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THE HIDDEN THREAT: UNRAVELING DRUG-INDUCED NEPHROTOXICITY

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ABSTRACT

Drug-induced nephrotoxicity (DIN) is a leading cause of acute and chronic kidney injury, posing a significant challenge in clinical practice. The kidneys' unique physiology, including high blood flow and extensive drug metabolism, makes them particularly susceptible to toxic insults. This review explores the epidemiology, risk factors, and normal kidney function to provide a foundation for understanding nephrotoxicity. Various drug classes, such as aminoglycosides, NSAIDs, contrast agents, chemotherapeutics, and immunosuppressants, induce kidney damage through mechanisms like tubular toxicity, oxidative stress, altered renal hemodynamic, and immune-mediated injury. Identifying high-risk patients and understanding these mechanisms are critical for early intervention and prevention. Future research should focus on developing safer drug formulations, refining renal protective strategies, and improving clinical monitoring to reduce the incidence of DIN and improve patient outcomes.

INTRODUCTION

Drug-induced nephrotoxicity (DIN) is a significant clinical concern, accounting for approximately 20% of acute renal failure cases acquired in both hospital and community settings. Notably, older adults are disproportionately affected, with up to 66% of this population experiencing some degree of drug-induced kidney injury. This heightened vulnerability is often attributed to the increased prevalence of comorbid conditions such as diabetes and cardiovascular disease, polypharmacy, and the frequent use of diagnostic and therapeutic procedures that pose a risk to renal function.[1,5]

While drug-induced renal impairment is often reversible with the prompt discontinuation of the offending medication, it remains a considerable burden on healthcare systems. Renal dysfunction may necessitate prolonged hospitalization, additional diagnostic procedures, and therapeutic interventions, thereby increasing healthcare costs and patient morbidity.[2,5] The spectrum of drug-induced nephrotoxicity varies widely, ranging from acute tubular injury with electrolyte imbalances to chronic reductions in glomerular filtration rate (GFR) and even nephrotic syndrome.[1,5]

Traditionally, the diagnosis of DIN has relied heavily on serum creatinine measurements to estimate GFR. However, creatinine elevation is often a late marker of kidney injury, limiting the potential for early intervention. This delay in diagnosis underscores the urgent need for more sensitive and specific biomarkers that can detect renal injury at an earlier stage, potentially mitigating irreversible damage and improving patient outcomes.[3,5]

Emerging biomarkers such as Kidney Injury Molecule-1 (KIM-1), clusterin, and cystatin C offer promising alternatives for the early detection of drug-induced nephrotoxicity. KIM-1, an adhesion molecule expressed in the proximal convoluted tubule, has shown heightened urinary levels in response to nephrotoxic agents like cisplatin, gentamicin, and cyclosporine. Similarly, clusterin, a protein involved in apoptosis regulation, has demonstrated enhanced diagnostic accuracy in cases of tubular injury, particularly in patients receiving vancomycin, tacrolimus, or aminoglycosides. Furthermore, cystatin C, produced by all nucleated cells and freely filtered by the glomeruli, has exhibited superior sensitivity compared to creatinine in detecting nephrotoxicity induced by amphotericin B, polymyxins, and cisplatin.[4,5]

This review aims to provide a comprehensive overview of drug-induced nephrotoxicity, exploring its epidemiology, pathophysiology, and risk factors. Additionally, the role of traditional diagnostic approaches will be compared to the emerging utility of novel biomarkers in facilitating early detection and improving clinical outcomes. Through a better understanding of these advancements, clinicians may be empowered to adopt proactive strategies in the prevention and management of drug-induced renal injury.[5]

Epidemiology

Drug-induced nephrotoxicity (DIN) remains a substantial contributor to acute kidney injury (AKI), accounting for approximately 25% of cases. However, the reported incidence of AKI can vary depending on the diagnostic criteria applied and the characteristics of the healthcare

settings in which the studies are conducted. In severe cases, around 20% of patients with drug-induced AKI require renal replacement therapy (RRT), which is often associated with a significantly increased risk of mortality, particularly in resource-limited settings where mortality rates can exceed 60%.[6,8]

A notable challenge in determining the primary etiology of AKI is the absence of reliable diagnostic assays to identify the specific cause of renal injury. Patients commonly present with a combination of contributing factors, including septicaemia, hypotension, dehydration, and exposure to potentially nephrotoxic medications, complicating the identification of the exact cause. To establish a causal relationship between a drug and AKI, several criteria are generally applied:

- Temporal association: The patient must have been exposed to the suspected drug for at least 24 hours before the onset of kidney injury.
- Mechanistic plausibility: The drug should have a well-established mechanism of renal injury relevant to the clinical presentation.
- Exclusion of alternative causes: Other possible causes of nephropathy must be systematically ruled out through clinical and laboratory investigations.

Identifying populations at risk is essential for the early detection and prevention of drug-induced nephrotoxicity. Several factors predispose individuals to a higher risk of renal injury, particularly those leading to increased drug concentrations within the renal tubules. These include the presence of medications with vasoconstrictive effects, diuretics that reduce renal perfusion, and drugs that interfere with tubular secretion transporters, thereby increasing intracellular drug accumulation. For example, nephrotoxic agents such as cisplatin and aminoglycosides are well known to cause tubular damage through these mechanisms. Additionally, individuals with reduced renal functional reserve, characterized by a diminished capacity of the remaining glomeruli to increase the filtration rate, are particularly vulnerable to developing AKI.[7,8]

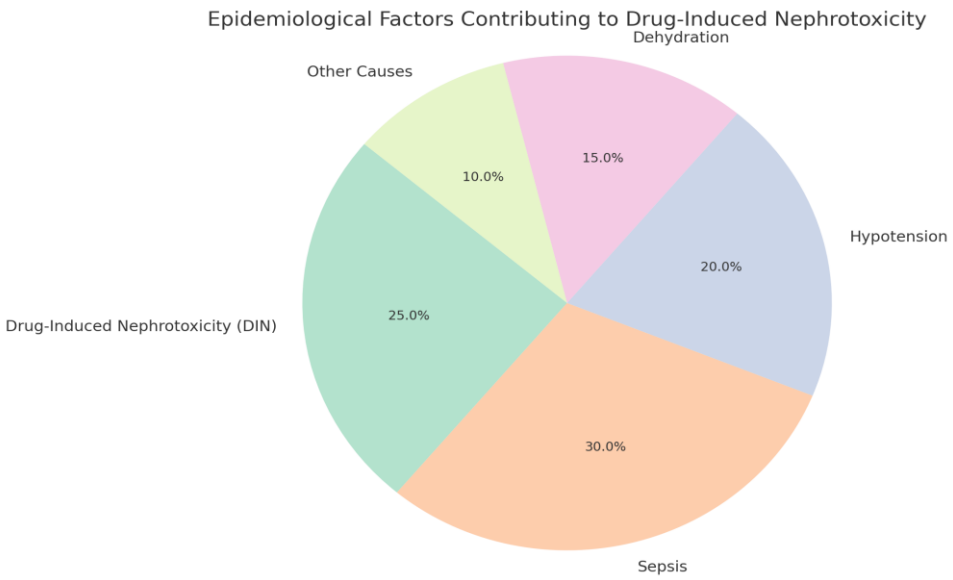

Fig. 1: Epidemiology of drug induced nephrotoxicity.

Patient-Related Risk Factors

Patient-related risk factors for drug-induced nephrotoxicity (DIN) can vary depending on the specific nephrotoxic agent involved. However, certain factors are commonly associated with an increased susceptibility to kidney injury.[9,23] These include advanced age, particularly individuals over 60 years, pre-existing renal insufficiency with a glomerular filtration rate (GFR) below 60 mL/min/1.73 m², intravascular volume depletion, concurrent exposure to multiple nephrotoxins, diabetes mellitus, heart failure, and sepsis.[10,23] Patients with a combination of these risk factors are at a significantly higher risk of developing acute renal failure (ARF), necessitating vigilant monitoring of renal function, especially during the initiation of new medications or dose adjustments.[11,23]

The role of ethnicity, genetic variability, and sex in the predisposition to drug-induced renal injury remains unclear, with conflicting evidence regarding whether males are more susceptible to AKI than females. Nevertheless, personalized risk assessment is essential when managing patients with predisposing factors.[12,23]

Both absolute and effective intravascular volume depletion are recognized as significant contributors to drug-induced renal impairment. Absolute volume depletion occurs in conditions involving severe diuresis, prolonged diarrhoea, gastroenteritis, or inadequate oral fluid intake, leading to a reduction in circulating blood volume.[13,23] On the other hand, effective intravascular volume depletion refers to a perceived reduction in blood volume detected by renal and atrial baroreceptors.[14,23] This phenomenon is commonly observed in

patients with fluid sequestration into third-space compartments due to conditions such as ascites, pancreatitis, heart failure, or sepsis. Recognizing and addressing these risk factors through appropriate hydration, renal function monitoring, and cautious use of nephrotoxic medications can significantly reduce the incidence of drug-induced nephrotoxicity.[15,23]

Table 1[16]

Table 1. Patient-Related Risk Factors for Drug-Induced Nephrotoxicity

Absolute" or "effective" intravascular volume depletion
Age older than 60 years
Diabetes
Exposure to multiple nephrotoxins
Heart failure
Sepsis
Underlying renal insufficiency (glomerular filtration rate < 60 mL per minute per 1.73 m²)

Drug-Related Risk Factors

Certain medications, including aminoglycosides, amphotericin B, cisplatin, contrast dye, and cyclosporine, are inherently nephrotoxic.[17,23] For other drugs, nephrotoxicity may be dose-dependent or associated with prolonged use, leading to conditions like crystal deposition or chronic interstitial nephritis.[18,23] The risk of kidney injury increases further when multiple nephrotoxic agents are used concurrently, resulting in synergistic nephrotoxicity.

Contrast-induced nephropathy (CIN) is particularly notable as the third most common cause of acute renal failure in hospitalized patients.[19,23] The likelihood of developing CIN is influenced by factors such as the type and dosage of the contrast agent, the presence of underlying renal dysfunction, and additional comorbidities.[20,23] Patients with chronic kidney disease (CKD), defined by a glomerular filtration rate (GFR) below 60 mL/min/1.73 m², face the highest risk, especially if they have diabetes. Other contributing factors include dehydration, heart failure, advanced age (over 70 years), and concurrent use of nephrotoxic medications.[21,23] Careful consideration of these risk factors, along with appropriate preventive strategies, is essential to minimize the incidence of drug-induced nephrotoxicity.[22,23]

Table 2[16]

Table 2. Drug-Related Risk Factors for Drug-Induced Nephrotoxicity

MEDICATION	RISK FACTORS
Drugs altering intraglomerular hemodynamics	
ACE inhibitors, ARBs. NSAIDS	Underlying renal insufficiency, intravascular volume depletion; age older than 60 years; concomitant use of ACE inhibitors, ARBs; NSAIDs, cyclosporine (Neoral), or tacrolimus (Prograf)
Cyclosporine, tacrolimus	As above, plus: excessive dose, concomitant use with other nephrotoxic drugs or drugs that infibit cyclosporine or tacrolimus metabolism
Drugs associated with tubular cell toxicity	
Aminoglycosides	Underlying renal insufficiency, duration of therapy > 10 days, trough concentrations > 2 mcg per mL, concomitant liver disease, Hypoalbuminemia
Amphotericin B	Underlying renal insufficiency, rapid infusion, large daty dosage, deorycholate formulations more so than lied formenations, protonet duration of therapy
Contrast dye	Underlying renal insufficiency, age older than 70 vars. diabetes. Neart ailure, volume depletion, repeated exposures
Drugs associated with chronic interstitial nephropathy	
Acetaminophen, aspirin,NSAIDS	History of chronic pain, age older than 60 years, female sex, cumulative consumption of analgesic > 1 gram per day for more than two years
Lithium	Elevated drug level
Drugs associated with crystal nephropathy	
Acyclovir (Zavirax),methotrexate, sulfa antibiotics, triamterene (Dyrenium)	Volume depletion, underlying renal,insufficiency, excessive dose, intravenous administration

Kidney physiology

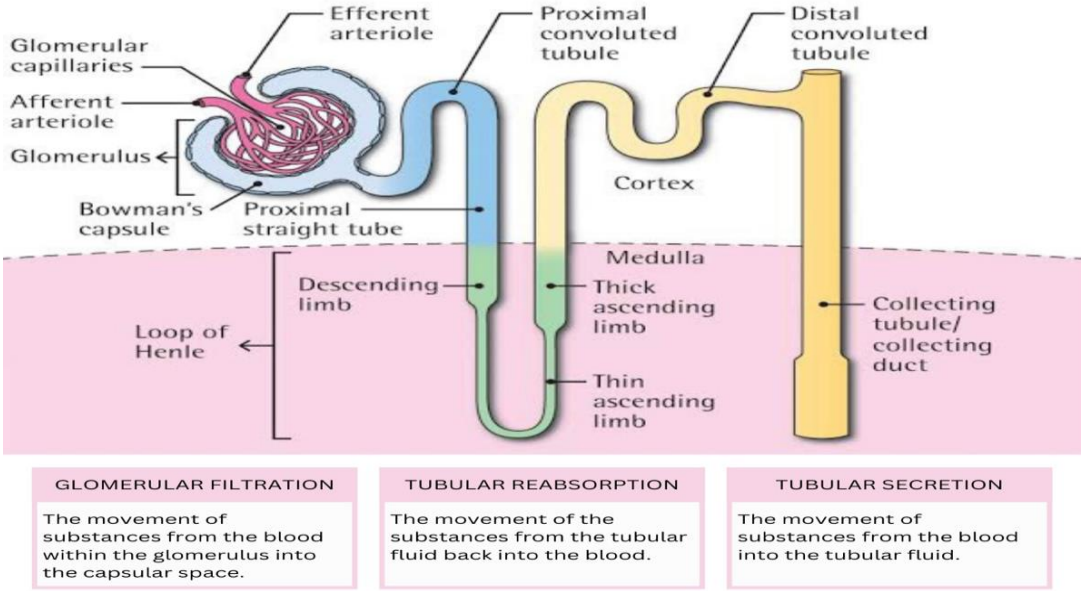

Fig. 2: Normal physiology.[24]

Kidney glomerular physiology

Glomerular filtration is the initial step in urine formation, where hydrostatic pressure passively drives fluid and solutes across a specialized filtration membrane. This membrane consists of three layers: The fenestrated endothelium of the glomerular capillaries, the basement membrane acting as a negatively charged barrier to prevent protein filtration, and the podocyte foot processes that provide selective filtration. The net filtration pressure, primarily determined by the glomerular capillary hydrostatic pressure (55 mmHg), influences the glomerular filtration rate (GFR), which typically ranges from 120 to 125 mL/min.[25]

The GFR is regulated by both intrinsic and extrinsic mechanisms. Intrinsic control involves the myogenic and tubuloglomerular feedback systems, which adjust the resistance of the afferent arterioles. When blood pressure rises, the myogenic mechanism constricts the afferent arteriole to maintain GFR, while a drop in pressure results in dilation. Tubuloglomerular feedback, mediated by macula densa cells in the nephron loop, detects sodium chloride (NaCl) concentrations to modulate afferent arteriole tone. High NaCl levels induce vasoconstriction, reducing GFR, while low levels promote vasodilation.[26]

Extrinsic control primarily involves the sympathetic nervous system and the renin-angiotensin-aldosterone system (RAAS). During significant fluid loss or low blood pressure, norepinephrine and epinephrine trigger vasoconstriction, reducing renal blood flow and GFR.

Additionally, renin release is stimulated by three mechanisms: activation of beta-1 adrenergic receptors in the kidneys, macula densa sensing low NaCl levels, and reduced renal perfusion pressure. Renin subsequently activates the RAAS cascade, promoting vasoconstriction and sodium retention to restore blood pressure and GFR.[27]

Understanding these regulatory mechanisms is crucial for assessing glomerular function and recognizing alterations in conditions like drug-induced nephrotoxicity, where impaired renal autoregulation can exacerbate kidney injury.[28]

Tubular reabsorption

Tubular reabsorption is a crucial process in the kidneys, with each segment of the nephron contributing uniquely to the reabsorption of water, electrolytes, and other solutes. The proximal convoluted tubule (PCT) is the primary site of reabsorption, responsible for reclaiming all glucose, amino acids, and nearly 65% of sodium and water under normal conditions. Sodium ions are reabsorbed through primary and secondary active transport mechanisms, as well as passive paracellular diffusion driven by electrochemical gradients. Water follows via osmosis, facilitated by the osmotic gradient created by solute reabsorption. Lipid-soluble substances are reabsorbed through passive diffusion, while urea is reabsorbed through paracellular diffusion.[29]

Following the PCT, the filtrate enters the nephron loop (loop of Henle), which consists of descending and ascending limbs with distinct functions. The descending limb, rich in aquaporins, allows for the reabsorption of water through osmosis, but it is impermeable to solutes. Conversely, the ascending limb is impermeable to water but enables the active reabsorption of sodium, potassium, and chloride ions through a symporter in its thick segment. The thin segment facilitates passive sodium transport along its concentration gradient. The sodium-potassium ATPase pump on the basolateral membrane maintains the ionic gradient necessary for this process. Additionally, calcium and magnesium ions are reabsorbed in the ascending limb through passive paracellular diffusion.[30]

The distal convoluted tubule (DCT) serves as the final major site for tubular reabsorption. Sodium reabsorption in the DCT occurs via Na-Cl symporters and sodium channels on the apical membrane, with further regulation by aldosterone. This hormone enhances sodium reabsorption at the distal end of the nephron, ensuring the maintenance of electrolyte balance

and blood pressure. Together, these tubular reabsorption processes play a critical role in maintaining homeostasis by regulating fluid and electrolyte levels.[31]

Tubular secretion

The purpose of tubular secretion is to get rid of things like medicines and metabolites that attach to plasma protein. Additionally, tubular secretion eliminates urea and uric acids that were passively reabsorbed. The removal of excess potassium via aldosterone hormone regulation at the collecting duct and distal DCT is one of the roles of tubular secretion. Hydrogen ions are removed when the blood pH deviates from the normal range. Then, as the blood pH rises above normal, bicarbonate acid is released, causing chloride ions to be reabsorbed.

Ammonia, creatinine, and a number of other organic acids and bases are released.[32]

Storage of urine

When urine production is complete, the pee travels via a structure called the ureter before being directed to the bladder for storage.[33] The left and right ureters are located on either side of the human body. These are thin tubes with three layers: the muscularis, which is made up of the external circular layer and the interior longitudinal layer; the adventitia, which is a fibrous connective tissue covering the ureter's exterior; and the mucosa, which is made up of a transitional epithelial tissue.[34] When urine flows through the ureters, the smooth muscle expands, creating peristaltic contractile waves that help move the urine into the bladder.[35] The ureter's oblique insertion at the posterior bladder wall stops urine from flowing backward. Once the pee is within the bladder, the particular structure of the bladder enables effective urine storage.[36]

Micturition process

Micturition, the process of urine expulsion, involves the coordinated relaxation of the internal and external urethral sphincters and the contraction of the detrusor muscle. In infants under the age of three, micturition is regulated by a spinal reflex. As urine accumulates in the bladder, the resulting stretch stimulates receptors in the bladder wall. These receptors send signals via visceral afferent nerves to the sacral spinal cord, where interneurons inhibit sympathetic activity and stimulate parasympathetic neurons. This leads to detrusor muscle contraction and relaxation of the internal urethral sphincter. The somatic efferent nerves,

responsible for maintaining the external sphincter closure, reduce their firing, resulting in involuntary urination.[37]

After the age of three, conscious control over the external urethral sphincter develops, allowing voluntary regulation of urination. The pontine micturition center (PMC) in the brainstem plays a key role in this process. When the bladder reaches its capacity, the PMC activates parasympathetic pathways, promoting detrusor contraction and sphincter relaxation while suppressing sympathetic activity. Conversely, the pontine storage center becomes active when the bladder is not full, maintaining sympathetic tone to relax the detrusor muscle and keep the urethral sphincters closed. This dynamic regulation ensures effective urine storage and timely voiding, contributing to urinary continence and homeostasis.[38]

Drug associated with nephrotoxicity

Table 3[39]

Table 3. Overview of nephrotoxic drugs and their mechanism

CLASS	DRUG	TYPE OF RENAL INJURY
Antiretrovirals	Adefovir cidofovir, tenofovir	Tubular cell toxicity
	Indinavir (Crixivan)	Acute interstitial nephritis, crystal nephropathy
Benzodiazepines	Calcineurin inhibitors	Rhabdomyolysis
	Cyclosporine (Neoral)	Altered intraglomerular hemodynamics chronic interstitial nephritis, thrombotic microangiopathy
	Tacrolimus	Altered intraglomerular hemodynamics
Cardiovascular agents	Angiotensin-converting enzyme inhibitors, angiotensin receptor blockers	Altered intraglomerular hemodynamics
	Clopidogrel (Plavix), ticlopidine (Ticlid)	Thrombotic microangiopathy
	Statins	Rhabdomyolysis
Chemotherapeutics	Carmustine, semustine (investigational)	chronic interstitial nephritis
	Cisplatin	chronic interstitial nephritis, Tubular cell toxicity.
	Interferon-alfa	glomerulonephritis
	Methotrexate	Crystal nephropathy
	Mitomycin-C	Thrombotic microangiopathy
Drugs of abuse	Cocaine, heroin, ketamine, methamphetamine	Rhabdomyolysis
Proton pump inhibitors	omeprazole, Pantoprazole	Acute interstitial nephritis

CLASS	DRUG	TYPE OF RENAL INJURY
Analgesic	Acetaminophen, Aspirin, Nonsteroidal anti- inflammatory drugs	Chronic interstitial nephritis Acute interstitial nephritis, altered intraglomerular hemodynamics, chronic interstitial nephritis, glomerulonephritis.
Antidepressants/mood stabilizers:	Amitriptyline, doxepin, fluoxetine	Rhabdomyolysis
	Lithium	Chronic interstitial nephritis, glomerulonephritis, rhabdomyolysis
Antihistamines:	Diphenhydramine, doxylamine	Rhabdomyolysis
Antimicrobials:	Acyclovir (Zovirax)	Acute interstitial nephritis, crystal nephropathy
	Aminoglycosides	Tubular cell toxicity
	Amphotericin B	Tubular cell toxicity
	Beta lactams (penicillins, cephalosporins)	Acute interstitial nephritis, glome-rulonephritis (ampicillin, penicillin)
	Foscarnet	Crystal nephropathy, tubular cell toxicity
	Ganciclovir	Crystal nephropathy
	Pentamidine	Tubular cell toxicity
	Quinolones	Acute interstitial nephritis, crystal nephropathy
	Rifampin	Acute interstitial nephritis
	Sulfonamides	Acute interstitial nephritis, crystal nephropathy
	Vancomycin	Acute interstitial nephritis

Acyclovir

Acyclovir is a selective antiviral agent that effectively inhibits viral replication with minimal toxicity to host cells. It is a synthetic analogue of the purine nucleoside guanosine, existing in an inactive form that requires phosphorylation within infected cells to convert into its active triphosphate state.[40] Following administration, 62% to 91% of acyclovir is excreted unchanged by the kidneys. However, its limited solubility in urine increases the risk of

crystallisation, particularly in the distal renal tubules.[41] Intravenous bolus injections further contribute to the intratubular precipitation of crystals, leading to obstructive tubulopathy and crystal nephropathy, which typically manifest within 24 to 48 hours of treatment. A study by Sawyer reported acute renal insufficiency in four patients with chronic fatigue syndrome who received high-dose intravenous acyclovir. Among five instances of acute kidney injury (AKI), urine analysis using polarised microscopy revealed birefringent, needle-shaped crystals within leukocytes in three patients.[42] In the most severe case, serum creatinine levels surged to 8.6 mg/dL, while renal biopsy findings indicated interstitial inflammation without tubular necrosis. Elevated acyclovir concentrations were detected in urine, blood, and renal tissue, supporting the diagnosis of obstructive nephropathy caused by crystalluria. To prevent acyclovir-induced nephrotoxicity, adequate hydration is essential during high-dose therapy to enhance drug solubility and minimise crystal formation. Regular monitoring of renal function and timely intervention can reduce the risk of severe renal complications, ensuring safer therapeutic outcomes.[43]

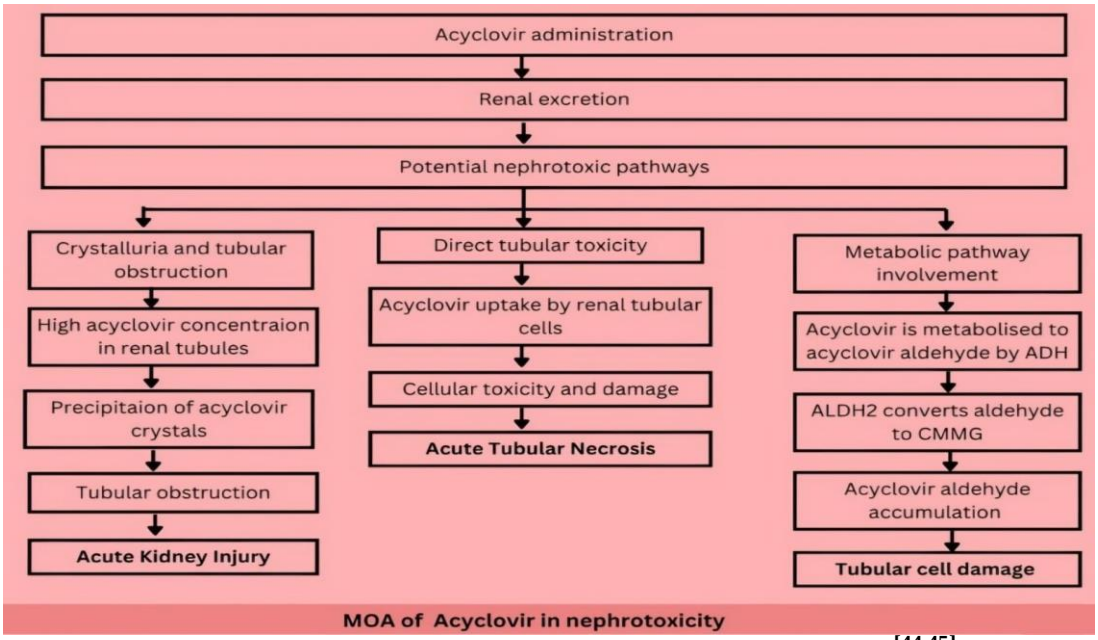

Fig. 3: Mechanism of acyclovir induced nephrotoxicity.[44,45]

Aminoglycosides

Aminoglycosides are associated with nephrotoxicity in up to 25% of treated patients, primarily through three key mechanisms:

- Renal tubular toxicity
- Reduced glomerular filtration
- Diminished renal blood flow [46]

As renal damage progresses, serum creatinine levels rise, accompanied by increased potassium and sodium excretion. Aminoglycosides reduce the glomerular filtration rate (GFR) by inducing mesangial cell contraction in the glomerulus.[47] This contraction is driven by elevated intracellular calcium levels, mediated through several pathways. These include the production of vasoconstrictors like endothelin-1 and thromboxane A2, activation of the renin-angiotensin-aldosterone system, stimulation of platelet-activating factor secretion, and increased oxidative stress caused by reactive oxygen species.[48] The resulting mesangial constriction reduces the filtration surface area, leading to a decline in GFR. In addition to GFR reduction, aminoglycosides also decrease renal blood flow by increasing vascular resistance within the renal vascular bed.[49] This compensatory response aims to prevent further fluid and electrolyte loss following proximal tubular damage.[50] However, the sustained release of endothelin-1 and thromboxane A2 exacerbates vasoconstriction, further restricting renal perfusion and contributing to the overall decline in renal function. Effective monitoring and early intervention are crucial to mitigate aminoglycoside-induced nephrotoxicity and preserve renal health.[51]

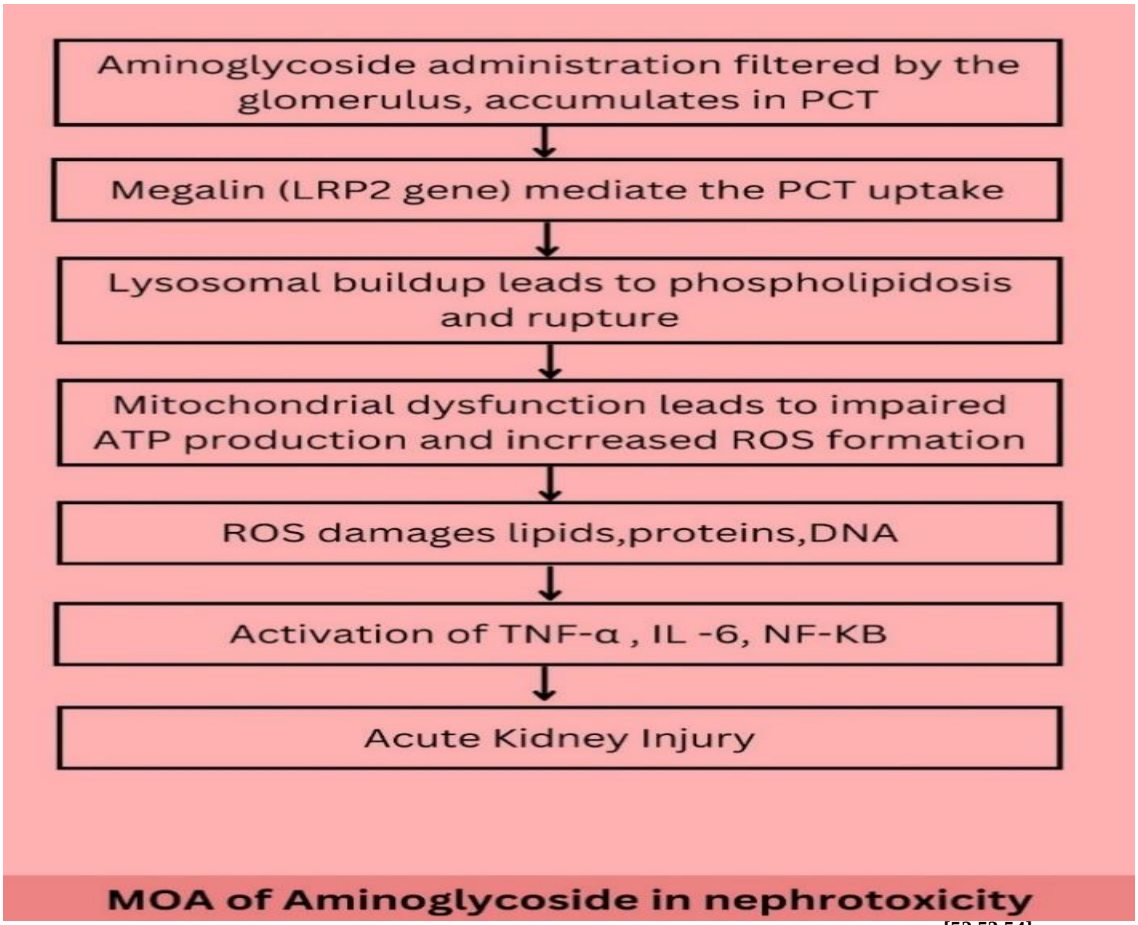

Fig. 4: Mechanism of aminoglycoside induced nephrotoxicity.[52,53,54]

Vancomycin

Animal studies suggest that vancomycin induces nephrotoxicity primarily through oxidative stress, although the exact mechanisms remain incompletely understood. Vancomycin administration in rats leads to increased urinary excretion of malondialdehyde, a marker of oxidative stress, and N-acetyl-D-glucosaminidase, an indicator of tubular injury, along with reduced activities of key antioxidant enzymes such as catalase and superoxide dismutase. These findings, along with evidence of increased oxygen consumption by proximal tubule cells following vancomycin exposure, support the involvement of free radicals in the drug's renal toxicity.[55] Moreover, vancomycin appears to impair mitochondrial function and disrupt energy-dependent reabsorption processes in the proximal tubule.[56] It is proposed that an energy-dependent transport mechanism across the basolateral membrane facilitates vancomycin entry into tubular cells, leading to oxidative damage and subsequent renal tubular ischemia. Notably, the use of antioxidants and cilastatin has shown promise in preventing vancomycin-induced kidney injury, underscoring the critical role of oxidative stress in its pathogenesis.[57]

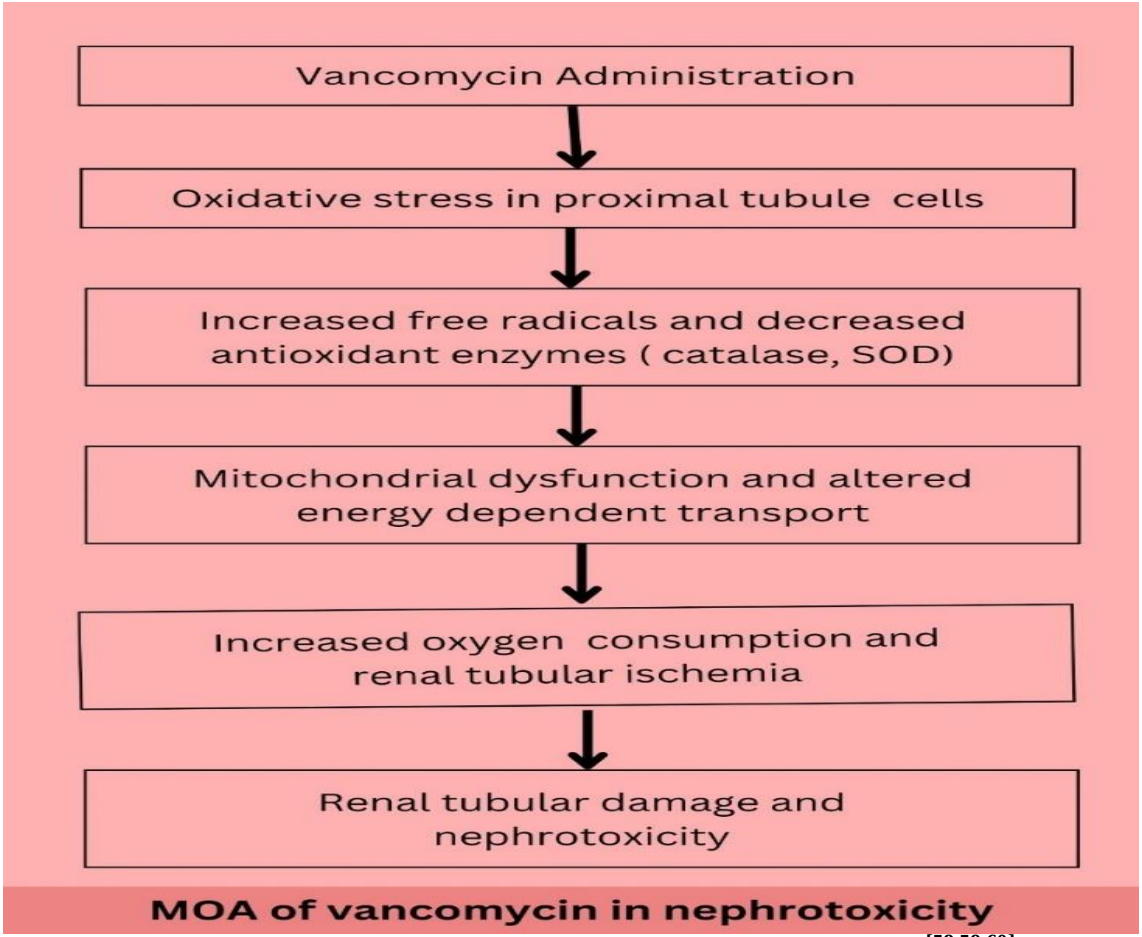

Fig. 5: Mechanism of Vancomycin induced nephrotoxicity.[58,59,60]

Non-steroidal anti-inflammatory drugs

Nonsteroidal anti-inflammatory drugs (NSAIDs) are widely used to alleviate pain and inflammation and are among the most commonly available over-the-counter medications due to their efficacy and relative safety.[61] However, global estimates indicate that 1% to 5% of users experience renal side effects, and NSAIDs are recognized as one of the leading causes of drug-induced kidney injury because of their extensive use. The renal complications associated with NSAIDs include prerenal azotemia, acute tubular necrosis, membranous nephropathy, hypertension, and hyponatremia.[62] These adverse effects are largely attributed to the inhibition of prostaglandin synthesis. Prostaglandins play a crucial role in maintaining renal perfusion through vasodilation, and their suppression by NSAIDs alters renal hemodynamics, particularly in hypovolemic patients or those concurrently receiving angiotensin converting enzyme inhibitors. Furthermore, prostaglandins stimulate renin and angiotensin-mediated aldosterone release; thus, their inhibition can lead to hyperkalemia and metabolic acidosis, a condition sometimes referred to as hyporeninemic hypoaldosteronism. NSAIDs may also interfere with the antidiuretic hormone-mediated water reabsorption in the distal collecting tubules, contributing to hyponatremia, while impaired prostaglandin activity can promote sodium retention, resulting in edema and hypertension.[63]

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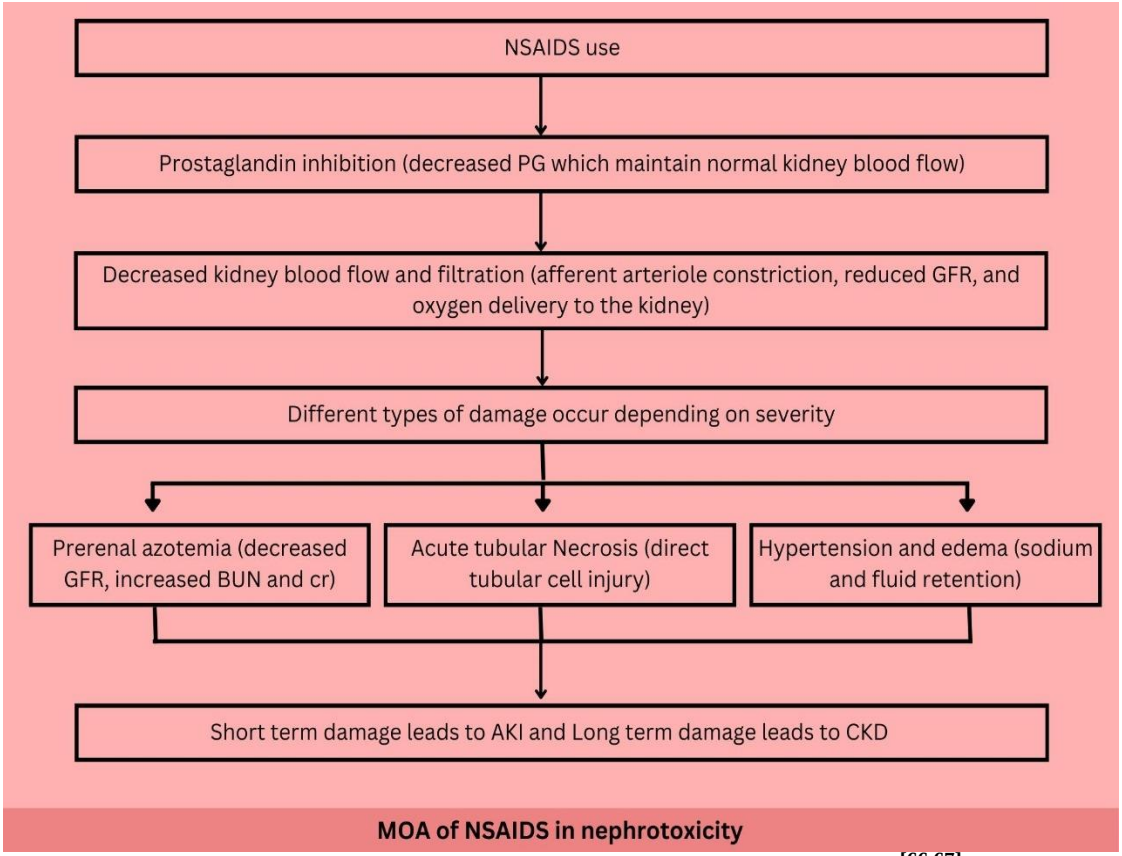

Fig. 6: Mechanism of NSAIDs induced nephrotoxicity.[66,67]

Cisplatin

Cisplatin is primarily eliminated via tubular secretion and glomerular filtration, yet it accumulates in renal parenchymal cells at levels exceeding those in the bloodstream due to active uptake by membrane transporters. Two key transporters facilitate this process: the copper transporter Ctr1 and the organic cation transporter OCT2. Ctr1, which is abundantly expressed on the basolateral membrane of the proximal tubule, plays a crucial role in cisplatin uptake, as evidenced by reduced cellular toxicity and drug absorption when its expression is downregulated in vitro, although its in vivo contribution remains to be fully elucidated.[68] OCT2, on the other hand, has been directly linked to cisplatin nephrotoxicity; its inhibition by substrates such as cimetidine and its deletion in animal models result in decreased drug uptake and reduced renal injury, with genetic variations (e.g., SNP rs316019) further influencing toxicity risk. Beyond transporter-mediated uptake, cisplatin-induced nephrotoxicity involves multiple pathways, including the intrinsic mitochondrial apoptotic cascade (marked by Bax translocation and cytochrome C release), the extrinsic apoptotic pathway via TNF receptors and Fas, and an ER stress-mediated route involving caspase-12 activation.[69] These apoptotic mechanisms are compounded by oxidative stress and inflammation—reactive oxygen species (ROS) inflict cellular damage while TNF-α triggers

inflammatory responses.[70] Cellular regulators such as p21 and p53 modulate these processes by either delaying cell cycle progression to allow DNA repair or promoting apoptosis through mediators like PUMA-α and PIDD.[71] Additionally, autophagy serves as a protective mechanism by clearing damaged cellular components, whereas its suppression accelerates apoptosis, and MAPK signaling pathways (ERK, p38, JNK) further contribute to renal injury. Collectively, these findings underscore the multifactorial nature of cisplatin nephrotoxicity and suggest that strategies employing antioxidants, iron chelators, caspase inhibitors, and free radical scavengers may hold promise in mitigating renal damage.[72]

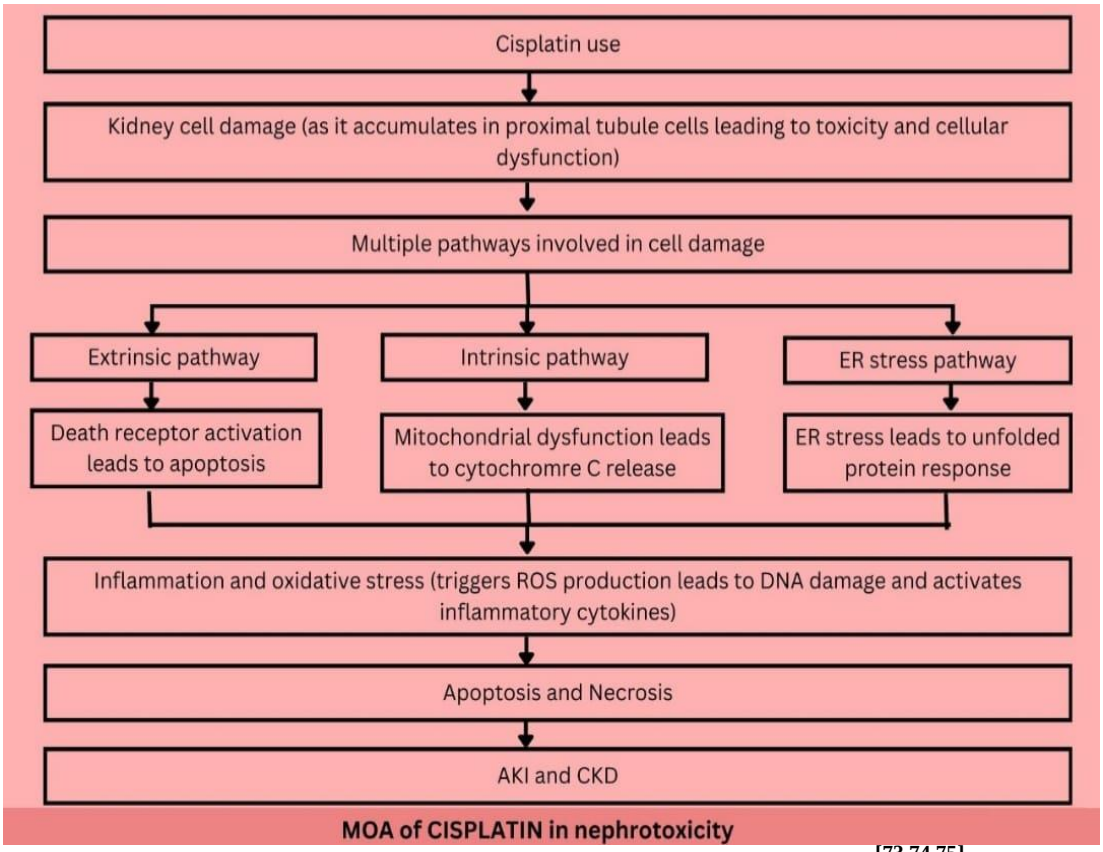

Fig 7: Mechanism of cisplatin induced nephrotoxicity.[73,74,75]

Overall perspectives

Drug-induced nephrotoxicity remains a significant clinical concern, contributing to a substantial burden of acute and chronic kidney disease worldwide. Given the kidney's vital role in drug excretion and its susceptibility to toxic insults, understanding the epidemiology, risk factors, and underlying mechanisms of nephrotoxicity is crucial for early identification and prevention. Various classes of drugs, including aminoglycosides, NSAIDs, contrast agents, and chemotherapeutic agents, exert nephrotoxic effects through different pathways, such as oxidative stress, tubular toxicity, altered renal hemodynamics, and immune-mediated

damage. Despite advancements in renal protective strategies, drug-induced kidney injury continues to be a challenge in clinical practice. A thorough understanding of normal kidney physiology and the specific mechanisms of nephrotoxicity can aid in developing safer therapeutic strategies, improving drug monitoring, and minimizing renal injury. Future research should focus on identifying biomarkers for early detection, optimizing dosing regimens, and exploring novel renoprotective interventions to mitigate nephrotoxicity risk. Ultimately, increasing awareness among healthcare professionals and promoting individualized patient management are essential steps toward reducing the incidence of drug-induced nephrotoxicity and improving renal outcomes.

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