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REVIEW

Nephrotoxins and nephrotoxic acute kidney injury

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Abstract

Although the concept of nephrotoxicity has been recognized for more than 80 years, interest in nephrotoxins has intensified dramatically over the past two decades. Much of this attention has rightfully been focused on pharmaceutical agents and iatrogenic harm; however, it is important for providers to recognize that nephrotoxins can be found in naturally occurring substances as well. Although nephrotoxins exist in a myriad of forms, the means by which they induce injury can be organized into a few categories. For most of these agents, regardless of the mechanism, the final common pathway is acute kidney injury (AKI). Unfortunately, therapeutic options are limited and no treatments currently exist to reverse nephrotoxic AKI once it occurs. As a result, current strategies focus on increased awareness, nephrotoxin avoidance, early injury detection, and mitigation of disease severity. The goal of this review is to summarize our current understanding of nephrotoxic mechanisms and the epidemiology of nephrotoxic AKI. Additionally, avoidance and preventative strategies are discussed, screening approaches are suggested, and chronic monitoring recommendations are made.

Keywords Acute kidney injury · AKI · Nephrotoxin

Introduction

The concept of "toxin nephropathy" was first introduced by Dr. George Schreiner in 1965. He coined this term to describe "any adverse functional or structural changes in the kidney due to the effect of a chemical or biological product that is inhaled, ingested, injected or otherwise absorbed, or that yields toxic metabolites with an identifiable adverse effect to the kidneys" [1]. Since that time, nephrotoxins, defined generally as agents capable of causing such a nephropathy, have been widely studied in the nephrology literature.

In 1967, Balter et al. highlighted several of the more prevalent nephrotoxic exposures, focusing on hydrocarbons, heavy metals, drugs of abuse, analgesics, and antimicrobials [2]. Even then, the authors emphasized the importance of prevention and early detection. In 1987, Kleinknecht et al. provided pathologic evidence of nephrotoxicity, describing the clinical course and biopsy findings in 81 patients with "drug-associated renal failure" [3]. The authors identified seven major medication classes implicated in injury, including non-steroidal anti-inflammatory drugs (NSAIDs), antibiotics, glafenin, contrast media, diuretics, chemotherapy, and paracetamol. Notably, NSAIDs and antibiotics were responsible for 30% and 27% of cases, respectively. The biopsies revealed the most common pathologic findings in the setting of nephrotoxin exposure were acute tubular necrosis (ATN) and acute interstitial nephritis (AIN) [3, 4]. Over the next two decades, publications on this subject increased substantially. Specific drugs were studied more comprehensively and medications with particularly high risk for injury were identified. Additionally, the concept of "nephrotoxin burden" was introduced. In 2000, Merlin Thomas coined the term "triple whammy," describing the three drug cocktail commonly prescribed to adults with heart failure consisting of an angiotensin-converting enzyme (ACE) inhibitor, an NSAID, and a diuretic; he reported that over 50% of iatrogenic episodes of acute renal failure could be attributed to administration of one or more of these medications. This study also highlighted the impact underlying comorbidities have on the severity of nephrotoxic injury and underscored the potential risk for chronic renal impairment following exposure [5].

The concepts derived from these early studies have greatly informed our current approach. Although the injurious potential of specific single agents is important, clinicians should

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focus on the cumulative effect of concurrent nephrotoxin exposure. Providers should also be aware that patient and disease factors can amplify the nephrotoxic potential of medications. Patients who develop nephrotoxicity are at risk for chronic renal injury, which can persist well beyond the initial peri-administration period. Finally, despite the research performed to date, treatment strategies remain focused on increased awareness, prevention and early detection. With those concepts in mind, the goals of this manuscript are to review the mechanisms of renal injury common to nephrotoxins, describe categories of nephrotoxic agents, highlight the ramifications of nephrotoxic AKI, illustrate preventative strategies designed to improve patient care, and provide longitudinal monitoring recommendations [6].

Mechanisms of nephrotoxicity

At the most basic level, nephrotoxins are compounds capable of injuring the kidney. Nephrotoxicity, the term for such injury, has at times been strictly defined as damage inflicted directly to renal cells. However, given the evidence surrounding cumulative nephrotoxin burden and the potential for mechanistic interactions, this review will address nephrotoxicity more generally, defining the term as any effect that adversely impacts renal structure or function.

In that context, it is important to note that while there are many different nephrotoxic agents, they can be categorized by their primary mechanisms of injury:

1. *Vasoconstriction/hemodynamic alterations*: This phenomenon occurs when patients experience decreased blood flow into the glomerulus and/or increased blood flow out of the glomerulus with a resultant reduction in intraglomerular pressure. Examples of medications capable of causing injury in this way include NSAIDs, ACE inhibitors, and angiotensin receptor blockers (ARBs) and calcineurin inhibitors. Patients with hypovolemia, vasodilatation, and/or reduced systemic perfusion are particularly susceptible to this type of injury.
2. *Direct tubular toxicity*: Not only do the kidneys receive a high relative proportion of blood flow (augmented delivery of nephrotoxins), but the renal tubules reabsorb the glomerular filtrate, which concentrates agents intracellularly; these factors increase exposure to nephrotoxins and dramatically increase the risk of injury. Medications which cause injury primarily via direct tubular injury include aminoglycosides, amphotericin, cisplatin, ifosfamide, calcineurin inhibitors, methotrexate, cocaine, and radiocontrast agents.
3. *Interstitial nephritis*: Certain medications can cause a hypersensitivity or allergic reaction which manifests as renal inflammation. The hallmark of acute interstitial nephritis (AIN) is an inflammatory infiltrate in the interstitial and tubular compartment. This phenomenon is often idiopathic and not necessarily dependent on the dose of the medication administered. AIN can occur days to weeks after nephrotoxin exposure but tends to occur more quickly after subsequent exposures. Medications causing injury via this mechanism include NSAIDS, sulfonamides, ciprofloxacin, diuretics (loop and thiazide), anticonvulsants, and cocaine.
4. *Crystal formation*: Many medications (or their metabolites) are poorly soluble in the urine and, depending on urine pH and concentration, can form urinary crystals. These crystals accumulate in the urinary space and can cause ATN. Medications that can cause crystal formation include methotrexate, acyclovir, and sulfonamides.
5. *Thrombotic microangiopathy*: The final common pathway of thrombotic microangiopathy (TMA) is creation of platelet-rich thrombi in the microvasculature. The characteristics in addition to AKI include microangiopathic hemolytic anemia and thrombocytopenia. Medications implicated in this type of injury include cyclosporine, quinine, tacrolimus, interferon, clopidogrel, and cocaine [7].
6. *Glomerular injury/podocytopathy*: Some agents specifically cause glomerular injury which can manifest as a podocytopathy. Lithium, although best known for causing diabetes insipidus, can cause significant proteinuria thought to be related to renal epithelial cell injury [8, 9]. Sirolimus, an mTOR inhibitor, has been associated with significant proteinuria and nephrotic syndrome [10]. NSAIDs commonly cause an interstitial nephritis; however, podocytopathy and nephrotic syndrome have also been described. Although the exact mechanism is not completely understood, these phenomena are thought to be mediated by glomerular epithelial cell injury.
7. *Osmotic nephrosis*: In certain situations, injury can occur when hyper-oncotic solutions are administered to patients. The mechanisms include direct tubular injury and/or modifying the glomerular filtration pressure. Mannitol is the agent most commonly associated with this type of injury.

While these are the most well-described mechanisms of nephrotoxic kidney injury, much is unknown about the injury that is occurring on the molecular level. To date, few animal models exist, the majority of studies have been performed in adults, and biopsies are rarely performed. These factors have left us with significant knowledge gaps, and it is likely that these categories will be further refined in the future. Ongoing research focused on elucidating the specific types of injury that occur will allow practitioners to better mitigate injury and develop targeted therapies [7].

Specific nephrotoxins

Nephrotoxins can be sub-categorized by type, and while the term "nephrotoxin" is ubiquitously used to describe pharmaceutical agents capable of causing injury, it is important to remember that non-pharmaceutical nephrotoxins exist which are capable of causing significant morbidity and mortality. The number of potential nephrotoxins a patient may be exposed to is vast and diverse, and physicians must recognize naturally occurring agents and environmental causes of nephrotoxic kidney injury in addition to the more ubiquitous pharmaceutical exposures [11–15].

Medications

Without a doubt, the most widely studied and discussed nephrotoxins are the nephrotoxic pharmaceutical agents which cause iatrogenic harm and AKI alongside their intended effect. While there is no definitive, consensus list of nephrotoxins, almost every provider is familiar with and considers AKI risk when administering vancomycin, aminoglycosides, acyclovir, calcineurin inhibitors, amphotericin, and intravenous contrast. Indeed, the 2012 Kidney Disease: Improving Global Outcomes (KDIGO) AKI guidelines specifically highlight aminoglycosides, amphotericin, and IV contrast [11]. Perhaps the best attempt at developing a comprehensive list of nephrotoxins, at least in children, is the Nephrotoxic Injury Negated by Just-In-time Action (NINJA) collaborative. This multi-center nephrotoxin awareness and AKI prevention consortium generated a consensus-based list of nephrotoxic medications; the most current iteration of the nephrotoxin list is shown in Table 1 [16].

Natural nephrotoxins

Beyond the aforementioned pharmaceutical agents, there are many naturally occurring nephrotoxins which clinicians should be aware of. A number of foods can become nephrotoxic when ingested in large enough quantities; examples include Vichy water, Worcestershire sauce, milk, licorice, rhubarb, bile of carp, and starfruit [12, 13]. In these cases, nephrotoxicity occurs as a result of "toxin" accumulation—milk can be associated with hypercalcemia from vitamin D excess, rhubarb ingestion can result in oxalic acid overload, and licorice can be toxic due to accumulation of glycyrrhizic acid. Many plants can be toxic as well. Some of the most commonly described nephrotoxic plants are autumn crocus (colchicine), water hemlock (cicutoxin), castor beans (ricin), and toxic mushrooms (*Amanita phalloides* and *Cortinarius* species). Finally, animal venoms from a variety of species are known to be nephrotoxic. The animal's venoms most commonly associated with nephrotoxicity include those belonging to scorpions, the brown recluse spider, various bees and wasps found throughout the world, and several snakes including the Black Mamba, Pit viper, Rattlesnake, and Water moccasin. Snakebites can be particularly dangerous and can lead to enough renal injury to cause overt renal failure. In many of these animal venom examples, the mechanism of action is toxin-mediated hemolysis, rhabdomyolysis, coagulopathy, and profound hemodynamic collapse [12].

Environmental nephrotoxins

In addition to some of these naturally occurring nephrotoxins, a number of environmental exposures can be associated with renal injury as well. For example, ethylene glycol is the active ingredient in anti-freeze; when ingested, it leads to direct tubular injury through the formation of oxalate crystals. Heavy metals including lead, mercury, gold, bismuth, copper, arsenic, cadmium, uranium, and thallium can all lead to kidney injury. Though the mechanism of injury varies slightly by agent, most cause mitochondrial dysfunction, direct injury to the proximal tubule, and ATN [12, 14]. Over the past several decades, drugs of abuse have emerged as another category of nephrotoxins. Synthetic cannabinoids, synthetic cathinone/bath salts, cocaine, and heroin are all known to cause ATN. Anabolic steroids cause ATN, AIN, and bile acid nephropathy. Inhaled solvents are known to cause distal or type I RTA and/or Fanconi syndrome. Heroin can cause crystal nephropathy or even AA amyloidosis. Finally, methylenedioxymethamphetamine/MDMA/ecstasy can lead to ATN with associated hyponatremia [15].

Nephrotoxins, renal dysfunction and acute kidney injury

Over time, these medications and chemicals capable of causing renal injury have come to be known as nephrotoxins. Although these agents may cause damage via different pathophysiologic mechanisms, the final common pathway of nephrotoxin exposure is usually acute kidney injury (AKI). AKI is an extraordinarily common complication in hospitalized children; the prevalence is approximately 5% and 25% in children receiving acute and critical care, respectively [17–19]. In 2011, Moffett & Goldstein published one of the first pediatric studies to describe the association between nephrotoxic medications and AKI; they found that among children who developed AKI, 86% had been exposed to at least one nephrotoxin. Additionally, there was a dose-dependent effect as each additional nephrotoxin increased AKI risk [6]. Risk factors for nephrotoxic AKI include younger age, co-morbidities such as chronic kidney disease (CKD), liver failure, cardiovascular disease, malignancy, and hemodynamic instability (Fig. 1) [16, 20].

Table 1 Nephrotoxic medication list derived from NINJA collaborative [16]

Acyclovir	Enalapril	Ketorlac	Sulfasalazine
Amikacin	Enalaprilat	Lisinopril	Tacrolimus
Amphotericin B	Foscarnet	Lithium	Tenofovir
Amphotericin B (liposomal)	Ganciclovir	Losartan	Ticarcillin/clavulanic acid
Aspirin	Gentamicin	Mesalamine	Tobramycin
Captopril	Ibuprofen	Methotrexate	Topiramate
Carboplatin	Ifosfamide	Mitomycin	Valacyclovir
Celecoxib	Indomethacin	Nafcillin	Valgancyclovir
Cidofovir	Iodixanol	Naproxen	Valsartan
Cisplatin	Iohexol	Pamidronate	Vancomycin
Colistimethate	Iopamidol	Pentamidine	Zoledronic acid
Cyclosporine	Iopromide	Piperacillin	Zonisamide
Deferasirox	Ioversol	Piperacillin/tazobactam	
Diatrizoate meglumine	Ioxaglate	Polymixin B	
Diatrizoate sodium	Ioxilan	Sirolimus	

Early studies suggested that nephrotoxicity was responsible for approximately 15% of pediatric AKI [6, 21]. However, more recent data describe an incidence closer to 25% in non-critically ill pediatric patients exposed to a significant nephrotoxin burden [16]. The best data likely come from studies of specific nephrotoxins in isolation. Aminoglycoside antibiotics, which cause direct proximal tubule epithelial cell injury, are one of the most extensively studied nephrotoxic medications. Recent studies found AKI rates of 20–33% in children receiving aminoglycosides [22]. It is important to note that, in children, aminoglycosides are used most ubiquitously in populations which carry particularly high underlying AKI risk (neonates and patients with cystic fibrosis) which may exacerbate their nephrotoxic effect [22]. Vancomycin is another commonly prescribed nephrotoxic antibiotic which was first classified as a nephrotoxin in the 1950s [23]. In the most recent pediatric studies, AKI rates up to 40% have been described in patients receiving vancomycin, with the highest incidence in the critically ill [23]. It is important to note that AKI can occur even when vancomycin levels remain in the targeted therapeutic range [24–26]. Perhaps the most extensively studied nephrotoxic medication is iodinated contrast media. Contrast-induced nephropathy (CIN) was ubiquitous enough that the 2012 KDIGO AKI guidelines proposed specific recommendations regarding risk assessment and prevention strategies [11]. Recently, however, several studies have

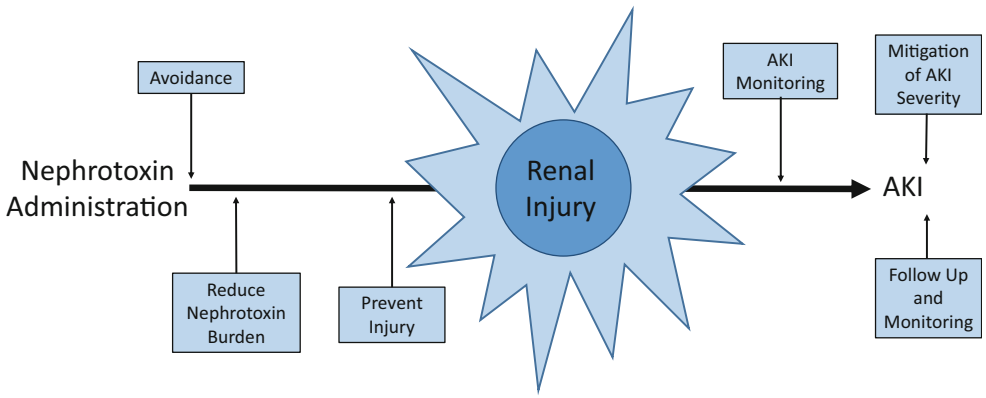

Fig. 1 Intervention strategies for nephrotoxic AKI. Although therapeutic options to treat nephrotoxic AKI do not exist, increased awareness and preventative strategies can be effective. Avoidance is effective and providers should use non-nephrotoxic agents when possible. Often, however, nephrotoxins are unavoidable and in these situations, it is important to reduce cumulative nephrotoxin burden to the extent possible; nephrotoxins which are no longer necessary should be stopped and less injurious agents should be considered. If effective preventative strategies exist (i.e., acyclovir and fluid administration), they should be employed. Even under ideal conditions, however, injury can occur, and it is imperative that monitoring for AKI should be implemented; this is especially true for agents which are cleared by the kidney as reduced renal excretory function can augment toxicity. If AKI develops, every attempt should be made to reduce AKI risk factors in order to mitigate further injury and disease severity. Finally, patients who develop AKI require monitoring to assess renal recovery and the subsequent development of chronic renal dysfunction

questioned the association between contrast and the development of AKI. These studies have focused on the fact that CIN epidemiology is highly confounded by underlying morbidities such as pre-existing CKD, cardiovascular disease, hypertension, diabetes, and concomitant administration of other medications; additionally, few of the earliest studies included control groups [27, 28]. Newer studies which focus on the safer, low osmolarity contrast agents and contain appropriate control groups capable of reducing confounder effect suggest that the incidence of CIN is overestimated [27–31].

Although it is challenging to determine the exact proportion of AKI due entirely or in part to nephrotoxin exposure, it is clear that nephrotoxicity is one of the most common risk factors for AKI in hospitalized children. Indeed, as the epidemiology of pediatric AKI continues to shift towards more severe systemic disease, greater comorbidity, and high complexity of care, the number of AKI events due to nephrotoxin exposure is likely to increase.

Implications and outcomes following nephrotoxin-induced AKI

Nephrotoxic AKI carries substantial implications. AKI in general has been associated with higher mortality in critically ill children [32]. Additionally, it has been associated with longer lengths of stay and greater costs across both ICU and non-ICU pediatric populations [6, 16, 32–34]. Beyond these short-term, in-hospital ramifications, AKI has also been associated with long-term renal morbidity [16, 35, 36]. Pediatric studies have described an increased risk for CKD following the development of AKI, with CKD rates as high as 30–66% [21, 35, 37–40]. It is important to note, however, that many of these studies focus on critically ill patients and lack control populations.

Poorer outcomes have also been described specifically in children who develop nephrotoxic AKI. In one single-center study of children receiving aminoglycoside antibiotics, those who developed AKI experienced longer lengths of stay and higher costs than those who did not [6, 33]. Another study which examined nephrotoxins more generally found that children who develop AKI while receiving nephrotoxins experience higher total costs ($82,600 ± $77,000 vs. $48,300 ± $38,800, $p < 0.05$) and longer hospital stays (12.3 ± 9.4 days vs. 7.1 ± 4.2 days, $p < 0.05$) [6]. These effects are in line with those seen in general, non-specific AKI studies. For example, a study of US children who developed AKI while hospitalized found that AKI increased the length of stay approximately twofold [34]. Similarly, a large study from China found that AKI increased length of stay and hospital costs by 16% and 18%, respectively [41]. Studies have also examined the relationship between nephrotoxic AKI and the subsequent development of CKD. For example, Menon et al. found that more than 70% of patients who experienced nephrotoxin-associated AKI developed some evidence of CKD after exposure: in this study, 6 months after the AKI event, 68.5% of the patients had proteinuria, 37.6% had hypertension, and 20% had an eGFR between 60 and 90 mL/min/1.73 m^2 [42]. For the sake of comparison, Mammen et al. described CKD findings among children who developed AKI while receiving intensive care [36]. Of the AKI survivors, 9.5% developed proteinuria, 3.2% developed hypertension, and 39% developed an eGFR < 90 mL/min/1.73 m^2. Thus, it certainly seems that children who develop AKI specifically due to nephrotoxin exposure have outcomes at least as poor as those who develop AKI from other causes.

Many of the aforementioned studies also highlight the under-recognition of the relationship between nephrotoxic AKI and the development of chronic renal dysfunction. In the study by Menon et al., despite the high prevalence of renal abnormalities detected, fewer than 20% of those children received nephrology follow up after discharge [42]. This lack of recognition is significant as there is evidence that with appropriate identification, high-quality follow-up care can be delivered. In fact, specific recommendations have been implemented in certain patient populations which are at particularly high risk for nephrotoxin exposure and/or the development of AKI. For example, the Children's Oncology Group published recommendations in 2008 which were based upon specific medication exposures (*Children's Oncology Group Long Term Follow Up Guidelines*). The guidelines clearly outline risk factors based on nephrotoxin exposure as well as potential long-term sequelae and suggest health counseling. The guidelines call for baseline screening including blood pressure measurement, serum electrolyte determination, and a urinalysis. Furthermore, they recommend annual monitoring with a urinalysis and blood pressure measurement followed by prompt referral to a pediatric nephrologist if abnormalities are detected [43]. Patients in the neonatal intensive care unit (NICU) are another population which is exposed to a high nephrotoxin burden. This is especially important as neonates have unique risk factors for CKD (i.e., prematurity). Given this, there has been a push to monitor nephrotoxin administration in the NICU, as well as more routine nephrology follow-up for neonates who experience AKI postnatally [44].

Currently, there are no definitive approaches to nephrotoxic AKI identification, monitoring, and care. To date, the most comprehensive program in children is the Nephrotoxic Injury Negated by Just-in-time Action (NINJA) collaborative. This quality improvement initiative, which was originally developed at Cincinnati Children's Hospital, focuses on identifying nephrotoxin exposures and screening for AKI events. NINJA defines "high" nephrotoxin exposure as the receipt of three nephrotoxins concurrently or the administration of aminoglycosides/vancomycin for three or more consecutive

days [6, 16, 20, 45]. This approach is effective as it supports the concept of overall cumulative nephrotoxin burden, yet emphasizes certain medications which are associated with particularly high AKI risk. In these patients who are at high AKI risk, NINJA recommends screening for AKI nominally via daily serum creatinine monitoring while exposed. Although no data exist regarding the optimal frequency of creatinine monitoring, daily screening seems reasonable given what we know about creatinine and AKI. Serum creatinine, despite its ubiquitous use in AKI definitions, is a functional marker which tends to rise 24–72 h after an injury has occurred [46]. Thus, a nephrotoxic injury detected by a rise in creatinine likely occurred days prior. Monitoring creatinine less frequently could increase the interval between injury and detection, and a vital interventional window might be missed. Follow-up care and monitoring is likely to be equally important in children who develop nephrotoxic AKI. The 2012 KDIGO guidelines on AKI recommend that all patients who experience AKI undergo evaluation within 3 months [11]. However, the Acute Dialysis Quality Initiative (ADQI) group has refined this universal approach, stating that the frequency, duration, and exhaustiveness of follow-up care should be based upon the severity of the AKI episode [47]. We agree with the KDIGO recommendation that patients who experience nephrotoxic AKI should be evaluated within 3 months to assess for resolution and sequelae. In accordance with the ADQI statement, patients with more severe AKI episode should receive earlier, more enduring, and more comprehensive assessments. Thus, a patient who developed stage 1 (mild) AKI which fully resolved might benefit from blood pressure monitoring and a urinalysis; this could easily be performed by the patient's primary medical doctor. A patient who had stage 2/3 (severe) AKI might benefit from serial evaluation, including serum creatinine determination, blood pressure monitoring, and more specific testing for proteinuria (i.e., urinary protein/creatinine and albumin/creatinine ratios). Patients who experience more severe AKI events likely warrant nephrology referral. This especially holds true for patients with pre-existing CKD or those with significant CKD risk factors. As we begin to understand more about the chronic ramifications of nephrotoxin exposure and nephrotoxic AKI, more specific and advanced guidelines will likely become available.

Treatment and prevention of nephrotoxic AKI

Unfortunately, no treatments currently exist for AKI once it develops; this is true regardless of the underlying etiology. As a result, contemporary care strategies are focused on prevention and mitigation [48]. One such intervention is fluid administration. In certain populations and disease states, fluids can reduce nephrotoxicity risk for specific medications. Intravenous fluid loading has been particularly beneficial in patients receiving cisplatin, acyclovir, amphotericin, and iodinated contrast [49–51]. In these situations, fluid administration reduces the risk of renal injury and/or its severity and is particularly beneficial in the setting of hypovolemia. Fluid therapy in these cases should be carefully monitored as fluid overload can occur should AKI develop [52–54]. In many situations, fluids are administered in conjunction with diuretics (i.e., furosemide or mannitol). Although there is no evidence that administration of diuretics is beneficial in these cases, forced diuresis can help maintain euvolemia should AKI and fluid overload develop. Beyond this, no other interventions have been shown to be effective at preventing nephrotoxic AKI. Aminophylline/theophylline has been used in asphyxiated neonates and patients with super-therapeutic calcineurin inhibitor levels to prevent AKI with some degree of success [11, 55–58]. However, in studies of specific nephrotoxins, these agents have not been shown to reduce the risk of injury [59]. *N*-acetylcysteine is another agent which has been used historically to treat and prevent AKI, most frequently in the setting of contrast-induced nephropathy. However, the efficacy of *N*-acetylcysteine has been much debated and, based upon the best available data, it is not thought to be effective and its use is no longer used recommended [60–65]. Despite the lack of effective therapeutic options available currently, novel interventions may be on the horizon. As an example, observational studies in adults have suggested that the sedative dexmedetomidine reduces AKI risk in patients undergoing cardiac surgery [66–68]. Kwiatkowski et al. identified a similar effect in children [69]. While these data need to be confirmed by prospective studies, they underscore the potential for discovery.

Given the fact that prevention strategies have limited success and treatments do not currently exist, perhaps the most effective intervention for nephrotoxic AKI is avoidance. Benoit et al. prospectively studied the effect of nephrotoxin avoidance in a cohort of children undergoing hematopoietic stem cell transplantation [70]. In this single-center study, the intervention consisted of using cefepime in lieu of piperacillin-tazobactam and limiting the duration of vancomycin therapy when culture results did not warrant its use. The study found that this intervention reduced nephrotoxin exposure by 33% and, more importantly, it reduced nephrotoxic AKI by 50%; this was accomplished without increasing infection rates or treatment failures. The cornerstone of such avoidance strategies is increased nephrotoxin awareness. This is perhaps best demonstrated by the early NINJA findings [6, 7, 16, 20, 45]. Implemented at a single center, this intervention was wildly successful, reducing AKI intensity by 64% [16, 20]. A multicenter study of the NINJA intervention is currently underway, testing the efficacy across a diverse set of institutions.

Summary

The concept of nephrotoxicity is well established and potentially injurious agents come in a variety of forms including foods, animal/insect venoms, environmental toxins, drugs of abuse, and pharmaceutical agents. Although many nephrotoxic agents have been identified, only a few mechanisms of action exist and the primary final common pathway is AKI. Despite our extensive historical experience with nephrotoxins, therapeutic interventions are limited and current strategies focus almost exclusively on avoidance, prevention, and mitigation. The best data available suggest that improved awareness, avoidance, and early injury detection are the keys to preventing short- and long-term morbidity.

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