharmacist's intervention group.

Computerized prescriber order entry with or without CDS can assist in reducing many medication errors. CDS, for example, could alert a prescriber when a patient has risk factors for AKI that are related to the drug being prescribed. Although computerized prescriber order entry and CDS have shown promise in improving patient safety, they have been met with skepticism. In addition to the aforementioned studies, numerous authors have found less than optimal compliance when these systems have been put into practice (75–77).

Conclusion

Drug-induced AKI is common in critical illness and accounts for 15% to 25% of all cases of renal failure seen in this population. It is associated with increased mortality, length of stay, and hospital cost. A better understanding of the proposed mechanisms of injury and the associated clinical course will assist the clinician when evaluating patients with suspected drug-induced AKI. In addition, preventive strategies (e.g., computerized prescriber order entry with CDS focused on renal dosing) should be implemented whenever possible to decrease the likelihood of injury. Other approaches include identifying the at-risk patient (e.g., patients with preexisting renal dysfunction, elderly, and those with other acute insults to the kidney), using protection/prevention strategies (hydration before and during intravenous contrast administration), and, if possible, avoiding medications known to be nephrotoxic.

References

1. Hou SH, Bushinsky DA, Wish JB, et al: Hospital-acquired renal insufficiency: a prospective study. *Am J Med* 1983; 74:243–248
2. Nash K, Hafeez A, Hou S: Hospital-acquired renal insufficiency. *Am J Med* 2002; 39: 930–936
3. Kohli HS, Bhaskaran MC, Muthukumar T, et al: Treatment-related acute renal failure in the elderly: A hospital-based prospective study. *Nephrol Dial Transplant* 2000; 15: 212–217
4. Uchino S: The epidemiology of acute renal failure in the world. *Curr Opin Crit Care* 2006; 12:538–543
5. Hoste E, Kellum JA: Incidence, classification, and outcomes of acute kidney injury. *Contrib Nephrol* 2007; 156:32–38
6. Dasta JF, Kane-Gill S, Durtschi AJ, et al: Costs and outcomes of acute kidney injury (AKI) following cardiac surgery. *Nephrol Dial Transplant* 2008; 23:1970–1974
7. Hoitsma AJ, Wetzels, JF, koene RA: Drug-induced nephrotoxicity. *Drug Saf* 1991; 6:131–147
8. Uchino S, Kellum JA, Bellomo R, et al: Acute renal failure in critically ill patients: A multinational, multicenter study. *JAMA* 2005; 294:813–818
9. Mehta RL, Pascual MT, Soroko S, et al: Spectrum of acute renal failure in the intensive care unit: The PICARD experience. *Kidney Int* 2004; 66:613–1621
10. Taber SS, Pasko DA: The epidemiology of drug-induced disorders: The kidney. *Expert Opin Drug Saf* 2008; 7:679–690
11. Guo X, Nzerue C: How to prevent, recognize, and treat drug-induced nephrotoxicity. *Cleve Clin J Med* 2002; 69:289–312
12. Schetz M, Dasta J, Goldstein S, et al: Drug-induced acute kidney injury. *Curr Opin Crit Care* 2005; 11:555–565
13. Farrugia E, Larson TS: Drug-induced renal toxicity. *Postgrad Med* 1991; 90:241–248
14. Whelton A: Nephrotoxicity of nonsteroidal anti-inflammatory drugs: Physiologic foundations and clinical implications. *Am J Med* 1999; 106:13S–24S
15. Whelton A, Hamilton CW: Nonsteroidal anti-inflammatory drugs: Effects on kidney function. *J Clin Pharmacol* 1991; 31:588–598
16. Brater DC, Harris C, Redfern JS, et al: Renal Effects of COX-2-Selective Inhibitors. *Am J Nephrol* 2001; 21:1–15
17. Ahmad SR, Kortepeter C, Brinker A, et al: Renal failure associated with the use of celecoxib and rofecoxib. *Drug Saf* 2002; 25: 537–544
18. Swan SK, Rudy DW, Lasseter KC, et al: Effect of cyclooxygenase-2 inhibition on renal function in elderly persons receiving a low-salt diet. A randomized, controlled trial. *Ann Intern Med* 2000; 133:1–9
19. Cruz CS, Cruz LS, Silva GR, et al: Incidence and predictors of development of acute renal failure related to treatment of congestive heart failure with ACE inhibitors. *Nephron* 2007; 105:77–83
20. Hricik DE, Browning PJ, Kopelman R, et al: Captopril induced functional renal insufficiency in patients with bilateral renal artery stenosis, or stenosis in a solitary kidney. *N Engl J Med* 1983; 308:377–381
21. Textor SC, Novick AC, Steinmuller DR, et al: Renal failure limiting antihypertensive therapy as an indication for renal vasocularization. *Arch Intern Med* 1983; 143:2208–2211
22. Bakris GL, Weir MR: Angiotensin-converting

enzyme inhibitor-associated elevations in serum creatinine: Is this a case for concern? *Arch Intern Med* 2000; 160:685–693
23. Olyaei AJ, de Mattos AM, Bennett WM: Nephrotoxicity of immunosuppressive drugs: New insight and preventive strategies. *Curr Opin Crit Care* 2001; 7:384–389
24. Naesens M, Kuypers DR, Sarwal M: Calcineurin inhibitor nephrotoxicity. *Clin J Am Soc Nephrol* 2009; 4:481–508
25. Stallone G, Infante B, Gesualdo L: There is a choice for immunosuppressive drug nephrotoxicity: Is it time to change? *J Nephrol* 2009; 22:326–332
26. Farkas SA, Schnitzbauer AA, Kirchner G, et al: Calcineurin inhibitor minimization protocols in liver transplantation. *Transpl Int* 2009; 22:49–60
27. Olyaei AJ, de Mattos AM, Bennett WM: Immunosuppressant-induced nephropathy: pathophysiology, incidence and management. *Drug Saf* 1999; 21:471–488
28. Bobadilla NA, Tapia E, Franco M, et al: Role of nitric oxide in renal hemodynamic abnormalities of cyclosporine nephrotoxicity. *Kidney Int* 1994; 46:773–779
29. Lanese DM, Conger JD: Effects of endothelin receptor antagonists on cyclosporine-induced vasoconstriction in isolated rat renal arterioles. *J Clin Invest* 1993; 91:2144–2149
30. Remuzzi G, Perico N: Cyclosporin-induced renal dysfunction in experimental animals and humans. *Kidney Int* 1995; 52:S70–S74
31. Rho M, Perazella MA: Nephrotoxicity associated with antiretroviral therapy in HIV-infected patients. *Curr Drug Saf* 2007; 2:147–154
32. Markowitz GS, Fine PL, Stack JI, et al: Toxic acute tubular necrosis following treatment with zoledronoate, *Kidney Int* 2003; 64: 281–289
33. Mingeot- Leclercq MP, Tulkens PM: Aminoglycosides: Nephrotoxicity. *Antimicrob Agents Chemother* 1999; 43:1003–1012
34. Swan SK: Aminoglycoside nephrotoxicity. *Semin Nephrol* 1997; 17:27–33
35. Olbricht CT, Fink M, Gutjahr E: Alterations in lysosomal enzymes of the proximal tubule in gentamicin nephrotoxicity. *Kidney Int* 1991; 39:639–646
36. Humes HD: Aminoglycoside nephrotoxicity. *Kidney Int* 1988; 33:900–911
37. Humes HD, Weinberg JM, Krauss TC: Clinical and pathophysiologic aspects of aminoglycoside nephrotoxicity. *Am J Kidney Dis* 1982; 2:5–29
38. Bennett WM, Wood CA, Houghton DC, et al: Modification of experimental aminoglycoside nephrotoxicity. *Am J Nephrol* 1986; 8:292–296
39. Meyer RD: Risk factors and comparisons of clinical nephrotoxicity of aminoglycosides. *Am J Med* 1986; 80:119–125
40. Matzke GR, Lucarotti RL, Shapiro HS: Controlled comparison of gentamicin and tobramycin nephrotoxicity. *Am J Nephrol* 1983; 3:11–17
41. Pannu N, Nadim MK: An overview of drug-induced acute kidney injury. *Crit Care Med* 2008; 36:S216–S223
42. Oliveira J, Silva CA, Barbieri CD, et al: Prevalence and risk factors for aminoglycoside nephrotoxicity in intensive care units. *Antimicrob Agents Chemother* 2009; 53: 2887–2891
43. Turnidge J: Pharmacodynamics and dosing of aminoglycosides. *Infect Dis Clin North Am* 2003; 17:503–528
44. Burgess DS: Pharmacodynamic principles of antimicrobial therapy in the prevention of resistance. *Chest* 1999; 115:S19–S23
45. Anaissie EJ, Vartivarian SE, Abi-Said D, et al: Fluconazole versus amphotericin B in the treatment of hematogenous candidiasis: A matched cohort study. *Am J Med* 1996; 101: 170–176
46. Sabra R, Branch RA: Amphotericin B nephrotoxicity. *Drug Saf* 1990; 5:94–108
47. Deray G: Amphotericin B nephrotoxicity. *J Antimicrob Chemother* 2002; 49:S37–S41
48. Dupont B: Overview of the lipid formulations of amphotericin B. *J Antimicrob Chemother* 2002; 49:S31–S36
49. Weisbord SD, Mor MK, Resnick AL, et al: Prevention, incidence, and outcomes of contrast-induced acute kidney injury. *Arch Intern Med* 2008; 168:1325–1332
50. McCullough PA: Contrast-induced acute kidney injury. *J Am Coll Cardiol* 2008; 51: 1419–1428
51. Persson PB, Hansell P, Liss P: Pathophysiology of contrast medium-induced nephropathy. *Kidney Int* 2005; 68:14–22
52. McCullough PA, Adam A, Becker CR, et al: Risk prediction of contrast-induced nephropathy. *Am J Cardiol* 2006; 98:27K–36K
53. Dangas G, Iakovou I, Nikolsky E, et al: Contrast-induced nephropathy after percutaneous coronary interventions in relation to chronic kidney disease and hemodynamic variables. *Am J Cardiol* 2005; 95:13–19
54. Mehran R, Aymong ED, Nikolsky E, et al: A simple risk score for prediction of contrast-induced nephropathy after percutaneous coronary intervention: Development and initial validation. *J Am Coll Cardiol* 2004; 44: 1393–1399
55. Krumlovsky FA, Simon N, Santhanam S, et al: Acute renal failure: Association with administration of radiographic contrast material. *JAMA* 1978; 239:125–127
56. Barrett BJ, Carlisle EJ: Meta-analysis of the relative nephrotoxicity of high- and low-osmolality iodinated contrast media. *Radiology* 1993; 188:171–178
57. Rudnick MR, Goldfarb S, Wexler L, et al: Nephrotoxicity of ionic and nonionic contrast media in 1196 patients: a randomized trial: The Iohexol Cooperative Study. *Kidney Int* 1995; 47:254–261
58. Davidson C, Stacul F, McCullough PA, et al: Contrast medium use. *Am J Cardiol* 2006; 98:42K–58K
59. Brar SS, Hiremath S, Dangas G, et al: Sodium bicarbonate for the prevention of contrast induced-acute kidney injury: A systematic review and meta-analysis. *Clin J Am Soc Nephrol* 2009; 4:1584–1592
60. Stacul F, Adam A, Becker CR, et al: Strategies to reduce the risk of contrast-induced nephropathy. *Am J Cardiol* 2006; 98:59K–77K
61. Michel DM, Kelly CJ: Acute interstitial nephritis. *J Am Soc Nephrol* 1998; 9:506–515
62. Dickenmann M, Oettl T, Mihatsch MJ: Osmotic nephrosis: acute kidney injury with accumulation of proximal tubular lysosomes due to administration of exogenous solutions. *Am J Kidney Dis* 2008; 51:491–503
63. Visweswaran P, Massin EK, Dubose TD: Mannitol-induced acute renal failure. *J Am Soc Nephrol* 1997; 8:1028–1033
64. Sawyer MH, Webb DE, Balow JE, et al: Acyclovir-induced renal failure. Clinical course and histology. *Am J Med* 1988; 84:1067–1071
65. Keeney RE, Kirk LE, Bridgen D: Acyclovir tolerance in humans. *Am J Med* 1982; 73: 176–181
66. Briden D, Rosling AE, Woods N: Renal function after acyclovir intravenous injection. *Am J Med* 1982; 73:182–185
67. Treon SP, Chabner BA: Concepts in use of high-dose methotrexate therapy. *Clin Chem* 1996; 42:1322–1329
68. Adamson PC, Widemann BC: Understanding and Managing Methotrexate Nephrotoxicity. *Oncologist* 2006; 11:694–703
69. Kohn LT, Corrigan JM, Donaldson MS:To Err is Human: Building a Safer Health Care System. Washington, DC, National Academy Press, 1999
70. Bates DW, Cullen DJ, Laird N, et al: ncidence of adverse drug events and potential adverse drug events. Implications for prevention. ADE Prevention Study Group. *JAMA* 1995; 274:29–34
71. Lesar TS, Briceland LL, Delcoure K, et al: Medication prescribing errors in a teaching hospital. *JAMA* 1990; 263:2329–2334
72. Lesar TS, Briceland LL, Stein DS: Factors related to errors in medication prescribing. *JAMA* 1997; 277:312–317
73. Chertow GM, Lee J, Kuperman GJ, et al: Guided medication dosing for inpatients with renal insufficiency. *JAMA* 2001; 286: 2839–2844
74. Nash IS, Rojas M, Hebert P, et al: Reducing excessive medication administration in hospitalized adults with renal dysfunction. *Am J Med Qual* 2005; 20:64–69
75. Gallanter WL, Didomenico RJ, Polikaitis A: A trial of automated decision support alerts for contraindicated medications using computerized physician order entry. *J Am Med Inform Assoc* 2005; 12:269–273
76. Weingart SN, Toth M, Sands DZ, et al: Physicians' decisions to override computerized drug alerts in primary care. *Arch Intern Med* 2003; 163:2625–2631
77. Rind DM, Safran C, Phillips RS, et al: Effect of computer-based alerts on the treatment and outcomes of hospitalized patients. *Arch Intern Med* 1994; 154:1511–1517