An overview of drug-induced acute kidney injury

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The complex nature of critical illness often necessitates the use of multiple therapeutic agents, many of which may individually or in combination have the potential to cause renal injury. The use of nephrotoxic drugs has been implicated as a causative factor in up to 25% of all cases of severe acute renal failure in critically ill patients. Acute tubular necrosis is the most common form of renal injury from nephrotoxin exposure, although other types of renal failure may be seen. Given that this is a preventable cause of a potentially devastating complication, a comprehensive strategy should be used to avoid nephrotoxicity in critically ill patients including: accurate estimation of pre-existing renal function using serum creatinine–based glomerular filtration rates, avoidance of nephrotoxins if possible, ongoing monitoring of renal function, and immediate discontinuation of suspected nephrotoxins in the event of renal dysfunction. (Crit Care Med 2008; 36[Suppl.]:S216–S223)

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Acute kidney injury (AKI) is a relatively common condition in the intensive care unit and occurs in 20% to 30% of critically ill patients, with approximately 6% eventually requiring renal replacement therapy (1). The development of AKI in this setting is associated with increased mortality, increased hospital length of stay, and increased healthcare resource use and costs (2). The complex nature of critical illness often necessitates the use of multiple therapeutic agents, many of which may individually or in combination have the potential to cause renal injury. While in most cases the etiology of AKI is multifactorial (e.g., sepsis, ischemia/hypoperfusion), several recent large epidemiologic studies have shown that nephrotoxic drugs were contributing factors in 19% to 25% of cases of severe acute renal failure in critically ill patients (3, 4).

The use of potentially nephrotoxic medications is often unavoidable; however, the contribution of treatment-induced renal injury is frequently overlooked as a preventable cause of AKI. This article will review several types of nephrotoxicity associated with therapeutic agents commonly used in the intensive care unit and outline recommendations with respect to the usage and monitoring of these medications in critical illness.

Mechanisms of Nephrotoxicity

Drugs with direct nephrotoxic effects may induce renal injury by several mechanisms (Table 1). Most commonly, renally excreted drugs can exert direct toxic effects on renal tubules, inducing cellular injury and death in acute tubular necrosis, or induce inflammation in the renal interstitium in acute interstitial nephritis (AIN).

Other types of nephrotoxic tubular injury include osmotic nephrosis induced by hypertonic solutions and tubular obstruction by drug precipitation (e.g., crystalline nephropathy). Nephrotoxic acute tubular necrosis is generally a dose-dependent phenomenon that predictably occurs in patients at high risk for renal injury (older patients, pre-existing renal disease, multiple nephrotoxic agents used) and is characteristically noninflammatory in nature. In contrast, acute (allergic) interstitial nephritis is an idiosyncratic inflammatory response to drug exposure. Drugs also may be indirectly vnephrotoxic by modulating intrarenal blood flow, thus rendering the kidneys vulnerable to ischemia and injury in the case of decreased renal blood flow. Therapeutic agents have been associated with the development of glomerular disease or vasculitis; however, these are relatively rare complications of medical therapy and will not be discussed in detail in this review.

Drug-Induced Acute Tubular Necrosis

Aminoglycosides. Aminoglycosides (AGs) continue to be commonly used for the management of severe Gram-negative infections, despite well established ototoxicity and nephrotoxicity. AKI as defined by a 0.5–1 mg/dL increase in serum creatinine values is a relatively common complication of treatment with a reported frequency ranging between 10% and 20% (5, 6). Aminoglycosides are non–protein bound drugs that are not metabolized and are primarily excreted by glomerular filtration. The cationic properties of these agents facilitate binding to the tubuloepithelial membrane in the proximal tubule, resulting in rapid intracellular transport (7, 8). The number of cationic groups on the molecules determines the facility with which these drugs are transported across the cell membrane and are an important determinant of toxicity (5, 9). Neomycin is associated with the most nephrotoxicity; gentamicin, tobramycin, and amikacin are intermediate, and streptomycin is the least nephrotoxic (9–12). Several hypotheses have been proposed to explain the nephrotoxic effects of these agents. Intracellular accumulation of AG within lysosomes is thought to interfere with normal cellular function, such as protein synthesis and mitochondrial function, eventually leading to cell death (13). AGs

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Table 1. Mechanisms of nephrotoxin-induced acute renal failure

Direct nephrotoxicity
Tubuloepithelial injury
Acute tubular necrosis (e.g., aminoglycosides)
Osmotic nephrosis (e.g., hypertonic solutions, intravenous immune globulin)
Interstitial nephritis
Acute allergic interstitial nephritis (e.g., penicillins)
Chronic interstitial nephritis (e.g., calcineurin inhibitors)
Papillary necrosis (e.g., NSAIDs)
Glomerular disease
Glomerulonephritis (e.g., gold, penicillamine, ACE inhibitors)
Renal vasculitis (e.g., hydralazine)
Obstructive uropathy
Crystalline nephropathy (e.g., acyclovir, indinavir)
Indirect nephrotoxicity
Decreases intrarenal blood flow (e.g., ACE inhibitors, NSAIDs)

ACE, angiotensin-converting enzyme; NSAIDs, nonsteroidal anti-inflammatory drugs.

also are known to stimulate the calcium-sensing receptor on the apical membrane, which induces cell signaling and cell death (14, 15).

Risk factors for aminoglycoside nephrotoxicity include the type of AG, high peak serum levels, cumulative dose, the duration and frequency of administration, and patient-related factors such as age, pre-existing renal dysfunction, hypoalbuminemia, liver dysfunction, decreased renal perfusion, and the use of concomitant nephrotoxic drugs (16–20).

Several approaches have been evaluated in both animals and humans as potential treatments to attenuate the nephrotoxicity of aminoglycosides. Several investigators have demonstrated that calcium supplementation reduces the nephrotoxic effect, likely through competitive inhibition of calcium channels in the proximal tubule (21–23). Similarly, calcium channel blockers also have been shown to attenuate aminoglycoside nephrotoxicity (24). The protective effect of concomitant use of B lactam antibiotics has been recognized for several years, although the mechanism by which this may occur is somewhat unclear (25–27). More recent investigations have evaluated the role of antioxidants in renoprotection (28–30). Aminoglycoside therapy induces the generation of reactive oxygen intermediates and the release of iron by cortical mitochondria (31). Antioxidants such as vitamins E (30) and C (32), selenium (30), and probucol (28), as well as deferoxamine (32), have shown protective effects in animal studies; however, large-scale studies of these interventions have not been attempted, and none of these approaches are commonly used in clinical practice.

Once-daily dosing of aminoglycosides is the only clinical approach that is commonly used to reduce nephrotoxicity (6). The rationale for the efficacy of consolidated aminoglycoside dosing against Gram-negative bacteria is based on two pharmacodynamic properties of AG: a) the bacteriocidal mechanism of action is concentration dependent; and b) prolonged postantibiotic effect (33). The uptake of aminoglycosides in the proximal tubule is saturable; therefore, the administration of large doses may not result in increased renal uptake, and in fact is associated with decreased uptake because the drug is given less often (34). The clinical and bacteriologic efficacy of once-daily antibiotic administration has been studied extensively over the past decade. To date, at least five meta-analyses have been published that have shown similar efficacy and decreased cost with once-daily dosing; however, none has shown a significant reduction in nephrotoxicity (35–39). There were significant differences among the studies with respect to coadministration of nephrotoxic drugs and type of aminoglycosides used; therefore, the studies may not have been suitable for pooled analysis. Nonetheless, even with consolidated dosing, AG nephrotoxicity remains common in high-risk subsets such as the elderly, where up to 15% of patients develop renal dysfunction (40).

Appropriate monitoring of AG drug levels remains a controversial topic. Conventionally, a nomogram has been used to determine dosing intervals for consolidated dosing regimens; however, this approach assumes stability of renal function, which may be inappropriate in critically ill patients. Monitoring of trough levels has been one recommended approach for addressing this issue (41, 42), although trough levels have not been shown to be associated with nephrotoxicity in multiple daily dosing regimens (43), and renal toxicity can occur despite careful monitoring of drug levels.

Clinical evidence of AG-induced acute tubular necrosis is seen within 5 to 10 days of initiation of AG treatment. AG-induced acute renal failure is generally nonoliguric, and may be associated with decreased urine-concentrating ability and urinary magnesium wasting. It is generally reversible after discontinuation of the drug; however, supportive renal replacement therapy may be required. We recommend that alternative antimicrobials should be considered when possible in patients at high risk for AG nephrotoxicity. If required and consolidated AG dosing is used, renal function should be assessed daily to monitor for changes in renal function, and trough levels should be followed to guide dosage adjustments.

Amphotericin B. The use of antifungals has become more commonplace in intensive care units, as the prevalence of fungemia (specifically candidemia) has increased in critically ill patients. For decades, amphotericin B was the drug of choice because of its broad spectrum of activity and its wide availability; however, its use has been sharply curtailed in recent years because of its considerable side effects (specifically, nephrotoxicity) and the availability of newer less toxic agents.

Approximately 80% of patients who receive treatment with amphotericin B will experience some renal dysfunction (44). There are several mechanisms by which amphotericin B is thought to induce renal dysfunction: by directly binding to tubular epithelial cells in the cortical collecting duct, resulting in altered cell permeability; by causing sodium, potassium, and magnesium wasting; and by directly causing afferent arteriolar (preglomerular) vasoconstriction (45, 46). Risk factors for amphotericin B nephrotoxicity include pre-existing renal insufficiency, hypokalemia, volume depletion, the use of concomitant nephrotoxins, and large individual and cumulative dosages (47–49). A number of preventive strategies have been studied to minimize the associated nephrotoxicity, including sodium loading (50) and longer infusion rates (51). While some have shown a reduction in nephrotoxicity, these studies are very small and used low-risk patients. Lipid-based formulations of amphotericin B also are available, which may produce less nephrotoxicity. However, these agents are considerably more expensive. The recent introduction of alternative antifungal agents such as itraconazole, voriconazole, and caspofungin has largely supplanted the use of amphotericin B in high-risk patients with renal impairment; however, it continues to be used widely in patients with normal renal function because of its relatively low cost and broad spectrum of activity.

Given the presence of many underlying risk factors for nephrotoxicity in critically ill patients, we recommend that amphotericin B should be avoided in this patient population if alternative therapies are available. If it is used, sodium loading with intravenous hydration is recommended to attenuate vasoconstrictive effects, and longer infusion times also should be considered. Renal function and serum electrolytes (specifically potassium) should be monitored during treatment.

Vancomycin. Vancomycin hydrochloride is the standard therapy for treatment of methicillin-resistant *Staphylococcus aureus* infections (52). Recent data from the 2004 Centers for Disease Control and Prevention National Nosocomial Infections Surveillance system indicate that the prevalence of methicillin-resistant *S. aureus* exceeds 50% in U.S. hospitals (53). The synergistic nephrotoxicity of combination therapy involving vancomycin and aminoglycosides is well established, with a reported frequency of acute renal failure in the range of 20% to 30% (54); however, the nephrotoxicity of vancomycin alone increasingly is being recognized as high-dose therapy has become more common for the treatment of methicillin-resistant *S. aureus*.

Vancomycin is excreted by glomerular filtration, 80% to 90% in an unaltered form. The reported frequency of vancomycin-related nephrotoxicity ranges from 6% to 30% (55); however, most reported cases have had additional risk factors for acute renal failure, which makes it difficult to determine the true risk of treatment. The mechanism by which it exerts its nephrotoxicity is unknown. Independent risk factors for nephrotoxicity include the use of concomitant nephrotoxic agents, age, duration of therapy, and drug levels achieved (55, 56). Trough levels >15 μg/mL are associated with increased risk of nephrotoxicity and peak levels also have been associated with increased nephrotoxicity.

The dosing of vancomycin requires careful consideration of renal function and estimated glomerular filtration rate. Trough levels should be monitored frequently in patients with fluctuating renal function.

Nephrotoxic Acute Interstitial Nephritis

Acute interstitial nephritis (AIN) is an acute inflammatory condition that specifically affects the renal tubules and interstitium and occurs as a hypersensitivity reaction to medications, most commonly antibiotics, but may also be associated with other conditions including sepsis, immune-mediated disease, and glomerular diseases. AIN is associated with a wide variety of drugs, many of which are commonly used in the critical care setting (Table 2), and accounts for 3% to 15% of all drug-induced acute renal failure (34). Renal dysfunction usually occurs 7–14 days after exposure, but may occur earlier in a previously sensitized individual. Systemic symptoms may be associated with B lactam antibiotics and sulfa drugs including fever, eosinophilia, and rash. Renal manifestations include sterile pyuria, eosinophiluria, and characteristic findings of an inflammatory infiltrate in the renal interstitium, as well as granulomas on renal biopsy. Reactions are generally idiosyncratic, and management involves removal of the suspected causative agent and supportive therapy. In most cases, AIN is self-limited and reversible; however, recovery may take weeks to months and a small proportion of patients may require temporary renal replacement therapy. Several case series suggest that treatment of biopsy-proven AIN with steroids (prednisone, 1 mg/kg/day) for up to 4 wks may accelerate the rate of recovery (57–59).

Table 2. Drugs commonly associated with acute interstitial nephritis

NSAIDs, including selective COX-2 inhibitors
Penicillins and cephalosporins
Rifampin
Sulfonamides, including trimethoprim-sulfamethoxazole, furosemide, bumetanide, thiazide-type diuretics
Ciprofloxacin
Cimetidine
Allopurinol
Omeprazole and lansoprazole
Indinavir
5-aminosalicylates

NSAIDs, nonsteroidal anti-inflammatory drugs; COX, cyclooxygenase.

AIN should be considered in any critically ill patient who develops acute renal failure while on any of the medications outlined above in the absence of another explanation. There have been conflicting reports regarding the efficacy of steroid treatment for AIN; however, given the relatively low toxicity of a short-term steroid regimen, it should at least be considered in cases of AIN not associated with nonsteroidal anti-inflammatory drugs (NSAIDs).

Hemodynamically Mediated Nephrotoxic Acute Renal Failure

Angiotensin-Converting Enzyme Inhibitors and Angiotensin Receptor Blockers. Intraglomerular pressure and consequently glomerular filtration rate (GFR) are normally regulated by the vasomotor tone of the afferent (preglomerular) and the efferent (postglomerular) arterioles. In situations of decreased renal blood flow, intraglomerular pressures are maintained by vasodilation of the afferent arteriole and vasoconstriction of the efferent arteriole. Medications that affect the renin angiotensin system also have the potential of causing or exacerbating acute renal failure by modulating intrarenal blood flow. Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers decrease intraglomerular pressure by selective inhibition of angiotensin II–mediated vasoconstriction at the efferent arteriole. As a consequence, the serum creatinine may increase by as much as 30% after initiating angiotensin-converting enzyme inhibitors or angiotensin receptor blockers without being a cause for concern, a reflection of angiotensin II inhibition (60, 61). This apparent decline in GFR is seen 3–5 days after initiating therapy and stabilizes within 7 days. This action is beneficial in proteinuric renal disease or diabetic renal disease in which high intraglomerular pressures are associated with progression of renal disease; however, in situations involving a reduction in renal perfusion (bilateral renal artery stenosis, shock of any cause, or decreased intravascular volume) these drugs will further decrease intraglomerular pressure, precipitating prerenal failure.

The most common scenario in which angiotensin-converting enzyme inhibitors may be associated with AKI is in the presence of decompensated heart failure. Several recent studies show that 20% to 25% of patients admitted with congestive heart failure will develop renal dysfunction (62, 63). Reasons for progressive renal failure in this setting include overdiuresis resulting in intravascular volume depletion, critical renal artery stenosis, or patients with acute decompensation who have a precipitous drop in cardiac output. Even with optimal management, however, some patients are so angiotensin II-dependent that discontinuation of

these agents may be required in favor of alternative agents for afterload reduction (nitrates and hydralazine) (64). The plasma creatinine and potassium concentrations should be carefully monitored in critically ill patients.

Nonsteroidal Anti-inflammatory Drugs (NSAIDs). In most circumstances, NSAIDs do not pose a significant risk to patients with normal renal function. However, in situations in which renal perfusion may be diminished (decreased effective circulating volume), which are relatively common with critically ill patients, the inhibition of prostaglandin-induced vasodilation with the use of NSAIDs may further compromise renal blood flow and exacerbate ischemic injury. The renal effects of NSAIDs do seem to be dependent on the type, dose, and duration of treatment (65). Indomethacin is thought to be the most likely drug to impair renal function, and aspirin the least likely (65). Patients at high risk of NSAID-induced nephrotoxicity include patients with pre-existing renal dysfunction, severe cardiovascular or hepatic failure, or the concomitant use of other potentially nephrotoxic medications, such as aminoglycosides, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers (65, 66).

Cyclooxygenase (COX)-2 inhibitors were introduced with speculation that they would reduce the frequency of NSAID-induced end-organ toxicity by sparing the homeostatic COX-1 enzyme, which is necessary for normal cell function. While differences in gene regulation between the COX isomers provide a molecular basis for specific COX-2 selective inhibitors, in fact the COX-2 isoform also is constitutively expressed and up-regulated in the kidney, where it plays a role maintaining homeostasis, particularly in the state of effective circulating volume depletion (67, 68). AKI and hyperkalemia attributable to the use of COX-2 inhibitors has been reported; however, all patients also had additional risk factors including pre-existing renal dysfunction and true or effective volume depletion (69–71). Despite the initial promise of a more favorable side-effect profile, COX-2 inhibitors essentially are equivalent to other classes of NSAIDS with respect to their nephrotoxic potential (69).

The requirement for NSAIDS should be considered carefully in high-risk critically ill patients. If used, indomethacin should be avoided and consideration should be given to using NSAIDs with shorter half lives, such as sulindac.

Vasopressors. Critically ill patients with hemodynamic compromise often are treated with vasopressor agents to support tissue and organ perfusion. Vasoconstrictor agents may cause renal ischemia if used in patients who have been inadequately volume-resuscitated. Despite the lack of evidence to support its use, low dose or "renal" dose dopamine is still commonly used to treat or to prevent renal dysfunction in this setting. Several meta-analyses have been published on this topic. None has found a benefit with respect to overall survival or avoidance of dialysis (72–74).

There is no evidence to support the routine use of low-dose dopamine for nephroprotection. Adequate resuscitation requires volume repletion in addition to the judicious use of vasopressors when indicated.

Calcineurin Inhibitors. Despite the dramatic improvement in both allograft half-life and patient survival since the introduction of calcineurin inhibitors (CNI) in 1983, clinical use of CNIs often is limited by their nephrotoxic effect, which can be presented as two distinct and well-characterized forms: acute and chronic nephrotoxicity. Calcineurin inhibitor–induced AKI may occur as early as a few weeks or months after initiation of therapy. The clinical manifestations of CNI-induced renal dysfunction include reduction of GFR, hyperkalemia, hypertension, renal tubular acidosis, increased resorption of sodium, and oliguria. The acute adverse effects of calcineurin inhibitors on renal hemodynamics are thought to be directly related to the cyclosporine (CsA) or tacrolimus dosage and blood concentration and can be managed by dose reduction. This is in contrast to calcineurin inhibitor–induced chronic nephropathy, which is largely irreversible and can occur independently of acute renal dysfunction, CNI dosage, or blood concentration.

Although the exact mechanism of nephrotoxicity is not fully understood, several factors have been implicated in the pathogenesis of CNI nephrotoxicity (75). Experimental models of acute CsA toxicity revealed that CsA administration is associated with afferent and efferent arteriolar vasoconstriction, with predominating preglomerular vasoconstriction that results in a significant reduction of renal plasma flow and GFR (76–78). The precise mechanism by which CsA induces renal vasoconstriction has not been established clearly. Results from several studies indicate that vascular dysfunction induced by CsA results from an increase in vasoconstrictor factors that include endothelin, thromboxane, and angiotensin II, as well as a reduction of vasodilator factors such as prostacyclin and nitric oxide (79–82).

Cyclosporine and tacrolimus differ with respect to side effects; however, the available data comparing nephrotoxicity are conflicting. While some studies have suggested that tacrolimus may be associated with a decreased severity of renal dysfunction in comparison to CsA (83–89), other investigators have demonstrated no difference between the two CNIs (90).

With the introduction of sirolimus in transplantation, it was hoped that its lack of nephrotoxicity in animal models would be translated in humans to improve immunosuppression with minimal effect on renal function. Unfortunately, several recent studies suggest that sirolimus has inherent nephrotoxicity, such as development of proteinuria and delay in recovery from ischemia-reperfusion injury. In addition, several studies have shown that the nephrotoxicity associated with CNIs is exacerbated when used in combination with sirolimus (91).

Studies have been conflicting on the protective effect of calcium channel blockers on the preservation of renal function for patients receiving CNIs. In a multicenter, prospective, randomized, placebo-controlled study in 118 cadaveric renal transplant recipients receiving CSA, the use of calcium channel blocker resulted in a significantly better allograft function at 2 yrs and demonstrated an improvement in graft function as assessed by serum creatinine and GFR, which was independent of lowered blood pressure (92).

Osmotic Nephrosis

The purported nephrotoxic effect of hyperosmolar therapeutic agents has been debated vigorously. Changes in proximal tubular cells and incipient renal failure after the administration of intravenous sucrose were first observed in the early 1940s (93). Since that time, similar pathological changes and the development of AKI have been observed in association with a number of other hyperosmolar agents, including high osmolar radiocontrast, intravenous immune globulin (IVIG) (94), and hydroxyethyl starches (95).

IVIG is often prescribed for the management of immune-mediated disorders in the intensive care unit. The basis for IVIG nephrotoxicity is speculated to be the sucrose that is added to these solutions as a stabilizing substance. More than 50 cases of IVIG nephrotoxicity have been reported (96). IVIG-related nephrotoxicity appears to follow a predictable clinical course. Most reported patients have had pre-existing renal impairment and are elderly, which may be a surrogate for unrecognized renal impairment. Renal failure develops within 2–4 days of administration and tends to be oliguric and reversible, although renal replacement therapy has been required in approximately one third of reported cases. Renal biopsy shows a distinctive pattern of injury: swollen proximal tubular cells with cytoplasmic vacuolization, and narrowing and occlusion of the tubular lumen from cellular edema with characteristic sparing of the glomeruli. While no studies specifically have addressed the issue of reducing nephrotoxicity, the administration of IVIG over a longer duration may reduce its nephrotoxic potential.

Hydroxyethyl starches also are commonly used to expand plasma volume in hemodynamically unstable patients. Renal injury resembling osmotic nephrosis has been associated with the use of these products, although the data for this is controversial. High molecular weight hydroxyethyl starches, and hydroxyethyl starches with a high C2–C6 molar substitution ratio, may be more nephrotoxic (97, 98). Given this association, these products should be used cautiously in patients with pre-existing renal impairment. If they are used, lower osmolality agents are preferable and the daily dosage (33 mL/kg/day) should not be exceeded.

Tubular Obstruction

Treatment and life expectancy of patients infected with human immunodeficiency virus have improved dramatically since the initiation of highly active antiretroviral therapy. Despite evidence of prevention and slowing of the progression of human immunodeficiency virus–associated nephropathies with the use of highly active antiretroviral therapy, over the past decade there has been a growing literature of case reports describing the nephrotoxicities associated with these antiretroviral therapies. Among all of the antiretroviral medications, the protease inhibitor indinavir and the reverse transcriptase tenofovir most commonly have been associated with nephrotoxicity.

Indinavir has been known to cause crystal-induced renal failure, the development of nephrolithiasis and AKI due to tubulointerstitial nephritis, or obstructive nephropathy. Approximately two thirds of patients receiving indinavir develop asymptomatic crystalluria. Besides the usual risk factors for nephrolithiasis (decreased fluid intake), high dose indinavir, urine pH >6, and concomitant treatment with trimethoprim-sulfamethoxazole or acyclovir also are risk factors for the development of indinavir-associated nephrolithiasis (99).

Tenofovir has been associated with a reversible proximal tubule dysfunction, including the development of a Fanconi syndrome, nephrogenic diabetes insipidus, and AKI. Although low-grade proteinuria has been described, nephrotic range proteinuria is rare. The onset is usually within 5–12 months after initiation of therapy, and recovery usually occurs within a few months following the discontinuation of tenofovir (100). While the exact mechanism of tenofovir-induced nephrotoxicity is not known (because many of the patients who developed nephrotoxicity also were receiving ritonavir, a protease inhibitor), some have suggested that the concomitant use of ritinavir may raise the plasma concentration of tenofovir and increase the risk for renal dysfunction (101).

Three recent reviews provide a more comprehensive review of nephrotoxicity associated with highly active antiretroviral therapy, in addition to dosing modifications in patients with reduced renal function, drug-drug interaction involving these medications, and renal toxicities of other antiretroviral agents (102–104).

CONCLUSIONS

Emerging data demonstrate that even small reversible changes in renal function in critically ill patients are associated with adverse outcomes (105). Medication-related renal dysfunction is common in the critically ill for a number of possible reasons, including increased patient complexity with other coexistent risk factors for AKI (e.g., sepsis, hypotension); polypharmacy; overestimation of preexisting renal function, particularly in elderly patients; and inaccurate and insensitive methods of assessing acute changes in renal function.

Surprisingly little information is available to guide us with respect to avoiding these complications in critical illness; therefore, we make the following opinion-based recommendations. 1) Identify patients at high risk of kidney injury (the elderly, pre-existing chronic kidney disease, hemodynamic instability, sepsis). Serum creatinine–based GFR estimation equations may be helpful in detecting occult pre-existing chronic kidney disease (106). These equations have the same limitations as serum creatinine and overestimate renal function in hospitalized patients, but may be slightly more accurate in detecting baseline renal disease, which has implications for drug dosing. 2) Avoid nephrotoxins in high-risk patients if alternatives exist. 3) Ensure all medications are dosed to estimated GFR and carefully monitor and re-evaluate renal function. 4) A clinical pharmacist in the critical care setting can reduce dosing errors and may prevent or limit nephrotoxin exposure (107). 5) When in doubt about the nephrotoxic effect of a medication, hold all potentially offending drugs. Consider AIN in your differential diagnosis.

Despite the fact that drug-induced renal dysfunction is a common and preventable condition in critically ill patients, there is a paucity of information available regarding the epidemiology of this problem or about effective measures to prevent it. Given the grave consequences of renal dysfunction in this patient population, future research efforts should be directed toward better defining this problem and testing systematic strategies for prevention.

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