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Drug-Associated Acute Kidney Injury: Who's at risk?

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Abstract

The contribution of nephrotoxic medications to the development of acute kidney injury (AKI) is becoming better understood with the rise in incidence of AKI in children. Treatment of AKI is not yet available, so prevention continues to be the most effective approach. There is an opportunity to mitigate severity and prevent the occurrence of AKI if children at increased risk are identified early and nephrotoxins are used judiciously. Early detection of AKI is limited by the dependence on serum creatinine as an indicator. Promising new biomarkers may offer early detection of AKI prior to the rise in serum creatinine. Early detection of AKI is evolving and offers opportunities for better management of nephrotoxins. However, identification of patients at increased risk will remain an important first step both to focus the use of biomarker testing and to aid in its interpretation.

Keywords

Acute Kidney Injury (AKI); Nephrotoxic; Drug-Associated; Critical Illness; Drug-Related Side Effects; Adverse Drug Reactions; Pharmacovigilance

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Introduction

The incidence of acute kidney injury (AKI) is rising and the associated mortality is significant with a 25.3% 28-day mortality in critically ill children [1]. It is prudent to develop preventative measures, risk stratification models, and treatment strategies to address this significant public health problem. It is necessary to identify patients at highest risk for developing AKI to promote increased monitoring and minimize or eliminate exposure to potential risk factors. Among hospitalized children, nephrotoxic drug exposure is one of the most common contributors to AKI [2] and accounts for approximately 16% of cases of AKI [3]. Critically ill patients are at the highest risk for drug-associated AKI given comorbidities, sepsis, hypotension, polypharmacy, and poor estimation of renal function [4, 5]. Unfortunately, no effective treatment for AKI is available and avoidance of nephrotoxic medications is one of the few modifiable risk factors; although, this can be a challenge, particularly in critically ill patients. It is useful to identify the children most susceptible to drug-associated AKI to find the balance between using a medication (or combinations) with known nephrotoxic potential and delaying nephrotoxin initiation in a patient who requires the medication. Risk factors for drug-associated AKI may not be the same as those of AKI from other causes, however there are no large-scale studies done to assess this comparison [6]. Risk factors specific to some populations are described in the literature and will be discussed in this review. We will also discuss the definition of AKI, pediatric populations susceptible to drug-associated AKI, nephrotoxic medication use as an exposure for AKI, and ongoing research for prevention.

What is AKI?

In order to identify AKI, we first need to define it. Identifying AKI based on ICD-9 codes grossly underestimates the prevalence of AKI when compared to staging based on serum creatinine values [7, 8]. In 2012, in response to the need for standardized definitions for AKI, the Kidney Disease Improving Global Outcomes (KDIGO) AKI subcommittee developed a staging system for acute kidney injury (Table 1) [9]. This was a unifying definition, taking into account the Risk, Injury, Failure, Loss, End Stage (RIFLE) and Acute Kidney Injury Network (AKIN) criteria which had been previously used and validated [9], as well as the pRIFLE system developed for children [10]. Ultimately the KDIGO criteria was developed to include the elements described in these prior staging systems, but added qualifiers of a glomerular filtration rate (GFR) of less than 35 mL/min/1.73m² for individuals less than 18 years of age or the initiation of renal support for the maximum stage of AKI [11]. The goals of defining a universal staging system for AKI include quality assurance, standardization of comparison for epidemiologic and clinical studies, and to correlate AKI with clinical outcomes such as death and dialysis [12]. The KDIGO criteria have been validated in both critically ill and non-critically ill pediatric populations showing increased length of mechanical ventilation, hospital length of stay, cost and mortality with stepwise increase in AKI stage [13, 14].

Limitations of serum creatinine and urine output

The current method of assessing renal function is reliant on measurements of serum creatinine and urine output. It is best to assess AKI by stage using both serum creatinine and urine output, when available, to best categorize patients for outcome stratification and management [15]. Although serum creatinine is the current standard biomarker to assess renal function, it is suboptimal. The half-life of serum creatinine in an adult male is estimated at 3.85 hours, but can increase to 77 hours with declining renal function [16]. Given the significant adaptability and functional reserve of the kidney, serum creatinine only starts to rise when more than 50% of renal functional mass has been lost [17], serving as a late marker for renal dysfunction. Failure to correct serum creatinine for fluid overload may also underestimate serum creatinine [18]; thus fluid resuscitation in critically ill patients can cause dilution of serum creatinine with subsequent inaccurate calculation of estimated GFR as well as inaccurate diagnosis and staging of AKI [19, 20]. Finally, with prolonged critical illness, less creatinine is produced making it less reflective of renal function [19, 20].

Who develops AKI?

Prior studies have shown that the prevalence of AKI ranges from 5 to 41% depending on the definition of AKI that was used, as well as which population was being studied [21–23]. This includes both community-acquired and hospital-acquired AKI, which are sometimes difficult to differentiate. In critically ill pediatric patients who develop AKI, renal dysfunction occurs within the first 24 hours of admission in about half of patients [24], which often suggests community-acquired AKI. Overall, the rates of AKI, or its identification, have increased by more than nine fold between the 1980's and early 2000's [25], and the etiology of AKI has changed from primarily intrinsic renal disease to systemic illness and nephrotoxic medication use [17, 26, 27]. Most cases of AKI are multifactorial in nature [3, 28].

Of the many known risk factors and patient-specific susceptibilities that contribute to AKI (see Table 2), nephrotoxic medication administration provides one of the few potentially modifiable risk factors if the drug in question can be removed or replaced. Incidence and risk factors for drug-associated AKI are described in a number of population sub-sets (Table 2). Several large studies identified that in 16–25% of cases, nephrotoxic medication exposure is linked to the development of AKI in the adult population [29–31]. In the same population, there is a 53% greater odds of developing AKI for each nephrotoxic medication administered to a patient [30]. In non-critically ill children exposed to three or more nephrotoxic medications or at least three days of intravenous aminoglycoside therapy, the incidence of AKI is reported to be 30% [32]. Non-critically ill children who developed AKI had a significantly greater odds of exposure to at least one nephrotoxic drug, and the intensity of AKI increased with increased nephrotoxic drug exposure [2]. Conversely, increasing age can be a protective factor against developing drug-associated AKI in non-critically ill children [2].

While these studies are insightful, there is a notable lack of standardization for identifying and grading nephrotoxic agents [33]. Many studies use a list of nephrotoxic medications derived from formularies, and some of the most commonly described nephrotoxic

medications are listed in Table 3. Several studies used definitions of significant medication exposure as concomitant administration of three or more potentially nephrotoxic agents [32, 34]. While several medications were studied for nephrotoxic potential, the actual contribution of each medication to development of renal dysfunction remains unclear. AKI is often multifactorial in nature, so indication bias is a major confounding variable. For example, patients with sepsis are also more likely to receive nephrotoxic medications, so the degree of contribution of either medication use or the underlying condition (e.g. sepsis, heart failure) to development of AKI is often difficult to parse out.

Mechanism of Drug-Associated AKI

Categorizations of drug-associated AKI are made based on the underlying mechanism of renal injury. Direct nephrotoxicity occurs from tubuloe epithelial injury, interstitial nephritis, glomerular injury or obstructive nephropathy whereas indirect nephrotoxicity develops from decreased renal blood flow [4, 31]. There are pro-inflammatory processes and alterations in the renal vasculature that cause cell injury, and cellular-based changes associated with AKI have been identified and continue to be under investigation [27]. Animal models show that AKI produces a pro-inflammatory response with increased levels of inflammatory cytokines including tumor necrosis factor and interleukins-1 β , -6, and -8 [35].

Phenotypes of Drug-Associated AKI

A panel of international pediatric and adult nephrologists and pharmacists developed a standardized description of the phenotype for drug-associated kidney disease in hospitalized patients [36]. The four general categories include AKI, glomerular disorders, nephrolithiasis and tubular dysfunction, and underlying mechanisms can either be dose-dependent or dose-independent (as in acute interstitial nephritis) [36]. The authors concede that multi-drug exposures and concurrent AKI risk factors make the use of these criteria challenging. While this phenotype description still requires validation, the hope is to improve the recognition of drug-associated kidney disease.

Who is at risk for drug-associated AKI?

Critical Illness

Critically ill children are at increased risk for AKI from any cause and are particularly susceptible to drug-associated AKI. Studies in adults show that sepsis is the most common contributing factor for AKI in critically ill patients [29]. The kidney undergoes a decrease in renal perfusion as well as increase in exposure to inflammatory mediators in sepsis, and damage can be exacerbated by hypotension and development of acute tubular necrosis (ATN) [20]. While necessary management in hypotensive patients, vasopressors have been identified as a risk factor for AKI in critically ill adults [30]. High abdominal pressures due to injury, surgery, or ascites from poor hepatic function can cause renal vascular compression and decreased renal perfusion [20]. Not only can critical illness contribute to AKI, prolonged mechanical ventilation can be a direct effect of AKI. Critically ill children who developed AKI were ventilated for 2.3 days longer than their counterparts who did not develop AKI and there was a step-wise increase in length of mechanical ventilation by AKI

stage [13]. Cardiac dysfunction, which is often present concomitantly with critical illness, will be discussed further in the following section.

Children with systemic disease may develop AKI from either multi-organ dysfunction itself, or from its treatment (use of nephrotoxic therapy) [3]. A pediatric-focused study showed that intensive care unit (ICU) patients who developed AKI were exposed to more nephrotoxic medications with between 2.3 and 18.5 times increased odds of developing AKI when exposed to beta-lactam antibiotics, glucocorticoids, non-steroidal anti-inflammatory drugs (NSAID) and opioids [23].

Critically ill patients have constantly fluctuating pharmacokinetics because of factors such as changing serum creatinine and alterations in fluid status, which makes medication dosing difficult and adds to the risk of AKI [20]. For critically ill adults receiving aminoglycoside therapy, there can be up to an 83% variability in pharmacokinetics and pharmacodynamics between two successive doses of the medication [37] and risk for aminoglycoside-associated AKI increases in patients with hypoalbuminemia [38]. There has to be a balance between giving a high enough medication dose to ensure adequate concentration at the site of infection, address bacterial resistance, account for increased volume of distribution and altered protein binding while avoiding medication toxicity and addressing altered renal clearance [5]. Critically ill patients with AKI are about 16 times more likely to experience an adverse drug event, particularly because of changing organ function (with changing GFR), alterations in pharmacokinetics, and polypharmacy [39].

Cardiac dysfunction

Children who have cardiac dysfunction are at increased risk for renal dysfunction. Heart failure leads to decreased renal perfusion with potential for development of ATN, which would be exacerbated by addition of agents that decrease renal perfusion such as angiotensin converting enzyme-inhibitors (ACE-I), angiotensin receptor blockers (ARB), or NSAIDs [20]. In children admitted with heart failure, AKI often develops and is associated with prolonged length of stay, mortality and need for mechanical ventilation [40]. Poor cardiac output and decreased renal blood flow may lead to fluid retention and increased systemic vascular resistance, which can worsen heart failure symptoms [40], proving that AKI is both a symptom of and contributor to other organ dysfunction. In children who underwent cardiac surgery, AKI occurred in 42% of cases, and of those patients, a significant proportion were exposed to either gentamicin or NSAIDs in the post-operative period [41]. Furosemide, which is often used as an afterload reducer in children with cardiac dysfunction, may potentiate AKI when used in conjunction with vancomycin or NSAID therapy [42, 43].

Oncologic disease

Advances in diagnosis, treatment and bone marrow transplant in oncologic diseases have improved patient survival. This group of patients are at particularly high risk for AKI and long-term renal sequelae because of the advances in this field, specifically in relation to nephrotoxic exposure. In one study assessing AKI in the pediatric ICU, HUS and hemato-oncologic pathologies represented 36% of the cases [21]. Rapid cell breakdown, which may result from initiation of chemotherapy in children with leukemia and lymphoma, can lead to

uric acid nephropathy or crystallization of calcium phosphate in the kidney [44]. Renal injury associated with tumor lysis syndrome is associated with either blockage of the tubular lumen from crystal precipitation or alterations in renal blood flow [27].

Nephrotic Syndrome

Children who are hospitalized with nephrotic syndrome are at increased risk for AKI via multiple mechanisms including intravascular volume depletion, infection, and exposure to potential nephrotoxic medications. A recent retrospective multicenter study showed that the incidence of AKI in children hospitalized with active nephrotic syndrome was significant, with 58.6% of children having at least one episode of AKI during their hospital stay [45]. Exposure to nephrotoxic medications was associated with increased risk for development of AKI. Over half of the episodes of AKI developed after admission to the hospital, and half of the children were given at least one nephrotoxic medication [45], showcasing that judicious use of nephrotoxic medications may help prevent some of these episodes of AKI. ACEs and ARBs should be used with caution in patients with nephrotic syndrome since it increases the risk of AKI in those who are already intravascularly volume-depleted [26].

Neonates

The incidence of AKI in critically ill neonates ranges between 8% and 24%, associated with varying mortality rates between 10% and 61% [46]. One of the difficulties in researching neonatal AKI is the lack of a unified definition for AKI. Using serum creatinine to define AKI is particularly ineffective in the neonatal period given a rapidly changing GFR in the first two weeks of life with alterations in renal blood flow [46]. Premature neonates are suspected to be at an even higher risk for development of any cause AKI given renal underdevelopment, which should encourage limited use of nephrotoxic agents [47]. Although much remains unknown regarding specific nephrotoxic agents used in the newborn period, neonates are known to have an increased susceptibility to aminoglycoside-associated AKI [26]. Low nephron mass may lead to CKD later in life [46], although serum creatinine may be normal in the neonatal period. Newborns who sustain AKI in the neonatal period may not develop changes in their GFR (measured by serum creatinine) until adolescence when they go through a growth spurt [48], so ongoing renal function monitoring is important in this population.

Patients with Intravascular volume depletion

It is unclear whether episodes of pre-renal azotemia are less hazardous than episodes of intrinsic AKI, and it is sometimes difficult to distinguish the two. The possibility of using tubular injury or cell-cycle arrest biomarkers in the future to help distinguish pre-renal azotemia from injury that has progressed to tubular damage is promising [19]. Medications that inhibit renal blood flow are particularly risky to use in individuals who have intravascular volume depletion.

What drugs are the biggest offenders?

Antibiotics

Either alone or in combination, vancomycin and piperacillin/tazobactam are both commonly used antibiotics in critically ill children for broad coverage, but are known to have nephrotoxic potential. The continued nephrotoxic risk of vancomycin monotherapy has been debated since introduction of the drug in the 1950's and after improvements in purification procedures [49]. Vancomycin purity is currently estimated at about 95% [50], and nephrotoxicity is thought to be limited. However, evidence of detrimental oxidative effects of vancomycin on proximal tubule cells has been shown [26, 50, 51]. In three pediatric studies, 7.2–14.4% of children who received intravenous vancomycin for more than 48 hours developed AKI [43, 52, 53]. One study proposed that AKI that occurs in critically ill children in the cardiac ICU receiving vancomycin was more likely related to underlying illness than directly related to vancomycin toxicity [52]. Nephrotoxicity with vancomycin is likely increased in children with concomitant nephrotoxic medication use [50, 51, 53], higher mean vancomycin troughs [43, 51], higher dose [53], longer duration of therapy [51, 53], or concomitant furosemide use [43]. Simultaneous use of vancomycin and piperacillin/tazobactam has been linked to development of AKI in non-critically ill children [2]. Two adult studies showed that compared to vancomycin monotherapy, when vancomycin is used in conjunction with piperacillin/tazobactam the odds of hospitalized non-critically ill adult patients developing AKI increased by 2.48 to 5 times [54, 55], though indication bias is difficult to control for. A more recent study showed no increased risk of AKI using this drug combination in critically ill adults [56], so this risk may differ by population studied. Finally, there is even some evidence suggesting more substantial nephrotoxicity associated with piperacillin/tazobactam independent of vancomycin [2].

Synergistic nephrotoxicity and development of AKI with combination therapy of aminoglycosides and vancomycin is as high as 30% in critically ill adults [31]. A study of critically ill children found only several individual medications associated with increased risk of AKI, but overall increased nephrotoxic medication exposure in children who developed AKI [23], suggesting a significant role for multiple medication exposures in the development of AKI [2]. Aside from limiting individual nephrotoxic medication use in children at high risk for AKI, it is likely most imperative to avoid use of multiple nephrotoxic agents.

Aminoglycosides

While the nephrotoxic potential of aminoglycosides has been well-established, their use is often necessary in patients with cystic fibrosis for lung infections secondary to resistant organisms. Aminoglycosides primarily cause damage to tubular epithelial cells leading to ATN but can also add to renal dysfunction via the renin-angiotensin-aldosterone system activation and alterations of glomerular endothelial cells [27, 37]. The risk of aminoglycoside-associated AKI increases with higher peak serum levels, African American race, higher baseline renal function, longer hospital stay, longer duration of therapy as well as clinical circumstances including poor renal blood flow and concomitant nephrotoxic medication use [31] (see Table 2). Longer courses of aminoglycoside therapy will lead to

increased cumulative exposure in the proximal tubule, increasing risk for nephrotoxicity. In critically ill adults, lower GFR seemed to be a protective factor in aminoglycoside-related AKI, which may be related to cautious use of the medication by providers in patients with known poor kidney function [57]. Interestingly another study found conflicting evidence showing that in children with cystic fibrosis receiving aminoglycoside therapy, concomitant nephrotoxic medication use was actually not associated with increased risk of AKI [38]. Regardless, it has been recommended that aminoglycosides be used with extended interval dosing to help minimize risk of AKI [31, 37, 58]. Strategies such as inhalational use of aminoglycosides are also gaining popularity as a way to deliver medication to the site of infection while reducing systemic exposure.

Chemotherapy

Patients with malignancy, bone marrow transplant, multivisceral and liver transplant are overrepresented when assessing children exposed to nephrotoxic medications [8]. Several of the chemotherapeutic agents including platins and methotrexate can cause AKI [26]. Children who receive bone marrow (and solid organ) transplants are generally treated with a calcineurin-inhibitor (CNI) as a form of immunosuppression. CNI's can cause AKI via renal vasoconstriction [26], as well as contribute to CKD from chronic use. Cyclosporin A (a CNI) which continues to be used in the pediatric bone marrow transplant population, can also cause AKI from hemolytic uremic syndrome [26]. Children with exposure to radiation therapy, surgical nephrectomy, or chemotherapy including ifosfamide, methotrexate and platins should be screened for CKD, since these agents are known contributors to its development [17, 27].

NSAIDs

NSAIDs inhibit prostaglandin synthesis which reduces renal perfusion [26, 31]. In a study of pediatric non-critically ill patients, NSAIDs were one of the only individual classes of medications that were used more often in children who developed AKI [32]. Children with acute gastroenteritis have decreased intravascular volume, and use of NSAIDs can increase their risk for AKI by 2-fold, even after adjusting for degree of dehydration [59]. NSAID-associated AKI accounted for 2.7% of AKI cases in one institution, and included a significant portion of children who took only the recommended dose [28]. All NSAID-associated AKI is not necessarily due to poor renal perfusion and/or progression to ATN, as NSAIDs can also be associated with acute interstitial nephritis. NSAID use requires careful consideration for regular administration, as often times it may be a non-essential drug selection and use of NSAIDs with other nephrotoxins requires further scrutiny [20].

What are the consequences of AKI?

An overwhelming number of studies in both the pediatric and adult literature have shown that patients who develop AKI, from any cause, have increased hospital length of stay, increased hospital cost, and higher mortality compared to those who do not develop AKI [10, 13, 14, 21–24, 60–62]. In a recent study assessing critically ill children, mortality was almost nine times higher for children who developed AKI compared with those who didn't, with a stepwise increase in mortality across KDIGO AKI stage [1], highlighting the clear

need for further research regarding prevention and treatment of this disease. While AKI is generally thought to be a result of other organ dysfunction, it likely also exacerbates delay in recovery of other organ dysfunction [1].

In recent years, investigators have discovered that individual episodes of AKI affect long-term renal health. At hospital discharge, 35% of children with a history of AKI had either decreased renal function or required continued dialysis [61]. In critically ill children with AKI and significant nephrotoxic medication exposure, up to 70% of survivors displayed at least one sign of persistent renal dysfunction six months after the insult [63]. And in follow-up studies at 1–3 years after an AKI event, 10.3% of patients had chronic kidney disease (CKD) and almost half were at risk for CKD which manifested as slightly decreased GFR, hypertension, and/or hyperfiltration [64]. Multiple other studies have demonstrated similar evidence of CKD after episodes of AKI in both children [27] and adults [26].

The effects of length of AKI have now become more evident. Adults who have longer duration of AKI have worse long-term outcomes [15] and critically ill children who had resolution or improvement of AKI severity had a lower mortality rate than those who had persistent AKI [1].

What can we do once AKI is diagnosed?

Current practice aimed toward decreasing incidence of AKI is primarily driven by prevention. Current KDIGO AKI treatment recommendations can be seen in Figure 1. Multiple studies have shown that the use of dopamine, which was used to improve renal blood flow, in fact does not provide any benefit in patients with AKI as once believed [27]. We rely on diligent monitoring and withdrawal or replacement of modifiable risk factors when AKI is identified [6]. Studies show that automatic triggers in electronic medical record systems can increase the ability to identify nephrotoxic medication exposure (particularly the use of radiocontrast) [34]. Additionally, the severity of AKI has been shown to decrease in non-critically ill children after initiation of an electronic screening trigger to encourage daily serum creatinine screening and decreased use or withdrawal of nephrotoxic medications [32]. With the increased risk of mortality in critically ill pediatric patients, studies assessing prevention strategies would be of particular importance in this young population [1]. Given the significant long-term health sequelae as described above, it is essential that children with AKI events be followed after the episode to screen for development of CKD. They also need to be monitored closely to help avoid further nephrotoxin exposure.

What's next?

Biomarkers

One of the major scientific breakthroughs in AKI research has been the development of new biomarkers to aid in prediction and early detection of AKI. If we are only using serum creatinine and/or oliguria as markers for renal injury, then AKI is being detected late. There are two major categories of promising biomarkers: tubular injury markers and cell cycle arrest markers. In a study assessing pediatric critically ill, mechanically ventilated patients,

urinary neutrophil gelatinase associated lipocalin (NGAL), a tubular injury marker, was noted to be six-fold higher in children who sustained AKI compared to controls, and this change persisted from 48 hours before to 48 hours after development of AKI [65]. Specific to drug-associated AKI, kidney injury molecule-1 (a tubular injury marker) has been most studied and is specific to injury in the S3 portion of the proximal renal tubule [66]. While further validation studies are necessary, microRNAs are proving to be promising urinary biomarkers for drug-associated AKI as well [67]. MicroRNAs function intracellularly as post-transcriptional regulators of gene expression [68], but are also found extracellularly in the blood and other body fluids including urine [67]. Deregulation of microRNA expression can be associated with organ dysfunction including renal injury [67]. Sensitive and specific biomarkers like microRNAs could be useful for detection of subclinical and clinical AKI as well as in drug development testing for nephrotoxicity. MicroRNAs also provide a potential future drug target for treatment of AKI [69].

Renal Angina

A “Renal Angina Index” model has been proposed as a way to help predict AKI and guide clinical evaluation, much like chest pain guides the use of troponins in patients with suspected myocardial ischemia [70]. The renal angina index includes risk factors and clinical presentation in an effort to risk-stratify patients, and most effectively use biomarkers for detection and prediction of AKI (i.e. have a high negative predictive value for AKI) [70]. Ideally, a risk prediction tool could be implemented to detect AKI in real-time, providing clinicians with feedback about potentially modifiable risk factors [71].

Future Direction

Based on underlying pathophysiology of AKI, possible future treatments could include anti-oxidant therapy, anti-adhesion molecule therapy, or administration of vascular mediators or mesenchymal stem cells [61]. Eventually, we may be able to assess genetic predisposition for susceptibility to particular nephrotoxic medications [6]. Ideally, wide-spread use of tubular injury, cell cycle arrest biomarkers and/or microRNAs, in conjunction with a risk-stratifying model could aid in predicting patients who are going to develop AKI. This would be particularly valuable in identifying patients in whom nephrotoxic medications should be most avoided and in whom renal replacement therapy should be initiated early.

Conclusion

The morbidity, mortality and excessive healthcare costs associated with AKI have been clearly defined, and the impetus is to prevent AKI in children who are at high risk. Prevention of AKI will improve with earlier detection of renal injury using promising biomarkers and development of risk stratification models implemented with the electronic health record. Drug-associated AKI remains an important and potentially modifiable sub-category of AKI. We need to understand which populations are at highest risk for drug-associated AKI, and encourage judicious use of nephrotoxic medications and frequent monitoring in these populations, particularly when a combination of nephrotoxic agents is used. Once AKI has occurred, nephrotoxic agents should be avoided as much as possible to aid in renal recovery and prevention of recurrent AKI.

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References

1. Sanchez-Pinto LN, Goldstein SL, Schneider JB, Khemani RG. Association Between Progression and Improvement of Acute Kidney Injury and Mortality in Critically Ill Children. *Pediatr Crit Care Med*. 2015; 16:703–710. [PubMed: 26132741]
2. Moffett BS, Goldstein SL. Acute kidney injury and increasing nephrotoxic-medication exposure in noncritically-ill children. *Clin J Am Soc Nephrol*. 2011; 6:856–863. [PubMed: 21212419]
3. Hui-Stickle S, Brewer ED, Goldstein SL. Pediatric ARF epidemiology at a tertiary care center from 1999 to 2001. *Am J Kidney Dis*. 2005; 45:96–101. [PubMed: 15696448]
4. Perazella MA. Renal vulnerability to drug toxicity. *Clin J Am Soc Nephrol*. 2009; 4:1275–1283. [PubMed: 19520747]
5. Lewis SJ, Mueller BA. Antibiotic Dosing in Patients With Acute Kidney Injury: “Enough But Not Too Much”. *J Intensive Care Med*. 2014; 31:164–176. [PubMed: 25326429]
6. Kane-Gill SL, Goldstein SL. Drug-Induced Acute Kidney Injury: A Focus on Risk Assessment for Prevention. *Crit Care Clin*. 2015; 31:675–684. [PubMed: 26410137]
7. Siew ED, Basu RK, Wunsch H, Shaw AD, Goldstein SL, Ronco C, Kellum JA, Bagshaw SM. Optimizing administrative datasets to examine acute kidney injury in the era of big data: workgroup statement from the 15(th) ADQI Consensus Conference. *Can J Kidney Health Dis*. 2016; 3:12. [PubMed: 26925248]
8. Schaffzin JK, Dodd CN, Nguyen H, Schondelmeyer A, Campanella S, Goldstein SL. Administrative data misclassifies and fails to identify nephrotoxin-associated acute kidney injury in hospitalized children. *Hosp Pediatr*. 2014; 4:159–166. [PubMed: 24785560]
9. Section 2: AKI Definition. *Kidney Int Suppl* (2011). 2012; 2:19–36. [PubMed: 25018918]
10. Akcan-Arikan A, Zappitelli M, Loftis LL, Washburn KK, Jefferson LS, Goldstein SL. Modified RIFLE criteria in critically ill children with acute kidney injury. *Kidney Int*. 2007; 71:1028–1035. [PubMed: 17396113]
11. Levi TM, de Souza SP, de Magalhães JG, de Carvalho MS, Cunha AL, Dantas JG, Cruz MG, Guimaraes YL, Cruz CM. Comparison of the RIFLE, AKIN and KDIGO criteria to predict mortality in critically ill patients. *Rev Bras Ter Intensiva*. 2014; 25:290–296.
12. Kellum JA. Diagnostic Criteria for Acute Kidney Injury: Present and Future. *Crit Care Clin*. 2015; 31:621–632. [PubMed: 26410133]
13. Selewski DT, Cornell TT, Heung M, Troost JP, Ehrmann BJ, Lombel RM, Blatt NB, Luckritz K, Hieber S, Gajarski R, Kershaw DB, Shanley TP, Gipson DS. Validation of the KDIGO acute kidney injury criteria in a pediatric critical care population. *Intensive Care Med*. 2014; 40:1481–1488. [PubMed: 25079008]
14. Sutherland SM, Byrnes JJ, Kothari M, Longhurst CA, Dutta S, Garcia P, Goldstein SL. AKI in hospitalized children: comparing the pRIFLE, AKIN, and KDIGO definitions. *Clin J Am Soc Nephrol*. 2015; 10:554–561. [PubMed: 25649155]
15. Kellum JA, Sileanu FE, Murugan R, Lucko N, Shaw AD, Clermont G. Classifying AKI by Urine Output versus Serum Creatinine Level. *J Am Soc Nephrol*. 2015; 26:2231–2238. [PubMed: 25568178]
16. Chiou WL, Hsu FH. Pharmacokinetics of creatinine in man and its implications in the monitoring of renal function and in dosage regimen modifications in patients with renal insufficiency. *J Clin Pharmacol*. 1975; 15:427–434. [PubMed: 1133219]
17. Goldstein SL, Devarajan P. Acute kidney injury in childhood: should we be worried about progression to CKD? *Pediatr Nephrol*. 2010; 26:509–522. [PubMed: 20936523]
18. Basu RK, Andrews A, Krawczeski C, Manning P, Wheeler DS, Goldstein SL. Acute Kidney Injury Based on Corrected Serum Creatinine Is Associated With Increased Morbidity in Children

- Following the Arterial Switch Operation. *Pediatr Crit Care Med*. 2013; 14:e218–e224. [PubMed: 23439467]
19. Chen L-X, Koyner JL. Biomarkers in Acute Kidney Injury. *Crit Care Clin*. 2015; 31:633–648. [PubMed: 26410134]
 20. Perazella MA. Drug use and nephrotoxicity in the intensive care unit. *Kidney Int*. 2010; 81:1172–1178. [PubMed: 21124300]
 21. Bailey D, Phan V, Litalien C, Ducruet T, Merouani A, Lacroix J, Gauvin F. Risk factors of acute renal failure in critically ill children: A prospective descriptive epidemiological study. *Pediatr Crit Care Med*. 2007; 8:29–35. [PubMed: 17251879]
 22. Naik S, Sharma J, Yengkom R, Kalrao V, Mulay A. Acute kidney injury in critically ill children: Risk factors and outcomes. *Indian J Crit Care Med*. 2014; 18:129–33. [PubMed: 24701061]
 23. Glanzmann C, Frey B, Vonbach P, Meier CR. Drugs as risk factors of acute kidney injury in critically ill children. *Pediatr Nephrol*. 2015; 31:145–151. [PubMed: 26260379]
 24. Schneider J, Khemani R, Grushkin C, Bart R. Serum creatinine as stratified in the RIFLE score for acute kidney injury is associated with mortality and length of stay for children in the pediatric intensive care unit. *Crit CareMed*. 2010; 38:933–939.
 25. Vachvanichsanong P, Dissaneewate P, Lim A, McNeil E. Childhood acute renal failure: 22-year experience in a university hospital in southern Thailand. *Pediatrics*. 2006; 118:e786–e791. [PubMed: 16894011]
 26. Patzer L. Nephrotoxicity as a cause of acute kidney injury in children. *Pediatr Nephrol*. 2008; 23:2159–2173. [PubMed: 18228043]
 27. Andreoli SP. Acute kidney injury in children. *Pediatr Nephrol*. 2009; 24:253–263.
 28. Misurac JM, Knoderer CA, Leiser JD, Naliescu C, Wilson AC, Andreoli SP. Nonsteroidal Anti-Inflammatory Drugs Are an Important Cause of Acute Kidney Injury in Children. *J Pediatr*. 2013; 162:1153–1159. [PubMed: 23360563]
 29. Uchino S, Kellum JA, Bellomo R, Doig GS, Morimatsu H, Morgera S, Schetz M, Tan I, Bouman C, Macedo E, Gibney N, Tolwani A, Ronco C. Acute renal failure in critically ill patients: a multinational, multicenter study. *JAMA*. 2005; 294:813–818. [PubMed: 16106006]
 30. Cartin-Ceba R, Kashiouris M, Plataki M, Kor DJ, Gajic O, Casey ET. Risk factors for development of acute kidney injury in critically ill patients: a systematic review and meta-analysis of observational studies. *Crit Care Res Pract*. 2012; 2012:691013. [PubMed: 23227318]
 31. Pannu N, Nadim MK. An overview of drug-induced acute kidney injury. *Crit Care Med*. 2008; 36:S216–S223. [PubMed: 18382197]
 32. Goldstein SL, Kirkendall E, Nguyen H, Schaffzin JK, Bucuvalas J, Bracke T, Seid M, Ashby M, Foertmeyer N, Brunner L, Lesko A, Barclay C, Lannon C, Muething S. Electronic health record identification of nephrotoxin exposure and associated acute kidney injury. *Pediatrics*. 2013; 132:e756–e767. [PubMed: 23940245]
 33. Kane-Gill SL, Sileanu FE, Murugan R, Trietley GS, Handler SM, Kellum JA. Risk Factors for Acute Kidney Injury in Older Adults With Critical Illness: A Retrospective Cohort Study. *Am J KidneyDis*. 2015; 65:860–869.
 34. Kirkendall ES, Spires WL, Mottes TA, Schaffzin JK, Barclay C, Goldstein SL. Development and Performance of Electronic Acute Kidney Injury Triggers to Identify Pediatric Patients at Risk for Nephrotoxic Medication-associated Harm. *Appl Clin Inform*. 2014; 5:313–333. [PubMed: 25024752]
 35. Faubel S. Pulmonary complications after acute kidney injury. *Adv Chronic Kidney Dis*. 2008; 15:284–296. [PubMed: 18565479]
 36. Mehta RL, Awdishu L, Davenport A, Murray PT, Macedo E, Cerdad J, Chakaravarthi R, Holden AL, Goldstein SL. Phenotype standardization for drug-induced kidney disease. *Kidney Int*. 2015; 88:226–234. [PubMed: 25853333]
 37. Boyer A, Gruson D, Bouchet S, Clouzeau B, Hoang-Nam B, Vargas F, Gilles H, Molimard M, Rogues AM, Moore N. Aminoglycosides in septic shock: an overview, with specific consideration given to their nephrotoxic risk. *Drug Saf*. 2013; 36:217–230. [PubMed: 23508544]

38. Downes KJ, Patil NR, Rao MB, Koralkar R, Harris WT, Clancy JP, Goldstein SL, Askenazi DJ. Risk factors for acute kidney injury during aminoglycoside therapy in patients with cystic fibrosis. *Pediatr Nephrol.* 2015; 30:1879–1888. [PubMed: 25912993]
39. Kane-Gill SL, Kirisci L, Verrico MM, Rothschild JM. Analysis of risk factors for adverse drug events in critically ill patients. *Crit Care Med.* 2011; 40:823–828.
40. Price JF, Mott AR, Dickerson HA, Jeffries FL, Nelson DP, Change AC, O'Brian Smith E, Towbin JA, Dreyer WJ, Denfield SW, Goldstein SL. Worsening renal function in children hospitalized with decompensated heart failure: evidence for a pediatric cardiorenal syndrome? *Pediatr Crit Care Med.* 2008; 9:279–284. [PubMed: 18446113]
41. Li S, Krawczeski CD, Zappitelli M, Devarajan P, Thiessen-Philbrook H, Coca SG, Kim RW, Parikh CR. Incidence, risk factors, and outcomes of acute kidney injury after pediatric cardiac surgery: A prospective multicenter study. *Crit Care Med.* 2011; 39:1493–1499. [PubMed: 21336114]
42. Lee BS, Byun SY, Chung ML, Chang JY, Kim HY, Kim EA, Kim KS, Pi SY. Effect of Furosemide on Ductal Closure and Renal Function in Indomethacin-Treated Preterm Infants during the Early Neonatal Period. *Neonatology.* 2010; 98:191–199. [PubMed: 20234144]
43. McKamy S, Hernandez E, Jahng M, Moriawaki T, Deveikis A, Le J. Incidence and Risk Factors Influencing the Development of Vancomycin Nephrotoxicity in Children. *J Pediatr.* 2011; 158:422–426. [PubMed: 20888013]
44. Mirrakhimov AE, Voore P, Khan M, Ali AM. Tumor lysis syndrome: A clinical review. *World J Crit Care Med.* 2015; 4:130–138. [PubMed: 25938028]
45. Rheault MN, Zhang L, Selewski DT, Kallash M, Tran CL, Seamon M, Katsoufis C, Ashoor I, Hernandez J, Supe-Markovina K, D'Allessandri-Silva C, DeJesus-Gonzalez N, Vasylyeva TL, Formeck C, Woll C, Gbadegesin R, Geier P, Devarajan P, Carpenter SL, Kerlin BA, Smoyer WE. AKI in Children Hospitalized with Nephrotic Syndrome. *Clin J Am Soc Nephrol.* 2015; 7:2110–2118.
46. Askenazi DJ, Ambalavanan N, Goldstein SL. Acute kidney injury in critically ill newborns: what do we know? What do we need to learn? *Pediatr Nephrol.* 2008; 24:265–274. [PubMed: 19082634]
47. Hanna MH, Askenazi DJ, Selewski DT. Drug-induced acute kidney injury in neonates. *Curr Opin Pediatr.* 2016; 28:180–187. [PubMed: 26735892]
48. Goldstein SL. Renal recovery at different ages. *Nephron Clin Pract.* 2014; 127:21–24. [PubMed: 25343815]
49. Levine DP. Vancomycin: a history. *Clin Infect Dis.* 2005; 42(Suppl 1):S5–12.
50. Elyasi S, Khalili H, Dashti-Khavidaki S, Mohammadpour A. Vancomycin-induced nephrotoxicity: mechanism, incidence, risk factors and special populations. A literature review. *Eur J Clin Pharmacol.* 2012; 68:1243–1255. [PubMed: 22411630]
51. Totapally BR, Machado J, Lee H, Paredes A, Raszynski A. Acute kidney injury during vancomycin therapy in critically ill children. *Pharmacotherapy.* 2013; 33:598–602. [PubMed: 23526674]
52. Moffett BS, Hilvers PS, Dinh K, Arian AA, Checchia P, Bronicki R. Vancomycin-associated acute kidney injury in pediatric cardiac intensive care patients. *Congenit Heart Dis.* 2014; 10:E6–10. [PubMed: 24934335]
53. Sinclair EA, Yenokyan G, McMunn A, Fadrowski JJ, Milstone AM, Lee CK. Factors Associated With Acute Kidney Injury in Children Receiving Vancomycin. *Ann Pharmacother.* 2014; 48:1555–1562. [PubMed: 25186624]
54. Burgess LD, Drew RH. Comparison of the Incidence of Vancomycin-Induced Nephrotoxicity in Hospitalized Patients with and without Concomitant Piperacillin-Tazobactam. *Pharmacotherapy.* 2014; 34:670–676. [PubMed: 24855041]
55. Kim T, Kandiah S, Patel M, Rab S, Wong J, Xue W, Easley K, Anderson AM. Risk factors for kidney injury during vancomycin and piperacillin/tazobactam administration, including increased odds of injury with combination therapy. *BMC Research Notes.* 2015; 8:579. [PubMed: 26476979]
56. Hammond DA, Smith MN, Painter JT, Meena NK, Lusardi K. Comparative Incidence of Acute Kidney Injury in Critically Ill Patients Receiving Vancomycin with Concomitant Piperacillin-

- Tazobactam or Cefepime: A Retrospective Cohort Study. *Pharmacotherapy*. 2016; 36:463–471. [PubMed: 26952639]
57. Oliveira JFP, Silva CA, Barbieri CD, Oliveira GM, Zanetta DM, Burdmann EA. Prevalence and risk factors for aminoglycoside nephrotoxicity in intensive care units. *Antimicrob Agents Chemother*. 2009; 53:2887–2891. [PubMed: 19364846]
 58. Kellum JA, Lameire N. Diagnosis, evaluation, and management of acute kidney injury: a KDIGO summary (Part 1). *Crit Care*. 2013; 17:204. [PubMed: 23394211]
 59. Balestracci A, Ezquer M, Elmo ME, Molini A, Thorel C, Torrents M, Toledo I. Ibuprofen-associated acute kidney injury in dehydrated children with acute gastroenteritis. *Pediatr Nephrol*. 2015; 30:1873–1878. [PubMed: 25895445]
 60. McGregor TL, Jones DP, Wang L, Danciu I, Bridges BC, Fleming GM, Shirey-Rice J, Chen L, Byrne DW, Van Driest SL. Acute Kidney Injury Incidence in Noncritically Ill Hospitalized Children, Adolescents, and Young Adults: A Retrospective Observational Study. *Am J Kidney Dis*. 2015; 67:384–390. [PubMed: 26319754]
 61. Askenazi DJ, Feig DI, Graham NM, Hui-Stickle S, Goldstein SL. 3–5 year longitudinal follow-up of pediatric patients after acute renal failure. *Kidney Int*. 2005; 69:184–189.
 62. Zappitelli M, Moffett BS, Hyder A, Goldstein SL. Acute kidney injury in non-critically ill children treated with aminoglycoside antibiotics in a tertiary healthcare centre: a retrospective cohort study. *Nephrol Dial Transplant*. 2010; 26:144–150. [PubMed: 20591815]
 63. Menon S, Kirkendall ES, Nguyen H, Goldstein SL. Acute kidney injury associated with high nephrotoxic medication exposure leads to chronic kidney disease after 6 months. *J Pediatr*. 2014; 165:522–527. e2. [PubMed: 24928698]
 64. Mammen C, Abbas AI, Skippen P, Nadel H, Levine D, Collet JP, Matsell DG. Long-term risk of CKD in children surviving episodes of acute kidney injury in the intensive care unit: a prospective cohort study. *Am J Kidney Dis*. 2011; 59:523–530. [PubMed: 22206744]
 65. Zappitelli M, Washburn KK, Arikian AA, Loftis L, Ma Q, Devarajan P, Parikh CR, Goldstein SL. Urine neutrophil gelatinase-associated lipocalin is an early marker of acute kidney injury in critically ill children: a prospective cohort study. *Crit Care*. 2007; 11:R84. [PubMed: 17678545]
 66. Fuchs TC, Hewitt P. Biomarkers for Drug-Induced Renal Damage and Nephrotoxicity—An Overview for Applied Toxicology. *AAPS J*. 2011; 13:615–631. [PubMed: 21969220]
 67. Zhou X, Qu Z, Zhu C, Lin Z, Huo Y, Wang X, Wang J, Li B. Identification of urinary microRNA biomarkers for detection of gentamicin-induced acute kidney injury in rats. *Regul Toxicol Pharmacol*. 2016; 78:78–84. [PubMed: 27074385]
 68. Pavkovic M, Robinson-Cohen C, Nicoara O, Chua A, Cardenas-Gonzalez M, Bijol V, Ramachandran K, Hampson L, Piromohamed M, Antoine DJ, Frendl G, Jimmelfarb J, Waikar SS, Vaidya VS. Detection of Drug-induced Acute Kidney Injury in Humans Using Urinary KIM-1, miR-21, -200c and -423. *Toxicol Sci*. 2016; doi: 10.1093/toxsci/kfw077
 69. Pavkovic M, Vaidya VS. MicroRNAs and drug-induced kidney injury. *Pharmacol Ther*. 2016; 163:48–57. [PubMed: 27126472]
 70. Basu RK, Kaddourah A, Terrell T, Mottes T, Arnold P, Jacobs J, Andringa J, Goldstein SL. Assessment of Worldwide Acute Kidney Injury, Renal Angina and Epidemiology in critically ill children (AWARE): study protocol for a prospective observational study. *BMC Nephrol*. 2015; 16:24. [PubMed: 25882434]
 71. Sutherland SM, Chawla LS, Kane-Gill SL, Hsu RK, Kramer AA, Goldstein SL, Kellum JA, Ronco C, Bagshaw SM. Utilizing electronic health records to predict acute kidney injury risk and outcomes: workgroup statements from the 15(th) ADQI Consensus Conference. *Can J Kidney Health Dis*. 2016; 3:11. [PubMed: 26925247]
 72. Leblanc M, Kellum JA, Gibney RT, Lieberthal W, Tumlin J, Mehta R. Risk factors for acute renal failure: inherent and modifiable risks. *Curr Opin Crit Care*. 2005; 11:533–536. [PubMed: 16292055]
 73. Nolin TD, Himmelfarb J. Mechanisms of drug-induced nephrotoxicity. *Handb Exp Pharmacol*. 2009:111–130.

Key Summary Points

- Acute kidney injury is associated with increased morbidity, mortality, and length of hospital stays in the pediatric population
- Nephrotoxic medications are one of the few potentially modifiable risk factors for AKI
- Populations at increased risk for drug-associated AKI should be monitored frequently and nephrotoxic medications should be used with caution
- With no AKI treatments available, prevention is key and alerting systems that include biomarkers and a risk factor assessment may be beneficial

Figure 1. Stage-Based Management of AKI (KDIGO) [9], used with permission. Shading of boxes indicates priority of action; solid shading indicates actions that are equally appropriate at all stages whereas graded shading indicates increasing priority as intensity increases.

Table 1

Acute Kidney Injury Stages, per Kidney Diseases Improving Global Outcomes (KDIGO) Criteria [9, 58]

Stage	Serum Creatinine	Urine Output
1	1.5 to 1.9 times baseline or 0.3 mg/dL increase	< 0.5 mL/kg/hr for 6–12 hours
2	2 to 2.9 times baseline	< 0.5 mL/kg/hr for 12 hours
3	3 times baseline OR Increase in serum creatinine to 4 mg/dL OR Initiation of renal replacement therapy OR In patients < 18 years, decrease in eGFR to < 35 mL/min/1.73m ²	< 0.3 mL/kg/hr for 24 hours or anuria for 12 hours

eGFR, estimated glomerular filtration rate

Table 2**AKI Risk Factors**

AKI	Population	Risk factors
AKI, any cause [58, 72]	Adults	Exposures: Sepsis, critical illness, hypotension/shock, burns, trauma, cardiac surgery, major noncardiac surgery, nephrotoxic medications (including radiocontrast use), rhabdomyolysis, solid organ transplantation, abdominal compartment syndrome Susceptibilities: Intravascular volume depletion, hypoalbuminemia, extremes of age, black race, pre-existing chronic kidney disease, comorbidities (cardiac, liver, or respiratory dysfunction, diabetes, cancer, arterial vascular disease, diabetes), anemia
Vancomycin-Associated AKI[50]	Adults	Older age, longer duration of therapy, concomitant nephrotoxic medication use, high trough levels, critical illness, pre-existing compromised renal function
Drug-Associated AKI [4]	Critically Ill Adults	Chronic: Age > 65, AKI/CKD, diabetes, malignancy, cardiovascular disease, liver disease/cirrhosis, chronic pulmonary disease, hypertension, peripheral vascular disease, underlying genetic vulnerability to AKI Acute: sepsis/infection, volume depletion (true and effective), acute decompensated heart failure, hypotension, major surgery, trauma, mechanical ventilation, excessive drug dosing
Aminoglycoside-Associated AKI [37, 57]	Critically Ill Adults	Older age, diabetes, cirrhosis, hypoalbuminemia, reduced renal function, hypotension longer duration of therapy, high daily AUC, high trough concentrations, concomitant use of other nephrotoxic medications (including contrast, vancomycin, amphotericin B, piperacillin/tazobactam, cephalosporins, foscarnet, allopurinol, NSAIDs, ACE-Is, cyclosporine, cisplatin)
AKI after Cardiac Surgery [41]	Children	Longer cardiopulmonary bypass time, younger age, lower weight, lower pre-operative creatinine, mechanical ventilation
Aminoglycoside-Associated AKI [26]	Children	Neonates, increased drug dosage, duration of therapy, pre-existing renal disease, volume depletion, hepatic dysfunction, sepsis, and concomitant nephrotoxic medications
Drug-Associated AKI [2, 59]	Non-Critically Ill Children	Young age, serum creatinine values per admit day, higher baseline GFR, nephrotoxic medication doses, and days of nephrotoxic medication use
Aminoglycoside-Associated AKI [38, 62]	Non-Critically Ill Children	African American race, longer treatment duration, higher baseline eGFR, treated with AG in the past month, longer hospital stays prior to starting AG, admitted under Heme/Onc service, hypoalbuminemia, concomitant use with trimethoprim/sulfamethoxazole
AKI, any cause [28, 60]	Non-Critically Ill Children	Younger, lower weight-for-age, lower baseline serum creatinine, and higher peak serum creatinine values
AKI, any cause [21, 22, 28]	Critically Ill Children	Younger age, (older age [21]), higher PRISM score, presence of cardiac disease, mechanical ventilation, hypoxemia, administration of nephrotoxic medications, hypotension/need for vasopressors, coagulopathy, thrombocytopenia

AKI, acute kidney disease; CKD, chronic kidney disease; AUC, area under the curve; NSAID, non-steroidal anti-inflammatory drug; ACE-I, angiotensin converting enzyme inhibitors; GFR, glomerular filtration rate; AG, aminoglycoside; PRISM, pediatric risk of mortality

Table 3**Drugs Associated with AKI [20, 73]**

Hemodynamic AKI: Non-steroidal anti-inflammatories, Angiotensin converting enzyme-inhibitors, Angiotensin receptor blockers, Calcineurin inhibitors, Vasopressors
Tubuloe epithelial Injury and Acute Tubular Necrosis: Antimicrobials, Radiocontrast, Aminoglycosides, platins, Amphotericin, Calcineurin inhibitors, Adefovir/Cidofovir/Tenofovir, Pentamidine, Foscarnet, Zoledronate
Osmotic Nephropathy: Radiocontrast, Intravenous Immunoglobulin (IVIG)
Crystal Nephropathy: Highly active antiretroviral therapy (HAART), Acyclovir, Ciprofloxacin, Sulfonamides, Indinavir, Foscarnet, Methotrexate
Nephrocalcinosis: Sodium phosphate solution
Papillary Necrosis: Non-steroidal anti-inflammatories
Acute Interstitial Nephritis: Antibiotics (Penicillins, Ciprofloxacin), NSAIDs, Proton pump inhibitors, H2 blockers, Antiepileptics, Loop diuretics
Chronic Tubulointerstitial Disease: Cyclosporine, Lithium
Glomerular Disease: Angiotensin converting enzyme-inhibitors (glomerulonephritis), Hydralazine (Vasculitis) [31], Lithium, Non-steroidal anti-inflammatories, Pamidronate, Gold
Renal vasculitis and thrombosis: Hydralazine, Allopurinol, Penicillamine, Gemcitabine, Mitomycin C, Methamphetamines, Calcineurin inhibitors