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DRUG-INDUCED NEPHROTOXICITY OF COMMONLY USED DRUGS: MECHANISMS AND PREVENTION

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ABSTRACT
Drug-induced nephrotoxicity (DIN) is a frequent, under-recognised cause of acute kidney injury (AKI) and progression to chronic kidney disease (CKD). The kidney's unique physiology-high perfusion, concentrated solute load, many xenobiotic transporters, and high metabolic demands-renders it particularly vulnerable to injury from therapeutic agents. Common drug classes implicated in nephrotoxicity include non-steroidal anti-inflammatory drugs (NSAIDs), aminoglycosides, radiocontrast media, chemotherapeutics, calcineurin inhibitors, antivirals and antifungals. The mechanisms of injury are heterogeneous, involving intraglomerular haemodynamic alterations, direct tubular cytotoxicity, crystal nephropathy, thrombotic microangiopathy, rhabdomyolysis-mediated injury, and interstitial inflammation. Early recognition of risk factors (e.g., older age, baseline renal impairment, dehydration, polypharmacy) and application of preventive strategies-such as dose adjustment, hydration, monitoring of renal function and novel biomarkers-can significantly reduce the incidence and severity of DIN. This review summarises mechanistic pathways of drug-related nephrotoxicity, examines major nephrotoxic drug classes, considers emerging biomarkers and new prevention strategies, and provides a synthesis of best-practice recommendations.

Keywords: *Drug-induced nephrotoxicity; acute kidney injury; chronic kidney disease; renal tubular toxicity; glomerular haemodynamics; biomarkers; prevention strategy; nephroprotection.*

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INTRODUCTION
The kidneys play a central role in fluid and electrolyte homeostasis, acid-base balance, and the excretion of endogenous waste and xenobiotics. Because of the organ's high blood flow (~20–25% of cardiac output) and the concentrating mechanisms of the nephron, renal tissues are exposed to high levels of circulating drugs and their metabolites. The proximal tubule, in particular, reabsorbs ~60–70% of the filtered load and is reliant on mitochondrial ATP production and transporter activity-making it a frequent target for nephrotoxic injury [1].

Drug-induced nephrotoxicity (DIN) refers to a broad spectrum of renal injuries caused by therapeutic agents, manifesting as acute decreases in glomerular filtration rate (GFR), tubular dysfunction (e.g., Fanconi syndrome, acute tubular necrosis), interstitial nephritis, glomerular disease, or progressive CKD. While some cases resolve completely, delayed recognition often results in persistent renal dysfunction, higher morbidity and healthcare costs. The purpose of this review is to summarise the mechanistic basis, identify commonly implicated drug classes, and to present practical prevention and monitoring strategies for clinicians [2].

MECHANISMS OF DRUG-INDUCED NEPHROTOXICITY
DIN arises through multiple mechanistic pathways. Often more than one mechanism is operative in a given patient.

Alteration of intraglomerular haemodynamics
The glomerulus maintains filtration via autoregulatory mechanisms in afferent and efferent arterioles: prostaglandin-mediated afferent dilation and angiotensin II-mediated efferent constriction. Drugs that inhibit prostaglandins (e.g., NSAIDs) or interfere with angiotensin II signalling (ACE inhibitors, ARBs) can reduce intraglomerular pressure, decrease GFR and precipitate AKI especially in states of volume depletion or impaired renal reserve.

Calcineurin inhibitors (e.g., cyclosporine, tacrolimus) cause afferent arteriolar vasoconstriction, reduced renal perfusion, and GFR decline [3].

Tubular cell toxicity

The proximal tubule is exposed to high concentrations of drugs and their metabolites due to filtration + secretion + reabsorption. This exposure, plus high metabolic demands, confer vulnerability. Mechanistic injury pathways include:

- Mitochondrial damage, impaired ATP production, leading to loss of transporter function and cell death.
- Reactive oxygen species (ROS) and oxidative stress, triggering apoptosis or necrosis.
- Interruption of tubular transporter systems (organic anion transporters OATs, organic cation transporters OCTs) or accumulation via these transporters.
- Lysosomal disruption (e.g., aminoglycosides) and phospholipidosis.

The clinical consequence is acute tubular necrosis (ATN), proximal tubulopathy (e.g., Fanconi syndrome), or chronic tubular injury with interstitial fibrosis [4].

Crystal nephropathy and tubular obstruction

Certain drugs (or high metabolite loads) precipitate as crystals in the tubular lumen (especially in acidic urine), causing physical obstruction, intraluminal pressure increase, local ischemia, and interstitial inflammation. Examples include sulfonamides, high-dose acyclovir, methotrexate, ciprofloxacin.

Thrombotic microangiopathy (TMA)

Some drugs provoke endothelial injury or immune responses that result in microvascular thrombosis in glomeruli and arterioles (TMA). The resultant microcirculatory injury can cause severe AKI. Drugs implicated include ticlopidine, some immunosuppressants (e.g., cyclosporine) and quinine [5].

Rhabdomyolysis-related nephropathy

Several drugs may cause skeletal muscle breakdown (rhabdomyolysis), releasing myoglobin and other intracellular contents into the plasma. Myoglobin is directly toxic to tubular cells, causes oxidative injury, casts formation and obstructive injury in distal tubules. Statins (rarely), illicit drugs, or drugs interacting to cause muscle toxicity fall in this category [6].

Inflammation and interstitial nephritis

Drug-hypersensitivity or direct toxic effects may lead to acute interstitial nephritis (AIN), characterised by interstitial inflammation, tubular damage, and often reversible if caught early. Chronic interstitial nephritis may develop with long-term use of certain drugs (e.g., analgesics, lithium, calcineurin inhibitors) via tubulointerstitial fibrosis [7].

Oxidative stress, mitochondrial dysfunction and apoptosis

Many modern nephrotoxic drugs trigger ROS production, mitochondrial membrane damage, endoplasmic reticulum (ER) stress, autophagy/mitophagy imbalance, and programmed cell death (apoptosis/necroptosis). These cellular events can occur before overt GFR decline; hence novel biomarkers may detect early injury.

Summary: The mechanistic diversity of DIN means that one-size prevention will not fit all. Typing the likely mechanism for a given drug (haemodynamic vs tubular cytotoxic vs crystalline vs vascular) aid in appropriate monitoring and prevention [8].

MAJOR DRUG CLASSES AND NEPHROTOXICITY

Here we review key commonly used drug classes with well-recognised nephrotoxic potential, summarising mechanisms, clinical features and prevention remarks.

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

NSAIDs are among the most widely used drugs. By inhibiting cyclooxygenase (COX) enzymes, they reduce prostaglandin synthesis. Prostaglandins (especially PGE2, PGI2) mediate afferent arteriolar dilation, particularly under conditions of reduced renal perfusion (e.g., volume depletion). NSAIDs reduce afferent vasodilation → reduced renal perfusion → drop in GFR → possible AKI. They may also trigger AIN, papillary necrosis or glomerular injury [9].

Risk factors: older age, pre-existing CKD, heart failure, volume depletion, concomitant ACEi/ARB + diuretic ("triple whammy").

Prevention: avoid NSAIDs (or use lowest dose for shortest duration) in high-risk patients; ensure adequate hydration; monitor renal function.

Aminoglycoside antibiotics (e.g., gentamicin, amikacin)

Aminoglycosides accumulate in proximal tubular epithelial cells via megalin-mediated endocytosis, causing phospholipidosis, lysosomal rupture, mitochondrial injury, oxidative stress and apoptosis. Clinically, rising creatinine, mild proteinuria/glycosuria, electrolyte abnormalities, oliguria. Because toxicity is dose- and concentration-dependent, once-daily dosing regimens, therapeutic drug monitoring (TDM) and limiting duration reduce risk [10].

Radiographic contrast media

Contrast-induced nephropathy (CIN) remains a significant iatrogenic cause of AKI, especially in patients with pre-existing CKD, diabetes or dehydration. Mechanisms include renal vasoconstriction (secondary to tubular-medullary hypoxia), direct tubular cytotoxicity (ROS generation) and tubular obstruction by precipitated contrast.

Prevention: identify at-risk patients, use lowest volume of contrast, isotonic saline hydration before and after procedure, avoid repeat exposures closely spaced [10].

Chemotherapeutic agents and targeted therapies

Many anticancer drugs cause nephrotoxicity via tubular injury, vascular injury, glomerular disease and interstitial fibrosis. For example:

Cisplatin: causes proximal tubule DNA damage, mitochondrial dysfunction, ROS, hypomagnesemia, cumulative injury and long-term CKD risk.

Methotrexate: may crystallise in tubules especially with poor hydration or acidic urine.

Ifosfamide: proximal tubular injury / Fanconi syndrome.

Prevention: adequate hydration, dose reduction, use of nephroprotectants (e.g., amifostine in cisplatin therapy), close monitoring of electrolytes and renal function [11].

Calcineurin inhibitors (CNIs) – e.g., Cyclosporine and Tacrolimus

CNIs are used widely in transplant medicine and autoimmune disease. They cause afferent arteriolar narrowing, decreased renal perfusion, increased vasoconstrictors (endothelin) and proliferation of fibrotic pathways. Chronic CNI nephrotoxicity manifests as interstitial fibrosis, glomerular sclerosis and gradual GFR loss. Prevention: minimise duration/dose, monitor drug levels, blood pressure and volume status, consider alternative immunosuppressants when possible.

Antiviral agents (e.g., Tenofovir, Cidofovir, Foscarnet)

Tenofovir (especially older formulation) is associated with proximal tubular dysfunction (Fanconi syndrome), AKI and GFR decline. Mechanism: mitochondrial toxicity in proximal tubule cells, transporter-mediated uptake and intracellular injury.

Foscarnet: crystalline nephropathy and tubular cytotoxicity.

Prevention: baseline renal assessment, dose adjustment in renal impairment, avoid other nephrotoxins, monitor phosphate, bicarbonate, urine protein, and consider switch to less nephrotoxic agents [12].

Antifungal/Amphotericin B, Vancomycin and Other Miscellaneous Agents

- Amphotericin B: causes afferent vasoconstriction and direct tubular damage (especially classic formulation). Prevention: lipid formulations, hydration, electrolyte monitoring.
- Vancomycin: increasingly recognised for nephrotoxicity, often in high doses, ICU setting, concomitant nephrotoxins and volume depletion.
- Other agents: high-dose sulfonamides, cisplatin, lithium, proton-pump inhibitors (rare interstitial nephritis) etc [13].

Analgesic nephropathy, contrast additives, herbal and OTC preparations

Chronic analgesic misuse (NSAIDs + acetaminophen + phenacetin) has historically led to "analgesic nephropathy" via interstitial fibrosis and papillary necrosis. Herbal and over-the-counter (OTC) preparations may contain nephrotoxins (aristolochic acid, heavy metals). Though not always strictly "drugs", they contribute to cumulative nephrotoxicity [14].

Risk Factors for Drug-Induced Nephrotoxicity

Identifying risk factors is critical for prevention.

- **Patient-related factors:** older age (>60 years), pre-existing renal impairment (eGFR < 60 mL/min/1.73 m^2), underlying CKD, diabetes, heart failure, volume depletion/hypotension, sepsis, anaemia and use of multiple nephrotoxins.
- **Drug-related factors:** high dose, prolonged therapy, narrow therapeutic index, multiple nephrotoxic agents, drugs cleared by kidney, transporter-mediated accumulation, and drugs with renal secretion [15].
- **Clinical context**: ICU setting, surgery, contrast administration, major illness, dehydration.
- **Genetic/personalised factors**: polymorphisms in transporters (OATs, OCTs), mitochondrial DNA variants, variable drug metabolism may affect individual susceptibility.

By assessing these factors prior to drug initiation, clinicians can stratify risk and implement mitigation [16].

BIOMARKERS AND EARLY DETECTION

Reliance on serum creatinine and BUN is limited: these lag behind injury and lack specificity. Emerging biomarkers for early detection of DIN include:

- Kidney Injury Molecule-1 (KIM-1): marker of proximal tubular injury.
- Neutrophil Gelatinase-Associated Lipocalin (NGAL): rises early in tubular injury.
- Interleukin-18 (IL-18), osteopontin, cystatin C, urinary microalbumin, β2-microglobulin: markers of tubular/ glomerular injury.
- Implementation of biomarkers in drug development and toxicity screening ground is increasing.

However, widespread clinical adoption remains limited due to cost, standardisation issues and variable specificity/sensitivity. Continuous research is needed to validate these biomarkers and integrate them into routine practice [17-18].

PREVENTION AND MANAGEMENT STRATEGIES

Prevention and early intervention are the cornerstones of reducing DIN.

Prevention

Pre-treatment evaluation: assess baseline renal function (eGFR, urine protein, electrolytes), identify risk factors.

Drug choice: where possible, select less nephrotoxic alternatives especially in high-risk patients.
Dose adjustment: tailor drug dosing to renal function, body weight, comorbidities.
Hydration and volume status: ensure euvolemia and avoid hypotension/volume depletion, particularly when using haemodynamic nephrotoxins (NSAIDs, contrast).
Therapeutic drug monitoring (TDM): especially for aminoglycosides, vancomycin, CNIs.
Avoid or limit concomitant nephrotoxins: e.g., combine NSAID + diuretic + ACEi is high risk.
Minimise duration/volume: e.g., lowest effective dose for shortest period; minimal contrast volume; minimise cumulative cisplatin.
Monitoring: serial assessment of renal function, electrolytes, tubular function (in case of antiviral/chemotherapy). Biomarkers where available.
Protective adjuncts: e.g., amifostine for cisplatin, lipid-form amphotericin, isotonic saline for contrast hydration.
Educate clinicians/patients: about early signs of AKI, importance of hydration, avoiding OTC nephrotoxins in vulnerable patients [19].

MANAGEMENT

Early recognition: rising creatinine, falling urine output, rising biomarkers.
Stop or reduce offending agent where feasible; replace with safer alternative.
Optimize hemodynamics: ensure adequate perfusion, avoid further insults (hypotension, volume depletion, sepsis).
Avoid further nephrotoxins: and adjust other drug dosages accordingly.
Supportive care: manage electrolytes, acid–base balance, monitor for complications (hyperkalemia, fluid overload).
Renal replacement therapy(RRT) when indicated in severe AKI as per standard guidelines.
Assess for recovery: many DIN cases are reversible if caught early; persistent dysfunction warrants nephrology referral and evaluation for CKD.
Research setting: some nephroprotective strategies (mitochondrial-protectants, anti-fibrotic agents, antioxidant therapies) are under investigation [20].

EMERGING TRENDS AND FUTURE PERSPECTIVES

Several evolving themes are of interest:
Pharmacogenomics & personalised medicine: transporter polymorphisms (e.g., OAT1/OAT3, OCT2/MATE1) may influence drug uptake by tubular cells and risk of injury.
Mathematical modelling & simulation (M&S): simulation approaches may better predict nephrotoxicity during drug development, enabling earlier "renal-safe" screening.
Predictive analytics & AI: e.g., machine-learning models to predict rising creatinine in ICU settings with vancomycin use.
Biomarker panels and early detection: as biomarker research matures, earlier detection of tubular injury (pre-creatinine rise) may allow preventive intervention.
New therapeutic/nephroprotective agents: mitochondrial protectants, anti-fibrotic drugs, ROS modulators are being explored in preclinical and early clinical phases. Nonetheless, key challenges remain: lack of universal definition for DIN, standardisation of biomarkers, translation of research into practice, and the need for clinician awareness [21].

DISCUSSION

DIN is a common, multifactorial and often preventable complication of pharmacotherapy. Despite significant improvements in understanding mechanisms, many gaps persist. For example, the absence of a universally-accepted definition of DIN makes epidemiological assessment difficult [1, 3, 22]. Additionally, clinical trials of new drugs frequently exclude patients with impaired renal reserve, limiting data on real-world risk. Most importantly, the heterogeneity of mechanisms (haemodynamic vs cytotoxic vs crystalline vs vascular) implies that prevention cannot be generic; it must be tailored to the drug, patient and context [23-24].
In many clinical settings, polypharmacy and multimorbidity (e.g., diabetes, CKD, heart failure) increase risk and complicate attribution of renal injury to a single agent. Prevention efforts must emphasise risk-stratification and incorporate renal-safe prescribing guidelines. Early detection remains suboptimal: reliance on creatinine alone delays recognition of injury. Integration of biomarkers and predictive tools into routine care may shift the paradigm toward pre-emptive nephroprotection [25].
Clinical vigilance, renal monitoring and interdisciplinary collaboration (nephrology + pharmacy + prescribing physician) are key to reducing the burden of DIN. Implementation science (how to embed prevention protocols in real-world practice) remains a priority area.

CONCLUSION

Drug-induced nephrotoxicity remains a significant iatrogenic cause of kidney injury. Although common, it is often under-recognised and under-prevented. A clear understanding of the mechanistic pathways, combined with identification of high-risk drugs and patients, application of early detection via biomarkers and vigilant monitoring, and implementation of preventive strategies can substantially reduce the incidence and severity of

DIN. With advancing tools in pharmacogenomics, predictive modelling and biomarker science, the future holds promise of personalised "renal safe" pharmacotherapy. Until then, clinician awareness, careful prescribing and timely monitoring remain the foundation of safeguarding kidney health.

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