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Review Article

A review on antibiotics induced nephrotoxicity

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ABSTRACT

One of the common causes of acute kidney injury (AKI) is drug nephrotoxicity. AKIs around 20-60% in hospitalised patients are caused by drug-induced nephrotoxicity, which is also linked to higher morbidity and death both in children and adults. Antibiotics are one of the most frequently prescribed drug classes worldwide and, also one of the leading contributors to nephrotoxicity. Nephrotoxicity has been related to a wide range of antimicrobial medications, although the characteristics of kidney damage vary depending on the agent, the site of toxicity and the mechanism of injury within the renal. Acute tubular necrosis, acute interstitial nephritis, crystal nephropathy, and proximal/distal tubulopathy with electrolyte problems are the most frequent mechanisms. Pre-existing chronic renal disease and concurrent use of medications with nephrotoxic potential are two general risk factors for antimicrobial-induced AKI. The various types of antimicrobial-induced nephrotoxicity especially antibiotics will be discussed in this review and offer guidance on how to prevent AKI and recognize it early in order to reduce it and prevent morbidity.

Keywords: Acute kidney injury, Chronic kidney disease, Antibiotics, Nephrotoxicity

INTRODUCTION

Being a primary organ for drug excretion exposes to high levels of concentrations of potentially harmful drugs. Both inpatient and outpatient settings can experience drug-induced nephrotoxicity, a frequent and possibly serious side effect of pharmaceutical delivery. Although the words acute kidney damage (AKI) and nephrotoxicity are frequently used interchangeably, AKI refers to a decrease in kidney function. A wide variety of drugs, including antibacterial, antihypertensive, chemotherapeutic, immunosuppressive, and anti-inflammatory medications, have been linked to nephrotoxicity.[1] In hospitalised patients, drug toxicity is thought to be responsible for 20% to 60% of AKI. The majority of cases of allergic interstitial nephritis, 35% of all cases are acute tubular necrosis, changes in renal hemodynamics, and post-renal obstruction may all be caused by in-hospital medication usage.[2] Antibiotics are among the most widely used drugs, and more than half of hospitalized patients receive antibiotics.[3] Frequent episodes of adverse drug reactions (ADR) following antimicrobial therapy were reported.[4,5] Kidney injury is the most important adverse reaction that was reported with antibiotics.[6,7] The incidence of antibiotic induced nephrotoxicity alone may be as high as 36%.[8] Most recent reviews imply rates of 5% to 15%. Aminoglycoside nephrotoxicity has been recorded in up to 58% of patients undergoing aminoglycoside medication.[9,10] Due to its unique ability to remove hazardous compounds, the kidney is a common target for toxic xenobiotics.[11] The most frequent antibiotics thought to cause AKI are aminoglycosides and beta-lactams, which are mostly responsible for acute tubular necrosis (ATN) and acute interstitial nephritis (AIN), respectively. Therefore, understanding the risk variables associated with patients, drugs, and renal damage is necessary for effective prevention.[12] The proposed mechanisms, incidence, and risk factors for antibiotic-induced nephrotoxicity are covered in this article, along with measures to take in order to prevent long-term consequences (Figure 1).

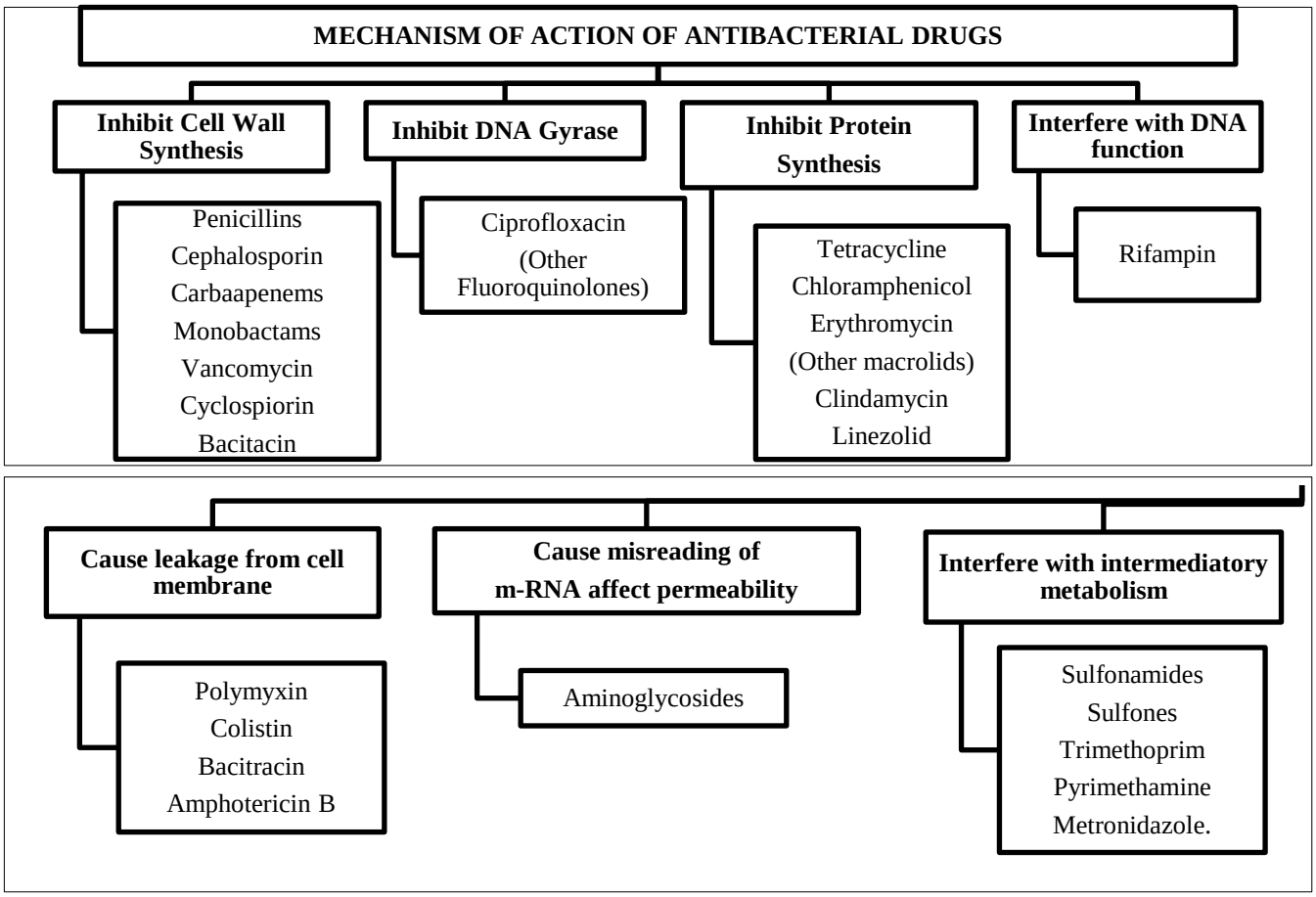

Figure 1: Mechanism of antibacterial drugs.

NEPHROTOXICITY MECHANISM

The majority of medications that have been linked to nephrotoxicity do so through one or more well-known pathogenic pathways. Inflammation, alteration, tubular cell toxicity, and crystal nephropathy are all effects of antibiotics.

Tubular cell toxicity

Because of their function in concentrating and reabsorbing glomerular filtrate, renal tubular cells, in particular proximal tubule cells, are vulnerable to drug toxicity.[13] Aminoglycosides are drugs that damage mitochondrial function, interfere with tubular transport, up the level of oxidative stress, or produce free radicals. These drugs are responsible for tubular cell toxicity.[13-16]

Inflammation

Renal fibrosis and scarring can be caused by drug-induced inflammatory changes in the glomerulus, renal tubular cells, and surrounding interstitium. Patients with glomerulonephritis, an inflammatory condition predominately brought on by immunological mechanisms, typically have proteinuria in the nephrotic range.[17] Acute interstitial nephritis is an idiosyncratic, non-dose-dependent condition that might be brought on by an allergic reaction to a suspected medication. Acute interstitial nephritis medications are hypothesised to attach to antigens in the kidney or act as antigens that are then transferred into the interstitium, producing an immune response.[18] However, the traditional signs of an allergic reaction, such as a fever, rash, and eosinophilia, are not always present.[19] Antibiotics, particularly beta lactams, quinolones, rifampin, sulfonamides, and vancomycin, have been implicated. Acute interstitial nephritis is more likely to be drug-induced than chronic interstitial nephritis. Because persistent interstitial nephritis has been linked to end-stage renal disease, early detection is critical.

Crystal nephropathy

Drugs that cause crystals in human urine can have a negative impact on the kidneys. In most cases, the distal tubular lumen is where the crystals precipitate, blocking urine flow and causing an interstitial response. Antibiotics are a class of drugs that are frequently administered and connected to the formation of crystals. The drug concentration present in the urine and the pH of the urine determine crystal precipitation. Individuals with fluid reduction and pre-existing kidney failure are particularly vulnerable to crystal nephropathy.[12]

CLASSIFICATION OF ANTIBIOTICS

Aminoglycosides

The nephrotoxins known as aminoglycosides cause a dose-dependent 10–20% of patients have AKI, which results in a 50% loss in kidney function.[20] After administration, approximately 5–10% of the dose will remain in the renal cortex. These drugs are 99% eliminated by the urine without prior metabolism. The most frequent reason for aminoglycoside-induced renal damage is toxicity to the proximal tubule. Once the aminoglycoside passes through the glomerular filtration barrier freely and is reabsorbed in the S1 and S2 segments of the proximal renal tubule, nephrotoxicity sets in. In organelles such the mitochondria, Golgi complex, and nucleus, the aminoglycoside enters the cytoplasm and builds up. The interruption of protein synthesis and mitochondrial dysfunction seen in aminoglycoside nephrotoxicity are explained by this mechanism.[21] Among these drugs, gentamicin is known to be the most nephrotoxic, followed by tobramycin and amikacin. Neomycin has the strongest affinity for the proximal convoluted tubule (PCT) yet has significant nephrotoxic, neurotoxic, and ototoxic potential (PCT). The occurrence of comorbidities or clinical situations like sepsis, volume depletion, or sepsis may cause a delay in this recovery.[22] An important implication is reduced clearance of the antibiotics resulting in higher and more persistent blood level. Streptomycin is the least nephrotoxicity aminoglycoside.

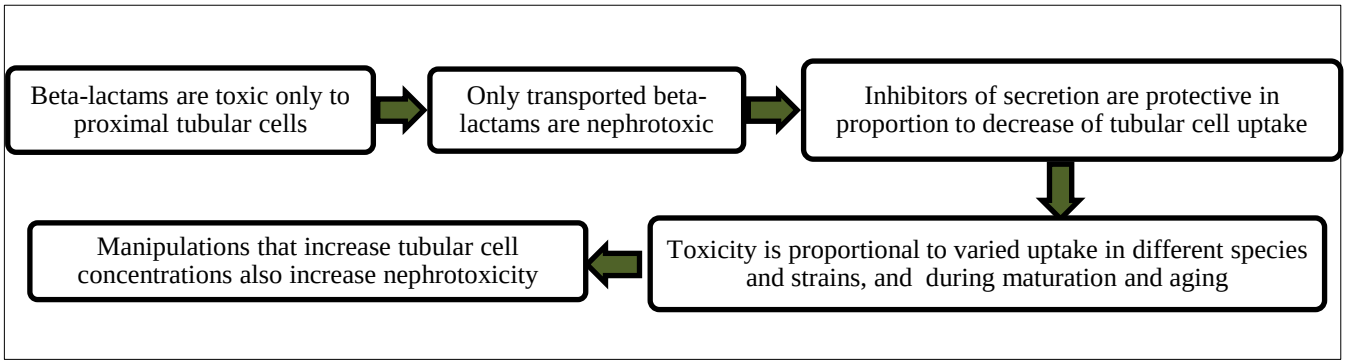

Figure 2: Beta-lactam nephrotoxicity: a pathogenic function for tubular cell transport antibiotics.

Beta-lactams

Beta-lactams are well-known nephrotoxins. These bactericides inhibit the final step in bacterial wall synthesis. Penicillins, cephalosporins, carbapenems, and monobactams are included in this group. Beta-lactam antibiotics acylate and inactivate a series of proteins required for bacterial reproduction. The mobility of a beta-lactam across bacterial cell walls and its lactam ring reactivity are two characteristics that enable it to have this effect (acylating potential). Beta-lactam nephrotoxicity, a selective acute proximal tubular necrosis, increases in proportion to the secretory uptake of the antibiotic by the tubular cell, as well as the acylation and inactivation of mitochondrial substrate transporters, or in the case of cephaloridine, lipid peroxidation. The most often seen mechanism of injury include translocation into the tubular cell, acylation of target proteins, and lipid peroxidation (Figure 2).[23]

Fluoroquinolones

These are commonly prescribed broad-spectrum antibiotics. Despite being quite effective, they are known to cause cardiac arrhythmia, hypersensitivity reactions, and central nervous system side effects include agitation and insomnia.[24-26] Fluoroquinolones prevent the production of bacterial DNA. Ciprofloxacin has the highest estimated risk for AKI of any fluoroquinolone, followed by moxifloxacin and levofloxacin. The primary underlying mechanism of kidney injury appears to be AIN, though some cases also exhibit granulomatous interstitial nephritis and acute tubular necrosis, which are characterised by histiocyte and T lymphocyte infiltration of the renal tissue, which results in the development of granulomas.[27,28] When urine pH is higher than 6.8, crystalluria has been documented, along with multiple cases of acute renal damage brought on by crystal formation.[29] Although it is believed that fluoroquinolones cause acute kidney injury through acute hypersensitivity reactions, renin-angiotensin-system blockers impact renal hemodynamics by widening the efferent arteriole, which lowers intraglomerular pressure and raises serum creatinine levels.[30] The study by Bird et al, discovered a minor but substantial increase in the guys' vulnerability to acute kidney damage individuals take fluoroquinolones orally, as well as a substantial interaction between the Fluoroquinolones and renin-angiotensin system blockers are both used simultaneously. Although it is obvious that the risks associated with using fluoroquinolones outweigh the danger of death from major infections, the possibility of acute renal injury highlights the significance of careful prescribing.[31]

Trimethoprim/sulfamethoxazole

The most used sulfa-based antibiotic is probably sulfamethoxazole (SMX). As a combination antibacterial drug, it is typically prescribed along with trimethoprim

(TMP), which acts synergistically. Clinicians frequently choose SMX-TMP because of its low cost and excellent spectrum of antibacterial activity. The prevalence of skin infections caused by methicillin-resistant Staphylococcus aureus has recently grown, which has resulted in increased use of this medication. Multiple harmful renal consequences of SMX-TMP exist. TMP can cause an increase in the observed serum creatinine because it prevents proximal tubular creatinine secretion.[32,33] This result is not indicative of AKI because it is not accompanied by a fall in real GFR. TMP can potentially cause hyperkalemia by preventing potassium excretion by blocking the epithelial sodium channel at the distal convoluted tubule.[34,35] In a prior retrospective cohort, the overall incidence of SMX-TMP-associated renal illness was reported to be modest; however, more recent data indicate that the overall incidence may be as high as 11.2%.[36,37] Acute interstitial nephritis is the most prevalent subsequent condition to AKI from sulfa-based antimicrobials (AIN). Rarely, use of high doses of sulfadiazine might also result in crystal nephropathy.[38,39] In this instance, urine microscopy may show the distinctive, needle-shaped, birefringent crystals grouped in a "shocks of wheat" pattern. Acidic urine and low-flow conditions can result in crystal precipitation. Therefore, alkalinizing the urine and consuming lots of fluids may help to prevent the formation of crystalluria.[35]

Vancomycin

Methicillin-resistant *Staphylococcus aureus* infections and severe *Clostridium difficile* colitis are treated with vancomycin, a glycopeptide antibiotic. Vancomycin use has increased in the era of highly resistant pathogens and treatment of patients with multiple comorbidities in order to reduce mortality in critical illness. Vancomycin carries a higher risk of AKI than penicillin, is much less risky than aminoglycosides or amphotericin B, but riskier than daptomycin or linezolid, according to numerous randomised clinical trials.[40,41] The onset of AKI occurs after 4-8 days of therapy with subsequent improvement after discontinuation of the medication. Numerous investigations have found that pro-inflammatory oxidation, mitochondrial malfunction, and cellular death are the fundamental mechanisms that cause proximal tubular damage and, when severe, also ATN. AIN has been observed in a number of cases, frequently with cutaneous symptoms. Given the limited availability of renal biopsy, the poor quality of serum and urine biomarkers, and the frequent use of antibiotic combinations with a high nephrotoxic potential, the precise prevalence of ATN or AIN is yet unknown. However, intrinsic variables like the total daily dose, the area under the curve, and the manner of administration have a significant impact on the pathogenesis of AKI. There are not many preventive measures available, however dosing by vancomycin level and adjusting the dose for weight and decreased glomerular filtration rate (GFR) have been demonstrated to dramatically lower the incidence of AKI.[42]

Polymyxins

Polymyxin B and colistin are polypeptide antibiotics. Gram-negative bacteria's membrane lipopolysaccharides interact with polymyxins to disrupt the stability of the cell membrane, and promotes a bactericidal effect. Cationic displacement serves as a mediator for this interaction (mainly Ca and Mg).[43,44] Nephrotoxicity is the most concerning of the known side effects, which is why parenteral polymyxin use was stopped in 1960. ATN, proteinuria, and cylindruria are some of the clinical symptoms of polymyxin-induced nephrotoxicity.[45] The postulated mechanism of nephrotoxicity is similar to their antibacterial mechanism of action. In the proximal tubule, polymyxins are filtered and almost completely reabsorbed. Similarities between LLC-PK1 cells and human proximal tubule cells can be seen in their membrane transport capabilities, membrane enzyme expression, and microvilli.[46] In addition, endocytosis at the apical membrane mediates polymyxin B uptake into LLC-PK1 cells. A second antimicrobial in this class, colistin (polymyxin E), has also been linked to an increased risk of AKI, with a few cases exhibiting characteristics of AIN. Polymyxins promote ion and water influx through increased permeability of tubular epithelial cell membranes, which results in cellular swelling and cell death (Table 1).[42,47]

RISK FACTORS AND PREVENTION

The incidence of renal toxicity is often low in medications that are frequently prescribed in clinical settings. It is evident when evaluating the incidence of nephrotoxicity that the majority of renal injury tends to cluster around particular people and particular clinical circumstances. The clinical utility of many diagnostic and therapeutic medicines may be restricted by nephrotoxicity, thus it's critical to be aware of the risk factors for renal injury. Patient-related, drug-related, or the result of drug association or interaction variables are possible causes of renal damage.[48]

Patient-related risk factors

Age (older than 60 years), sex, race; prior renal insufficiency specific diseases (diabetes mellitus, multiple myeloma, diseases with proteinuria, lupus); states retaining sodium (cirrhosis, heart failure, nephrosis); volume loss and dehydration depletion of potassium, magnesium, and acidosis, hyperuricemia, hyperuricosuria sepsis and shock renal transplantation; in patients with gastroenteritis, persistent diarrhoea, aggressive diuresis, or low oral intake, absolute intravascular volume loss may develop; effective intravascular volume is the amount of blood that the right atrium and kidney baroreceptors can detect; and sequestration of fluid into third space compartments causes a decrease in effective circulating blood volume, which is linked to sepsis, heart failure, ascites, or pancreatitis.

Drug-related risk factors

Aminoglycosides, polymyxins, and cyclosporine are a few medications that are fundamentally nephrotoxic.[49,50] Others, such those linked to crystal deposition and chronic interstitial nephritis, have nephrotoxicity that is dose-dependent or related to a prolonged duration of treatment.[51] Multiple nephrotoxins combined in combination therapy may cause synergistic nephrotoxicity, raising the risk of kidney damage. According to reports, contrast-induced nephropathy is the third most frequent reason for acute renal failure in hospitalised patients.[52] The risk of contrast-induced nephropathy is higher in patients with chronic renal disease (i.e., a GFR <60ml/min, particularly in the presence of diabetes.[53] Dehydration, heart failure, being older than 70 years old, and concomitant use of nephrotoxic medications are other risk factors.[52] Patients at risk for contrast-induced nephropathy, particularly those with several risk factors, need preventive measures before imaging.[54] Acetylcysteine pre- and post-imaging have both been explored as preventative therapies, as have normal saline or sodium bicarbonate infusions. Because of the mixed outcomes of clinical trials, the function of acetylcysteine hasn't yet been established.[52]

Preventive measures

Considering fairly effective but non-nephrotoxic pharmaceutical wherever possible, decreasing risk factors for nephrotoxicity, evaluating average renal function before starting therapy, optimising the dosage of medication for renal dysfunction, and avoidance nephrotoxic drug combinations are all general preventive measures.[55] The modification of diet in renal disease (MDRD) formula, the Cockcroft-Gault formula, or the Schwartz formula can be used to estimate baseline renal function at the patient's bedside.[56] The MDRD formula is recommended by the National Renal Foundation for the early diagnosis and staging of chronic kidney disease.[57] Programs for mobile devices including MedCalc, Archimedes, InfoRetriever, Epocrates, and Micromedex contain GFR estimate equations. Some of the proposed mechanisms to prevent nephrotoxicity induced by antimicrobials are the following: adjust medication dosages using the Schwartz or Cockcroft-Gault formula (for adults) (in children); determine the patient's renal function before prescribing a new medication by utilising the MDRD equation to determine their baseline renal function; avoid nephrotoxic combinations, prevent nephrotoxicity by addressing risk factors before starting a medication regimen; maintain appropriate hydration before and throughout treatment with possible nephrotoxins; whenever possible, use equally effective non-nephrotoxic medications; when available, assay and adjustment based on trough or random levels; monitoring antibiotic indications on a daily basis and, when appropriate, using brief antibiotic courses; if a long-term antibiotic is required, kidney function should be monitored on a frequent basis. The prevention of antimicrobial-induced AKI has been mentioned in certain papers as a benefit of substances like vitamin E, vitamin C, N-acetylcysteine, erythropoietin, a-lipoic acid, curcumin, or statins. However, there is a lack of convincing evidence and they are not frequently utilised in clinical practise.

Table 1: Summary of antibiotics-induced nephrotoxicity mechanisms.

Class	Medication	Mechanism
Aminoglycosides	Streptomycin, gentamycin, amikacin, kanamycin, tobramycin, sisomicin, netilmicin	Retention of the aminoglycosides by the proximal tubular cells disrupts calcium-mediated transport process. This result in kidney damage ranging from mild, reversible renal impairment to severe, potentially irreversible, cell death and acute tubular necrosis
Beta-lactams	Penicillin, cephalosporin, monobactams, carbapenems	Transport into the tubular cell, which is mostly accomplished via the antiluminal organic anion secretory carrier; acylation of target proteins, which results in respiratory toxicity by inactivating mitochondrial anionic substrate carriers; and lipid peroxidation
Cotrimoxazole	Trimethoprim/ sulfamethoxazole	TMP can cause an increase in the observed serum creatinine because it prevents proximal tubular creatinine secretion. Acute interstitial nephritis is the most prevalent subsequent condition to AKI from sulfa-based antimicrobials (AIN)
Quinolones	Fluoroquinolones (gatifloxacin, ciprofloxacin, norfloxacin, levofloxacin)	Allergic tubular nephritis, necrotizing vasculitis, granulomatous interstitial nephritis and tubular necrosis are some of the several names for this condition
Glycopeptide	Vancomycin	Pro inflammatory oxidation, mitochondrial dysfunction, and cellular apoptosis leading to proximal tubular injury and, when extensive, also ATN
Polypeptide	Polymyxins	Bioavailability at the apical surface was present in proximal tubular (LLC-PK1) cells from the swine's renal. If polymyxin B develops a strong affinity for renal tissue, it has the potential to be nephrotoxic and cause injury to renal tubular cells. This uptake causes polymyxin B to accumulate within renal tubular cells, which can result in various types of cellular harm or death

Continued.

CONCLUSION

Antimicrobials play a significant role in AKI. Antimicrobial administration can result in a clinically significant reduction of renal function either directly through cytotoxic effects, indirectly via immune-mediated pathways, or through the persistence of other repetitive nephrotoxic events. Although nephrotoxicity may be unavoidable or unexpected, such as when the mechanism is AIN, physician utilise knowledge of the toxic dynamics of antimicrobial drugs to develop customised regimens that lower the risk of toxicity for patients.

In high-risk patients those on several nephrotoxic medications and with underlying renal disease or previous AKI or those with haemodynamic instability - when alternative medications are not viable, careful observation of renal function, urinary output, and hydration level is necessary. In high-risk individuals, it is also advisable to regularly use dosing/administration techniques that reduce nephrotoxicity, [i.e. aminoglycosides (oculus dexter), Area under curve (AUC)-targeted vancomycin].

Antimicrobials play a crucial role in maintaining people of all ages' health and preventing disease. Despite being one of the most often prescribed groups of medications in both hospitalized and outpatient, nephrotoxicity is a significant and frequently predictable adverse effect of many antimicrobial treatments. To guarantee the safe delivery of these medications, periodic monitoring of serum creatinine alone is insufficient. It's also critical to be aware of the patient's haemodynamics, concomitant medications, and urine output/hydration status. When available, therapeutic drug monitoring (TDM) should also be used to give efficient and secure doses that aim for known PK/PD.

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