Spotlights on Antibiotic-induced Acute Kidney Injury
The Evidence to Date

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Acute kidney injury (AKI) is a frequent and wide complication of antibiotics therapy. In the present review article, we assessed the epidemiology, pathogenesis, risk factors, and clinical manifestation of antibiotic-induced AKI. The risk factors for the occurrence of antibiotic-induced AKI include medical comorbidities, coexisting drug therapies and the dosage, and therapeutic period of antibiotics. The prognosis of antibiotic-induced AKI varies by antibiotics types. This review summarizes the clinical controversy of antibiotic treatment and the future clinical recommendations.

INTRODUCTION

Due to their physiological function, the kidneys are exposed to many drugs; drug-associated acute kidney injury (AKI) is a common complication in hospitalized patients,1 and the antibiotics are one of the most widely used drugs, which involve more than half of hospitalized patients.2 A large number of studies have investigated the frequent onset of AKI after antibacterial therapy.3,4 Although dialysis delivery and sophisticated continuous renal replacement therapy have been carried out, the hospitalization is still long. More importantly, the dose and appropriate level of antibiotic treatment are still controversial.

In the present article, we summarized the epidemiology, risk factors, mechanisms, clinical manifestation, and preventive strategies of antibiotic-induced AKI. This review summarizes the clinical controversy of antibiotic treatment and the future clinical recommendations.

EPIDEMIOLOGY

According to the RIFLE (Risk, Injury, Failure, Loss, and end-stage renal disease) standard, the Acute Renal Injury Network standards and the Kidney Disease Improving Global Outcomes standard,5-7 it has been suggested that the global burden of AKI is up to 13.3 million cases per year, and the prevalence of AKI in developing countries is estimated to be higher than that in developed countries.5,9 Globally, drug nephrotoxicity contributes to 17% to 26% of AKIs,10,11 and the ratio is higher in Asian countries.12 In China, around 40% of AKIs are due to drug toxicity and antimicrobial agents are the most common types of nephrotoxic drugs.13 One study displayed that 166 out of 347 drug-induced AKI events was associated with antibiotics.14 The incidence of antibiotics-induced AKI increased in antibiotics combination.5,6,14

Based on the literature, aminoglycosides are the most frequent in antibiotic-induced AKI.14,15 Among patients admitted to intensive care units, antibiotic-induced AKI is a catastrophic life-threatening event with the mortality rate range from 30% to 60%.16,17

RISK FACTORS AND MECHANISMS

Identification of patients at high risk for antibiotic-induced AKI is of major importance. Understanding the risk profile of antibiotic-induced AKI may be of benefit in the early prevention and treatment. Recent studies have identified some potentially modifiable risk factors for antibiotic-induced AKI,18-21 which is summarized in Table 1 and Figure 1.

Antibiotics are a wide-spread class of drugs.
Antibiotic-induced Acute Kidney Injury—Yang et al

and the principal cause of antibiotic-associated nephropathy is varied. Different mechanisms have been identified: a decrease in kidney perfusion pressure, cytotoxicity, hypersensitivity reactions, and crystalline nephropathy. Normally, acute interstitial nephritis (AIN) and acute tubular necrosis (ATN) appear in antibiotic-induced AKI. Most of the cases of antibiotic-induced renal failure are related to ATN. Two important causal agents of ATN are aminoglycosides and amphotericin B. Acute interstitial nephritis also presents the signs of an allergic reaction. It is usually self-limiting, but in some studies, it is claimed that steroids may promote recovery. The symptoms of AIN are variable and often not specific; thus, kidney biopsy is required to make a firm diagnosis.

Table 1. Risk Factors for Antibiotic-induced Acute Kidney Injury18-21

<table>
<thead>
<tr>
<th>Category</th>
<th>Risk Factor</th>
</tr>
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<tbody>
<tr>
<td>Patients</td>
<td>Advanced age (an age older than 60 years)</td>
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<tr>
<td></td>
<td>Obesity</td>
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<tr>
<td></td>
<td>Dehydration upon admission</td>
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<tr>
<td>Medical comorbidities</td>
<td>Hypertension</td>
</tr>
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<td></td>
<td>Cirrhosis</td>
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<td></td>
<td>Preexisting renal disease</td>
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<tr>
<td></td>
<td>Diabetes</td>
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<td></td>
<td>Congestive heart failure</td>
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<tr>
<td></td>
<td>Hypotensive episodes</td>
</tr>
<tr>
<td>Coexisting drug therapies</td>
<td>Diuretics</td>
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<tr>
<td></td>
<td>Nonsteroidal anti-inflammatory drugs</td>
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<tr>
<td></td>
<td>Renin-angiotensin-mediated drugs</td>
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<tr>
<td></td>
<td>Nephrotoxic agents</td>
</tr>
<tr>
<td>Antibiotics per se</td>
<td>High dose</td>
</tr>
<tr>
<td></td>
<td>Antibiotic combination</td>
</tr>
<tr>
<td></td>
<td>Therapy exceeding</td>
</tr>
</tbody>
</table>

Figure 1. The pathogenic mechanisms of antibiotic-induced nephrotoxicity.
The clinical syndromes of antibiotic-induced nephrotoxicity can be recognized in acute kidney failure, nephrotic syndrome, and chronic nephritis. The underlying mechanics of antibiotic-induced AKI are summarized in Figure 2 and the details of cytotoxicity are shown in Figure 3.

ANTIBIOTICS
Aminoglycosides
Aminoglycosides are effective broad-spectrum drugs for the treatment of serious infections caused by gram-negative and some gram-positive bacteria. The employment of aminoglycosides is complicated by nephrotoxicity and ototoxicity. The hierarchy of the risk of nephrotoxicity for aminoglycosides is in the order of neomycin, gentamicin, tobramycin, amikacin, netilmicin, and streptomycin. The incidence of aminoglycosides-induced AKI varies between 5% and 25%, and it usually occurs after at least a week of treatment.

Aminoglycosides are selectively accumulated within proximal tubule epithelial cells and mesangial matrix cells. The former is the major site of accumulation of aminoglycosides. This choice is related to the multi-ligand receptor megalin, which is a ligand for numerous low-molecular-weight proteins. When inside these cells, aminoglycosides cause structural changes and functional impairment of the endoplasmic reticulum, mitochondria, and lysosomes in these cells, leading to cells death, as demonstrated in Figure 2. Therefore, the tubule and glomeruli damage not only induced the AKI and then decreased glomerular filtration rate, also the tubule damage induced the electrolyte abnormalities, eg,

Figure 2. The underlying mechanics of antibiotic-induced acute kidney injury. Antibiotics are a wide-spread class of drugs and the principal cause of antibiotics-associated nephropathy varied. Different mechanisms have been identified: a decrease in kidney perfusion pressure, the formation of encounter complex, cytotoxicity, hypersensitivity reactions and crystalline nephropathy. ATN indicates acute tubular necrosis; AIN, acute interstitial nephritis; and AKI, acute kidney injury.
Antibiotic-induced Acute Kidney Injury—Yang et al

Antibiotic-induced Acute Kidney Injury—Yang et al

13

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hypokalemia, hypomagnesemia, and hypocalcemia. Furthermore, renal vasoconstriction caused by the application of aminoglycosides may also contribute to AKI. 34

In the prevention of AKI, prolonged interval dosing of aminoglycosides may be safer for the kidneys. Clinical trial show that the increase in urine N-acetyl-beta-D-glucosaminidase was 33% less with once daily dosing compared to the three daily doses. 35 Limiting exposure to less than 7 days, ensure pharmacokinetic monitoring occurs with target troughs less than 1.0 mg/dL will help decrease the incidence of nephrotoxicity.27

Statins have been shown to reduce gentamicin accumulation in renal cells through a mechanism involving geranyl isoprenoids. 36 Of note, aminoglycosides can be effectively cleared by hemodialysis, which have relatively small volumes of distribution, minimal protein binding, and small molecular weights ranging from 465 Da to 600 Da. Approximately 10% to 15% of the aminoglycosides concentration will be removed per hour by hemodialysis. 37 In this review, we have highlighted certain antibiotic-specific preventive strategies for reducing the incidence of AKI in Table 2.

Antituberculous Drugs

The first line antituberculous (TB) drugs refer to isoniazid, rifampicin, ethambutol, pyrazinamide, and streptomycin, but adverse events from these drugs are not uncommon. Anti-TB drug-induced AKI is a severe complication.38,39 The incidence of AKI is up to 7.1% during anti-TB treatment.40 The proportion of occurrence of AIN 83(84%) patients were in AKI Stage 1, 10 (10%) in stage 2, and 6 (6%) in stage 3, 40 and rifampicin is the most common drug.38-40

Some studies41,42 provide a possible mechanism for the anti-TB drug-induced AKI. Anti-TB drugs-dependent immune complexes widely deposited in renal tubulars, glomeruli, and the interstitial area, result in ATN and AIN. This serum immune complexes can be found in many multiple visceral organs, suggesting that the lesion is a multisystem autoimmune disease, which was accompanied by gastrointestinal symptoms, eg, abdominal pain, nausea, vomiting, and diarrhea, flu-like symptoms, and blood system diseases such as anemia, leukocytosis, and thrombocytopenia when a patient is suffering from AKI.43,44 Interestingly, in a Kaplan-Meier analysis, fever, gastrointestinal

Figure 3. Antibiotic-induced cytotoxicity. Megalin and cubilin of proximal tubule form the giant endocyctic complex. This complex transports gentamicin by endocytosis, then accumulates mostly in lysosomes, the golgi, and endoplasmic reticulum. When the concentration of gentamicin in endosomal structures exceeds an undetermined threshold, their membrane is disrupted, the drug is poured into the cytosol that act on mitochondria directly and indirectly by impairing ATP production, producing oxidative stress, increasing bax levels, lead to the cell death. In fact, lysosomes also damage the cell death directly. Endoplasmics reticulum activates apoptosis through impairing translational accuracy.
disturbance, and skin rash, rather than what we usually say AKI stage, age, and comorbidities, were proved to be the independent predictors of renal recovery.\textsuperscript{40}

Clinically, timely termination of anti-TB treatment may have an excellent response; no further therapy (steroids or hemodialysis) was required.\textsuperscript{41} Days after discontinuing anti-TB drugs, serum creatinine concentration begins to recover.\textsuperscript{44} Therefore, early diagnosis and discontinuation of anti-TB drugs are of fundamental importance for recovering kidney function. Apart from pyrazinamide, other first-line anti-TB drugs are difficult cleared by hemodialysis.\textsuperscript{45} This is due to these drugs’ large molecular weight, wide distribution into tissues, high protein binding, and rapid hepatic clearance or adherence of drug to the dialysis membrane.

**Amphotericin B**

Amphotericin B, a treatment for leishmaniasis, fungal, and fever of unknown origin, can directly cause damage to renal tubular cells by harming cell membrane permeability as the possible mechanisms underlying the AKI.\textsuperscript{46} Tubular dysfunction manifests as renal tubular acidosis, electrolyte abnormalities, notably hypokalemia and hypomagnesemia. Another mechanism for amphotericin B-induced AKI is the direct renal vasoconstriction and subsequent reduction in renal blood flow.\textsuperscript{47} According to the Kidney Disease Improving Global Outcomes criteria, the incidence of amphotericin B-induced AKI reached to 58.6% in the inpatients and the median time for the diagnosis of amphotericin B-induced AKI reduced to 4 days.\textsuperscript{48}

Several large-scale prospective studies have identified an average daily dose of amphotericin B above 35 mg can enhance the risk of amphotericin B-induced AKI.\textsuperscript{49} Use of liposomal amphotericin B resulted in lower incidence of AKI than conventional amphotericin B.\textsuperscript{50} Oral N-acetylcysteine and saline loading (150 mEq/d) before or during amphotericin B infusion were also proved to be effective in preventing amphotericin B-induced AKI reduced to 4 days.\textsuperscript{51}

### Table 2. Mechanisms and Prevention of Acute Kidney Injury Induced by Different Types of Antibiotics

<table>
<thead>
<tr>
<th>Antibiotics</th>
<th>Related drugs</th>
<th>Mechanisms</th>
<th>Preventions</th>
<th>Hemodialysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aminoglycosides</td>
<td>Gentamicin, Amikacin, Streptomycin</td>
<td>Cytotoxicity, Decrease in kidney perfusion pressure</td>
<td>Statins, Prolonged interval dosing, Nebulised aminoglycosides</td>
<td>Effective clearance\textsuperscript{37}</td>
</tr>
<tr>
<td>Antituberculous</td>
<td>Isoniazid, Rifampicin, Ethambutol</td>
<td>Hypersensitive reactions</td>
<td>...</td>
<td>Effective clearance (pyrazinamide)</td>
</tr>
<tr>
<td>Amphotericin B</td>
<td>Amphotericin B</td>
<td>Cytotoxicity, Decrease in kidney perfusion pressure</td>
<td>Liposomal amphotericin B, Nacetylcysteine, Saline loading, Slowing infusion speed</td>
<td>Poor clearance (wide volume of distribution, high molecular weight &gt; 90%)\textsuperscript{34}</td>
</tr>
<tr>
<td>Beta-lactams</td>
<td>Carbpamems, Cephalosporins, Penicillins</td>
<td>Cytotoxicity, Hypersensitive reactions</td>
<td>Reduce the combination with Vancomycin</td>
<td>Effective clearance\textsuperscript{51}</td>
</tr>
<tr>
<td>Macrolides</td>
<td>Azithromycin, Clarithromycin, Roxithromycin</td>
<td>Hypersensitive reactions</td>
<td>...</td>
<td>Poor clearance (wide volume of distribution, high molecular weight 700 Da to 1100 Da)\textsuperscript{69}</td>
</tr>
<tr>
<td>Quinolones</td>
<td>Levofloxacin, Ciprofloxacin, Norfloxacin</td>
<td>Hypersensitive reactions, Crystalline nephropathy</td>
<td>Appropriate hydration</td>
<td>Effective clearance\textsuperscript{75}</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>Vancomycin</td>
<td>Cytotoxicity</td>
<td>Cilastatin, Antioxidants</td>
<td>Effective clearance\textsuperscript{83,84}</td>
</tr>
</tbody>
</table>
adults and 0.4 to 8.3 L/kg in children), lipophilicity, bulky size (924 Da), and being highly protein bound (> 90%). Thus, these characteristics suggest that hemodialysis will not clear amphotericin B from plasma. Cases described the use of continuous venovenous hemodiafiltration for patients receiving therapeutic dose of amphotericin B and the drug was found to be poorly dialyzable.

**Beta-Lactams**

Although AKI has been recorded, the main adverse reaction of beta-lactams is allergy. The potential to cause AKI decreases in turn: carbapenems, cephalosporins, penicillins, and monobactams. The major mechanism of AKI is thought to be the direct damage of beta-lactams to tubular cells. Moreover, tubular cells and lymphocytes were observed in renal biopsy tissues what has been reported in some cases. As a result, it is assumed that cell mediated immunological reaction plays a role for beta-lactams-induced AKI. Once developing AKI, the patient’s prognosis may be more complex in the interaction of the two mechanisms. The benefit of early administration of corticosteroids in preventing chronic renal impairment after beta-lactams-induced AKI has been shown in some studies.

The combination of vancomycin and piperacillin-tazobactam has been routinely used for many years; however, reports of increased AKI risk is recently emerged. Recent evidence also suggests that rates of AKI among patients receiving this combination were approximately 3 times greater than that receiving vancomycin and cefepime, and the onset was more rapid in vancomycin and piperacillin-tazobactam patients compared to vancomycin and cefepime (3 versus 5 days, \( P < .001 \)). Fortunately, beta-lactams can be effective cleared by hemodialysis.

**Macrolides**

In clinical practice, azithromycin, clarithromycin, erythromycin, roxithromycin have been reported to cause AKI. Macrolide-induced AKI are observed that have a delayed effect which was presented in 10 days to 6 weeks after completion of therapy. Choosing to use low dose of corticosteroids can improve the extent of renal function recovery after AKI, avoiding long-term sequelae from renal injury. Studies indicated that the incidence of macrolide-induced AKI is associated with cell-mediated hypersensitivity reaction; therefore, the second episode exposed to macrolides was more severe than the first. There was exacerbation of the skin rash and blood eosinophilia and although both were treated with intensive corticosteroid therapy, kidney function remained impaired.

Macrolides can influence kidney function secondary to the interactions with other drugs, for example, the morbidity of AKI was increased when clarithromycin was coprescribed with calcium-channel blockers. A recent population-based cohort of older adults study also confirmed an increased risk of hospitalization with AKI after concurrent use of statins with erythromycin or clarithromycin (adjusted relative risk, 1.65; 95% confidence interval, 1.31 to 2.09). These findings give us current safety warnings regarding concurrent use of macrolides and calcium-channel blockers, and statins. Macrolides have wide volumes of distribution, relatively high molecular weights (700 Da to 1100 Da), and mostly is lipophilic antibiotics. The serum concentration of macrolides was decreased by 27% after 2 hours of conventional haemodialysis.

**Fluoroquinolones**

Fluoroquinolone-induced AKI is uncommon. The hierarchy of nephrotoxicity for fluoroquinolones decreases in turn is ciprofloxacin, followed by moxifloxacin and levofloxacin, with the relative risk of 2.76, 2.09, and 1.69, respectively. In general, cases of fluoroquinolone-induced AKI are described as immune-mediated interstitial nephritis. Studies suggested that early steroid treatment may improve the recovery of renal function in patients with drug-induced AIN.

Cases of AKI from crystal formation secondary to FQs have been documented depending on urine pH greater than 6.8, in particular ciprofloxacin. Khan and colleagues mentioned that conservative measures comprising intravenous hydration and avoidance of alkalinization of the urine can reverse this condition if applied in time, without any need for steroids, and appropriate hydration is helpful during the use of ciprofloxacin. Levofloxacin and ciprofloxacin, although lipophilics, widely distributed in tissues and body fluids, can be cleared by hemodialysis like the normal kidneys.
Figure 4. The diagnosis and treatment process of antibiotic-induced acute kidney injury. The Naranjo algorithm to further determine acute kidney injury as an adverse drug reaction due to antibiotics that categorize adverse reactions into definite, probable, possible, and doubtful. AKI indicates acute kidney injury; AIN, acute interstitial nephritis; and ATN, acute tubular necrosis.
Vancomycin
Vancomycin, the first-line agent for methicillin-resistant *Staphylococcus aureus* infections, is a glycopeptide antibiotic. The incidence of vancomycin-induced AKI has been reported up to 40%.76 Vancomycin-induced oxidative stress results in the tubular damage as the major factors in vancomycin-induced AKI.77 Therefore, various antioxidants have been shown to be beneficial for the prevention of vancomycin-induced AKI, such as erdosteine, vitamin E, caffeic acid phenethyl ester, and erythropoietin in animal experiments.78 A case of vancomycin-induced drug reaction with eosinophilia and systemic syndrome with dialysis-dependent AKI was determined to be an allergic reaction.79 Cilastatin attenuated vancomycin-induced AKI by decreasing apoptosis that could also be an approach to prevent AKI.80

A meta-analysis showed that trough concentrations of 15 mg/L and greater were associated with higher odds of AKI than trough less than 15 mg/L.81 Vancomycin has a moderate volume of distribution, minimal protein binding and molecular weight of 1486 Da. High-flux extract vancomycin as high as 30% to 46% of the administered dose can be cleared in a 3- to 4-hour hemodialysis session.82 Several severe cases showed complete remission of kidney function after hemodialysis.83,84

CLINICAL RECOMMENDATIONS
Most of the antibiotics are used in clinical treatments such as sepsis and septic shock. From studies by Angus and colleagues and Martin and colleagues, it can be found that the mortality rate of severely reported sepsis patients in the world is between 20% and 60%.86-90 Therefore, proper antibiotic treatment is essential. However, the dose and appropriate level of antibiotic treatment are still controversial.91-94

Therefore, choosing the right antibiotics is not enough. A sufficient dose of conventional antibiotic administration may not produce pharmacodynamic targets for infectious agents in this patient population. To provide sufficient antibiotic concentration at the site of infection must also be prescribed.95-98

It is best to identify the right antibiotics as soon as possible and then use them as safely as possible, especially in patients with sepsis and AKI. Patient monitoring should be as vigilant as possible to identify antibiotic toxicity as early as possible.99

CONCLUSIONS
Antibiotics are among the main causes of AKI worldwide. When signs of AKI are first noted, the patient’s medication list should be thoroughly reviewed for potential nephrotoxic antibiotics. In cases of antibiotic-induced AKI, rapid withdrawal of the offending antibiotics is necessary. Early use of steroids may be beneficial in some cases of severe antibiotic-induced AKI. Figure 4 shows the diagnosis and treatment process of antibiotic-induced AKI. The dose and appropriate level of antibiotic treatment are still controversial. This, in future clinical practice, we should not only be familiar with various antibiotics, but we also need to pay attention to the dose used. It is best to identify the right antibiotics as soon as possible and then use them as safely as possible.

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CONFLICT OF INTEREST
None declared.

REFERENCES


Antibiotic-induced Acute Kidney Injury—Yang et al


