IJKD KIDNEY DISEASES

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

Xiaoping Yang,[1] Hongfei Zhong,[2] Chengyun Xu,[1] Gaosi Xu[1]

[1]Department of Nephrology, the Second Affiliated Hospital of Nanchang University, China
[2]Grade 2015, The Second Clinical Medical College of Nanchang University, Nanchang, Jiangxi, China

Keywords. antibiotics, acute kidney injury, epidemiology, prevention, risk factors

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.

IJKD 2019;13:10-20
www.ijkd.org

Review

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.[8,9] 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

Table 1. Risk Factors for Antibiotic-induced Acute Kidney Injury[18-21]

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

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.[22-24] 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.[24] Two important causal agents of ATN are aminoglycosides and amphotericin B.

Acute interstitial nephritis also presents the signs of an allergic reaction.[25] It is usually self-limiting, but in some studies, it is claimed that steroids may promote recovery.[25] The symptoms of AIN are variable and often not specific; thus, kidney biopsy is required to make a firm diagnosis.

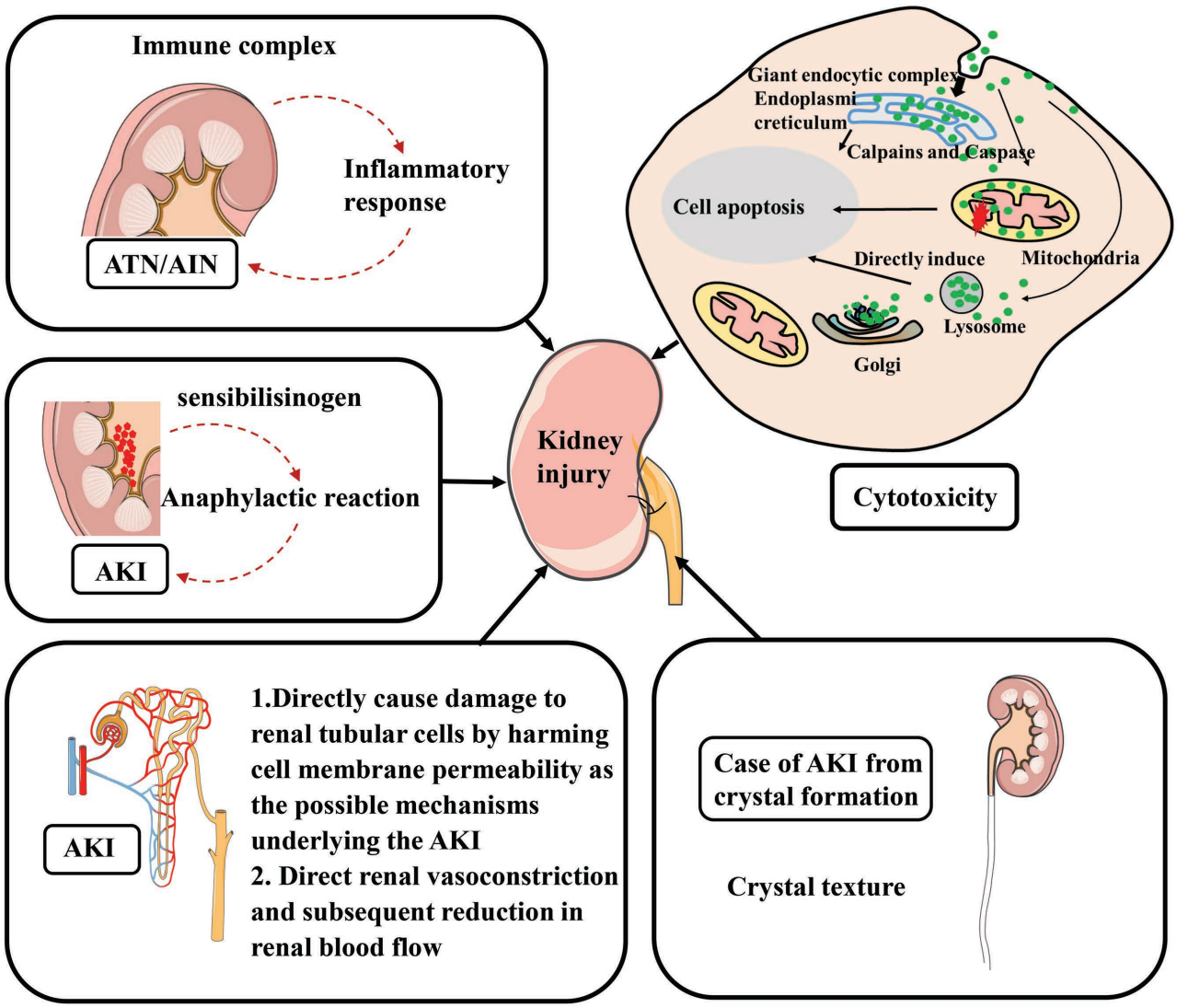

Figure 1. The pathogenic mechanisms of antibiotic-induced nephrotoxicity.

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.[26] The incidence of aminoglycosides-induced AKI varies between 5% and 25%,[27-29] and it usually occurs after at least a week of treatment.[30]

Aminoglycosides are selectively accumulated within proximal tubule epithelial cells and mesangial matrix cells.[31] 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,[32,33] 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,

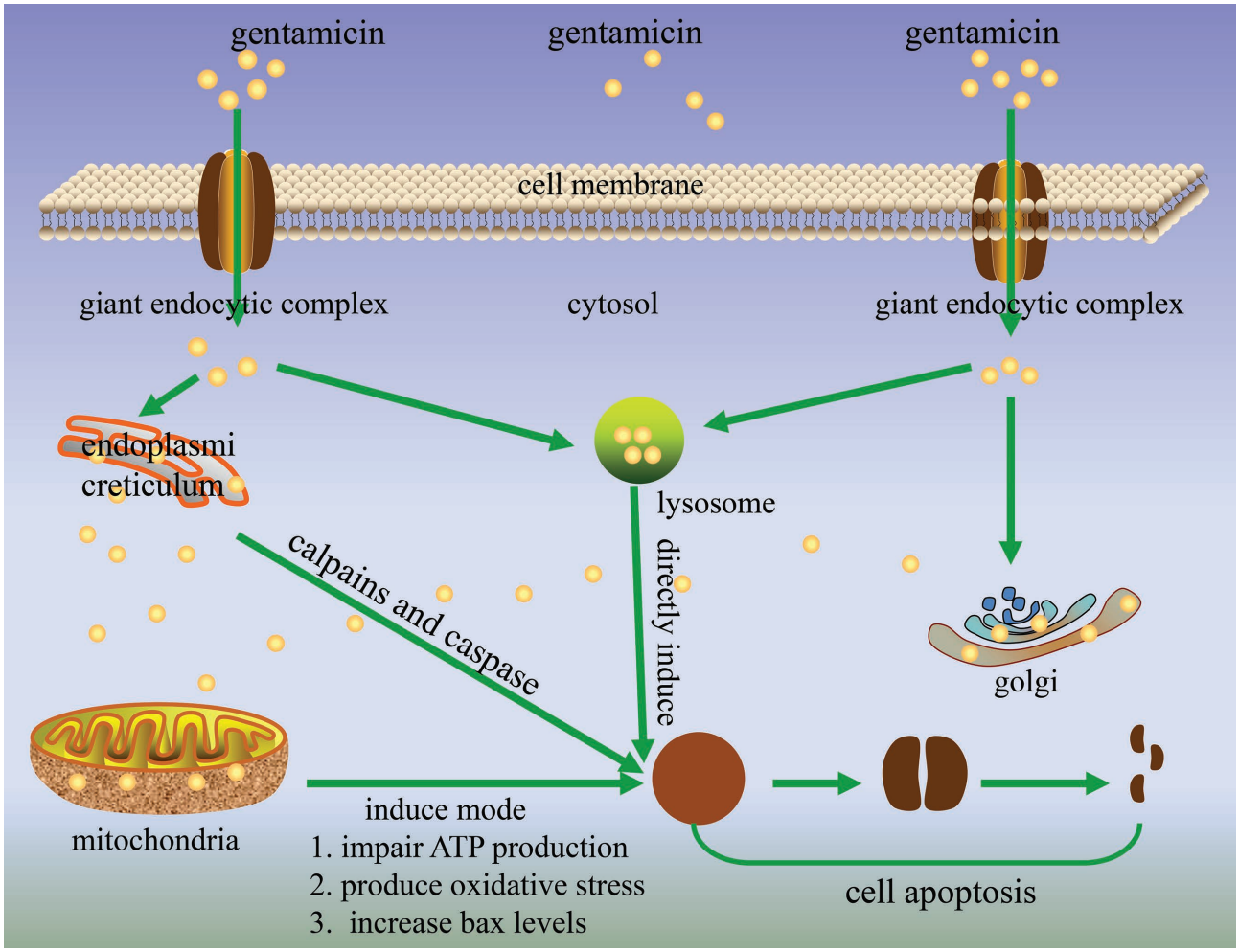

Figure 2. The underlying mechanics of antibiotic-induced acute kidney injury. Antibiotics are a wide-spread class of drugs and the principal cause of antibiotics -associated nephropathy varied. Different mechanisms have been identified: a decrease in kidney perfusion pressure, the formation of encounter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

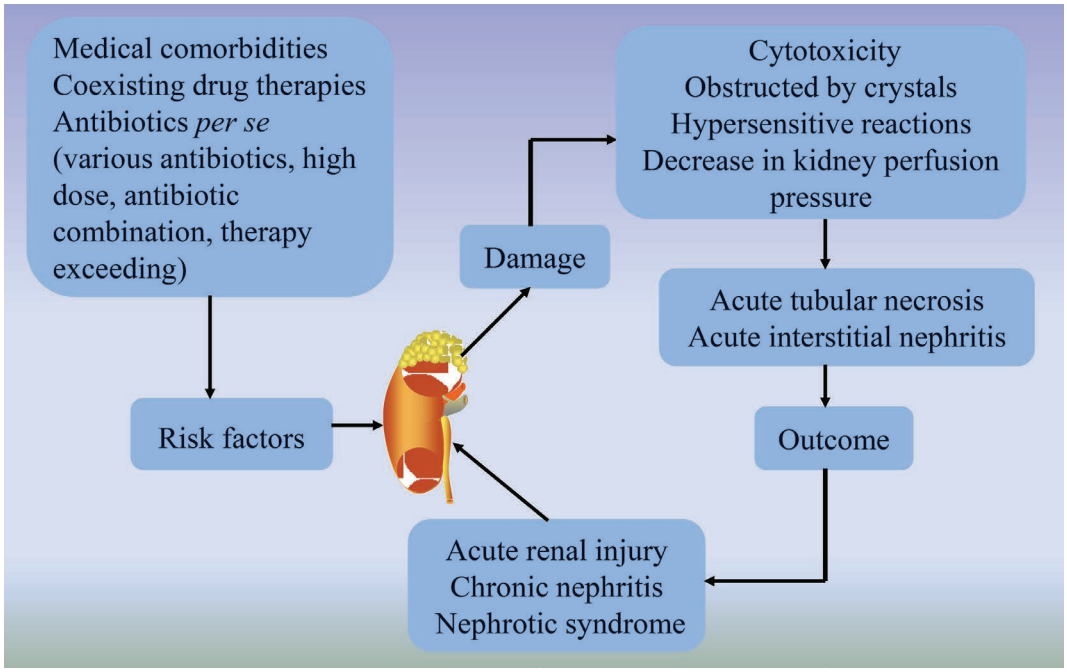

Figure 3. Antibiotic-induced cytotoxicity. Megalin and cubilin of proximal tubule form the giant endocytic complex. This complex transports gentamicin by endocytosis, then accumulates mostly in lysosomes, the golgi, and endoplasmic reticulum. When the concentration of gentamicin in endosomal structures 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.

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-glucosamidase 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 studies[41,42] 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

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

Antibiotics	Related drugs	Mechanisms	Preventions	Hemodialysis
Aminoglycosides	Gentamicin, Amikacin, Streptomycin	Cytotoxicity, Decrease in kidney perfusion pressure	Statins, Prolonged interval dosing, Nebulised aminoglycosides	Effective clearance[37]
Antituberculous	Isoniazid, Rifampicin, Ethambutol	Hypersensitive reactions	…	Effective clearance (pyrazinamide) Poor clearance (large molecularweight, wide distribution, high protein binding, rapid hepatic clearance or adherence to the dialyzer membrane of isoniazid, rifampicin and ethambutol)[41-45]
Amphotericin B	Amphotericin B	Cytotoxicity, Decrease in kidney perfusion pressure	Liposomal amphotericin B, Nacetylcysteine, Saline loading, Slowing infusion speed	Poor clearance (widely volume of distribution, lipophilicity, large size 924 daltons, and highly protein bound > 90%)[54]
Beta-lactams	Carbapenems, Cephalosporins, Penicillins	Cytotoxicity, Hypersensitive reactions	Reduce the combination with Vancomycin	Effective clearance[61]
Macrolides	Azithromycin, Clarithromycin, Roxithromycin	Hypersensitive reactions	…	Poor clearance (widely volumes of distribution, high molecular weights 700 Da to 1100 Da).[69]
Quinolones	Levofloxacin , Ciprofloxacin, Norfloxacin	Hypersensitive reactions, Crystalline nephropathy	Appropriate hydration	Effective clearance[75]
Vancomycin	Vancomycin	Cytotoxicity	Cilastatin, Antioxidants	Effective clearance[83,84]

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.[40]

Clinically, timely termination of anti-TB treatment may have an excellent response; no further therapy (steroids or hemodialysis) was required.[41] Days after discontinuing anti-TB drugs, serum creatinine concentration begins to recover.[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.[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.[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.[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.[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.[49] Use of liposomal amphotericin B resulted in lower incidence of AKI than conventional amphotericin B.[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.[51-53] Another strategy under discussion for prevention of AKI is to slow the infusion speed.[52] The pharmacokinetics of the conventional amphotericin B include a large volume of distribution (4 L/kg in

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.[54]

Beta-Lactams

Although AKI has been recorded, the main adverse reaction of beta-lactams is allergy.[55,56] 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.[56] As a result, it is assumed that cell mediated immunological reaction plays a role for beta-lactams-induced AKI.[57] 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.[57]

The combination of vancomycin and piperacillin-tazobactam has been routinely used for many years; however, reports of increased AKI risk is recently emerged.[58,59] 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, $P < .001$).[60] Fortunately, beta-lactams can be effective cleared by hemodialysis.[61]

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.[62,63] Choosing to use low dose of corticosteroids can improve the extent of renal function recovery after AKI, avoiding long-term sequelae from renal injury.[64] Studies indicated that the incidence of macrolide-induced AKI is associated with cell-mediated hypersensitivity reaction[65]; 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.[66]

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.[67] 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).[68] 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.[69]

Fluoroquinolones

Fluoroquinolone-induced AKI is uncommon. The hierarchy of nephrotoxicity for fluoroquinolones decreases in turn is ciprofloxacin, followed by moxifloxacin and levofloxacin,[70] 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.[71] Studies suggested that early steroid treatment may improve the recovery of renal function in patients with drug-induced AIN.[72]

Cases of AKI from crystal formation secondary to FQs have been documented depending on urine pH greater than 6.8, in particular ciprofloxacin.[73] 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,[74] 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.[75]

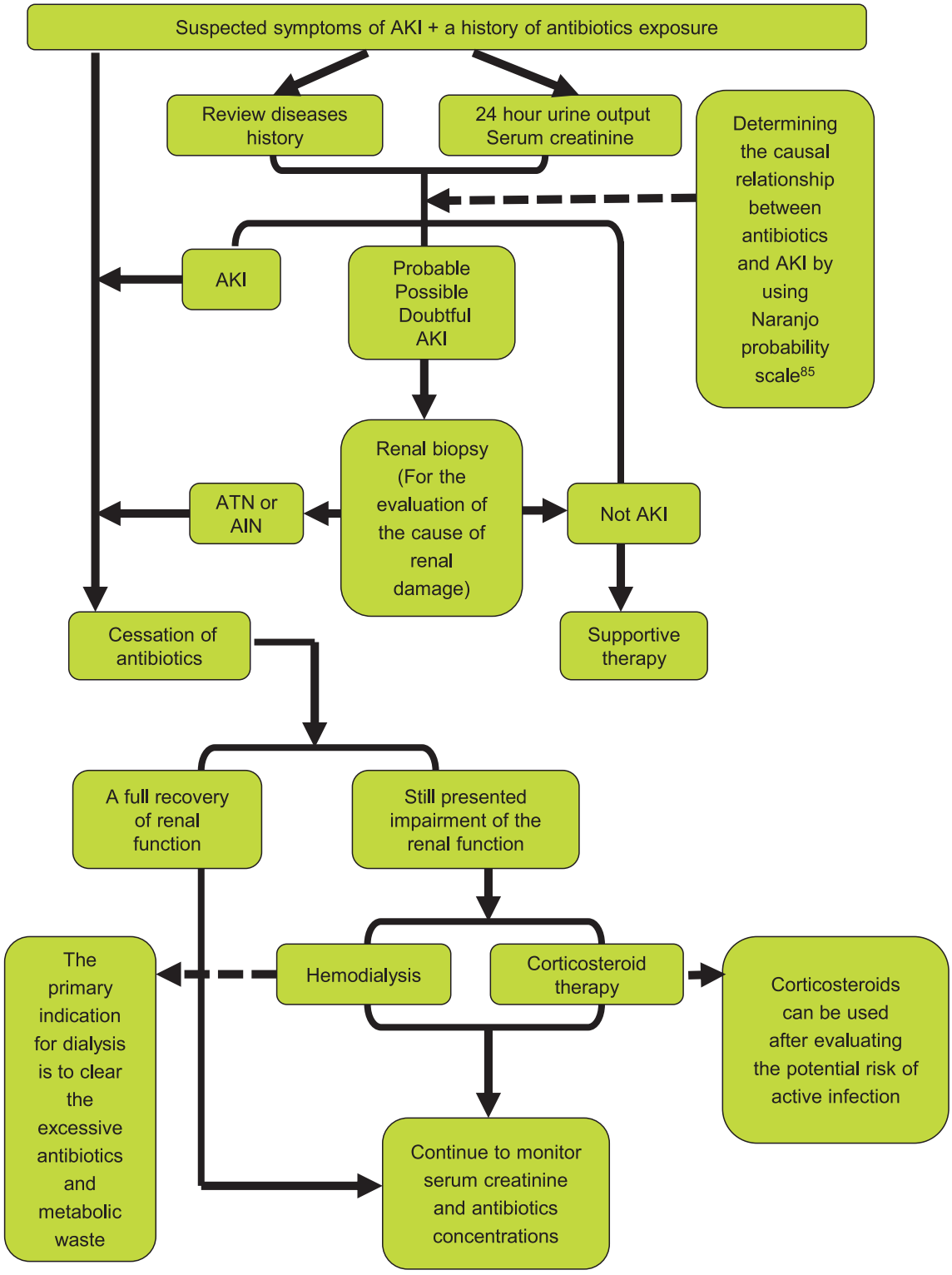

Figure 4. The diagnosis and treatment process of antibiotic-induced acute kidney injury.
The Naranjo algorithm to further determine acute kidney injury as an adverse drug reaction due to antibiotics that categorize adverse reactions into definite, probable, possible, and doubtful. AKI indicates acute 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.

FUNDING SUPPORT

This study was supported by the National Natural Science Foundation of China (No H0517/81560132), the Supporting Project for the Foregoers of Main Disciplines of Jiangxi Province (No 20162BCB22023), and the ''5511'' Innovative Drivers for Talent Teams of Jiangxi Province (No 20165BCB18018).

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Pazhayattil GS, Shirali AC. Drug-induced impairment of renal function. Int J Nephrol Renovasc Dis. 2014;7:457-68.
2. Stavreva G, Pendicheva D, Pandurska A, Marev R. Detection of adverse drug reactions to antimicrobial drugs in hospitalized patients. Trakia J Sci. 2008;6(Suppl 1):7-9.
3. Derungs A. Drug-induced acute kidney injury. Ther Umsch. 2015;72:717-27.
4. Khalili H, Bairami S, Kargar M. Antibiotics induced acute kidney injury: incidence, risk factors, onset time and outcome. Acta Med Iran. 2013;51:871-8.
5. Choudhury D, Ahmed Z. Drug-associated renal dysfunction and injury. Nat Clin Pract Nephrol. 2006;2:80-91.
6. Reis AM, Cassiani SH. Adverse drug events in an intensive care unit of a university hospital. Eur J Clin Pharmacol. 2011;67:625-32.
7. Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group AKI definition. Kidney Int Suppl. 2012;2:19-36.

8. Mehta RL, Burdmann EA, Tonelli M, et al. International Society of Nephrology's 0by25 initiative for acute kidney injury (zero preventable deaths by 2025): a human rights case for nephrology. Lancet. 2015;385:2616-43.
9. Susantitaphong P, Cruz DN, Cerda J, et al. World incidence of AKI: a meta-analysis. Clin J Am Soc Nephrol. 2013;8:1482-93.
10. Mehta RL, Pascual MT, Soroko S, et al. Spectrum of acute renal failure in the intensive care unit: the PICARD experience. Kidney Int. 2004;66:1613-21.
11. Uchino S, Kellum JA, Bellomo R, et al. Acute renal failure in critically ill patients: a multinational, multicenter study. JAMA. 2005;294:813-8.
12. Yang L. Acute Kidney Injury in Asia. Kidney Dis (Basel). 2016;2:95-102.
13. Xu X, Nie S, Liu Z, et al. Epidemiology and Clinical Correlates of AKI in Chinese Hospitalized Adults. Clin J Am Soc Nephrol. 2015;10:1510-8.
14. Che ML, Yan YC, Zhang Y, et al. Analysis of drug-induced acute renal failure in Shanghai. Zhonghua Yi Xue Za Zhi. 2009;89:744-9.
15. Pierson-Marchandise M, Gras V, Moragny J, et al. The drugs that mostly frequently induce acute kidney injury: a case - noncase study of a pharmacovigilance database. Br J Clin Pharmacol. 2017;83:1341-9.
16. Laake JH, Bugge, JF. Acute renal failure in critically ill patients. Tidsskr Nor Laegeforen. 2010;130:158-61.
17. Jensen JU, Hein L, Lundgren B, et al. Kidney failure related to broad-spectrum antibiotics in critically ill patients: secondary end point results from a 1200 patient randomised trial. BMJ Open. 2012;2:e000635.
18. Leblanc M, Kellum JA, Gibney RT, Lieberthal W, Tumlin J, Mehta R. Risk factors for acute renal failure: inherent and modifiable risks. Curr Opin Crit Care. 2005;11:533-6.
19. Schrier RW, Wang W. Acute renal failure and sepsis. N Engl J Med. 2004;351:159-69.
20. Nash K, Hafeez A, Hou S. Hospital-acquired renal insufficiency. Am J Kidney Dis. 2002;39:930-6.
21. Bellomo R. The epidemiology of acute renal failure:1975 versus 2005. Curr Opin Crit Care. 2006;12:557-60.
22. Martinez-Salgado C, Lopez-Hernandez FJ, Lopez-Novoa JM. Glomerular nephrotoxicity of aminoglycosides. Toxicol Appl Pharmacol. 2007;223:86-98.
23. Matsubara R, Kibe T, Nomura T. Crystalline nephropathy caused by tosufloxacin. Pediatr Int. 2016;58:1219-21.
24. Hosohata K. Role of Oxidative Stress in Drug-Induced Kidney Injury. Int J Mol Sci. 2016;17:1826.
25. Raghavan R, Shawar S. Mechanisms of Drug-Induced Interstitial Nephritis. Adv Chronic Kidney Dis. 2017;24:64-71.
26. McWilliam SJ, Antoine DJ, Smyth RL, Pirmohamed M. Aminoglycoside-induced nephrotoxicity in children. Pediatr Nephrol. 2017;32:2015-25.
27. Wargo KA, Edwards JD. Aminoglycoside-induced nephrotoxicity. J Pharm Pract. 2014;27:573-7.
28. Picard W, Bazin F, Clouzeau B, et al. Propensity-based study of aminoglycoside nephrotoxicity in patients with severe sepsis or septic shock. Antimicrob Agents Chemother. 2014;58:7468-74.
29. Lopez-Novoa JM, Quiros Y, Vicente L, Morales AI, Lopez-Hernandez FJ. New insights into the mechanism of aminoglycoside nephrotoxicity: an integrative point of view. Kidney Int. 2011;79:33-45.
30. Oliveira JFP, Cipullo JP, Burdmann EA. Aminoglycoside nephrotoxicity. Braz J Cardiovasc Surg. 2006;21:444-52.
31. Schmitz C, Hilpert J, Jacobsen C, Boensch C, Christensen EI, Luft FC, Willnow TE. Megalin deficiency offers protection from renal aminoglycoside accumulation. J Biol Chem. 2002;277:618-22.
32. Nagai J, Takano M. Entry of aminoglycosides into renal tubular epithelial cells via endocytosis-dependent and endocytosis-independent pathways. Biochem Pharmacol. 2014;90:331-7.
33. Denamur S, Boland L, Beyaert M, et al. Subcellular mechanisms involved in apoptosis induced by aminoglycoside antibiotics: Insights on p53, proteasome and endoplasmic reticulum. Toxicol Appl Pharmacol. 2016;309:24-36.
34. Martinez-Salgado C, Rodríguez-Barbero A, Eleno N, López-Novoa JM. Gentamicin induces Jun-AP1 expression and JNK activation in renal glomeruli and cultured mesangial cells. Life Sci. 2005;77:2285-98.
35. Smyth A, Tan KH, Hyman-Taylor P, et al. Once versus three-times daily regimens of tobramycin treatment for pulmonary exacerbations of cystic fibrosis--the TOPIC study: a randomised controlled trial. Lancet. 2005;365:573-8.
36. Antoine DJ, Srivastava A, Pirmohamed M, Park BK. Statins inhibit aminoglycoside accumulation and cytotoxicity to renal proximal tubule cells. Biochem Pharmacol. 2010;79:647-54.
37. Eschenauer GA, Lam SW, Mueller BA. Dose Timing of Aminoglycosides in Hemodialysis Patients: A Pharmacology View. Semin Dial. 2016;29:204-13.
38. Li Y, Zhu Y, Zhong Q, Zhang X, Shu M, Wan C. Serious Adverse Reactions From Anti-tuberculosis Drugs Among 599 Children Hospitalized for Tuberculosis. Pediatr Infect Dis J. 2017;36:720-5.
39. Wortham JM, Goggin M, Mora C, Vandehey L, Manangan L, Powell KM. Acute kidney injury during treatment for latent tuberculous infection with rifampin. Int J Tuberc Lung Dis. 2017;21:596-7.
40. Chang CH, Chen YF, Wu VC, et al. Acute kidney injury due to anti-tuberculosis drugs: a five-year experience in an aging population. BMC Infect Dis. 2014;14:23.
41. De Vriese AS, Robbrecht DL, Vanholder RC, Vogelaers DP, Lameire NH. Rifampicin-associated acute renal failure: pathophysiologic, immunologic, and clinical features. Am J Kidney Dis. 1998;31:108-15.
42. Martin SJ, Sabina EP. Amelioration of anti-tuberculosis drug induced oxidative stress in kidneys by Spirulina fusiformis in a rat model. Ren Fail. 2016;38:1115-21.
43. Munteanu L, Golea O, Nicolicioiu M, Tudorache V. Specific features of acute renal failure in patients treated with rifampicin. Pneumologia. 2002;51:15-20.
44. Muthukumar T, Jayakumar M, Fernando E M,

Muthusethupathi MA. Acute renal failure due to rifampicin: a study of 25 patients. Am J Kidney Dis. 2002;40:690-6.

45. Malone RS, Fish DN, Spiegel DM, et al. The effect of hemodialysis on isoniazid, rifampin, pyrazinamide, and ethambutol. Am J Respir Crit Care Med 1999;159:1580-4.
46. Yano T, Itoh Y, Kawamura E, et al. Amphotericin B-induced renal tubular cell injury is mediated by Na+ Influx through ion-permeable pores and subsequent activation of mitogen-activated protein kinases and elevation of intracellular Ca2+ concentration. Antimicrob Agents Chemother. 2009;53:1420-6.
47. Sabra R, Branch RA. Mechanisms of amphotericin B-induced decrease in glomerular filtration rate in rats. Antimicrob Agents Chemother 1991;35:2509-14.
48. Rocha PN, Kobayashi CD, de Carvalho Almeida L, de Oliveira Dos Reis C, Santos BM, Glesby MJ. Incidence, Predictors, and Impact on Hospital Mortality of Amphotericin B Nephrotoxicity Defined Using Newer Acute Kidney Injury Diagnostic Criteria. Antimicrob Agents Chemother. 2015;59:4759-69.
49. Karimzadeh I, Heydari M, Ramzi M, Sagheb MM. Frequency and Associated Factors of Amphotericin B Nephrotoxicity in Hospitalized Patients in Hematology-Oncology Wards in the Southwest of Iran. Nephrourol Mon. 2016;8:e39581.
50. Hamill RJ. Amphotericin B formulations: a comparative review of efficacy and toxicity. Drugs. 2013;73:919-34.
51. Karimzadeh I, Khalili H, Sagheb MM, Farsaei S. A double-blinded, placebo-controlled, multicenter clinical trial of N-acetylcysteine for preventing amphotericin B-induced nephrotoxicity. Expert Opin Drug Metab Toxicol. 2015;11:1345-55.
52. Karimzadeh I, Farsaei S, Khalili H, Dashti-Khavidaki S. Are salt loading and prolonging infusion period effective in prevention of amphotericin B-induced nephrotoxicity? Expert Opin Drug Saf. 2012;11:969-83.
53. Berdichevski RH, Luis LB, Crestana L, Manfro RC. Amphotericin B-related nephrotoxicity in low-risk patients. Braz J Infect Dis. 2006;10:94-9.
54. Gussak HM, Rahman S, Bastani B. Administration and clearance of amphotericin B during high-efficiency or high-efficiency/high-flux dialysis. Am J Kidney Dis. 2001;37:E45.
55. Moenster RP, Linneman TW, Finnegan PM, Hand S, Thomas Z, McDonald JR. Acute renal failure associated with vancomycin and beta-lactams for the treatment of osteomyelitis in diabetics: piperacillin-tazobactam as compared with cefepime. Clin Microbiol Infect. 2014;20:O384-9.
56. Mac K, Chavada R, Paull S, Howlin K, Wong J. Cefepime induced acute interstitial nephritis--a case report. BMC Nephrol. 2015;16:15.
57. González E, Gutiérrez E, Galeano C, et al. Early steroid treatment improves the recovery of renal function in patients with drug-induced acute interstitial nephritis. Kidney Int. 2008;73:940-6.
58. Burgess LD, Drew RH. Comparison of the incidence of vancomycin-induced nephrotoxicity in hospitalized patients with and without concomitant piperacillin-tazobactam. Pharmacotherapy. 2014;34:670-6.
59. Gomes DM, Smotherman C, Birch A, et al. Comparison of acute kidney injury during treatment with vancomycin in combination with piperacillin-tazobactam or cefepime. Pharmacotherapy. 2014;34:662-9.
60. Navalkele B, Pogue JM, Karino S, et al. Risk of Acute Kidney Injury in Patients on Concomitant Vancomycin and Piperacillin-Tazobactam Compared to Those on Vancomycin and Cefepime. Clin Infect Dis. 2017;64:116-23.
61. Lin SY, Huang JC, Shen MC, et al., Piperacillin-induced thrombocytopenia reversed by high-flux hemodialysis in an uremic patient. Hemodial Int. 2012;16(Suppl 1):S50-3.
62. Mansoor GA, Panner BJ, Ornt DB. Azithromycin-induced acute interstitial nephritis. Ann Intern Med 1993;119:636-7.
63. Persico C, Rocchi A, Edefonti A, Milani GP, Mazzoni MB, Fossali EF. The acute interstitial nephritis induced by azithromycin. NDT Plus. 2011;4:218.
64. Woodruff AE, Meaney CJ, Hansen EA, Prescott GM. Azithromycin-Induced, Biopsy-Proven Acute Interstitial Nephritis in an Adult Successfully Treated with Low-Dose Corticosteroids. Pharmacotherapy. 2015;35:e169-74.
65. Russell W, Smith W. Clarithromycin-induced acute interstitial nephritis and minimal change disease. NDT Plus. 2009;2:382-3.
66. Soni N, Harrington JW, Weiss R, Chander P, Vyas S. Recurrent acute interstitial nephritis induced by azithromycin. Pediatr Infect Dis J. 2004;23:965-6.
67. Gandhi S, Fleet JL, Bailey DG, McArthur E, Wald R, Rehman F. Calcium-channel blocker-clarithromycin drug interactions and acute kidney injury. JAMA. 2013;310:2544-53.
68. Mishima E, Maruyama K, Nakazawa T, Abe T, Ito S. Acute Kidney Injury from Excessive Potentiation of Calcium-channel Blocker via Synergistic CYP3A4 Inhibition by Clarithromycin Plus Voriconazole. Intern Med. 2017;56:1687-90.
69. Ma TK, Chow KM, Choy AS, Kwan BC, Szeto CC, Li PK. Clinical manifestation of macrolide antibiotic toxicity in CKD and dialysis patients. Clin Kidney J. 2014;7:507-12.
70. Bird ST, Etminan M, Brophy JM, Hartzema AG, Delaney JA. Risk of acute kidney injury associated with the use of fluoroquinolones. CMAJ. 2013;185:E475-82.
71. Muriithi AK, Leung N, Valeri AM, et al. Biopsy-proven acute interstitial nephritis, 1993-2011: a case series. Am J Kidney Dis. 2014;64:558-66.
72. Krishnan N, Perazella MA. Drug-induced acute interstitial nephritis: pathology, pathogenesis, and treatment. Iran J Kidney Dis. 2015;9:3-13.
73. Goli R, Mukku KK, Raju SB, Uppin MS. Acute Ciprofloxacin-Induced Crystal Nephropathy with Granulomatous Interstitial Nephritis. Indian J Nephrol. 2017;27:231-3.
74. Khan M, Ortega LM, Bagwan N, Nayer A. Crystal-induced acute kidney injury due to ciprofloxacin. J Nephropathol. 2015;4:29-31.
75. Pea F, Viale P, Pavan F, Furlanut M. Pharmacokinetic considerations for antimicrobial therapy in patients receiving renal replacement therapy. Clin Pharmacokinet. 2007;46:997-1038.

76. Elyasi S, Khalili H, Dashti-Khavidaki S, Mohammadpour A. Vancomycin-induced nephrotoxicity: mechanism, incidence, risk factors and special populations. A literature review. Eur J Clin Pharmacol. 2012;68:1243-55.
77. Filippone EJ, Kraft WK, Farber JL. The Nephrotoxicity of Vancomycin. Clin Pharmacol Ther. 2017;102:459-69.
78. Elyasi S, Khalili H, Hatamkhani S, Dashti-Khavidaki S. Prevention of vancomycin induced nephrotoxicity: a review of preclinical data. Eur J Clin Pharmacol. 2013;69:747-54.
79. Webb PS, Al-Mohammad A. Enigma: infection or allergy? Vancomycin-induced DRESS syndrome with dialysis-dependent renal failure and cardiac arrest. BMJ Case Rep. 2016;2016.
80. Im DS, Shin HJ, Yang KJ, et al. Cilastatin attenuates vancomycin-induced nephrotoxicity via P-glycoprotein. Toxicol Lett. 2017;277:9-17.
81. van Hal SJ, Paterson DL, Lodise TP. Systematic review and meta-analysis of vancomycin-induced nephrotoxicity associated with dosing schedules that maintain troughs between 15 and 20 milligrams per liter. Antimicrob Agents Chemother. 2013;57:734-44.
82. O'Donnell JN, Ghossein C, Rhodes NJ, et al. Eight unexpected cases of vancomycin associated acute kidney injury with contemporary dosing. J Infect Chemother. 2017;23:326-32.
83. Pallotta KE, Manley HJ. Vancomycin use in patients requiring hemodialysis: a literature review. Semin Dial. 2008;21:63-70.
84. Katikaneni M, Lwin L, Villanueva H, Yoo J. Acute Kidney Injury Associated With Vancomycin When Laxity Leads to Injury and Findings on Kidney Biopsy. Am J Ther. 2016;23:e1064-7.
85. Naranjo CA, Busto U, Sellers EM, et al. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther. 1981;30:239-45.
86. Angus DC, Lindezwirble WT, Lidicker J, et al. Epidemiology of severe sepsis in the United States: analysis of incidence, outcome, and associated costs of care. J Critic Care Med.. 2001;29:1303-10.
87. Martin GS, Mannino DM, Eaton S, et al. The epidemiology of sepsis in the United States from 1979 through 2000. N Engl J Med. 2003;348:1546-54.
88. Angus DC, Pereira CA, Silva E. Epidemiology of severe sepsis around the world. Endocr Metab Immune Disord Drug Targets. 2006;6:207-12.
89. Vincent JL, Rello J, Marshall J, et al. EPIC II Group of Investigators. International study of the prevalence and outcomes of infection in intensive care units. JAMA. 2009;302:2323.
90. Quenot JP, Binquet C, Kara F, et al. The epidemiology of septic shock in French intensive care units: the prospective multicenter cohort EPISS study. J Critic Care. 2013;17:R65.
91. Kollef MH, Sherman G, Ward S, Fraser VJ. Inadequate antimicrobial treatment of infections: a risk factor for hospital mortality among critically ill patients. J Chest. 1999;115:462-74.
92. Ibrahim EH, Sherman G, Ward S, VJ Fraser, MH Kollef. The influence of inadequate antimicrobial treatment of bloodstream infections on patient outcomes in the ICU setting. J Chest. 2000;118:146-55.
93. Harbarth S, Garbino J, Pugin J, et al. Inappropriate initial antimicrobial therapy and its effect on survival in a clinical trial of immunomodulating therapy for severe sepsis. Am J Med. 2003;115:529-35.
94. Shorr AF, Micek ST, Welch E C, et al. Inappropriate antibiotic therapy in Gram-negative sepsis increases hospital length of stay. J Critic Care Med. 2011;39:46.
95. Taccone F S, Laterre P F, Dugernier T, et al. Insufficient β-lactam concentrations in the early phase of severe sepsis and septic shock. J Critic Care. 2010;14:R126.
96. Seyler L, Cotton F, Taccone FS, et al. Recommended B-lactam regimens are inadequate in septic patients treated with continuous renal replacement therapy. Crit Care. 2011;15:R137.
97. Udy AA, Varghese JM, Altukroni M, et al. Subtherapeutic initial β-lactam concentrations in select critically ill patients: association between augmented renal clearance and low trough drug concentrations. J Chest. 2012;142:30-9.
98. Binder L, Schwörer H, Hoppe S, et al. Pharmacokinetics of meropenem in critically ill patients with severe infections. J Ther Drug Monitor. 2013;35:63-70.
99. Lewis S J, Mueller B A. Antibiotic Dosing in Patients With Acute Kidney Injury: "Enough But Not Too Much". J Intens Care Med. 2014;7:226-35.

Correspondence to:
Gaosi Xu, MD, PhD
Department of Nephrology, the Second Affiliated Hospital of Nanchang University, No 1, Minde Rd, Donghu District, Nanchang, China; Zip Code: 330006
Tel: +86 791 8631 1248
Fax: +86 791 8631 1248
E-mail: gaosixu@163.com

Xiaoping Yang and Hongfei Zhong contributed equally to this work as first author.

Received May 2018
Revised July 2018
Accepted July 2018