Review Article

Drug Induced Kidney Disease: Epidemiology, Pathophysiology and Management

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ABSTRACT

The incidence of acute kidney injury in population has grown over in previous decades. Medications cause renal failure through a variety of mechanisms. Drug-induced nephrotoxicity has been shown to contribute to 8–60% of AKI. The pathophysiology of DIKD is multifactorial and most drugs found to cause nephrotoxicity by one or more common pathogenic mechanisms. The main mechanisms of nephrotoxicity are vasoconstriction, altered intraglomerular hemodynamics, tubular cell toxicity, interstitial nephritis, crystal deposition, thrombotic microangiopathy and osmotic nephrosis. This review focuses on the epidemiology, pathophysiology and management of drug-induced kidney disease (DIKD).

Keywords: Nephrotoxicity, antibiotics, kidney injury, drug induced toxicity.

INTRODUCTION

Kidney is one of the vital organs of the body. A main function of the kidney is the concentration and excretion of toxic metabolites and drugs. It is therefore a frequent site of drug toxicity [1]. Our current understanding of the epidemiology of acute kidney injury (AKI) and its impact on morbidity, mortality, cost of medical care, and the development of chronic kidney disease is based almost exclusively on studies of patients who developed AKI while hospitalized. Although some patients develop AKI prior to hospitalization, termed community acquired AKI, the incidence of community-acquired AKI and its impact on patient outcomes are largely unknown. Drug-induced nephrotoxicity has been shown to contribute to 8–60% of AKI depending on patient population and definition of AKI [2].

Epidemiology of DIKD

There is no universally accepted definition of AKI[3]. Standard definition of AKI is lacking, leading to challenges in recognition and reporting. The clinical manifestations of drug induced nephrotoxicity often go unrecognized, particularly in the setting of short drug exposures. This poses challenges in assessing the incidence, severity and long-term consequences of drug induced nephrotoxicity. Our review focuses on the epidemiology, pathophysiology and management of drug induced nephrotoxicity. Prospective cohort studies of AKI have documented the frequency of drug-induced nephrotoxicity to be approximately 14-26% in adult populations [4-6]. Nephrotoxicity is a main concern in pediatrics with 16% of hospitalized AKI events caused primarily due to a drug [7]. Frequent use of specific drugs, such as tenofovir, has led to significant attention to tubular injuries with documented frequencies of 12–22% of treated subjects in cohort studies [8, 9]. Novel chemotherapeutic agents are increasingly being associated with glomerular injury[10]. DIKD associated with antibiotic toxicity and contrast-induced nephropathy, were reported to be significantly less common in community acquired vs. hospital-acquired[2]. Nephrotoxicity is a common in aminoglycosides such as gentamicin, amikacin, tobramycin which are commonly used for Gram-negative infections, ranging between 10 and 20% of patients prescribed these drugs [11, 12].

1. Pathophysiology of DIKD

The pathophysiology of DIKD is multifactorial and most drugs found to cause nephrotoxicity by one or more common pathogenic mechanisms. Certain drugs are nephrotoxic at any level of exposure (although a dose-response relationship for toxicity may still exist), such as aminoglycosides, amphotericin-B, cisplatin and contrast dye, whereas others may produces their toxic effects in a dose-dependent manner, depending on the duration of treatment[1]. Following are the pathogenic mechanisms of DIKD.

1.1. Intraglomerular heamodynamics alteration (Vasoconstriction)

This is the main mechanism of acute nephrotoxicity[1]. The kidney auto-regulates intra-glomerular pressure by controlling afferent and efferent arteriolar diameter to maintain the GFR. Drugs causing true intravascular volume depletion such as diuretics, or altered glomerular hemodynamics such as NSAIDs, angiotensin-converting enzyme inhibitors, ARBs, calcineurin inhibitors and sodium-glucose co-transporter-2 inhibitors may leads to hemodynamic AKI. Intravascular volume depletion stimulates prostaglandin synthesis and cause afferent arteriolar dilation to optimize renal blood flow. Inhibition

of prostaglandin-induced vasodilation with NSAIDs interferes with the auto-regulation of glomerular pressure and AKI may occur [13, 14-16]. These hemodynamic effects are also observed with drugs acting on the renin angiotensin system. Angiotensin converting enzyme inhibitors and Angiotensin receptor blockers (ARBs) decrease intra-glomerular pressure by the inhibition of angiotensin mediated efferent arteriolar vasoconstriction. The use of these drugs under normal circumstances with adequate renal perfusion does not cause AKI[13-15]. However, AKI may occur with angiotensin-converting enzyme inhibitors or ARBs in states of true or effective volume depletion (decompensated heart failure, decompensated cirrhosis), or with concomitant use with NSAIDs and diuretics [13-15]. Cacineurin inhibitors (tacrolimus, cyclosporine A) cause a dose-dependent vasoconstriction of the afferent arterioles, hence precipitating renal impairment and ischemia[17]. Moreover, drugs that increase the blood concentrations of calcineurin inhibitors (cytochrome P450 enzyme inhibitors such as diltiazem, azole antifungals) lead to an increase in nephrotoxicity in patients[18].

1.2. Tubular cell Toxicity

Renal tubular cells, particularly proximal convoluted tubule cells are susceptible to drug toxicity because their role in transporting and concentrating drugs and metabolites within the renal tubular epithelial cells with help of the human organic anion transporter[19]. Megalin-mediated endocytosis also plays crucial role in the development of drug and nephrotoxin-induced AKI[20]. Acute tubular necrosis (ATN) is usually a dose-dependent process [21]. It is commonly associated with antibiotics such as aminoglycosides, chemotherapeutic agents such as cisplatin, iodinated contrast agents and bisphosphonates (especially, zoledronic acid) [22]. Aminoglycosides are commonly used for gram-negative infections and Intracellular accumulation leads to cell apoptosis and necrosis leads nephrotoxicity in patients [11]. Other antibiotics commonly associated with ATN include amphotericin B and vancomycin. Amphotericin B is widely used for the treatment of fungal infections, owing to its broad spectrum of coverage. Approximately 80% of patients who receive conventional amphotericin B experience some renal dysfunction, mediated by its direct binding and toxicity to tubular epithelial cells causing increased cell permeability [14,22,23]. Vancomycin is a glycopeptide that is widely used to treat methicillin-resistant Staphylococcus aureus (MRSA) infections.

The exact mechanism of vancomycin-induced kidney injury is not completely understood; however, risk factors for toxicity include use of concomitant nephrotoxic agents, concomitant use of piperacillin–tazobactam and duration of exposure and drug concentrations achieved[24]. New evidence has recently been reported on vancomycin-induced cast nephropathy as the etiology of AKI [25.]

1.3. Glomerular Injury

It is less common than acute interstitial nephritis (AIN) and ATN. Drug-induced glomerular disease is seen with several commonly prescribed medications. These patients present with large amounts of proteinuria and microscopic hematuria, which is indicative of glomerular injury. The

patterns of glomerular injury relevant to drugs used by the elder patients include minimal change disease associated with NSAIDs and lithium and focal segmental glomerulosclerosis associated with pamidronate use [22].

1.4. Inflammation (Acute Interstitial Nephritis)

Drugs can cause inflammatory changes in the glomerulus, renal tubular cells, and the surrounding interstitium, leading to fibrosis and renal scarring. Glomerulonephritis is an inflammation primarily mediated by immune mechanisms and is often associated with proteinuria in the nephrotic range [22]. Medications such as gold therapy, hydralazine (K-propylthiouracil, and pamidronate (in high doses or prolonged courses) have been reported to cause glomerulonephritis [22, 26, 27].

Acute interstitial nephritis, which is an allergic response to a suspected drug, develops in an idiosyncratic, non–dose-dependent fashion[28]. Medications that cause acute interstitial nephritis are thought to bind to antigens in the kidney or act as antigens that are then deposited into the interstitium, inducing an immune reaction[28]. However, classic symptoms of a hypersensitivity reaction (i.e., fever, rash, and eosinophilia) are not always observed [26, 28]. Numerous drugs have been reported, including allopurinol; antibiotics (especially beta lactams, quinolones, rifampin, sulfonamides and vancomycin); antivirals (especially acyclovir and indinavir); diuretics (loops, thiazides); NSAIDs; phenytoin; proton pump inhibitors (especially omeprazole, pantoprazole and lansoprazole) and ranitidine [26, 28-31].

Chronic interstitial nephritis is less likely than acute interstitial nephritis to be drug induced; it is also insidious in onset and signs of hypersensitivity are often lacking[32]. Drugs associated with this mechanism of nephrotoxicity include calcineurin inhibitors (e.g., cyclosporine, tacrolimus), certain chemotherapy agents, Chinese herbals containing aristocholic acid and lithium[32-34]. Chronic interstitial nephritis has been reported with analgesics such as acetaminophen, aspirin and NSAIDs when used chronically in high dosages (i.e., more than 1 gram daily for more than two years) or in patients with preexisting kidney disease[35, 36]. Early recognition is important because chronic interstitial nephritis has been known to progress to end-stage renal disease[32]. Diagnosis may be difficult because most patients do not consider over-the-counter preparations to be medications and tend to under report frequency of use.

1.5 Rhabdomyolysis

Rhabdomyolysis is a syndrome in which skeletal muscle injury leads to lysis of the myocyte, releasing intracellular

contents including myoglobin and creatine kinase into the plasma. Myoglobin induces renal injury secondary to direct toxicity, tubular obstruction and alterations in GFR[37]. Drugs may induce rhabdomyolysis directly secondary to a toxic effect on myocyte function or indirectly by predisposing the myocyte to injury. Many drugs of abuse, such as cocaine, heroin, ketamine, methadone, and methamphetamine have been reported to cause rhabdomyolysis [37, 38]. Clinical manifestations of rhabdomyolysis include weakness, myalgia and tea-colored urine [38].

Statins are the most recognizable agents associated with rhabdomyolysis, but more than 150 medications and toxins have been implicated[37]. Rhabdomyolysis with statin monotherapy is rare, with an average reported incidence of 0.44 per 10,000 persons on years of therapy [39]. Drugs and alcohol are causative factors in up to 81 percent of cases of rhabdomyolysis, and up to 50 percent of patients subsequently develop acute renal failure [40].

1.6 Thrombotic Microangiopathy

Direct endothelial cell injury has been shown to result in drug induced thrombotic microangiopathy. Drugs commonly associated with thrombotic microangiopathy include anti-platelet agents and antineoplastic agents such as gemcitabine[41]. Moreover, the use of chemotherapeutic agents targeting angiogenesis, specifically inhibitors of vascular endothelial growth factor, has been shown to have various renal manifestations. Endothelial dysfunction from vascular endothelial growth factor inhibition results in new or worsening hypertension, proteinuria, and AKI. Kidney biopsies have been shown to have evidence of thrombotic microangiopathy as well as minimal change disease and collapsing focal segmental glomerulosclerosis[42].

1.7. Crystal-Induced Nephropathy

Drug crystallization and deposition in the tubules can cause AKI. The crystals precipitate owing to their insolubility in urine, and usually within the distal tubular lumen, resulting in an interstitial inflammatory reaction and intra-tubular obstruction of urine flow. Elderly patients at risk of dehydration and pre-existing kidney disease are predisposed to the development of crystal deposition and tubular obstruction. The precipitation of medications spans the spectrum of asymptomatic isolated crystalluria to obstructive stones. Crystalluria may also lead to AIN. Imaging such as renal ultrasound or computed tomography can detect nephrolithiasis but cannot detect crystals and microscopic tubular obstruction [22]. Drugs commonly associated with crystal nephropathy include acyclovir, high-dose methotrexate, indinavir and sulfonamides. Rarely, amoxicillin can also cause crystalluria and some recent data suggest that vancomycin can cause cast nephropathy [25, 43]. The prevention of crystal nephropathy includes the correction of hypovolemia, dose adjustment and maintenance of urinary pH, depending on the solubility characteristics of the drugs [44].

2. Diagnosis of Drug-Induced kidney disease (DIKD)

Serum creatinine is the most widely used marker for renal function in clinical practice. However, serum creatinine concentration is dependent on creatinine generation, volume of distribution and renal elimination. After an acute renal exposure, the rate and magnitude of increase in serum creatinine may be diminished in the elderly owing to a smaller amount of muscle mass and a decreased creatinine generation rate [45].

The diagnosis of drug-induced kidney injury is based on the AKI criteria mentioned previously (Table1), and changes in serum creatinine and urine output, in association with drug/nephrotoxin exposure. These criteria have been validated in several large studies [45].

Table 1: Criteria for acute kidney injury[12]

RIFLE Criteria	**Risk**	**SCr 1.5–1.9 times baseline or eGFR decrease ≥25%**	**UOP<0.5 mL/kg/h for>6 h**
	Injury	SCr 2–2.9 times baseline or eGFR decrease ≥50%	UOP<0.5 mL/kg/h for>12 h
	Failure	SCr≥3 times baseline or eGFR decrease ≥75% or SCr C4 mg/dL; acute rise ≥0.5 mg/dL	UOP<0.3 mL/kg/h for 24 h or anuria for 12 h
	Loss	Persistent acute renal failure with complete loss of function>4 weeks	---
	End-stage renal disease	Need for RRT3 months	---
AKIN criteria	Stage 1	SCr 1.5–2.5 times baseline or increase ≥0.3 mg/dL	UOP<0.5 mL/kg/h for>6 h
	Stage 2	SCr>2–3 times baseline	UOP<0.5 mL/kg/h for>12 h
	Stage 3	SCr>3 times baseline or Scr[4 mg/dL with acute increase of>0.5 mg/dL	UOP<0.3 mL/kg/h for 24 h or anuria for 12 h
KDIGO criteria	Stage 1	SCr 1.5–1.9 times baseline within the prior 7 days or ≥0.3 mg/dL increase within 48 h	UOP<0.5 mL/kg/h for>6 h
	Stage 2	SCr 2–2.9 times baseline within the prior 7 days	UOP<0.5 mL/kg/h for>12 h
	Stage 3	SCr ≥3 times baseline or increase to ≥4 mg/dL within the prior 7 days	UOP<0.3 mL/kg/h for 24 h or anuria for 12 h

A thorough history, specifically focusing on medication use and its timing, and other risk factors for AKI is essential in establishing the diagnosis. Additionally, examination of the urine sediment is helpful; for example, presence of muddy brown casts is indicative of ATN, white blood cells and casts are helpful in the diagnosis of AIN, dysmorphic red blood cells are pathognomonic for glomerular injury, and drug crystals in the urine can be specific for crystal nephropathy.

Historically, the presence of urine eosinophils (1% of urinary white cells) has been correlated with AIN, with test sensitivity ranging from 40 to 91% and specificity ranging from 52 to 95%. However, data from a recent study evaluating biopsy-proven diagnoses revealed positive urine eosinophils in a variety of kidney diseases besides AIN. Additionally, urine eosinophils showed 31% sensitivity and 68% specificity for the diagnosis of AIN and were not beneficial in distinguishing AIN from other renal pathology[46, 47]. Thus, while the presence of urine eosinophils may be helpful in suggesting AIN, their absence does not exclude this diagnosis. Kidney biopsy is usually safe in the elderly, with a low complication rate. Though it is a useful diagnostic tool, histologic findings may be difficult to interpret in elderly patients, given the presence of complex age-related changes, and concomitant arteriosclerosis or global sclerosis[48].

3. The therapeutic approach and strategies for the management of DIKD

The mainstay in the management of drug-induced kidney injury is prevention. Despite considerable progress, the treatment of kidney injury is often difficult due to its multifactorial etiology. Consequently, a global approach, requiring not one but several treatment modalities is needed for management of DIKD, instead of an approach localized to the organ. These preventive strategies can be divided into general and drug specific. It is imperative to have a reliable estimate of GFR in patients prior to drug administration to ensure correct dosing especially for those agents with narrow windows for toxicity. Still, there is no unanimously accepted method for the estimation of GFR in elderly subjects and serum creatinine is not a consistent marker for renal function. Estimation of GFR using prediction equations based on serum creatinine, age, sex, race, and weight are recommended [49-52].

In some studies, the Modification of Diet in Renal Disease formula has been shown to be more accurate in the elder patients than the Cockcroft– Gault equation (underestimates GFR) [49-52]. Another creatinine-based formula, the Chronic Kidney Disease Epidemiology Collaboration equation has been found to be more accurate than the Modification of Diet in Renal Disease formula, and is currently recommended for GFR estimation [49,50]. Recently, the Berlin Initiative Study equations have been developed and validated for GFR estimation in the elderly, using creatinine (Berlin Initiative Study 1) and creatinine-cystatin C (Berlin Initiative Study 2) [51,52]. However, some still recommend the Cockcroft–Gault equation in view of drug dose adjustments in the elderly population because this equation was originally used in dosing studies and data are limited on the use of other measures [53,54].

4.1 General measures

The first step in the treatment of DIKD is to correct the modifiable patient-related risk factors and drug-related risk factors coupled with vigilance and early intervention for drug induced kidney disease [1, 55]. Prevention should target the prescribing and monitoring of potential nephrotoxins in at-risk patients. Effort should be made to avoid or to find substitutes for drugs with negative impact of kidney function or risk factors should be corrected before drugs associated with nephrotoxicity are prescribed[56].

General preventive strategies include assessment of baseline creatinine clearance or GFR and adjusting medication dosing to renal function. Additionally, drugs should be prescribed for the shortest time, using the lowest effective dose, with monitoring of drug concentrations (if possible). Renal function should be monitored frequently, with subsequent medication changes or cessation. Hemodynamics must be monitored, particularly in the critically ill, with prompt recognition and treatment of hypovolemia and hypotension [15].

Drug specific preventive strategies are listed in Table 3. Moreover, new evidence is emerging on the role of cilastatin as a promising agent for inhibiting various forms of drug-induced kidney injury mediated via megalin in the clinical setting[57].

In one large cohort study of Medicare enrollees in the ambulatory setting, inadequate laboratory monitoring played a role in 36 percent of all preventable adverse drug events [58]. In addition, when assessing baseline renal function, physicians should consider monitoring serum creatinine levels after starting or increasing the dosage of drugs associated with nephrotoxicity, especially those used chronically in patients with multiple risk factors for renal impairment. A systems approach toward adopting an electronic medical record may provide a practical method for automated monitoring of all patients in general, and patients at risk of nephrotoxicity in particular.

4.2 Recognition and Early Intervention

Most episodes of drug-induced renal impairment are reversible. Renal function generally returns to baseline provided the impairment is recognized early and the offending medication is discontinued [52]. Failure to act on available information relating to clinical findings or laboratory results was the most common monitoring error, occurring in 37 percent of preventable adverse drug events, including those affecting the kidney, in older ambulatory patients[58]. A decrease in renal function as evidenced by a rise in serum creatinine levels following the initiation of a drug signals the possibility of drug-induced renal injury. An exception to this is an increase in serum creatinine following the initiation of cimetidine or trimethoprim, because they compete with creatinine for tubular secretion and are not associated with kidney damage or urine

abnormalities[59]. Although there are no standard guidelines used to interpret changes in serum creatinine, a 50 percent rise from baseline, an increase of 0.5 mg per dL (40 µmol per L) or more when baseline serum creatinine is less than 2 mg per dL (180 µmol per L), or an increase of 1 mg per dL (90 µmol per L) or more if baseline creatinine is greater than 2 mg per dL have been used as biochemical criteria of acute renal failure [55, 60, 61].

Table 2: Selected examples of polypharmacy-induced acute kidney injury

Cumulative effect	Drugs combinations	Mechanism of increased nephrotoxicity
Renal ischemia	NSAIDs + diuretics	NSAIDs: decreased prostaglandin synthesis, afferent arteriolar Vasoconstriction Diuretics: decreased effective blood volume, decreased renal blood flow, decreased renal perfusion pressure
	Diuretics + RAAS inhibitors	Diuretics: tubulo-glomerular feedback inhibition, compensatory activation of the RAAS, decreased effective blood volume,decreased renal blood flow, decreased renal perfusion pressure RAAS inhibitors: RAAS blockade and efferent vasodilation
	NSAIDS + diuretics + RAAS Inhibitors	NSAIDs: decrease in prostaglandin synthesis; afferent arteriolar vasoconstriction RAAS inhibitors: efferent arteriolar vasodilation Diuretics: reduction of plasma volume, decreased renal blood flow, decreased renal perfusion pressure
	CCBs + clarithromycin	Clarithromycin: CYP3A4 inhibition, increased CCBs concentrations hypotension
Increased risk of statin-induced rhabdomyolysis	Statins + macrolides	Macrolides: inhibition of the cytochrome 450 (CYP450), increased serum statin concentrations
	Statins + CCBs	CCBs: inhibition of the cytochrome 450 (CYP450), increased serum statin concentrations
	Simvastatin + cyclosporine	Cyclosporine: inhibition of the cytochrome 450 (CYP450) + inhibition of drug transporters, increased serum statin concentrations
	Statins + gemfibrozil	Gemfibrozil → inhibition of the organic anion-transporting polypeptide (OATP) → increased serum statin concentrations
Increased drugs Nephrotoxicity	Methotrexate (high doses) + NSAIDs	NSAIDs: decrease in prostaglandin synthesis, afferent arteriolar vasoconstriction, renal hypoperfusion, leading to increased Methotrexate concentrations
	Cyclosporine + ciprofloxacin	Ciprofloxacin: decrease in cyclosporine metabolism, increased cyclosporine concentrations (unclear as the two medications are metabolized through different CYP450 pathways)
	Vancomycin + piperacillin/ tazobactam	Piperacillin/tazobactam: decreased vancomycin clearance, increased vancomycin concentrations

Table 3: Preventive strategies for selected drugs

Drug	Preventive strategy
Aminoglycosides	Once-daily dosing, serum trough monitoring, limiting exposure
Vancomycin	Serum trough monitoring, limiting exposure, limiting use with piperacilin-tazobactam
Calcineurin inhibitors	Monitoring of trough concentrations
Iodinated contrast	Intravenous hydration, Limiting contrast volume, Use of iso-osmolar contrast, Role of agents such as N-acetylcysteine remains uncertain
Amphotericin B	Use of liposomal formulation, Maintenance of high urine flow rates by saline loading during administration
Methotrexate	Intravenous hydration, Urine alkalinization
Acyclovir	Intravenous hydration

At the first sign of renal dysfunction, the patient's medication list should be reviewed to identify offending agents. If multiple medications are present and the patient is clinically stable, physicians should start by discontinuing the drug most recently added to the patient's medication regimen. Attention should then be directed at avoiding further renal insults by supporting blood pressure, maintaining adequate hydration, and temporarily discontinuing all other possible nephrotoxins [62].

4.3 Medical Therapy

Discontinuation of offending medications and supportive therapy are the cornerstone of treatment in drug-induced kidney disease. Once kidney injury is established, the only beneficial measures are those avoiding additional insults and further deterioration. The preventative measures described earlier are therefore essential in therapeutic strategies as well. Though corticosteroids have been used for the specific therapy of AIN, most data are from retrospective studies [26]. Concerns exist about the tolerability of renal replacement therapy in the elderly, given increased co-morbid conditions, reduced cardiovascular reserve and autonomic dysfunction.

CONCLUSION

Nephrotoxicity is a widely prevalent cause of AKI in the population. Increasing age with its associated changes in renal structure and function as well as increasing co-morbidities makes the elderly particularly vulnerable to potential toxic kidney injuries. The manifestations of drug-induced AKI are varied, with limited specific therapeutic options. It is imperative to closely monitor drug prescriptions, with close attention to estimated GFR prior to drug dosing.

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REFERENCES

1. Schetz M, Dasta J, Goldstein S, Golper T. Drug-induced acute kidney injury. Current opinion in critical care 2005;555–65.
2. Schissler MM, Zaidi S, Kumar H. Characteristics and outcomes in community-acquired versus hospital-acquired acute kidney injury. Nephrology 2013; 18:183–7.
3. Himmelfarb J, Ikizler TA. Acute kidney injury: changing lexicography, definitions, and epidemiology. Kidney Int. 2007; 10:971–6.
4. Mehta RL, Pascual MT, Soroko S, Savage BR, Himmelfarb J, Ikizler TA. Spectrum of acute renal failure in the intensive care unit: the PICARD experience. Kidney Int 2004; 66(4):1613–21.
5. Uchino S, Kellum JA, Bellomo R, Doig GS, Morimatsu H, Morgera S. Acute renal failure in critically ill patients: a multinational, multicenter study. JAMA 2005; 294(7):813–8.
6. Hoste EA, Bagshaw SM, Bellomo R, Cely CM, Colman R, Cruz DN. Epidemiology of acute kidney injury in critically ill patients: the multinational AKI-EPI study. Intensive Care Med 2015; 41(8):1411–23.
7. Moffett BS, Goldstein SL. Acute kidney injury and increasing nephrotoxic medication exposure in non critically-ill children. Clin J American Soc Nephrol 2011;6(4):856–63.
8. Fux CA, Simcock M, Wolbers M, Bucher HC, Hirschel B, Opravil M.Tenofovir use is associated with a reduction in calculated glomerular filtration rates in the Swiss HIV Cohort Study. AntivirTher 2007; 12(8):1165–73.
9. Labarga P, Barreiro P, Martin-Carbonero L, Rodriguez-Novoa S, Solera C, Medrano J. Kidney tubular abnormalities in the absence of impaired glomerular function in HIV patients treated with tenofovir. Aids 2009; 23(6):689–96.
10. Eremina V, Jefferson JA, Kowalewska J, Hochster H, Haas M, Weisstuch J. VEGF inhibition and renal thrombotic microangiopathy. N Engl J Med 2008; 358(11):1129–36.
11. Humes HD. Aminoglycoside nephrotoxicity. Kidney Int 1988; 33:900–11.
12. Khan S, Loi V, Rosner MH. Drug-Induced Kidney Injury in the Elderly Drugs Aging. DOI 10.1007/s40266-017-0484-4.
13. Rosner MH. Acute kidney injury in the elderly. Clin Geriatr Med 2013;29:565–78.
14. Pannu N, Nadim M. An overview of drug-induced acute kidney injury. Crit Care Med. 2008; 36(4 Suppl.):S216–23.
15. Chronopoulos A, Cruz DN, Ronco C. Hospital-acquired acute kidney injury in the elderly. Nat Rev Nephrol 2010;6:141–9.
16. Dreischulte T, Morales DR, Bell S, Guthrie B. Combined use of nonsteroidal anti-inflammatory drugs with diuretics and/orrenin–angiotensin system inhibitors in the community increases the risk of acute kidney injury. Kidney Int 2015; 88:396–403.
17. Barros EJ, Boim MA, Ajzen H. Glomerular hemodynamics and hormonal participation on cyclosporine nephrotoxicity. Kidney Int. 1987; 32:19–25.
18. First MR, Schroeder TJ, Alexander JW, et al. Cyclosporine dose reduction by ketoconazole administration in renal transplantrecipients. Transplantation.1991; 51:365–70.
19. Morrissey KM, Stocker SL, Wittwer MB. Renal transporters in drug development. Annu Rev Pharmacol Toxicol 2013;53:503–29.
20. Mahadevappa R, Nielsen R, Christensen EI, Birn H. Megalin in acute kidney injury: foe and friend. Am J Physiol Renal Physiol 2014; 306:F147–54.
21. USRDS annual data report. http://www.usrds.org/2016/view/Default.aspx. Accessed 18 July 2017.
22. Perazella MA. Drug-induced nephropathy: an update. Expert Opin Drug Saf 2005;4:689–706.
23. Anaisse EJ, Vartivarian ES, Abi-Said D. Fluconazole vs amphotericin B in the treatment of hematogenous candidiasis. Am J Med 1996;101:170–6.
24. Hidayat LK, Hsu DI, Quist R. High-dose vancomycin therapy for methicillin-resistant Staphylococcus aureus infections: efficacy and toxicity. Arch Intern Med. 2006;166:2138–44.
25. Luque Y, Louis K, Jounneau C, et al. Vancomycin-associated cast nephropathy. J Am Soc Nephrol. 2017; 28:1723–8.
26. Markowitz GS, Perazella MA. Drug-induced renal failure: a focus on tubulointerstitial disease. ClinChimActa 2005; 351(1-2):31-47.
27. Markowitz GS, Appel GB, Fine PL. Collapsing focal segmental glomerulosclerosis following treatment with high-dose pamidronate. J Am SocNephrol 2001; 12(6):1164-1172.
28. Rossert J. Drug-induced acute interstitial nephritis. Kidney Int 2001; 60(2):804-817.

29. Geevasinga N, Coleman PL, Webster AC, Roger SD. Proton pump inhibitors and acute interstitial nephritis. ClinGastro enteral Hepatol 2006; 4(5):597-604.

30. Simpson IJ, Marshall MR, Pilmore H. Proton pump inhibitors and acute interstitial nephritis: report and analysis of 15 cases. Nephrology (Carlton) 2006; 11(5):381-385.

31. Kodner CM, Kudrimoti A. Diagnosis and management of acute interstitial nephritis. Am Fam Physician 2003;67(12):2527-2534.

32. 32.Ghane Shahrbaf F, Assadi F. Drug-induced renal disorders. J Renal Inj Prev 2015; 4(3): 57- 60.

33. Olyaei AJ, de Mattos AM, Bennett WM. Immunosuppressant-induced nephropathy: pathophysiology, incidence and management. Drug Saf. 1999; 21(6):471-488.

34. IsnardBagnis C, Deray G, Baumelou A, Le Quintrec M, Vanherweghem JL. Herbs and the kidney.Am J Kidney Dis 2004;44(1):1-11.

35. Fored CM, Ejerblad E, Lindblad P, et al. Acetaminophen, aspirin, and chronic renal failure. N Engl J Med 2001; 345(25):1801-1808.

36. Perneger TV, Whelton PK, Klag MJ. Risk of kidney failure associated with the use of acetaminophen, aspirin, and nonsteroidal antiinflammatory drugs. N Engl J Med 1994; 331(25):1675-1679.

37. Coco TJ, Klasner AE. Drug-induced rhabdomyolysis. CurrOpinPediatr. 2004; 16(2):206-210.

38. Huerta-Alardín AL, Varon J, Marik PE. Bench-to-bedside review: rhabdomyolysis—an overview for clinicans. Crit Care 2005; 9(2):158-169.

39. Graham DJ, Staffa JA, Shatin D, et al. Incidence of hospitalized rhabdomyolysis in patients treated with lipid-lowering drugs. *JAMA* 2004;292(21):2585-2590.

40. Prendergast BD, George CF. Drug-induced rhabdomyolysis-mechanisms and management. *Postgrad Med J*. 1993; 69(811):333-336.

41. Markowitz GS, Bomback AS, Perazella MA. Drug-induced glomerular disease: direct cellular injury. Clin J Am Soc Nephrol 2015; 10:1291–9.

42. Izzedine H, Escudier B, Lhomme C, et al. Kidney diseases associated with anti-vascular endothelial growth factor (VEGF):an 8 year observational study at a single center. Medicine (Baltimore). 2014; 93:333–9.

43. Zeller V, Puyraimond-Zemmour D, Sene´ T. Amoxicillin crystalluria, an emerging complication with an old and wellknown antibiotic. Antimicrob Agents Chemother.2016;60:3248.

44. Markowitz GS, Perazella MA. Drug-induced renal failure: a focus on tubulointerstitial disease. ClinChimActa 2005;35:31–47.

45. Coca SG. Acute kidney injury in elderly persons.Am J Kidney Dis 2010;56:122–31.

46. Murithi 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.

47. Muriithi AK, Nasr SH, Leung N. Utility of urine eosinophils in the diagnosis of acute interstitial nephritis. Clin J Am SocNephrol 2013;8:1857–62.

48. Nair R, Bell JM, Walker PD. Renal biopsy in patients over 80 years and older. Am J Kidney Dis. 2004; 44:618–26.

49. Levey AS, Stevens LA, Schmid CH. A new equation to estimate glomerular filtration rate.Ann Intern Med 2009;150:604–12.

50. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO clinical practice guideline for the evaluationand management of chronic kidney disease. Kidney Int Suppl 2012; 2013(3):1–150.

51. Schaeffner ES, Ebert N, Delanaye P, et al. Two novel equations to estimate kidney function in persons aged 70 years or older. Ann Intern Med 2012;157:471–81.

52. Alshaer IM, Kilbride HS, Stevens PE, et al. External validation of the Berlin equations for the estimation of GFR in the elderly.Am J Kidney Dis 2014;63:862–5.

53. Dowling TC, Wang ES, Ferrucci L, Sorkin JD. Glomerular filtration rate equations overestimate creatinine clearance in older individuals enrolled in the Baltimore Longitudinal Study on Aging: impact on renal drug dosing. Pharmacotherapy.2013;33:912–21.

54. Hellde´n A, Odar-Cederlo¨ f I, Nilsson G, et al. Renal function estimations and dose recommendations for dabigatran, gabapentin and valaciclovir: a data simulation study focused on the elderly. BMJ Open. 2013;3:e002686. doi:10.1136/bmjopen-2013-002686.

55. Guo X, Nzerue C. How to prevent, recognize, and treat drug-induced nephrotoxicity. Cleve Clin J Med2002;69(4):289-312.

56. Naughton CA. Drug-induced nephrotoxicity.Am Fam Physician2008;78(6):743-750.

57. Prieto-Garcı´a L, Pericacho M, Sancho-Martı´nez SM, et al. Mechanisms of triple whammy acute kidney injury. Pharmacol Ther 2016;167:132–45.

58. Gurwitz JH, Field TS, Harrold LR. Incidence and preventability of adverse drug events among older persons in the ambulatory setting. *JAMA*. 2003;289(9):1107-1116.

59. Choudhury D, Ahmed Z. Drug-associated renal dysfunction and injury. Nat ClinPractNephrol 2006;2(2):80-91.

60. Kaufman J, Dhakal M, Patel B, Hamburger R. Community-acquired acute renal failure. Am J Kidney Dis. 1991; 17(2):191-198.

61. Nash K, Hafeez A, Hou S. Hospital-acquired renal insufficiency. Am J Kidney Dis. 2002; 39(5):930-936.

62. Fry AC, Farrington K. Management of acute renal failure. Postgrad Med J. 2006; 82(964):106-116.