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Mechanisms of antimicrobial-induced nephrotoxicity in children

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Drug-induced nephrotoxicity is responsible for 20% to 60% of cases of acute kidney injury in hospitalized patients and is associated with increased morbidity and mortality in both children and adults. Antimicrobials are one of the most common classes of medications prescribed globally and also among the most common causes of nephrotoxicity. A broad range of antimicrobial agents have been associated with nephrotoxicity, but the features of kidney injury vary based on the agent, its mechanism of injury and the site of toxicity within the kidney. Distinguishing nephrotoxicity caused by an antimicrobial agent from other potential inciting factors is important to facilitate both early recognition of drug toxicity and prompt cessation of an offending drug, as well as to avoid unnecessary discontinuation of an innocuous therapy. This review will detail the different types of antimicrobial-induced nephrotoxicity: acute tubular necrosis, acute interstitial nephritis and obstructive nephropathy. It will also describe the mechanism of injury caused by specific antimicrobial agents and classes (vancomycin, aminoglycosides, polymyxins, antivirals, amphotericin B), highlight the toxicodynamics of these drugs and provide guidance on administration or monitoring practices that can mitigate toxicity, when known. Particular attention will be paid to paediatric patients, when applicable, in whom nephrotoxin exposure is an often-underappreciated cause of kidney injury.

Introduction

The kidney is a major organ of drug excretion and, thus, is exposed to high concentrations of potentially toxic medications. Drug-induced nephrotoxicity is a common and potentially serious complication of medication administration that occurs in both inpatient and outpatient settings. While the terms acute kidney injury (AKI) and nephrotoxicity are often interchanged, AKI specifically refers to a reduction in kidney function [i.e. glomerular filtration rate (GFR)], but nephrotoxicity more broadly encompasses the spectrum of medication- or toxin-induced kidney damage. Kidney injury must be substantial to affect traditional serum biomarkers, with 30%–50% parenchymal damage necessary before changes in creatinine can be detected.[1]

A broad range of medications have been associated with nephrotoxicity including various antimicrobial, antihypertensive, chemotherapeutic, immunosuppressant and anti-inflammatory agents, among others. Nephrotoxic medication exposure significantly contributes to AKI development in critically ill children, as well as in children cared for on general paediatric wards.[2,3] Anywhere from 20% to 60% of AKI in hospitalized patients is attributed to drug toxicity.[4–6] In non-critically ill children, AKI develops in roughly a quarter of those children administered nephrotoxins[7] and is associated with greater hospital costs and longer length of stay.[2]

Antimicrobials are one of the most commonly prescribed drug classes in children. In a global point prevalence study in 2012, 37% of hospitalized children across 226 hospitals were receiving antimicrobials on the survey date, including 61% of paediatric ICU

patients.[8] Although lifesaving and often critical, many antibiotics are unfortunately also nephrotoxic. It is well described that several antimicrobial classes and agents have potential to cause nephrotoxicity,[9] and the frequency of toxicity varies based on the properties of the individual agent, as well as the physiological status and underlying condition of the patient receiving the drug.[10] It is often difficult to tease out the relative contribution of antimicrobial exposure to AKI in hospitalized patients, since patients requiring antimicrobials are often sick (e.g. haemodynamically unstable), have underlying comorbidities and receive other potentially nephrotoxic drugs. Nevertheless, as a result of their frequent use, antimicrobials account for a large proportion of nephrotoxic medication exposures in hospitalized patients of all ages.[2,3,11]

The purpose of this review is to describe the mechanisms by which selected antimicrobials result in nephrotoxicity, highlighting the most common antimicrobial classes and agents to cause kidney injury in children. While AKI is most often multifactorial, it is important for clinicians to recognize the high-risk antimicrobials and strategies that may be employed in children to minimize toxicity. Alternatively, it is also imperative for clinicians to recognize when toxicity is not attributable to specific agents to avoid unnecessary medication changes. Understanding how antimicrobials induce kidney injury will support conscientious prescribing and therapeutic monitoring.

Mechanisms of nephrotoxicity

Drug-induced nephrotoxicity is classified as either dose dependent or dose independent.[12,13] Dose-dependent toxicities are predictable and related to the main pharmacological effect of the drug (type A reactions). For most drugs that cause type A reactions, AKI is linked to the degree of drug exposure over time and the toxicodynamic parameters associated with nephrotoxicity are either the drug's AUC or the peak concentration (C_{max}). Other agents, such as aminoglycosides, cause toxicity via drug accumulation and the trough (C_{min}) is more closely associated with renal injury. Dose-dependent toxicities can generally be mitigated by dose reductions, but sometimes cessation of therapy is necessary.

Dose-independent toxicities, known as type B reactions, are idiosyncratic, occur at any time during therapy and are highly variable from patient to patient. Hypersensitivity reactions are the most common dose-independent side effects. In the case of nephrotoxic AKI, drug exposure should precede changes in renal function, when characterized by changes in serum creatinine and/or a reduction in urine output, by at least 24 h, to be considered plausibly responsible.[12,14]

The mechanisms by which antimicrobials cause nephrotoxicity vary across classes and agents (Table 1) and several agents can cause multiple types of injury (Figure 1). Nephrotoxic effects can be categorized by the type of damage induced and resulting clinical presentation of the injury.[10,15] Acute tubular necrosis (ATN; tubuloepithelial injury), acute interstitial nephritis (AIN; tubulointerstitial disease) and crystal (obstructive) nephropathy are the primary means by which antimicrobials cause nephrotoxicity.[13] The distinguishing features of these types of nephrotoxic effects are summarized in Table 2. Osmotic nephrosis and chronic interstitial nephritis are untoward effects of some medications, but rarely of antimicrobials, and will not be discussed in detail in this review.

ATN

Tubuloepithelial injury results from the direct cytotoxic effects of drugs on proximal and/or distal tubule epithelial cells (Figure 2a).[15] Because this type of toxicity is dose dependent, it occurs along a spectrum from membrane or organelle damage to complete cell death and necrosis.[16] The term ATN is commonly used to describe tubuloepithelial injury, although actual cell necrosis is infrequent.[15,17] Aminoglycosides, vancomycin and amphotericin B are the most common antimicrobials to cause ATN, yet all elicit tubular damage through unique mechanisms (see below).

ATN is the most common form of drug-induced kidney injury and clinically manifests as a rise in creatinine with or without oliguria, an increased fractional excretion of sodium, microscopic haematuria and/or mild proteinuria.[15] Urinary biomarkers of tubular injury (KIM-1, NGAL and several others) are elevated, often prior to detectable changes in serum creatinine, but are not routinely measured clinically at the current time.[14] Tubular injury leads to a reduction in renal function via a complex tubuloglomerular feedback loop: tubular cell damage/death causes spilling of cellular components, which obstruct tubules, and impairs tubular reabsorption.[18] This causes excess water and electrolytes to be delivered to the distal nephron, increasing the hydrostatic pressure on the distal nephron and triggering compensatory vascular feedback mechanisms that reduce renal blood flow and glomerular filtration in efforts to limit the fluid and electrolyte losses.[19,20] In the setting of ongoing or severe tubular injury, oxidative stress and inflammation increase cellular damage, as well as the glomerular and vascular effects, potentiating ATN and leading to a further reduction in GFR.

AIN

AIN is characterized by tubular and interstitial inflammation that results from a non-IgE-mediated hypersensitivity reaction (Figure 2b).[21,22] Medications are the primary cause of AIN and antibiotics account for roughly one-third of drug-induced AIN cases;[23] penicillins, cephalosporins and sulphonamides are most often implicated. AIN is a much less frequent cause of nephrotoxic AKI in children than ATN, but may be responsible for up to 25% of unexplained AKI.[24] Following administration, drugs become immunogenic and induce a lymphocytic, cell-mediated inflammatory response that is accompanied by systemic signs of inflammation including fever (most patients) and rash (<50% of cases); peripheral eosinophilia is classically described in cases of AIN but rarely present. AIN generally develops after prolonged exposure to the drug (2–3 weeks), but can occur earlier in patients previously exposed to the offending agent.[16]

Drug-induced AIN presents as non-oliguric AKI with laboratory abnormalities including elevated serum creatinine, sterile pyuria, microscopic haematuria and tubular proteinuria, which consists of low molecular weight proteins (i.e. cystatin C, β-2-microglobulin, haemoglobin) rather than the larger proteins lost in glomerular diseases, such as albumin or immunoglobulins.[16,24] Eosinophils can be found in the urine in cases of AIN, although eosinophiluria is neither sensitive nor specific for AIN.[25] Kidney biopsy is required for

Table 1. Antimicrobials and their mechanisms of kidney injury

Agent	Mechanism(s) of kidney injury	Proposed approaches to minimize toxicity
Antibacterials		
aminoglycosides[a]	• accumulation of drug within proximal tubule cells leads to direct cytotoxicity • glomerular filtration reduced via tubuloglomerular feedback mechanism	• extended-interval dosing associated with decreased drug accumulation within proximal tubule cells and clearance of drug prior to re-administration of subsequent doses
β-lactam agents	• virtually all agents can cause a non-dose-dependent acute (allergic) interstitial nephritis • acute proximal tubule necrosis also reported for various agents	• avoidance of agents in individuals with prior hypersensitivity reactions may decrease subsequent episodes of AIN • piperacillin/tazobactam associated with increased rates of AKI (defined by serum creatinine changes) when given with vancomycin compared with vancomycin plus other β-lactam agents; clinicians should exercise caution when using this combination therapy
rifamycins	• AIN most common • some cases reported due to formation of rifampicin–antibody complexes with repeated exposures that cause direct damage to tubule cells	• avoidance of these agents in patients with prior reactions
polymyxins (colistin, polymyxin B)[a]	• drug accumulation within proximal tubule epithelial cells leads to cellular damage, increased membrane permeability and cell death, leading to ATN	• preclinical data suggest that use of larger, less frequent doses may minimize toxicity, but insufficient experience and data to support this strategy in paediatric patients
sulphonamides	• AIN • trimethoprim/sulfamethoxazole may inhibit tubular secretion of creatinine and falsely elevated serum creatinine (not true toxicity) • crystal formation also reported with sulfamethoxazole	• avoidance of these agents in patients with prior reactions • inhibition of tubular secretion of creatinine leads to small increases in serum creatinine (usually ∼25%) that rapidly return to normal upon cessation of drug; alternative measurements of estimated GFR will be unaffected (i.e. cystatin C)
vancomycin[a]	• oxidative stress on proximal tubule cells is the most common mechanism causing ATN; formation of tubular casts may also cause ATN • AIN via immunologically mediated process also described	• AUC-guided dosing may decrease toxicity, although AUC target not fully established in paediatric patients • use of continuous infusions may decrease toxicity, potentially due to administration of lower doses than with intermittent dosing
Antifungals		
amphotericin B products[a]	• bind to cholesterol in cell membranes causing tubular toxicity (increased tubule permeability and electrolyte wasting) and glomerular damage (impaired filtration)	• lipid formulations demonstrate decreased distribution into the kidney and reduced incidence of nephrotoxicity compared with amphotericin B deoxycholate • sodium loading or supplementation may reduce risk of nephrotoxicity with amphotericin B deoxycholate
Antivirals		
aciclovir[a], valaciclovir	• poor solubility in urine leads to formation of crystal deposits and tubular obstruction • crystal formation more likely with rapid infusions, high-dose therapy and in the setting of volume depletion • crystal formation often occurs early in therapeutic course (first 1–2 days)	• use of slow infusions and optimization of hydration status and urine output prior to administration decreases formation of crystals and reduces toxicity with intravenous aciclovir
atazanavir	• nephrolithiasis and crystal nephropathy	• ensure adequate hydration status throughout administration
cidofovir[a]	• dose-dependent proximal tubule cytotoxicity	• avoid in patients with underlying kidney disease/dysfunction • reduce co-administration with other nephrotoxic agents
foscarnet[a]	• ATN most common • can also cause formation of crystals within glomeruli and tubules	• ensure adequate hydration status and urine output throughout administration

Continued

Table 1. *Continued*

Agent	Mechanism(s) of kidney injury	Proposed approaches to minimize toxicity
	• may impair vasopressin responsiveness within the collecting ducts leading to nephrogenic diabetes insipidus	
ganciclovir, valganciclovir	• drug precipitation in renal tubules leads to crystal formation	• ensure adequate hydration status and urine output throughout administration
indinavir	• nephrolithiasis, crystalluria and tubular obstruction is common • asymptomatic crystalluria may lead to chronic kidney disease	• ensure adequate hydration status throughout administration • alternative agents should be considered
tenofovir	• proximal tubule damage as a result of mitochondrial injury, most often with prolonged therapy • may cause Fanconi syndrome (generalized tubulopathy) and nephrogenic diabetes insipidus	• use of tenofovir alafenamide associated with less toxicity than tenofovir disoproxil fumarate

[a]Incidence of nephrotoxicity in children >10%.

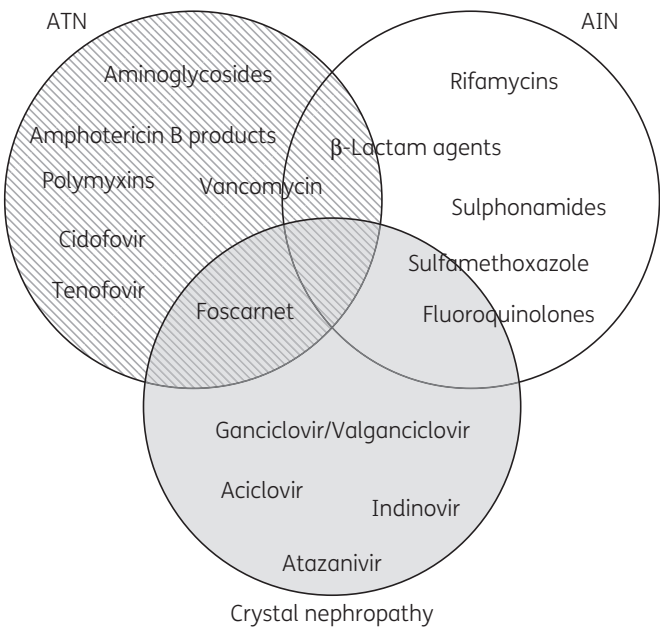

Figure 1. Diagram of the primary types of kidney injury caused by specific antimicrobial agents. Specific agents that have been reported to inflict multiple types of injury are displayed as overlapping.

diagnosis, which demonstrates characteristic histopathological changes including interstitial inflammation (predominantly lymphocytic, ±eosinophils), interstitial oedema and fibrosis, and tubulitis.[16,24,26] Because AIN is an immune-mediated process, corticosteroids are commonly used as treatment, particularly in patients who fail to improve following discontinuation of the offending agent.[26]

Crystal (obstructive) nephropathy

Some antimicrobials precipitate as crystals in the urinary system, causing damage to the tubular epithelium and obstruction of renal tubules (Figure 2c).[27] This most often manifests as AKI, but chronic kidney disease can develop, depending on the rapidity and extent of crystal formation.[28] Volume depletion is the major risk factor for crystal nephropathy, resulting in supersaturation of the urine and crystal formation in renal tubules; metabolic derangements and urinary pH may also predispose patients to crystal formation.[21,29] Crystal-induced tubule cell damage stimulates inflammation and necrosis, as described with ATN above, while obstruction of the tubular lumen, if significant, can affect the hydrostatic pressure within the kidney and promote the release of signals that decrease GFR. Antivirals, including aciclovir, indinavir and ganciclovir, are the antimicrobial agents most often associated with crystal nephropathy, which may develop following as little as a single dose of medication.[30–32] There have also been reports of sulfamethoxazole and fluoroquinolones causing crystaluria.[33–35] Dose reduction or slowing the rate of infusion, along with administration of intravenous fluids, may decrease the risk of crystal formation by promoting urine flow and limiting supersaturation.

Haemodynamically mediated kidney injury

Glomerular filtration is regulated via a complex balance of afferent and efferent blood flow through the glomerulus. Medications that reduce afferent blood flow (non-steroidal anti-inflammatory drugs, COX-2 inhibitors, calcineurin inhibitors) or increase efferent blood flow (angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers) alter the hydrostatic pressure in glomerular capillaries and glomerular filtration.[5,10] An inability to regulate the balance of afferent and efferent blood flow in patients receiving these drugs can lead to renal hypoperfusion or ischaemia, causing ATN, particularly in the setting of other haemodynamic insults, such as sepsis. Although no antimicrobials directly cause nephrotoxicity in this manner, patients receiving medications that affect renal blood flow (i.e. transplant recipients on calcineurin inhibitors) may be unable to compensate for the nephrotoxic insults caused by antimicrobials, potentiating their toxic effects.

Table 2. Features of drug-induced nephrotoxicity

	ATN	AIN	Crystal nephropathy
Mechanism of injury	direct cytotoxicity on tubular epithelial cells, most often proximal tubules	immunologically mediated damage to the interstitium	precipitation of drug as crystals causes damage to the tubular epithelium and/or tubular obstruction
Dose dependence	yes	no	yes; may also be infusion rate-dependent
Time course	days	usually 7–14 days, but can be sooner in previously sensitized individuals	any time during treatment; can occur as soon as following a single dose
Clinical features	elevated serum creatinine ±oliguria increased fractional excretion of sodium microscopic haematuria muddy brown casts proteinuria (usually mild) hypoalbuminaemia	elevated serum creatinine peripheral eosinophilia fever rash sterile pyuria, WBC casts microscopic haematuria tubular proteinuria (low molecular weight proteins) eosinophiluria (poor sensitivity)	elevated serum creatinine (acute or chronic) clinical signs of dehydration/volume depletion elevated urine specific gravity
Antimicrobials most commonly implicated	aminoglycosides amphotericin B cidofovir foscarnet polymyxins vancomycin	β-lactam agents fluoroquinolones rifamycins sulphonamides	aciclovir atazanavir foscarnet ganciclovir indinavir sulfamethoxazole

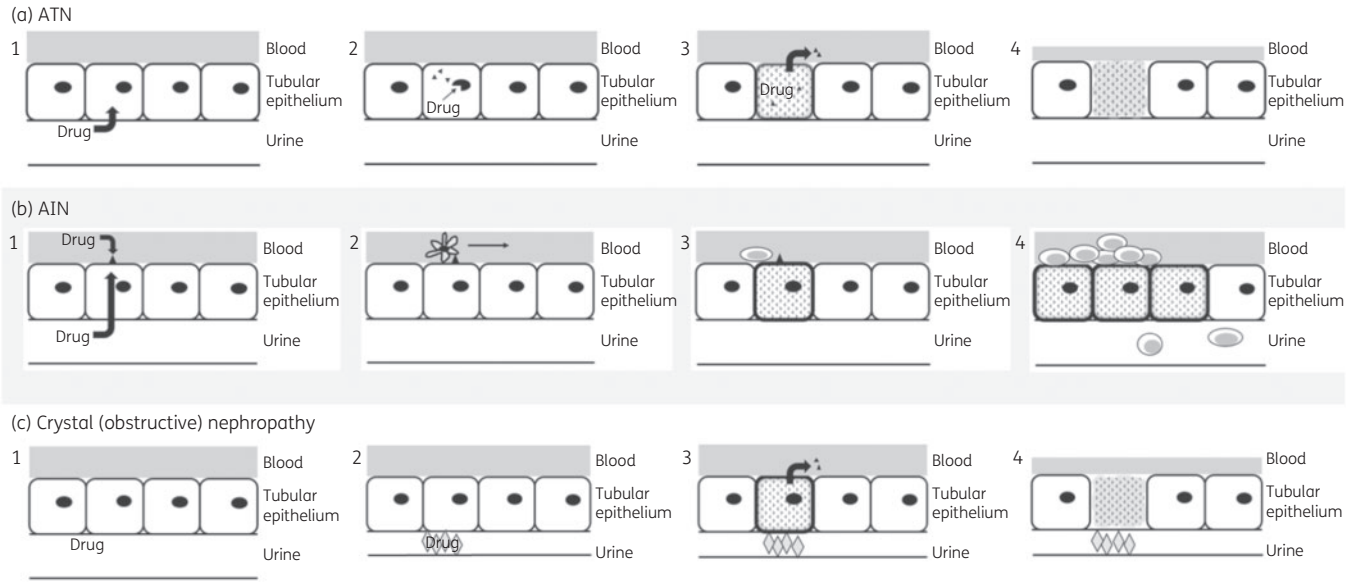

Figure 2. Mechanisms of antimicrobial-induced nephrotoxicity. (a) ATN: begins with endocytosis of drug from the urine into tubular epithelial cells (a1). Once inside the cell, the drug causes damage to cell organelles (a2). This initiates the process of cellular apoptosis and death, and release of systemic inflammatory signals (a3). Renal blood flow is then reduced (a4) as a result of tubuloglomerular feedback mechanisms. (b) AIN: antigen from either freely filtered drug or drug that is circulating in the blood is deposited on the basement membrane (b1). The antigen is recognized by dendritic cells (b2), which induce a T cell-mediated immune response (b3) and interstitial inflammation with pyuria (b4). (c) Crystal (obstructive) nephropathy: drug is filtered into the urine (c1). When the urine becomes supersaturated with drug, as in the setting of decreased urine flow, the drug precipitates (often as crystals) and obstructs the tubular lumen (c2). This leads to the release of inflammatory signals into the blood (c3), as well as induction of cellular apoptosis and reduced renal blood flow via tubuloglomerular feedback mechanisms (c4).

Specific medications/medication classes and mechanisms of nephrotoxicity

Vancomycin

Vancomycin is a glycopeptide antibiotic developed in the early 1950s.[36] It mainly acts by prevention of cell-wall biosynthesis of Gram-positive bacteria and is the first choice for the treatment of MRSA infections,[37,38] but its use is limited by adverse effects, most notably nephrotoxicity.[39] In a recent meta-analysis of eight paediatric studies,[40] renal toxicity was reported in 12.7% of vancomycin recipients (range across studies: 2.4%–24.3%), although there was variability in the AKI definitions used and patient populations studied. Vancomycin causes biopsy-proven ATN and AIN in both adult and paediatric patients.[41–46] AIN is mediated by an immunological reaction to vancomycin,[47] while two mechanisms have been suggested for ATN: vancomycin-induced direct oxidative stress and obstructive cast formation in proximal tubule cells.[48,49]

Oxidative stress is an imbalance between free radicals and antioxidants within cells that leads to mitochondrial dysfunction and cellular apoptosis. Vancomycin has been shown to stimulate oxidative phosphorylation in cultured cells and produce oxygen free radicals.[50,51] The free radicals induce lipid peroxidation and the superoxides produced cause depolarization of mitochondrial membrane potential with the release of cytochrome *c* and activation of downstream caspases involved in apoptotic cell death.[49,52]

Cast formation is another important mechanism for vancomycin-induced kidney injury. Uromodulin may interact with nanospheric vancomycin aggregates leading to tubular cast formation and subsequent ATN.[48] Luque *et al.*[48] detected vancomycin casts in nine patients with ATN and reproduced the obstructive vancomycin-associated cast nephropathy in mice. Recent preclinical data suggest that the vancomycin accumulation in proximal tubule cells is due to apical reabsorption at the brush border membrane via dehydropeptidase and megalin,[52,53] and that cilastatin inhibited vancomycin cellular uptake and reduced apoptosis of porcine renal proximal tubular epithelial cells in culture.[53]

In the clinical setting, vancomycin-associated nephrotoxicity is defined by increases in traditional markers of AKI such as creatinine and blood urea nitrogen and has been reported to occur at a median of 6–7 days into therapy.[54–56] In children, higher vancomycin troughs (i.e. those $\geq$15 mg/L) are associated with >2.5-fold more AKI in the non-critical care population and >3.5-fold more toxicity in the paediatric ICU.[40] Current vancomycin dosing guidelines focus on measurement of trough concentrations;[57] however, more recent data from our laboratory suggest that nephrotoxicity is more directly related to C_{max} or total plasma exposure (AUC_{0-24}) rather than troughs (C_{min}).[58,59] In adults, a 24 h AUC threshold of 650 mg·h/L has been reported[60] and a randomized trial of AUC- versus trough-driven vancomycin dosing demonstrated decreased nephrotoxicity among the AUC-guided therapy group.[61] Paediatric data support an AUC_{0-24}-toxicity threshold of 800 mg·h/L.[62] No studies have directly compared AUC-toxicity thresholds in adult and paediatric patients but adults may be more susceptible to the nephrotoxic effects of vancomycin than children (i.e. have decreased renal reserve), resulting in a lower observed AUC-toxicity cut-off.

Vancomycin efficacy is also AUC dependent but new data suggest that efficacy is similar even with higher exposures.[63,64] As a result, AUC-directed therapy may become more commonplace in children.[65] These findings are translating to the clinic as pharmacists are now monitoring vancomycin AUC:MIC concentrations in adult and paediatric patients.[66] Future dosing schemes may benefit from prolonging the infusion, although these studies have not yet been conducted in paediatric patients.[67]

Recently, numerous paediatric studies have reported an increased risk of AKI from combination therapy with vancomycin plus piperacillin/tazobactam compared with vancomycin alone or vancomycin plus cephalosporins or carbapenems. This finding has been established in adult patients as well. While the mechanism responsible for the increased AKI risk has not been elucidated, avoidance of this specific combination is generally recommended.

Aminoglycosides

Aminoglycoside antibiotics inhibit bacterial protein synthesis by binding to the 30S ribosomal subunit. They were first introduced in the 1940s and continue to play an important role in the treatment of Gram-negative infections in both adult and paediatric patients. Aminoglycoside-induced kidney injury has been well described and studies show that up to 33% of children exposed to aminoglycosides will develop AKI.[68] Despite known toxicity, aminoglycosides continue to be a mainstay of therapy due to their bactericidal activity and the increasingly prevalent resistance of Gram-negative bacteria to β-lactam agents.[19,69]

Aminoglycoside-induced kidney injury occurs when the drug accumulates within the proximal tubule epithelial cells of the renal cortex, leading to direct cytotoxicity.[70] After glomerular filtration, a portion of the drug binds to an endocytic receptor, megalin, located on the apical surface of the proximal tubule epithelial cell, and is endocytosed.[71] Expression of megalin is directly related to the degree of drug accumulation, as it is the principle receptor for aminoglycoside uptake in the kidney.[72] Following endocytosis, the drug traffics through the endosomal compartment and accumulates principally within lysosomes and then interacts with membrane phospholipids causing damage[73,74] in a process called phospholipidosis.[75] Drug is released into the cytosol, damages mitochondria and causes release of cytochrome *c*, activation of caspase-3 and induction of apoptosis.[74] Cell damage causes spilling of cellular components, which obstruct tubules,[18] impairs the excretory function of the nephron, increases the hydrostatic pressure and leads to proteinuria, enzymuria and loss of water and electrolytes in the urine.[76] In turn, glomerular filtration is reduced via the tubuloglomerular feedback mechanism.[19]

Traditionally, aminoglycosides are dosed multiple times per day; however, extended-interval dosing may mitigate kidney injury. Larger doses, given at extended intervals (i.e. once daily), optimize peak serum concentrations and the bactericidal killing of aminoglycosides.[77] Adult studies have found once-daily dosing to be equally efficacious, with lower rates of both ototoxicity and nephrotoxicity.[78–81] A meta-analysis of 24 paediatric randomized clinical trials found no significant differences in clinical failure or microbiological failure when comparing multiple-daily to extended-interval dosing.[82] The primary pooled nephrotoxicity outcome rates were similar between once-daily and multiple-daily dosing, as evidenced by any increase in serum creatinine levels or

decrease in CL_{CR}. However, pooled secondary nephrotoxicity rates, based on urinary excretion of proteins or phospholipids, were significantly lower in the once-daily [3/69 cases (4.3%)] versus multiple-daily [11/69 cases (15.9%)] (P=0.03) dosing arms.

Aminoglycosides require close therapeutic drug monitoring (TDM) in order to mitigate potential toxicities, including kidney injury. Peaks and troughs are most often measured during conventional, multiple-daily dosing regimens. However, these provide less informative data during extended-interval dosing regimens as a goal of extended-interval dosing is to ensure a trough below the level of quantification before re-dosing. Measurement of two concentrations during the post-distribution phase (i.e. at ≥1 and 6–9 h after the end of infusion) can promote estimation of the duration that plasma concentrations fall below the limits of quantification and confirm adequate drug clearance prior to administration of the next dose.[83,84]

Polymyxins

The polymyxins, a group of polypeptide antibiotics first discovered in 1947, demonstrate significant activity against Gram-negative pathogens.[85,86] In the 1970s, reports on renal and neurological adverse effects led to the gradual withdrawal of the polymyxins from clinical practice as newer antimicrobial agents with improved toxicity profiles were introduced.[87,88] However, recent progression of antimicrobial resistance, coupled with development of few new agents, have brought the polymyxins back into clinical use as a last line of defence.[89,90] The polymyxins consist of five chemically different compounds, i.e. polymyxins A–E.[86] Only polymyxin B and colistin (polymyxin E) have demonstrated clinical effectiveness in the treatment of Gram-negative infections.[91] Structurally, polymyxin B is similar to colistin but differs in one amino acid.[86] Colistin is the most widely used polymyxin in children and is clinically available as colistin sulphate and colistimethate sodium (CMS);[92–94] colistin sulphate is more potent and toxic. Both polymyxin B and colistin can be rapidly bactericidal by disruption of the bacterial cell membrane,[85,86,95] ultimately causing bacterial cell content leakage and cell death.[85,91,95]

The polymyxins cause renal toxicity that often limits clinical treatment.[93–95] Most studies in paediatric patients describe rates of nephrotoxicity between 3% and 10%; however, incidences over 20% have been reported.[92,96–98] Given the narrow therapeutic window and severity of nephrotoxicity, dose escalation of the polymyxins for resistant infections is often not advisable.[98–100]

Renal toxicity of polymyxins is a complex process. First, administration of polymyxins appears to induce renal vasoconstriction, sensitizing proximal tubule cells to direct cytotoxic effects of the drug.[101] Drug accumulation in proximal tubule cells is potentially driven by apical reabsorption at the brush border membrane via megalin-mediated endocytosis;[102,103] oxidative stress subsequently plays an important role in the development of renal toxicity.[103–105] Ultimately, drug accumulation within cells leads to organelle damage, increased membrane permeability, cell lysis and ATN.[99,100] Preclinical data indicate that accumulation of polymyxins may be a saturable, non-passive process, as with aminoglycosides.[106]

Dosing strategies for the polymyxins are based both on pharmacokinetic (PK) and pharmacodynamic (PD) properties. The PK for colistin and polymyxin differ substantially. CMS is excreted renally while polymyxin B and colistin are eliminated via non-renal mechanisms.[107] Thus, FDA recommendations exist for children to reduce the dose of CMS in the setting of renal failure.[108] The microbiological PD activity of the polymyxins is best described by the AUC:MIC ratio,[109] but fewer data exist on their toxicodynamics and whether renal toxicity is linked to C_{max} or overall AUC. Therefore, it is unclear whether daily doses of colistin or polymyxin B should be fractionated into smaller aliquots or given via continuous infusion. Abdelraouf *et al.*[106] conducted *in vitro* and *in vivo* studies that suggest that multiple-daily dosing of polymyxin B resulted in higher tissue accumulation and renal toxicity when compared with the equivalent once-daily dosing. This study may have important implications for dosing polymyxin B in paediatric patients; however, more data are needed. If toxicity occurs via a saturable mechanism, larger and fewer doses should result in less toxicity.[106,110,111]

Antivirals

Aciclovir [9-(2-hydroxyethoxymethyl)guanine] is an acyclic nucleoside in the class of nucleoside analogues.[112] It is a substrate and specific inhibitor of herpesvirus DNA polymerase, blocking DNA synthesis, and is effective against herpes simplex virus type 1 and 2 and varicella-zoster virus infections, as well as several other viruses. Aciclovir is primarily excreted via both glomerular filtration and tubular excretion and is eliminated mostly as unchanged drug.[112] One paediatric cohort study described an AKI incidence of 35% in children treated with intravenous aciclovir,[113] although few paediatric studies have evaluated the incidence of AKI from this drug.

The mechanism of nephrotoxicity most often described in aciclovir therapy is crystal nephropathy. Aciclovir has low urine solubility and may precipitate or crystallize in tubular lumens causing tubular obstruction,[114] particularly in the setting of low urine output. Use of high doses or administration via rapid intravenous bolus may further contribute to crystallization in the tubules. Also, crystal nephropathy can develop following a single dose of medication.[113] It is therefore recommended to administer aciclovir as a slower infusion rather than a rapid bolus and to avoid excessively high dosages when possible. It is also paramount to achieve and maintain adequate hydration throughout the course of treatment, including at initiation, to limit the potential for crystal nephropathy.[114]

Direct tubular toxicity is another important mechanism for aciclovir-induced nephrotoxicity. Preclinical models in rats have shown a dose-dependent elevation in urinary *N*-acetyl-β-D-glucosaminidase activity, which is a marker of renal tubular damage.[115] *In vitro* models are also consistent with direct injury to proximal tubular cells by aciclovir, possibly through aciclovir aldehyde, an intermediate metabolite that is produced in tubular cells.[116] These preclinical data are supported by case series of paediatric patients treated with aciclovir who demonstrated nephrotoxicity: renal biopsies in three patients showed tubulointerstitial nephritis or tubular epithelial damage and loss of proximal–distal tubular differentiation without intratubular crystals.[117,118]

Foscarnet is another intravenous antiviral agent with notable nephrotoxic potential,[114] particularly in immunocompromised children,[119] in whom it is used primarily to treat cytomegalovirus disease. A pyrophosphate analogue, foscarnet is eliminated via a combination of glomerular filtration and tubular secretion with

minimal tubular reabsorption.[120] ATN of proximal tubule cells is its most common form of nephrotoxicity, although several other types of kidney injury with this agent have been described.[121,122] Aggressive hydration with intravenous fluids throughout the treatment course appears to mitigate a significant portion of nephrotoxicity from foscarnet.[121,123]

Amphotericin B

Amphotericin B is a polyene antifungal with activity against a wide spectrum of fungal infections. It exerts its fungicidal activity by binding to the ergosterol of the lipid bilayer of the fungi and disrupting membrane permeability, leading to a loss of anions and glucose.[124] While active against most invasive fungal infections, it also produces serious infusion-related adverse effects, most notably dose-limiting nephrotoxicity.[125] Systemic imidazole and triazole antifungals have replaced amphotericin B as first-line treatment for many invasive fungal infections due to their efficacy and improved safety profiles.[126,127] However, amphotericin B is still utilized for life-threatening invasive fungal infections due to its broad spectrum of fungicidal activity.[126,128]

Clinically, amphotericin B-induced renal impairment manifests as increased levels of blood urea nitrogen and creatinine, electrolyte wasting, and a reduction in GFR of up to 40%–80%.[129,130] The mechanism of amphotericin B-induced nephrotoxicity has not been clearly defined, but it may be produced by a variety of mechanisms. One proposed mechanism of nephrotoxicity involves changes in cell permeability. Amphotericin B disrupts the fungal cell membrane by binding to ergosterol, which is structurally similar to cholesterol in mammalian cells. Therefore, amphotericin B may disrupt renal cell membranes to create transmembrane pores, thereby causing an electrolyte imbalance.[131] These pores cause a cascade of events whereby sodium enters the cells causing depolarization, voltage-gated calcium channels are triggered, allowing calcium to enter, and cell contraction is instigated. Multiple studies have shown that calcium channel blockers prevent afferent arteriole vasoconstriction, which supports this hypothesis.[132,133] Another hypothesis involves the direct vasoconstriction of the afferent arteriole of the glomerulus by amphotericin B.[133] This direct vasoconstriction can be attenuated by salt loading: an increased sodium concentration triggers the release of atrial natriuretic peptide and nitric oxide in the endothelium, thus inducing vasodilation, and has been shown to be clinically effective in preventing amphotericin B-induced nephrotoxicity.[134,135] Another possible mechanism is apoptosis of renal tubular epithelial and interstitial cells.[136] In the study by Varlam *et al.*,[136] renal cell lines from rats, dogs and pigs all demonstrated apoptosis and necrosis in a dose-dependent manner. These *in vitro* results were supported by *in vivo* studies in rats where dose-dependent toxicities and side effects were replicated and then attenuated when amphotericin B was administered concomitantly with the anti-apoptotic agent recombinant human insulin-like growth factor-1.

Aside from the reduction in renal blood flow and GFR, amphotericin B-induced nephrotoxicity also impairs the ability to acidify and concentrate urine. The aforementioned transmembrane pores created by amphotericin B explain poor urine acidification.[137,138] In a study by Kim *et al.*,[139] rats administered amphotericin B exhibited a reduction in aquaporin-2 expression and its regulator, adenylyl cyclase, as well as increased serum creatinine levels, high urinary flow rates and a markedly reduced urine osmolality, which is also observed in humans. These results suggest that the reduction in aquaporin-2, which is primarily expressed in the collecting ducts, is responsible for polyuria associated with amphotericin B administration.

The formulation of amphotericin B may also contribute to nephrotoxicity. In order to minimize the nephrotoxicity observed with traditional amphotericin B deoxycholate, new formulations have inserted the amphotericin B into liposomal structures.[140] All three lipid formulations of the drug [amphotericin B colloidal dispersion (ABCD), amphotericin B lipid complex (ABLC), liposomal amphotericin B] distribute well into tissues and have reduced kidney accumulation relative to amphotericin B deoxycholate. When amphotericin B is complexed with lipids, amphotericin B concentrates in phagocytes and is distributed to sites of inflammation.[141] As a result, less free amphotericin B is circulating, which reduces the overall side-effect profile.[140,142] Deoxycholate, which was added to amphotericin in the conventional formulation to improve solubility, is also nephrotoxic in itself.[143] Liposomal formulations also selectively target and bind to high-density lipoproteins of fungal organisms instead of mammalian cells.[144–146] While efficacy is similar between the formulations, the rate of nephrotoxicity with amphotericin B deoxycholate is between 12% and 50%, which is markedly higher than rates of the liposomal formulations, which range from 9% to 25%.[147] While some studies have reported decreased nephrotoxicity of continuous infusion compared with standard infusions (2–6 h),[148] the data are generally conflicting and do not universally support this practice.[134,135] Administration of supplemental intravenous sodium has been associated with decreased toxicity of amphotericin B deoxycholate in premature infants,[149] although not fully studied in other paediatric populations.

Future directions

As detailed above, most antimicrobials elicit kidney injury by causing ATN in a dose-dependent manner. When toxicodynamic endpoints are defined, such as for vancomycin, strong consideration should be given to implementation of effective TDM that aims to minimize toxicity risks. Reliance upon vancomycin troughs, for instance, is an inadequate approach to prevent vancomycin-associated nephrotoxicity in children, given that vancomycin displays AUC-dependent toxicity and estimation of AUCs from troughs is poor.[61] The use of bedside decision-support software can allow clinicians to estimate AUC more reliably using Bayesian approaches and derive personalized dosing regimens that achieve both effective and safe drug concentrations, not only for vancomycin but for all drugs in which clinical sampling can be performed. In addition, studies are needed to determine whether alternative administration strategies (i.e. continuous infusions for vancomycin) can mitigate drugs' toxic effects in paediatric patients.

Clinicians should also recognize that traditional biomarkers of kidney injury, blood urea nitrogen and serum creatinine, are insensitive and non-specific in children. Reliance on changes in these biomarkers will only detect patients who have already sustained significant injury. This reactive approach does not prevent AKI and is not a reliable tactic to mitigate toxicity in children receiving

nephrotoxic medications. While monitoring of traditional biomarkers remains the standard of care, largely due to cost, availability and interpretability, more sensitive markers of toxicity have been identified that more directly relate to the site of injury within the nephron (Figure S1, available as Supplementary data at *JAC* Online). Use of these sensitive urinary biomarkers may allow clinicians to recognize toxicity prior to the onset of significant damage and promote preemptive dose adjustments or medication changes. Both the US FDA and EMA have issued letters of support for KIM-1 and osteopontin.[150,151] In addition, KIM-1, clusterin and cystatin C have already been qualified for preclinical toxicological evaluations by the FDA, the EMA and the Pharmaceutical and Medical Devices Agency in Japan.[97] However, at the time of writing, there are no FDA-approved urinary biomarker tests available for clinical use in children. Additional studies will be needed to bring these tests into the paediatric TDM arena.

Conclusions

Antimicrobials are an important cause of AKI in children. Through direct cytotoxic effects, indirectly via immune-mediated mechanisms or via perpetuation of other concurrent nephrotoxic insults, antimicrobial administration can lead to a clinically meaningful impairment of renal function in paediatric patients. While nephrotoxicity may be unavoidable or unpredictable, such as when the mechanism is AIN, clinicians can utilize knowledge of the toxicodynamics of antimicrobial agents to develop personalized regimens that reduce the likelihood of toxicity for patients. When alternative agents are not feasible, close monitoring of kidney function, urine output and hydration status is imperative in high-risk patients—those receiving multiple other nephrotoxic medications, with underlying kidney disease or past AKI, or haemodynamic instability (i.e. impaired renal perfusion). Dosing/administration strategies known to minimize nephrotoxicity (i.e. once-daily aminoglycosides, AUC-targeted vancomycin, liposomal formulations of amphotericin B, concurrent hydration for aciclovir and foscarnet) should also be implemented routinely in high-risk patients.

Antimicrobials are vital to the preservation of health and the prevention of disease in people of all ages. They are, understandably, one of the most commonly prescribed classes of medications in both inpatient and ambulatory care settings; however, nephrotoxicity is a pertinent and often predictable adverse effect of many antimicrobial agents. Clinicians need to identify high-risk patients and implement strategies to allay toxicity or, at a minimum, detect it early. Periodic measurement of creatinine alone is insufficient to ensure safe administration of these drugs and awareness of patients' urine output/hydration status, haemodynamics and concurrent medications is important. TDM should also be used, when available, to deliver effective and safe doses that target known PK/PD endpoints.

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Disclaimer

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Supplementary data

Figure S1 is available as Supplementary data at *JAC* Online.

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