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Accidental and iatrogenic causes of acute kidney injury

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Abstract

Purpose of review—Ingestions and iatrogenic administration of drugs are all too common causes of acute kidney injury. This review will discuss these preventable causes of acute kidney injury.

Recent findings—Recent studies have examined the pathophysiology of acute kidney injury by several commonly used drugs. These studies have shown that drugs and toxins can cause acute kidney injury by altering renal hemodynamics, direct tubular injury or causing renal tubular obstruction.

Summary—Knowledge of the drugs that cause acute kidney injury and how this injury is manifested can lead to improved diagnosis and treatment with the ultimate goal of prevention.

Keywords

aminoglycosides; nephrotoxicity; nonsteroidal anti-inflammatory drugs; vancomycin

Introduction

Acute kidney injury (AKI) secondary to drugs is an increasingly important cause of morbidity and mortality in children. A recent retrospective analysis in children found that nephrotoxins [antibiotics, chemotherapy, non-steroidal anti-inflammatory drugs (NSAIDs)] were the second leading cause of AKI after renal ischemia, accounting for 16% of cases [1]. Drug-induced AKI in the hospital setting can be the result of a number of different nephrotoxic drugs, making it difficult to identify one specific cause. In addition, it is often a cumulative effect of multiple insults to the kidney that result in AKI. Of those patients with AKI secondary to nephrotoxins, only 77% survived [1]. A follow-up study was performed 3–5 years after hospital discharge which showed that the children who had AKI from all causes had a high incidence of death and long-term renal injury, illustrating the severity of the problem [2^{**}].

Sometimes it is difficult to recognize AKI based on serum creatinine alone, because serum creatinine is a poor marker of the glomerular filtration rate (GFR). Serum creatinine is a reflection of muscle mass [3], so if one is examining a chronically ill child with very little muscle mass, a serum creatinine within the 'normal range' may not accurately reflect that the child actually has a significant renal insult. In addition, one can have a decrease in GFR of 50% without an appreciable increase in serum creatinine. The purpose of this article is to review the most common causes of iatrogenic and accidental causes of AKI, and review the pathophysiology behind the injuries so that we can better understand how to prevent these injuries. This review will be divided into the different categories of how renal insults may cause injury.

Glomerular injury

Briefly described below are the common causes of AKI secondary to alterations in glomerular hemodynamics.

Normal glomerular hemodynamics

Under normal conditions, blood enters the afferent arterioles and then goes through the glomerular capillaries to the efferent arterioles which provide the blood supply to the tubules. The GFR is determined by Starlings forces; the hydrostatic and oncotic pressures across the glomerular capillaries. The kidneys have an impressive autoregulatory mechanism that keeps the GFR stable over a wide range of systemic blood pressures. The afferent and efferent arterioles can dilate or constrict as needed to maintain normal glomerular filtration under most circumstances. For example, with mild to moderate dehydration, there is an increase in catecholamines and angiotensin II resulting in a decrease in renal perfusion. Vasodilatory prostaglandins, which dilate the afferent arteriole, act as a safety valve so that there is preservation of GFR. With more severe dehydration, autoregulation and intraglomerular hemodynamics become impaired, and there is more marked renal vasoconstriction which decreases the GFR. This is a protective device to limit salt and water filtration and potentially urinary losses in face of volume depletion. In excess, there will be a reduction in renal perfusion to the extent that there will be inadequate blood flow and renal ischemia leading to AKI.

Nonsteroidal anti-inflammatory drugs

Nonsteroidal anti-inflammatory drugs are a class of drugs commonly used in children for the treatment of fever and pain. There have been multiple types of renal injuries reported in the literature in children, including acute reversible renal failure, irreversible renal failure, acute interstitial nephritis, chronic renal injury, proteinuria, nephrotic syndrome and electrolyte abnormalities [4–11]. The true incidence of renal injury associated with NSAID use in children is not known.

Nonsteroidal anti-inflammatory drugs work by inhibiting cyclooxygenase-dependent vasodilatory prostaglandin production [12]. Under normal or euvoletic conditions, there is very little glomerular prostaglandin production. In clinical situations such as volume depletion, there is increased synthesis of these vasodilatory prostaglandins which work to

protect renal blood flow and GFR by compensating for the effects of renal vasoconstriction. When NSAIDs are administered in the setting of volume depletion, vasoconstriction becomes unopposed, leading to a decrease in the GFR and potentially to renal ischemia [12–14]. This may cause mild or severe AKI that may even require transient renal replacement therapy.

There have been several conditions associated with an increased risk of NSAID-induced kidney damage, such as dehydration, hemorrhage, congestive heart failure, liver failure and hypoalbuminemia [12]. Patients who are concomitantly taking other classes of medications that alter the normal intraglomerular hemodynamics, such as angiotensin-converting enzyme inhibitors (ACEis) or angiotensin receptor blockers (ARBs), are also at increased risk [12].

An important thing to keep in mind is that the warning labels on these over-the-counter NSAIDs do not mention the risk for renal injury, and there is definitely not a warning to avoid these drugs in cases of dehydration. This is particularly concerning since one of the main indications for NSAID use in children is fever, which in children can easily be accompanied by varying degrees of dehydration. All practitioners should be aware of the potential complications and lack of warning on the labels of these medications and provide the appropriate counseling to families.

Angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers

ACE is and ARBs are classes of drugs that can also alter intraglomerular hemodynamics. ACE inhibitors work by blocking the conversion of angiotensin I to angiotensin II, thereby decreasing vasoconstriction of the efferent arterioles. ARBs block the receptor for angiotensin II. The normal compensatory response of the kidney in the face of volume depletion is to increase angiotensin II. Angiotensin II causes vasoconstriction of the efferent arterioles more than the afferent arterioles due to the presence of more angiotensin II receptors on the efferent arteriole. Thus, ACEi and ARB prevent the compensatory efferent arteriole vasoconstriction that can subsequently lead to a decrease in the GFR. Patients who are on these medications need close monitoring in times of illness to prevent hypotension and AKI.

Tubular injury

Tubular injury from aminoglycosides, vancomycin and contrast agents is another common cause of AKI.

Aminoglycosides

Aminoglycosides are a class of antimicrobial drugs that are widely used in pediatrics and are frequently associated with nephrotoxicity [15]. They are filtered by the kidney and excreted in the urine mostly unchanged [16]. It has long been known that high concentrations of aminoglycosides can be found in kidney tissue, with the majority concentrated in the proximal tubule [16–19]. The half life of gentamicin in the serum of rats has been shown to be 2 h, but the half life in the kidney was shown to be 109 h, with levels still detectable at

the 11th day [18], putting into perspective how easily nephrotoxicity can arise from the use of these drugs.

The exact cause of aminoglycoside-induced AKI is unknown, and is likely multifactorial. Aminoglycosides are filtered and then appear to be taken up by the proximal tubular cells and transported into the lysosomes [19,20]. Some of the mechanisms that have been proposed include activation of the renin–angiotensin system [21,22], alterations in the glomerular endothelial fenestrae [22], intratubular obstruction [23,24], and alterations in mesangial cells [25]. Renal failure associated with aminoglycoside nephrotoxicity is often detected late in the course of therapy, as aminoglycoside nephrotoxicity does not usually result in a decrease in urine output [24,26,27]. The mechanism for the polyuric renal failure is thought to be decreased proximal tubule fluid resorption secondary to extensive tubular cell necrosis and decreased papillary solute concentration from mechanisms that are unknown [24]. Other renal injuries that have been described with aminoglycoside use include acute interstitial nephritis and electrolyte imbalances such as Fanconi-like syndromes and a Bartter-like syndrome [28–32].

Several risk factors for developing nephrotoxicity associated with aminoglycosides have been identified, including increased creatinine at initiation of therapy, female sex, concomitant liver disease, elevated 1-h postdose and trough aminoglycoside levels, duration of aminoglycoside therapy and shock [33,34]. In the case of increased creatinine, it has been suggested that increased creatinine is only a risk factor if you do not correct the dose to account for creatinine clearance, and if you corrected the doses given to the patients then the risk would be the same. One study gave patients with impaired kidney function a smaller dose of gentamicin, and found no difference in the percentage of patients that developed AKI between those with chronic kidney disease (CKD) and those with normal renal function [35].

In an attempt to decrease the risk of nephrotoxicity, several studies have looked at one single dose per day versus multiple daily doses of aminoglycosides. A meta-analysis performed that analyzed all of the trials that included children found that once-daily dosing was preferred over multiple-daily doses [36**]. Not only did the single daily dose of aminoglycosides decrease the cost of administration, but it also made the monitoring and administration much simpler with comparable efficacy and safety [36**]. Whether this approach can be used in patients with CKD is unclear. The main point to be made is that patients on aminoglycoside therapy need frequent measurements of serum aminoglycoside and creatinine levels.

Vancomycin

Vancomycin was approved for use by the Food and Drug Administration (FDA) in 1958, and its use has dramatically increased in recent years due to the increasing numbers of methicillin-resistant *Staphylococcus aureus* (MRSA)-related infections [37]. Vancomycin is excreted almost entirely unchanged by the kidney [38,39]. It has been shown clinically that a decrease in renal function is associated with a significant reduction in vancomycin clearance, and anuric patients can have a vancomycin elimination half life of up to 100–200

h compared with 5–11 h in patients with normal renal function [39,40]. The mechanism(s) for the nephrotoxicity associated with vancomycin remain obscure, but animal studies suggest that oxidative stress to proximal tubular cells may be one of the mechanisms [41–46].

It is currently recommended that trough serum vancomycin levels be used to monitor vancomycin therapy [37,47^{*}]. However, there is conflicting evidence in the literature about what trough levels should be targeted. There has been the recent emergence of vancomycin intermediary *Staphylococcus aureus* (VISA) and vancomycin-resistant *S. aureus* (VRSA) [37]. Both VRSA and VISA are associated with higher rates of treatment failure, so it has been recommended in adults that the conventional target trough levels of vancomycin be increased to above 10 µg/ml to avoid development of resistance, and with more serious or complicated bacterial infections the trough should be maintained between 15 and 20 µg/ml [37,48^{**},49]. There have also been recommendations that the usual dose of vancomycin for children of 40 mg/kg/day divided every 6 h be increased to 60 mg/kg/day [50,51].

The original preparations of vancomycin were thought to be nephrotoxic secondary to impurities that are not found in the newer formulations, and the risk of nephrotoxicity associated with the newer formulations is thought to be only around 5% [52–54]. However, more nephrotoxicity is being seen when targeting trough levels between 15 and 20 µg/ml, ranging as high as 40% in adults [37,47^{*},55–57]. More research needs to be performed in children with the higher doses to see if the risk of nephrotoxicity increases, as has been seen with adults.

Iodinated contrast

Contrast-induced nephropathy (CIN) is usually defined as an increase in serum creatinine of more than 25% or 0.5 mg/dl within 3 days of intravascular contrast administration that cannot be explained by other causes [58^{*},59]. The exact mechanism(s) of CIN remains unknown. Some of the suggested mechanisms include direct tubular toxicity, generation of free oxygen radicals and renal hypoperfusion [60,61]. Patients who are at increased risk of CIN are those with pre-existing renal disease [estimated GFR (eGFR) <60 ml/min/1.73 m²], diabetes mellitus, volume depletion, nephrotoxic drug use (aminoglycosides, NSAIDs, cyclosporin, ACEi, ARB), hemodynamic instability, congestive heart failure, anemia or hypoalbuminemia [58^{*},62]. The more risk factors patients have, the higher the risk for CIN [62]. Patients who have normal renal function and no other risk factors have a low risk of CIN [59,63,64^{*}].

There have been many attempts to reduce the risk or to prevent CIN. The only intervention that has consistently been shown to be beneficial is intravenous hydration, but the optimal type of fluid and the length of hydration have not yet been established [64^{*}]. Forced diuresis with agents such as mannitol or furosemide should be avoided [64^{*}]. Low osmolar contrast media are now preferred over high osmolar agents [58^{*},59].

Gadolinium-based contrast agents

Gadolinium-based contrast agents (GBCAs) have been considered to be less nephrotoxic than iodinated contrast agents in patients with normal renal function [74*]. Patients who are at increased risk for developing nephrotoxicity are those who have CKD stages 4 and 5 (eGFR <30 ml/min/1.73 m² and eGFR <15 ml/min/1.73 m², respectively), patients who receive high dosages of the contrast and patients who have intra-arterial administration of the agents [74*]. The main concern with GBCAs today is nephrogenic systemic fibrosis (NSF). NSF was first described in 2000 in patients with renal insufficiency [75], but the first cases in children were not reported until 2004 [76]. The clinical features of NSF are varied and include mild to severe skin lesions, disabling contractures, and fatal systemic involvement [75–77]. Recent literature suggests that not all GBCAs are the same when comparing the risk for NSF. The current recommendations are that the nonionic linear agents such as gadodiamide be avoided in patients with renal insufficiency [78,79], and to date there have been no published cases of NSF after exposure to cyclic agents such as gadoteridol.

Obstructive injury

Acyclovir is a frequently prescribed antiviral medication, and has been associated with AKI in children [80,81,82**]. Acyclovir is filtered by the glomerulus and secreted by the tubules unchanged, and is relatively insoluble in urine [65,83]. The mechanism of renal injury with acyclovir is birefringent, needle-like crystal formation leading to tubular obstruction [65,83,84]. Risk factors for developing renal failure with acyclovir are rapid, high-dose intravenous infusions, volume depletion, concomitant use of nephrotoxic drugs and renal impairment [80,82**,84]. Current recommendations for prevention of acyclovir-induced renal failure include volume repletion before therapy with acyclovir and maintaining high urine flow rates during therapy, in addition to adjusting the dosage for baseline renal insufficiency and avoiding rapid infusions [80,81,82**,83,84]. Therefore, children with impaired renal function need close monitoring of their renal function while on acyclovir therapy.

Miscellaneous

Recreational drugs are also known to cause kidney damage. Heroin, ecstasy, cocaine, PCP, alcohol and LSD have all been associated with rhabdomyolysis-associated renal injury [66,85–89]. Ecstasy, 3,4-methylenedioxymethamphetamine, has been associated with a case of necrotizing renal vasculopathy that resulted in chronic renal failure [90]. Cocaine has been associated with thrombotic microangiopathy with associated malignant hypertension and renal failure [91,92], as well as with isolated renal infarction [93]. It is important to remember that a toxicology screen be included in the evaluation of acute kidney injury of unknown cause.

Prescription medications can cause rhabdomyolysis-associated kidney injury as well. Antipsychotics, specifically haloperidol, are a class of drugs that have been associated with rhabdomyolysis and kidney injury [88,94], as have antihyperlipidemic agents, specifically statins [88,95]. Table 1 lists medications that have been implicated in the cause of AKI.

Conclusion

There are many instances when the benefits of the drug outweigh the risks of nephrotoxicity, and it is important to remember not to withhold a class of drugs simply because the patient has some form of renal insufficiency. Correct assessment of kidney function before the medication is administered is of the utmost importance, and this knowledge gives the practitioner the opportunity to adjust dosages and take preventive measures such as hydration and therapeutic drug level monitoring to prevent kidney injury.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 259).

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Key points

- NSAIDs are an under-recognized cause of acute kidney injury.
- Aminoglycosides, vancomycin and acyclovir are important preventable causes of acute kidney injury.
- Contrast nephropathy is an important cause of acute kidney injury that should be considered prior to contrast administration.

Table 1**Nephrotoxic drugs**

Mechanism	Name or class of drug
Altered intraglomerular hemodynamics	ACEi/angiotensin receptor II blockers
	Calcineurin inhibitors
	Diuretics
	NSAIDS
Glomerulonephritis/ nephropathy	Ampicillin
	Captopril
	Gold
	Heroin
	Interferon-alpha
	Lithium
	Mercury
	NSAIDS
	Pamidronate
	Penicillamine
	Penicillin
	Sirolimus
Tubular cell toxicity	Adefovir
	Aminoglycosides
	Amphotericin B
	Cadmium
	Cidofovir
	Cisplatin
	Cocaine
	Intravenous contrast
	Foscarnet
	Ifosfamide
	IVIG
	Lead
	Lithium
	Mannitol
	Mercury
	Methotrexate
	Pamidronate
	Pentamidine
	Phosphorus
Acute interstitial nephritis	Tenofovir
	Uranium
	Abacavir
	Acyclovir

Mechanism	Name or class of drug
Chronic interstitial nephritis	Allopurinol
	Atazanavir
	Beta lactam antibiotics
	Carbamazepine
	Captopril
	Cephalosporins
	Chloramphenicol
	Cocaine
	COX-2 inhibitors
	Cyclosporin
	Diuretics (thiazides, loop and triamterene)
	Ethambutol
	H ₂ -blockers (cimetidine and ranitidine)
	Indinavir
	Interferon
	Lithium
	Macrolides
	Mercury
	Mesalamine
	Minocycline
	NSAIDS
	Phenobarbital
	Phenytoin
	Proton pump inhibitors
	Penicillamine
	Penicillin
	Quinolones (especially ciprofloxacin)
	Rifampin
	5-aminosalicylates
	Sulfonamides
	Tetracycline
	Valproic acid
	Vancomycin
Crystallopathy	Acetaminophen
	Calcineurin inhibitors
	Cisplatin
	Herbals (aristolochic acid)
	Interferon alpha
	Lead
	Lithium
	NSAIDS
	Acyclovir

Mechanism	Name or class of drug
Rhabdomyolysis	Ampicillin
	Ciprofloxacin
	Foscarnet
	Gancyclovir
	Indinavir
	Methotrexate
	Sodium phosphate solution
	Sulfadiazine
	Sulfonamides
	Triamterene
	Amphotericin B
	Antidepressants and antipsychotics (amitriptyline, amoxapine, doxepin, fluoxetine, fluphenazine, haloperidol, lithium, protriptyline, perphenazine, promethazine, chlorpromazine, trifluoperazine)
	Benzodiazepines
	Antihistamines (diphenhydramine, doxylamine)
	Antihyperlipidemic agents (statins, clofibrate and bezafibrate)
	Azathioprine
	Drugs of abuse [alcohol, amphetamine, cocaine, heroin, methadone, methamphetamine, lysergic acid diethylamide (LSD), phencyclidine (PCP)]
	Halothane
	Hypnotics and sedatives (benzodiazepines)
	Paracetamol
	Penicillamine
	Pentamidine
	Phenylpropanolamine
	Quinidine
	Salicylates
	Succinylcholine
	Terbutaline
	Theophylline
	Thiazides
	Vasopressin
Osmotic nephrosis	Contrast
	Dextran
	Hydroxyethyl starch (HES)
	IVIG
Thrombotic microangiopathy (HUS/TTP)	Mannitol
	Antiplatelet agents (clopidogrel, ticlopidine)
	Calcineurin inhibitors (tacrolimus and cyclosporin)
	Cisplatin
	Cocaine
	Indinavir
	Interferon

Mechanism	Name or class of drug
	Gemcitabine
	Lithium
	Mitomycin-C
	OKT3
	Quinine
	Oral contraceptives

Data from [65–73]. This table is a list of nephrotoxic drugs. It is not meant to be all inclusive. COX2, cyclooxygenase 2; HUS/TTP, Hemolytic Uremic Syndrome/Thrombotic Thrombocytopenic Purpura; IVIG, intravenous immunoglobulin.