

DRUG-INDUCED NEPHROTOXICITY: CURRENT CONCEPTS AND CLINICAL IMPLICATIONS

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Abstract: Drug-induced nephrotoxicity is a significant clinical problem and one of the leading causes of acute kidney injury, particularly among hospitalized patients, older adults, and individuals with chronic kidney disease. Due to the high blood flow through the kidneys, complex tubular functions, and active transport mechanisms, the kidneys are particularly susceptible to the harmful effects of drugs and their metabolites. It is estimated that drugs contribute to 20–25% of cases of acute kidney injury in adults, while the incidence is considerably higher among critically ill patients. The aim of this paper is to present current knowledge on the epidemiology, risk factors, classification, diagnosis, and clinical manifestations of drug-induced nephrotoxicity. Particular emphasis is placed to contemporary classification systems based on the site of injury, clinical phenotypes, and biomarkers of renal dysfunction and kidney injury. The most important mechanisms of kidney injury are presented, including hemodynamic disturbances, direct tubular toxicity, immune-mediated injury, crystal nephropathies, rhabdomyolysis, and thrombotic microangiopathy, with special emphasis on clinical presentation, preventive strategies, therapeutic options, and prognosis. In addition, the major groups of potentially nephrotoxic drugs encountered in everyday clinical practice are reviewed, including aminoglycosides, nonsteroidal anti-inflammatory drugs, renin-angiotensin-aldosterone system inhibitors, statins, and proton pump inhibitors. Timely recognition of risk factors, rational drug use, individualized dosing according to kidney function, and regular monitoring of renal parameters represent key measures for the prevention of nephrotoxicity. A better understanding of the pathophysiological mechanisms and clinical patterns of kidney injury enables earlier diagnosis, appropriate treatment, and reduction of the risk of permanent loss of kidney function.

Keywords: nephrotoxicity, acute kidney injury, drugs, acute interstitial nephritis, acute tubular necrosis, chronic kidney disease, prevention.

INTRODUCTION

The human kidneys are small paired organs that account for only 0.2–0.5% of total body mass, while receiving as much as 20–25% of the cardiac output. This intensive perfusion, together with the complex structure and function of the renal tubules, makes the kidneys particularly susceptible to the harmful effects of various drugs and chemicals. Most drugs and their metabolites are eliminated through glomerular filtration and/or tubular secretion. The elimination process is based on the capacity for drug metabolism through the oxidative-reductive phase of biotransformation, as well as on the conjugation of metabolites with specific carriers that facilitate their excretion into the urine [1–3].

Nephrotoxicity is defined as a rapid deterioration of kidney function caused by the toxic effects of substances, most commonly drugs, which may lead to acute kidney injury (AKI) and necessitate discontinuation of therapy

or even hemodialysis [4]. The proximal tubules are the nephron segment most susceptible to the nephrotoxic effects of drugs because of their intense metabolic activity, which, together with a high osmotic gradient and the presence of transport mechanisms, facilitates the accumulation of toxins and the development of injury [2].

Given the increasingly widespread use of drugs in modern therapy, understanding the mechanisms of nephrotoxicity and recognizing potentially harmful substances are of crucial importance for the prevention of kidney injury and the preservation of renal function.

EPIDEMIOLOGY

Drug-induced nephrotoxicity is currently considered to account for approximately 20% of all cases of nephrotoxicity, with hospitalized patients and those admitted to intensive care units being particularly vulnerable. Among older adults, the incidence reaches up to 66% owing to numerous comorbidities, polypharmacy, and

more frequent exposure to high-risk diagnostic and therapeutic procedures [5,2].

Nephrotoxicity may manifest as injury affecting different segments of the nephron and represents one of the etiopathogenetic factors of acute kidney injury (AKI) and chronic kidney disease (CKD). According to the results of prospective cohort studies, nephrotoxic drugs are responsible for AKI in 14–26% of adults,

whereas cross-sectional studies have reported rates of up to 37.5% [2,6]. Approximately 20% of all cases require kidney replacement therapy, with an associated mortality rate of 60%, even in developed countries [7].

Risk Factors

Risk factors for drug-induced nephrotoxicity include patient-related factors, kidney-related factors, and drug-related factors (Table 1).

Table 1. Risk factors for the development of drug-induced kidney disease²

Patient-related	Kidney-related	Drug-related
Older age (≥ 60 -65 years)	CKD with GFR <60 ml/min/ 1.73m^2	High doses of the drug or prolonged use
Female gender	Renal hypoperfusion	Direct nephrotoxic effects
Altered pharmacogenetics (genetic variations in hepatic CYP450 and kidney transporters)	Biotransformation of the drug into nephrotoxic metabolites and ROS	Exposure to multiple nephrotoxic agents
Comorbidities (cirrhosis, DM, HTN, HF, sepsis, active cancers)	High metabolic demand of proximal tubular cells despite relative hypoxia	Pharmacokinetic and/or pharmacodynamic drug interactions that increase the free fraction, interfere with biotransformation, or worsen drug/metabolite excretion
Metabolic perturbations (hypokalemia, hypercalcemia, hypomagnesemia acidosis)	Proximal tubular uptake of drugs: by the apical route or by the basolateral transporters	

Legend: CYP450, cytochrome P450; DM, diabetes mellitus; HTN, arterial hypertension; HF, heart failure; CKD, chronic kidney disease; GFR, glomerular filtration rate;

Patient-related risk factors may be non-modifiable (e.g., age, sex, and genetic variations) or at least partially modifiable, as in the case of chronic comorbidities and metabolic disorders. Both older age and female sex are associated with reduced lean body mass, lower total body water content, and decreased serum albumin concentrations, which may contribute to an increased free fraction of the drug. Furthermore, older individuals have been shown to have higher circulating levels of angiotensin II and endothelin, which contribute to vasoconstriction of the efferent arterioles, increased glomerular filtration, and a greater amount of drugs and metabolites reaching the renal tubules [3].

An increased risk of nephrotoxicity is undoubtedly associated with pre-existing CKD with a glomerular filtration rate (GFR) below 60 mL/min, as well as renal hypoperfusion, whether resulting from true or effective volume depletion. Additional contributing factors include intrarenal drug biotransformation, uptake of drugs by proximal tubular cells, and specific metabolic characteristics of tubular cells under hypoxic conditions.

One of the most important risk factors is the inherent nephrotoxicity of certain drugs. Some drugs, such as aminoglycosides, possess a high nephrotoxic potential and may cause kidney injury even in patients with minimal or no additional risk factors. In most cases, drug-induced nephrotoxicity is dose-dependent and/or associated with prolonged treatment duration. Such reactions are predictable because they are based on the known pharmacological properties of the drug and may be attenuated by dose reduction or drug discontinuation. Less frequently, nephrotoxicity develops as an unpredictable adverse reaction resulting from an immune-mediated response that is independent of dose and usually requires complete withdrawal of the offending drug for resolution of symptoms [3,5,8].

Exposure to multiple nephrotoxic agents and drug interactions affecting their pharmacokinetic and/or pharmacodynamic properties further increase the risk of nephrotoxicity.

CURRENT CLASSIFICATIONS OF DRUG-INDUCED NEPHROTOXICITY

Before 2002, the reported incidence of acute renal failure varied considerably due to the lack of a standardized definition. Since then, the RIFLE classification (Risk, Injury, Failure, Loss, End-stage Kidney Disease) has been developed and was first published in 2004 [9]. Soon thereafter, it became evident that even small increases in serum creatinine are clinically significant because they are associated with higher morbidity and mortality. Consequently, in 2007, the Acute Kidney Injury Network (AKIN) modified the RIFLE criteria (AKIN criteria) and introduced the term AKI instead of acute renal failure [10].

Classification of Drug-Induced AKI According to the Site of Injury

An important initial step in the evaluation of AKI is determining the primary site of injury. Accordingly, AKI can be classified as prerenal, renal (intrinsic), or postrenal (Table 2).

- Prerenal injury occurs primarily as a consequence of renal hypoperfusion. In the context of drug-induced nephrotoxicity, prerenal AKI may result from the use of nonsteroidal anti-inflammatory drugs (NSAIDs), calcineurin inhibitors (CNIs), and modulators of the renin-angiotensin-aldosterone system (RAAS).
- Renal or intrinsic injury may result from damage to any component of the kidney, including the renal tubules, glomeruli, vascular structures, interstitium, or tubular lumen. Acute tubular necrosis (ATN) and acute interstitial nephritis (AIN) are among the most common forms of intrinsic kidney injury, and anti-infective agents are the most frequent causative drugs.
- Postrenal injury resulting from obstruction leads to hydronephrosis and subsequent damage to the renal parenchyma. Drugs associated with tubular obstruction include acyclovir, methotrexate, and several antiretroviral agents [11].

Table 2. Potential causes of AKI and recovery expectations¹¹

Types of AKI	Nondrug-induced AKI	Drug-induced AKI	Recovery
Prerenal injury	Intravascular volume depletion, decreased CO, decreased SVR	<i>NSAIDs, ACEIs, ARBs, diuretics, calcineurin inhibitors</i>	Days to weeks
Renal injury			
ATN	Prolonged or severe prerenal states, toxin ingestion (ethylene glycol)	<i>Aminoglycosides, amphotericin B, rifampicin, cisplatin, cocaine, antiretrovirals</i>	Weeks to months; May require temporary RRT
AIN	Papillary necrosis, pyelonephritis, renal tuberculosis, fungal nephritis, FSGS, various viral infections	<i>Antimicrobials (betalactams, sulfonamides, quinolones, vancomycin), NSAIDs, allopurinol, diuretics</i>	Weeks to months; May require temporary RRT
Glomerulonephritis	Lupus	<i>Hydralazine, NSAIDs, ampicillin, lithium</i>	Weeks to months; May require temporary RRT
Postrenal injury	Tumor lysis syndrome, multiple myeloma, kidney stones, malignancy, BPH	<i>Acyclovir, methotrexate, sulfonamides, triamterene, some antiretrovirals, large doses of vitamin C</i>	Days to weeks; if reversal of obstruction is delayed, may not fully recover

Legend: AKI, acute kidney injury; ATN, acute tubular necrosis; AIN, acute interstitial nephritis; CO, cardiac output; SVR, systemic vascular resistance; FSGS, focal segmental glomerulosclerosis; BPH, benign prostatic hyperplasia; NSAIDs, non-steroidal anti-inflammatory drugs; ACEIs, angiotensin-converting enzyme inhibitors; ARBs, angiotensin-II receptor blockers; RRT, renal replacement therapy);

Classification of Drug-Induced Nephrotoxicity According to Clinical Presentation (Four Phenotypes)

Despite the previously described classification systems, uniform standards for the identification of drug-induced nephrotoxicity were still lacking, and kidney injury often remained unrecognized. Therefore, in 2015, Mehta et al. proposed four phenotypes of drug-induced kidney disease according to the underlying mechanism of injury: acute kidney injury (AKI), glomerular disorder, tubular dysfunction, and nephrolithiasis.

The clinical presentation of each phenotype is based on changes in biomarkers and other evidence of kidney injury, including serum creatinine (AKI), proteinuria or hematuria (glomerular disorders), electrolyte

abnormalities (tubular dysfunction), and ultrasonographic findings (nephrolithiasis). In order to standardize the initial phenotypic classification, primary and secondary criteria were developed, with at least one primary criterion being required to verify drug-induced nephrotoxicity (Table 3).

Drugs differ in the time course of nephrotoxic manifestations. Some agents cause acute injury (e.g., aminoglycosides and cephalosporins), whereas others are associated with a slower and more insidious onset (e.g., lithium). Taking into account conceptual models of the temporal evolution of kidney injury, Mehta classified drug-induced kidney disease into three categories: acute (1–7 days), subacute (8–90 days), and chronic (>90 days) [12].

Table 3. Primary and secondary criteria for the four main phenotypes¹²

Phenotype	Clinical features	Criteria	
		Primary	Secondary
Acute kidney injury	AIN ATN Osmotic nephrosis	Rise in sCr presents as or progresses to stage 2 AOB (KDIGO) 2.0–2.9 x reference sCr or higher OR Decline by at least 50% from peak Scr over 7 days in relationship to change in drug dosing adjustment or discontinuation within 2 weeks	Oliguric <500 ml/day or <0.5 ml/kg/hr for 12 hrs (KDIGO stage 2) Non-oliguric >500 ml per day Urinalysis findings: cylindruria consistent with ATN, eosinophils, proteinuria FeNa >1% Negative ultrasound findings Positive Gallium scan for AIN Clinical symptoms for AIN: fever, rash and joint pain
Glomerular disorder	Hematuria Proteinuria	Biopsy proven drug induced glomerular disease (within 4 weeks of stopping drug), AND Proteinuria: > 1 g/24h; UPC or UACR > 0.8; Urinalysis 2+ protein 100–300 mg/dL albumin Hematuria: >50 rbc/HPF	URINE: sterile pyuria, >50 wbc/HPF, casts, RBC; granular. Absence of secondary disorder that can cause GN: DM, lupus, infectious, hepatitis, etc Microangiopathic changes in the blood smear, LDH; haptoglobin Nephritic, nephrotic, mixed sy
Tubular dysfunction	RTA Fanconi syndrome Phosphaturia Diabetes insipidus SIADH	Hypophosphatemia OR Glucosuria: by urine analysis 3+ glucose without diabetes OR Hyperchloremic metabolic acidosis AND Hypokalemia or hyperkalemia Diabetes insipidus: Na>155 mEq/l; polyuria >3 l/day	Phosphaturia: FePO4 >5%; PO4 excretion >100 mg/24h Hypomagnesemia: serum Mg <1.2 mg/dl Hypouricemia: Serum Ac uric acid <2 mg/dl Tubular proteinuria: Urinalysis <2+, UPC <0.8; <1 g /24h; DI: serum osmolality >300 mOsm/kg, urine osmolality <100 mOsm/kg, urine Na <10 mEq/l
Nephrolithiasis	Crystalluria Nephrolithiasis Ultrasound findings of stone with or without obstruction	New onset after drug exposure with no previous history No evidence of congenital etiology for nephrolithiasis If obstructive, rise in Scr that presents as or progresses to stage 2 AOB (KDIGO) or higher; Without obstruction: Urinalysis with crystals Ultrasound with stone	Urine electrolytes Stone work up

Legend: AIN, acute interstitial nephritis; ATN, acute tubular necrosis; DM, diabetes mellitus; FeNa, fractional excretion of sodium; FePO4, fractional phosphorus excretion, GN, glomerulonephritis; HPF, high powered field; LDH, lactate dehydrogenase; SIADH, syndrome of inadequate antidiuretic hormone secretion; UPC, urinary protein/creatinine ratio; UACR, urinary albumin/creatinine ratio;

Biomarker-Based Classification of Nephrotoxicity

The following conceptual classification was proposed in 2019 by an international expert panel composed of nephrologists and pharmacists. This classification integrates both functional biomarkers and biomarkers of kidney damage, together with the predominant mechanisms of nephrotoxicity, and categorizes drugs into four groups: dysfunction without damage, damage without dysfunction, both dysfunction and damage, and neither dysfunction nor damage. Examples of drugs belonging to each category are provided to further illustrate this classification system, while possible transitions between categories are shown by arrows (Figure 1).

1. Neither dysfunction nor damage

This category includes drugs that cause an increase in serum creatinine without inducing kidney dysfunction or structural damage. For example, some drugs may reduce tubular creatinine secretion or increase creatinine production without affecting kidney function. These drugs are not truly nephrotoxic, and this clinical situation is referred to as pseudo-AKI.

2. Dysfunction without damage

This category includes drugs that impair kidney function by affecting systemic or intraglomerular

hemodynamics. By reducing renal perfusion, they decrease intraglomerular pressure, filtration fraction, and GFR, resulting in an increase in serum creatinine concentration. In some cases, this alteration in glomerular hemodynamics represents an adverse effect, whereas in others it reflects the intended therapeutic action of the drug. The most common examples are RAAS modulators and vasoactive agents.

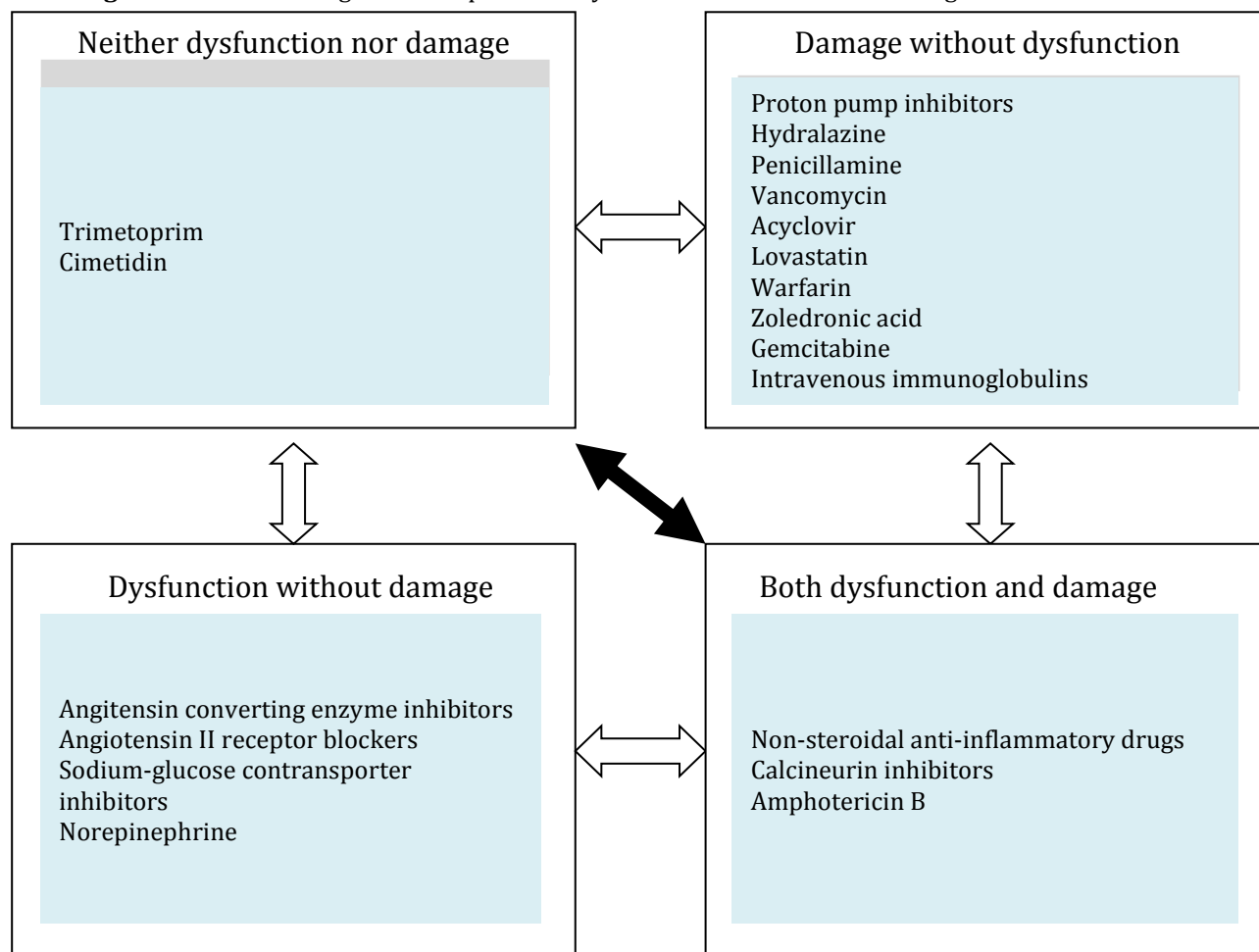
3. Damage without dysfunction

Kidney damage within this category may involve the glomeruli, tubules, or interstitium. Drugs may induce direct or indirect tubular damage/injury through crystal and cast formation, oxidative stress, inflammation, mitochondrial dysfunction, and immune-mediated reactions.

4. Both dysfunction and damage

This category includes drugs associated with both hemodynamic and non-hemodynamic mechanisms of AKI development. Non-hemodynamic features of AKI include glomerular, tubular, and interstitial injury occurring either alone or in combination. A given drug may induce functional changes through one mechanism and tissue damage through another, or both may result from the same pathogenic pathway. Typical examples are NSAIDs and CNIs [13].

Algorithm 1. Four categories of nephrotoxicity based on functional and damage biomarkers¹³



Drug-induced nephrotoxicity, similarly to other kidney diseases, can be diagnosed using simple blood and/or urine tests, including the measurement of serum creatinine and blood urea levels, as well as assessment of GFR using creatinine clearance. However, these tests are known to be imperfect markers of kidney function, as they are influenced by numerous renal and extrarenal factors.

Owing to continuous research efforts, novel biomarkers have been identified that are more sensitive and capable of detecting kidney injury at an earlier stage. Functional biomarkers include cystatin C, proenkephalin A (PENK), beta-trace protein (BTP), and neutrophil gelatinase-associated lipocalin (NGAL), which are measured in plasma. In addition, urinary biomarkers have been identified that may indicate injury to specific nephron segments. However, further studies are required before their routine clinical application can be recommended. Such studies should address several issues of crucial importance: when these biomarkers should be measured, whether they should be used to guide clinical decision-making, and what actions should be taken when their levels are elevated [14].

DRUG-INDUCED KIDNEY DISEASES

Acute Tubular Necrosis

ATN is a common cause of AKI in critically ill patients and is most often a consequence of

prolonged prerenal insults or exposure to nephrotoxins. Histological changes demonstrate necrosis of the renal tubular epithelium, with necrotic cells being shed into the tubular lumen, where they may cause extensive tubular injury. Regeneration is possible if the tubular basement membrane remains intact. The injury is usually reversible, although it may persist for days or weeks, and temporary renal replacement therapy (RRT) may be required. If ischemia is severe and prolonged, the injury may become irreversible [15,11].

Direct tubular injury may be caused by various classes of drugs, including antimicrobial agents, chemotherapeutic drugs, calcineurin inhibitors, bisphosphonates, and contrast media. Preventive strategies for many of these agents include volume expansion to correct hypovolemia and increase tubular flow, adjustment of drug dosage according to baseline GFR, and the use of alternative agents (e.g., mTOR inhibitors instead of calcineurin inhibitors or denosumab instead of bisphosphonates). For certain drugs, such as vancomycin and CNIs, therapeutic drug monitoring is required. Specific measures for vancomycin include avoidance of concomitant administration with piperacillin–tazobactam, whereas the nephrotoxicity of amphotericin B is significantly reduced when lipid-based or liposomal formulations are used (Table 4) [6].

Table 4. Drugs associated with acute tubular injury and preventative strategies⁶

Drug class	Medications	Preventative strategies
Antibiotics	Aminoglycosides	Once daily dosing, adjust dose for underlying GFR, administration of tobramycin over gentamicin if possible
	Vancomycin	Adjust dose for underlying GFR, therapeutic drug monitoring, avoiding combinations with piperacillin-tazobactam, use alternative agents
	Colistin	Adjust dose for underlying GFR, avoid prolonged administration, use alternative agents
Antifungals	Amphotericin B	Use lipid or liposomal form, IV isotonic crystalloids hydration
Antiviral agents	Cidofovir, tenofovir, adefovir	Adjust dose for underlying GFR, screen for tubular toxicity to identify early injury, use alternative agents
Analgesics	NSAIDs (and COX-2i) ↑Acetaminophen	Use alternative agents, avoid use in high-risk patients, avoid excessive dosing especially in liver disease
Chemotherapeutic agents	Cisplatin	Adjust dose for underlying GFR, IV isotonic crystalloid-induced diuresis, use of lower-dose regimens, use of cisplatin analogs, consider Na thiosulfate in high-risk pts
	Ifosfamide	Adjust dose for underlying GFR, limit dose Mesna and N-acetyl cysteine of unproven efficacy
Calcineurin inhibitors	Cyclosporin,	Reduce dose and follow drug levels.

	tacrolimus	Consider alternative agents such as mTOR inhibitors
Bisphosphonates	Pamidronate	Duration of infusion > 2hr, use lower doses, use alternative agents such as denosumab
	Zoledronic acid	Use lower dose especially if GFR <60 ml/min/1.73m ² , contraindicated in AKI and GFR <30ml/min/1.73m ² , use alternative agents such as denosumab

Legend: IV, intravenous; NSAIDs nonsteroidal anti-inflammatory drugs; COX, cyclo-oxygenase; mTOR, mammalian target of rapamycin;

Acute Interstitial Nephritis

AIN is an immune-mediated form of kidney injury, with drugs being responsible for more than 70% of cases (drug-induced acute interstitial nephritis, DI-AIN) [17]. Kidney biopsies performed in the evaluation of AKI indicate that the incidence of DI-AIN is

approximately 15%. To date, more than 250 drugs have been reported to cause AIN, with antibiotics, NSAIDs, proton pump inhibitors (PPIs), and immune checkpoint inhibitors being the most commonly implicated agents (Table 5) [6,17,18].

Table 5. Drugs associated with acute interstitial nephritis

Drug class	Individual medications
Antibiotics	Beta-lactam antibiotics (penicillins, cephalosporins), sulfonamides, fluoroquinolones, macrolides, rifampicin
Analgesics	NSAIDs (including COX2 inhibitors)
Acid-suppressive therapy	Proton pump inhibitors, histamine H2 receptor antagonists
Immunotherapy	PD-1 inhibitors, PD-L1 inhibitors, CTLA-4 inhibitors
Diuretics	Loop diuretics (Furosemide, Bumetanide) Thiazide diuretics (hydrochlorothiazide)
Antiviral agents	Acyclovir, Abacavir, Indinavir, Atazanavir, Foscarnet
Anticonvulsants	Phenobarbitone, Phenytoin
Angiogenesis inhibitors	Bevacizumab, tyrosine kinase inhibitors (sorafenib, sunitinib)
Other agents	Ifosfamide, Pemetrexed, Lithium, Allopurinol, Mesalazine and other 5-aminosalicylates

Legend: NSAIDs nonsteroidal anti-inflammatory drugs; COX, cyclo-oxygenase; PD-1i, Programmed Death-1 inhibitors; PD-L1i, Programmed Death Ligand-1 inhibitors; CTLA-4i, Cytotoxic T-Lymphocyte Antigen-4 inhibitors;

DI-AIN presents either as AKI or as a subacute decline in kidney function, indicating that symptoms may develop within a few days or several weeks to months after exposure to the drug that triggered the inflammatory cascade. The classic hypersensitivity triad consisting of rash, fever, and eosinophilia is observed only rarely (<10%). More commonly, patients present with nonspecific symptoms such as fatigue, malaise, and nausea, occasionally accompanied by flank pain. Many patients develop hypertension due to increased angiotensin II activity and the resulting arterial vasoconstriction in the setting of interstitial inflammation. Patients are usually non-oliguric unless advanced AKI develops, and some may even be polyuric because of impaired urinary concentrating ability [18,19].

Nephrotic syndrome may occur in cases induced by NSAIDs, although proteinuria of up to 1 g/24 h, sterile pyuria with leukocyte casts, and microscopic hematuria are more common findings. Although

laboratory findings may support a high clinical suspicion of DI-AIN, these tests have limited sensitivity and specificity; therefore, the definitive diagnosis is established by kidney biopsy. Novel urinary biomarkers may provide a noninvasive diagnostic alternative in the future.

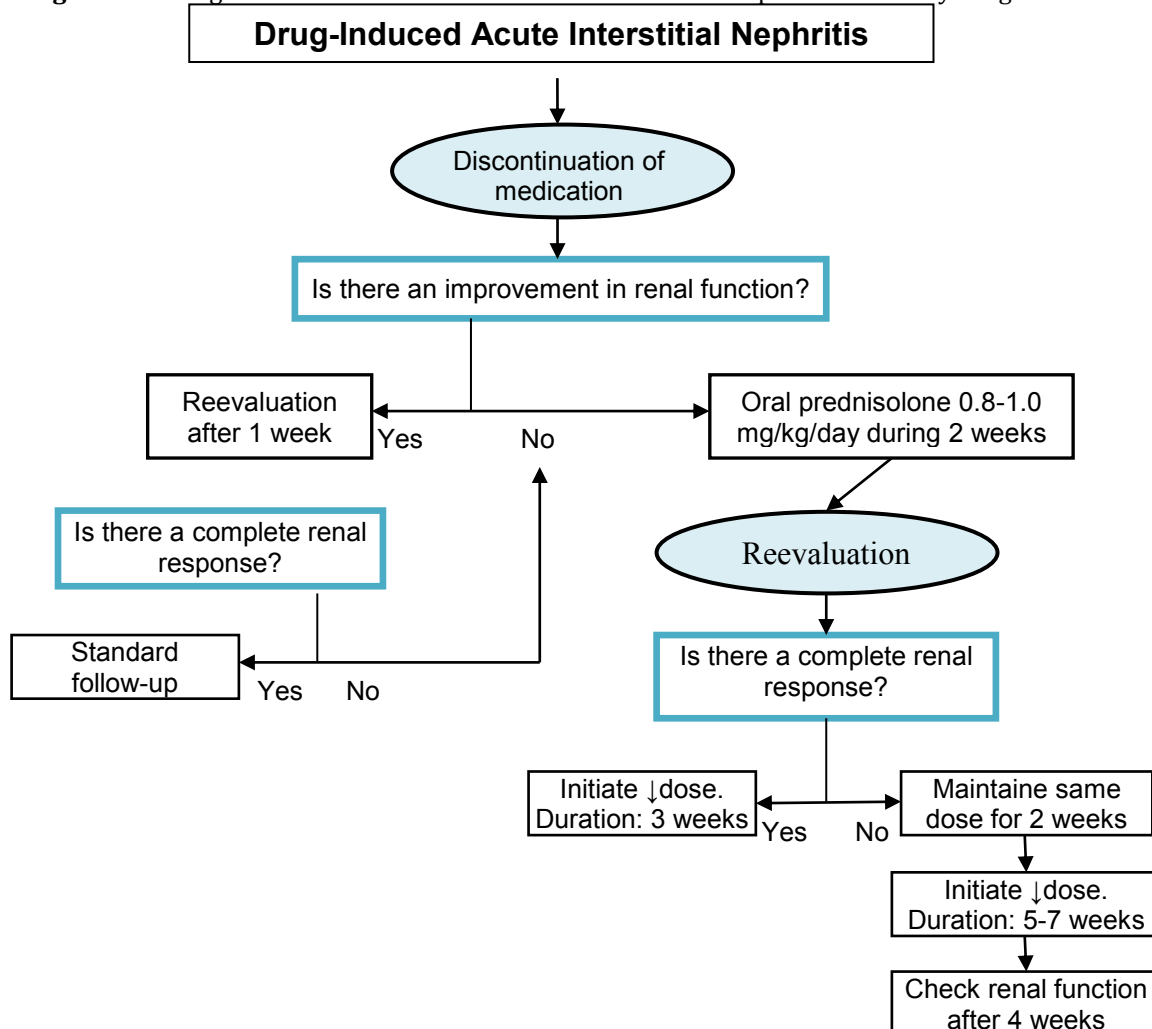
Histopathological findings indicate involvement of both the renal tubules and the interstitium. The characteristic feature is an extensive interstitial inflammatory infiltrate composed predominantly of lymphocytes and monocytes, although eosinophils, plasma cells, histiocytes, and polymorphonuclear leukocytes may also be present, and less commonly granulomas may be observed. Initially, the inflammatory infiltrate may be associated with interstitial edema; however, over time, interstitial fibrosis and tubular atrophy develop, findings that are characteristic of chronic interstitial nephritis [19,20]. Treatment and Prognosis of Drug-Induced Acute Interstitial Nephritis

Discontinuation of the suspected drug is generally considered the cornerstone of DI-AIN treatment, although identification of the offending agent may sometimes be challenging. Reassessment of serum creatinine is recommended one week after withdrawal of the suspected drug. In the absence of significant improvement, treatment with oral prednisolone at a dose of 0.8–1 mg/kg/day is recommended for 2 weeks. If a complete renal response is achieved, tapering of corticosteroid therapy should be initiated. In patients with an incomplete response, the same dose of prednisolone is recommended for an additional 2 weeks, followed by gradual dose reduction over a period of 5–7 weeks (Algorithm 1) [20].

Early reports of methicillin-associated AIN suggested that the disease was relatively benign and associated

with a favorable prognosis. However, this has proven to be far from reality, as incomplete recovery of kidney function is observed in approximately 40% of patients [21], and up to one-third of patients require dialysis treatment. Older adults are not only at a higher risk of developing the disease but also tend to have a poorer prognosis [20]. Prolonged impairment of kidney function is considered an unfavorable prognostic factor, whereas early diagnosis and timely initiation of treatment are associated with more favorable outcomes [22]. Histopathological findings undoubtedly have predictive value despite the inconsistencies reported in clinical studies: diffuse cellular infiltration, a greater degree of interstitial fibrosis and tubular atrophy, and the presence of granulomas have all been associated with a less favorable prognosis) [20].

Algorithm 1. Algorithm for the treatment of acute interstitial nephritis caused by drugs²⁰



Crystal Nephropathies Caused by Drugs

Crystal nephropathies are an important but often underrecognized cause of kidney disease and are characterized histologically by the presence of intrarenal crystal deposits that primarily affect the tubulointerstitial compartment. Clinically, patients present with urinary abnormalities such as crystalluria, proteinuria, and urinary casts, although tubulopathies, AKI, and CKD may also develop [23,24,25]. Microscopic identification of various pathological crystals and/or crystal-containing casts in the urine suggests the possibility of crystal nephropathy. Demonstration of crystals within the kidney by biopsy is crucial for establishing the diagnosis and requires evaluation of the underlying cause.

Drug-induced intrarenal crystal deposition occurs primarily as a consequence of renal excretion of the drug or its metabolites and drug supersaturation in urine. Conditions that favor

crystal formation include hypovolemia/dehydration (resulting in reduced urinary flow), drug overdose (leading to increased urinary drug concentrations), and urinary pH, the effect of which depends on the pKa of the respective drug (acidic urine for methotrexate and sulfadiazine, and alkaline urine for indinavir, atazanavir, and ciprofloxacin). The pathophysiological mechanisms involved in the development of drug-induced crystal nephropathy include substrate supersaturation, nucleation, aggregation, further crystal growth, cellular membrane injury, intratubular obstruction, direct and indirect cytotoxicity, inflammation, and necroinflammation [25]. The drugs most commonly associated with these processes are listed in Table 6, together with their clinical presentation and the basic preventive and therapeutic strategies.

Table 6. Drug-induced crystalline nephropathies²⁵

Medication	Renal syndromes	Preventive and therapeutic strategies
Methotrexate	Crystalluria, AKI and CKD	IV fluid before/during drug administration, alkalinize urine, adjust drug dose for kidney function, folic acid, glucarpidase if toxic level (<60h after drug)
Sulfo drugs (sulfadiazine, sulfamethoxazole)	Crystalluria, AKI, CKD and nephrolithiasis	Alkalinize urine, adjust drug dose for kidney function, assure euolemia before drug exposure
Ciprofloxacin, levofloxacin	Crystalluria and AKI	Assure euolemia during drug therapy and avoid alkaline urine (if possible)
Amoxicillin	Crystalluria and AKI	Assure euolemia and adjust drug dose for kidney function
Acyclovir	Crystalluria, AKI and CKD	Avoid rapid IV bolus, adjust drug dose for kidney function, ensure euolemia during drug therapy,
Indinavir, Atazanavir, Darunavir	Crystalluria, AKI, CKD and nephrolithiasis	Urine acidification does not play a role, assure euolemia during drug therapy, switch to different medication
Foscarnet	AKI, hematuria, proteinuria and CKD	Assure euolemia during drug therapy and adjust drug dose for kidney function
Triamterene	Crystalluria, AKI, CKD and nephrolithiasis	Alkalinize urine, assure euolemia during drug therapy

Legend: AKI, acute kidney injury; CKD, chronic kidney disease; IV, intravenous;

Drug-Induced Rhabdomyolysis

Rhabdomyolysis is a clinical syndrome in which skeletal muscle injury leads to myocyte lysis and the release of intracellular contents into the systemic circulation, including electrolytes, purines, enzymes such as creatine kinase (CK),

and myoglobin [26]. Myoglobin is considered responsible for renal toxicity through three principal mechanisms: renal vasoconstriction, formation of intratubular casts, and direct toxicity to renal tubular cells [27]. The typical signs and symptoms of rhabdomyolysis are

known as the classic triad and include acute or subacute myalgia, muscle weakness predominantly affecting the proximal muscles of the lower extremities, and dark tea-colored urine. Clinical manifestations range from subclinical elevations of serum CK, lactate dehydrogenase (LDH), and aspartate aminotransferase (AST) to severe electrolyte disturbances, cardiac arrhythmias, AKI, and disseminated intravascular coagulation [28].

The most common causes of rhabdomyolysis in adults include strenuous physical activity, illicit drugs (heroin, cocaine, methadone, and methamphetamine), alcohol abuse, medications, muscle diseases, trauma, neuroleptic malignant syndrome, seizures, and prolonged immobilization [29]. Drugs most commonly implicated in the development of rhabdomyolysis include statins, fibrates, sedative-hypnotics, anesthetic agents associated with malignant hyperthermia, neuroleptics, anabolic steroids/corticosteroids, and newer-generation anticonvulsants [26,28]. Treatment consists of discontinuation of the offending drug and restoration of intravascular volume in order to achieve a urine output exceeding 2 L/24 h. At present, there is insufficient evidence to support the routine use of loop diuretics, mannitol, or bicarbonate in the treatment of rhabdomyolysis. In patients with severe AKI and other life-threatening complications, such as hyperkalemia, hypocalcemia, or volume overload, RRT should be considered [30].

Drug-Induced Thrombotic Microangiopathy

Drug-induced thrombotic microangiopathy (TMA) accounts for 10–13% of all cases of TMA and approximately 20–30% of secondary forms, which are considerably more common than primary forms (80–90%). The classic triad of microangiopathic hemolytic anemia, thrombocytopenia, and kidney injury is rarely observed in its entirety. More frequently, patients present with subacute forms characterized by mild thrombocytopenia and a gradual decline in kidney function, or even with kidney-limited TMA, which is associated with a more favorable prognosis [31]. The key pathological feature is endothelial injury caused by heterogeneous mechanisms, most commonly involving an idiosyncratic acute antibody-mediated immune response or a direct toxic effect of the drug related to dosage or duration of therapy [32,33]. The list of drugs potentially associated with TMA is rapidly expanding and

includes numerous antimicrobial agents, immunosuppressive drugs, chemotherapeutic agents, antiplatelet drugs, as well as various other medications and illicit substances [31,32,33].

The cornerstone of treatment is discontinuation of the suspected drug and supportive care. Plasma exchange and rituximab should be considered only in patients with suspected immune-mediated TMA, particularly in cases potentially associated with ticlopidine or in patients who fail to improve after withdrawal of the offending drug. In severe cases, complement blockade with the monoclonal antibody eculizumab may be used as rescue therapy. By inhibiting complement factor C5, eculizumab prevents the formation of the membrane attack complex and thereby inhibits cell lysis and death [31].

(POTENTIALLY) NEPHROTOXIC DRUGS IN CLINICAL PRACTICE

Aminoglycosides

The nephrotoxicity of aminoglycosides is well recognized (occurring in 10–25% of cases); however, these agents continue to be used in the treatment of severe Gram-negative infections and infective endocarditis. In recent years, their use has even increased because of the progressive resistance to other antimicrobial agents and the lack of new therapeutic alternatives [34]. The mechanisms underlying aminoglycoside-induced nephrotoxicity include interaction with proximal tubular cells leading to cellular apoptosis and necrosis, as well as a reduction in renal blood flow resulting in parenchymal ischemia and promoting the development of AKI. Nephrotoxicity most commonly manifests as non-oliguric AKI, usually occurring 5–7 days after the initial exposure to the drug, or as proximal tubular dysfunction known as Fanconi syndrome, which is characterized by metabolic acidosis, hypophosphatemia, glycosuria, and aminoaciduria [6,35].

Strategies for the safer use of aminoglycosides have been defined in clinical guidelines, which recommend that:

- aminoglycosides should not be used for the treatment of infections unless no suitable alternative is available;
- in otherwise healthy and clinically stable patients, aminoglycosides should be administered as a single daily dose rather than in multiple daily doses;

• aminoglycoside serum concentrations should be monitored when multiple daily dosing is continued for more than 24 hours or when once-daily dosing is continued for more than 48 hours;

• topical or local administration of aminoglycosides (e.g., respiratory aerosols or instilled antibiotic beads) should be preferred over intravenous administration whenever feasible and clinically appropriate [36].

Treatment of aminoglycoside-induced nephrotoxicity consists of supportive care and discontinuation of the offending drug. Following drug withdrawal, the prognosis is generally favorable, and recovery of kidney function usually occurs within several days to several weeks. However, pre-existing kidney disease, advanced age, and prolonged exposure to aminoglycosides are associated with a high risk of incomplete recovery and progression to CKD. On the other hand, aminoglycoside-induced AKI in critically ill patients is associated with increased morbidity and mortality, particularly when complicated by sepsis, hypotension, or multiple organ dysfunction [37].

Nonsteroidal Anti-inflammatory Drugs

NSAIDs exert their analgesic, anti-inflammatory, and antipyretic effects through inhibition of cyclooxygenase (COX), the enzyme responsible for converting arachidonic acid released from cell membranes into various eicosanoids, including thromboxane, prostaglandin E₂, and prostacyclin. Within the kidney, prostaglandins exert vasodilatory effects and influence the tubular transport of water and electrolytes by reducing sodium and water reabsorption and increasing potassium secretion [38]. Prostaglandin production is increased in CKD as a mechanism aimed at improving perfusion of

the remaining nephrons ("prostaglandin-dependent state"). Therefore, in these patients, both selective and non-selective COX inhibition are considered equally hazardous. Current clinical guidelines recommend avoiding prolonged NSAID use when the glomerular filtration rate is 30–60 mL/min/1.73 m² and complete avoidance when the glomerular filtration rate is below 30 mL/min/1.73 m² [39]. The nephrotoxic effects of NSAIDs may manifest clinically in several ways:

- AKI, predominantly mediated by hemodynamic mechanisms, leading either to a reversible decline in GFR or to ischemic tubular injury;
- Fluid and electrolyte disorders, including hyperkalemia, occasionally metabolic acidosis, hyponatremia, and sodium and water retention, resulting in edema, worsening of congestive heart failure, and hypertension;
- AIN (NSAIDs account for 10–15% of cases);
- Proteinuria and nephrotic syndrome resulting from membranous nephropathy or minimal change disease as less common complications;
- Risk of CKD progression associated with cumulative drug exposure [38].

The use of NSAIDs is generally not considered excessively harmful in young individuals without kidney disease or significant comorbidities. However, because their nephrotoxic effects are dose-dependent, particular attention should be paid to chronic use, which increases the risk of nephrotoxicity. In CKD, NSAIDs directly affect kidney function through inhibition of prostaglandin synthesis; therefore, the indications for their use should be carefully evaluated, taking into account existing risk factors and the expected clinical benefit [40]. Risk factors for NSAID-induced nephrotoxicity are presented in Table 7 [38].

Table 7. Risk factors for NSAID-induced nephrotoxicity³⁸:

Acute kidney injury
True vascular volume depletion • exercise-induced, diarrhea, vomiting
Effective vascular volume depletion • nephrotic syndrome, liver cirrhosis, congestive heart failure
Exposure to high cumulative doses
Concurrent calcineurin inhibitors and other vasoconstrictors
Concurrent therapy with RAAS inhibitors and/or diuretics
Hyperkalemia
Concurrent use of drugs that promote hyperkalemia • RAAS inhibitors, trimethoprim, heparin, other drugs
Exposure to radiocontrasts with concomitant RAAS inhibitors
Age over 65 years,
Hyporeninemic hypoaldosteronism,
RTA type 4
Hyponatremia

Vascular volume depletion (true or effective)
Conditions associated with SIADH
Increased free water intake ± increased sodium losses
Use of thiazides in the elderly
Worsening of hypertension
Underlying HTN, including on effective treatment
Hyporeninemic status (in the elderly and DM)
Hypervolemia
Underlying comorbid conditions that promote sodium avidity (congestive heart failure, liver cirrhosis, nephrotic syndrome)
Progression of CKD
Age >65 year, high cumulative doses, coronary artery disease

Legend: RAAS, renin-angiotensin-aldosterone system; RTA, renal tubular acidosis; SIADH, syndrome of inadequate antidiuretic hormone secretion; HTN, arterial hypertension; DM, diabetes mellitus;

Renin-Angiotensin-Aldosterone System Inhibitors

The nephroprotective effects of RAAS inhibitors are well established, particularly in patients with kidney disease and diabetes mellitus. These effects are mediated through blood pressure reduction, slowing of GFR decline, reduction of proteinuria, and delay of progression to advanced stages of CKD [2,41]. Initial decline in eGFR after RAAS inhibitor initiation should not automatically be interpreted as nephrotoxicity. These drugs are rarely truly nephrotoxic, but their effects on intrarenal hemodynamics may result in a reversible decline in GFR and consequently AKI [2].

Such adverse renal effects may occur in patients with pre-existing impairment of glomerular autoregulation, which depends on prostaglandin-mediated vasodilation of the afferent arteriole and angiotensin II-mediated vasoconstriction of the efferent arteriole [42]. Nephrotoxicity may result from hypoperfusion associated with low mean arterial pressure (reduced cardiac output or low systemic vascular resistance), volume depletion (e.g., due to diuretic therapy), or pre-existing renovascular disease, such as bilateral renal artery stenosis or severe intrarenal arteriosclerosis [43]. The nephrotoxic potential of RAAS inhibitors may also become apparent as a result of drug interactions. A typical example is the concomitant chronic use of NSAIDs and RAAS inhibitors, particularly in older adults, with an additional increase in risk when a diuretic is also prescribed. This phenomenon is commonly referred to as the “triple whammy” interaction [44].

Management of patients with hemodynamic instability and AKI requires correction of hypovolemia and hypotension; therefore, temporary discontinuation of all

antihypertensive agents, including RAAS inhibitors, is a logical approach. However, after restoration of an adequate circulating volume, normalization of blood pressure, and recovery of GFR, these agents should be reintroduced according to the original indication for their use [41]. In patients with CKD, treatment with RAAS inhibitors should be continued unless serum creatinine increases by more than 30% within four weeks after initiation of therapy or dose escalation. Dose reduction or discontinuation of RAAS inhibitors should be considered in the presence of symptomatic hypotension or uncontrolled hyperkalemia despite medical treatment, or in order to reduce uremic symptoms during the management of kidney failure (estimated GFR <15 mL/min/1.73 m²) [45].

Statins

Statins (HMG-CoA reductase inhibitors) play an undisputed role in the primary and secondary prevention of cardiovascular disease, including among patients with predialysis CKD [45]. However, they may also exert nephrotoxic effects, making careful monitoring of kidney function during the first months of treatment advisable. Statin-induced nephrotoxicity has been directly associated with high drug doses and indirectly with interactions involving other agents that may increase serum statin concentrations [46]. Potential mechanisms of toxicity include alterations in cell membrane permeability, reduced ubiquinone levels, and depletion of isoprenoids resulting from inhibition of cholesterol synthesis [46]. Identified risk factors include advanced age, female sex, liver dysfunction, and diabetes mellitus. The clinical presentation of statin-induced nephrotoxicity includes rhabdomyolysis, ranging from mild elevations in serum creatine kinase levels and myalgia to severe muscle weakness, muscle cramps,

myositis, and rhabdomyolysis. In addition, statins may cause acute or subacute interstitial nephritis through immune-mediated mechanisms, which generally resolves following drug withdrawal and corticosteroid therapy [47].

Recent epidemiological studies have indicated a significantly increased risk of AKI, particularly among patients initiating treatment with high-potency statins [48]. However, these cases are often underreported, which may be explained by the characteristics of the population receiving these drugs. Patients treated with statins are generally older and frequently have comorbidities such as diabetes mellitus, hypertension, and atherosclerotic renovascular disease. In addition, they often receive concomitant medications, including RAAS inhibitors and diuretics, all of which may contribute to renal dysfunction. Furthermore, many patients are treated with antiplatelet agents, making kidney biopsy more difficult in the setting of AKI. Finally, statin-induced acute or subacute tubulointerstitial nephritis may develop insidiously and remain subclinical, thereby going unrecognized if kidney function is not routinely monitored [47,49].

Proton Pump Inhibitors

Proton pump inhibitors (PPIs) are among the most commonly used drugs worldwide, with an estimated 53–69% of prescriptions lacking an appropriate medical indication [50]. Although PPIs were considered safe for many years, evidence from observational studies suggests an association between PPI use and a variety of adverse effects, particularly adverse renal outcomes, including AKI, AIN, and CKD [50,51]. AIN may develop within hours to several months after initiation of therapy and rarely presents with the classic triad of fever, rash, and eosinophilia. However, sterile pyuria, hematuria, and eosinophiluria may be detected on urinalysis. A rapid decline in kidney function may precipitate AKI, or AIN may be complicated by the development of interstitial fibrosis and

tubular atrophy, resulting in chronic interstitial nephritis that gradually progresses to CKD. According to available studies, more than half of patients fail to achieve complete recovery of kidney function following AIN. Hypomagnesemia has also been reported as an adverse effect. Although the underlying mechanisms remain insufficiently understood, available evidence suggests an association with CKD [50,52].

Preventive measures include limiting excessive PPI use to appropriate medical indications, with careful attention to both dose and duration of therapy. Particular caution is warranted in patients with CKD or those at increased risk of developing CKD, and alternative therapeutic options should be considered whenever appropriate. When treatment with PPIs is clearly indicated, monitoring of GFR and serum magnesium levels is recommended, especially in patients receiving concomitant diuretic therapy [50].

CONCLUSION

Drug-induced nephrotoxicity is a significant cause of both acute and chronic kidney injury and represents an important contributor to morbidity and mortality in contemporary clinical practice. The risk of kidney injury is particularly pronounced in older adults, patients with pre-existing CKD, multiple comorbidities, and polypharmacy. Timely identification of risk factors, rational use of potentially nephrotoxic drugs, individualized dosing, and regular monitoring of kidney function constitute the cornerstone of prevention. Advances in the understanding of pathophysiological mechanisms and the development of novel biomarkers provide opportunities for earlier detection of kidney injury and more precise patient monitoring. Given that a substantial proportion of drug-induced kidney injuries are potentially preventable, physician education aimed at the early recognition of nephrotoxicity remains a key element in preserving kidney function and improving treatment outcomes.

LITERATURE:

1. Kalucki SA, Lardi C, Garessus J, Kfoury A, Grabherr S, Burnier M, et al. Reference values and sex differences in absolute and relative kidney size. A Swiss autopsy study. *BMC Nephrol.* 2020; 21: 289.
2. Dobrek L. A Synopsis of Current Theories on Drug-Induced Nephrotoxicity. *Life (Basel).* 2023; 13(2): 325.
3. Perazella MA. Pharmacology behind common drug nephrotoxicities. *Clin J Am Soc Nephrol.* 2018; 13: 1897–1908.
4. Al-Naimi MS, Rasheed HA, Hussien NR, Al-Kuraishy HM, Al-Gareeb AI. Nephrotoxicity: Role and significance of renal biomarkers in the early detection of acute renal injury. *J Adv Pharm Technol Res.* 2019; 10(3): 95–99.
5. Naughton CA. Drug-induced nephrotoxicity. *Am Fam Physician.* 2008;78(6):743–750.
6. Perazella MA, Rosner MH. Drug-induced acute kidney injury. *Clin J Am Soc Nephrol.* 2022; 17(8): 1220–1233.

7. Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group. KDIGO clinical practice guideline for acute kidney injury. *Kidney Int Suppl.* 2012; 2: 1–138.
8. Siddama A., Suneel I.M. Drug induced kidney disease. *Open Acc. J. Toxicol.* 2017; 2(5): 555576.
9. Bellomo R, Ronco C, Kellum JA, et al. Acute Dialysis Quality Initiative Workgroup Acute renal failure – definition, outcome measures, animal models, fluid therapy and information technology needs: the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. *Crit Care.* 2004; 8(4): R204–R212.
10. Coca SG, Peixoto AJ, Garg AX, Krumholz HM, Parikh CR. The prognostic importance of a small acute decrement in kidney function in hospitalized patients: a systematic review and meta-analysis. *Am J Kidney Dis.* 2007; 50(5): 712–720.
11. McDaniel BL, Bentley ML. The role of medications and their management in acute kidney injury. *Integr Pharm Res Pract.* 2015; 4: 21–29.
12. Mehta RL, Awdishu L, Davenport A, Murray PT, Macedo E, Cerda J, et al. Phenotype standardization for drug-induced kidney disease. *Kidney Int.* 2015; 88(2): 226–234.
13. Karimzadeh I, Barreto EF, Kellum JA, Awdishu L, Murray PT, Ostermann M, et al. Moving toward a contemporary classification of drug-induced kidney disease. *Crit Care.* 2023; 27(1): 435.
14. Parikh CR, Koyner JL. Biomarkers in acute and chronic kidney diseases. In: Chertow G, Luyckx V, Marsden P, Skorecki K, Taal M, Alan Y, editors. *Brenner and Rector's The Kidney*. 11. Elsevier; 2020.
15. Moore EM, Bellomo R, Nichol AD. The meaning of acute kidney injury and its relevance to intensive care and anaesthesia. *Anaesth Intensive Care.* 2012; 40(6): 929–948.
16. Perazella MA, Markowitz GS. Drug-induced acute interstitial nephritis. *Nat Rev Nephrol.* 2010; 6(8): 461–470.
17. Raghavan R, Shawar S. Mechanisms of Drug-Induced Interstitial Nephritis. *Adv Chronic Kidney Dis.* 2017; 24(2): 64–71.
18. Kodner CM, Kudrimoti A. Diagnosis and management of acute interstitial nephritis. *Am Fam Physician.* 2003;67(12):2527–2534.
19. Finnigan NA, Rout P, Leslie SW, et al. Allergic and Drug-Induced Interstitial Nephritis. [Updated 2023 Sep 12]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2026 Jan.
20. Sanchez-Alamo B, Cases-Corona C, Fernandez-Juarez G. Facing the Challenge of Drug-Induced Acute Interstitial Nephritis. *Nephron.* 2023;147(2):78–90.
21. Rossert J, Fischer E. Acute interstitial nephritis. *Comprehensive clinical nephrology.* Philadelphia: Elsevier Limited; 2018.
22. Muriithi AK, Leung N, Valeri AM, Cornell LD, Sethi S, Fidler ME, Nasr SH. Biopsy-proven acute interstitial nephritis, 1993–2011: a case series. *Am J Kidney Dis.* 2014;64(4):558–566.
23. Yarlagadda SG, Perazella MA. Drug-induced crystal nephropathy: an update. *Expert Opin Drug Saf.* 2008; 7(2): 147–158.
24. Daudon M, Frochot V, Bazin D, Jungers P. Drug-Induced Kidney Stones and Crystalline Nephropathy: Pathophysiology, Prevention and Treatment. *Drugs.* 2018;78(2):163–201.
25. Perazella MA, Herlitz LC. The Crystalline Nephropathies. *Kidney Int Rep.* 2021;6(12):2942–2957.
26. Keltz E, Khan FY, Mann G. Rhabdomyolysis. The role of diagnostic and prognostic factors. *Muscles Ligaments Tendons J.* 2014;3(4):303–312.
27. Petejova N, Martinek A. Acute kidney injury due to rhabdomyolysis and renal replacement therapy: a critical review. *Crit Care.* 2014;18(3):224.
28. Deng Z, Wang S, Wu C. Rhabdomyolysis associated with newer-generation anti-seizure medications (ASMs): a real-world retrospective and pharmacovigilance study. *Front Pharmacol.* 2023; 4:1197470.
29. Melli G, Chaudhry V, Cornblath DR. Rhabdomyolysis: an evaluation of 475 hospitalized patients. *Medicine (Baltimore).* 2005;84(6):377–385.
30. Yang BF, Li D, Liu CL, Luo Y, Shi J, Guo XQ, et al. Advances in rhabdomyolysis: A review of pathogenesis, diagnosis, and treatment. *Chin J Traumatol.* 2026;29(1):21–31.
31. Mazzierli T, Allegretta F, Maffini E, Allinovi M. Drug-induced thrombotic microangiopathy: An updated review of causative drugs, pathophysiology, and management. *Front Pharmacol.* 2023;13:1088031.
32. Al-Nouri ZL, Reese JA, Terrell DR, Vesely SK, George JN. Drug-induced thrombotic microangiopathy: a systematic review of published reports. *Blood.* 2015;125(4):616–618.
33. Abou-Isma MY, Kapoor S, Citla Sridhar D, Nayak L, Ahuja S. Thrombotic microangiopathies: An illustrated review. *Res Pract Thromb Haemost.* 2022;6(3):e12708.
34. Lopez-Novoa JM, Quiros Y, Vicente L, Morales AI, Lopez-Hernandez FJ. New insights into the mechanism of aminoglycoside nephrotoxicity: an integrative point of view. *Kidney Int.* 2011; 79(1): 33–45.
35. Campbell RE, Chen CH, Edelstein CL. Overview of Antibiotic-Induced Nephrotoxicity. *Kidney Int Rep.* 2023;8(11):2211–2225.
36. Khwaja A. KDIGO clinical practice guidelines for acute kidney injury. *Nephron Clin Pract.* 2012;120(4):c179–184.
37. Chowdary PJ, Kumar AS, Kumari NH, Sowjanya KK, Sravya D, Divakar D. A comprehensive review on drug-induced (aminoglycosides) acute kidney injury: mechanism, risk factors, diagnosis, and therapeutic approaches. *World J. Adv. Pharm. Sci.* 2025;2(2):73–80.
38. Baker M, Perazella MA. NSAIDs in CKD: Are They Safe? *Am J Kidney Dis.* 2020;76(4):546–557.
39. Shlipak MG, Tummalaipalli SL, Boulware LE, Grams ME, Ix JH, Jha V, et al; Conference Participants. The case for early identification and intervention of chronic kidney disease: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. *Kidney Int.* 2021;99(1):34–47.
40. Lucas GNC, Leitão ACC, Alencar RL, Xavier RMF, Daher EF, Silva Junior GBD. Pathophysiological aspects of nephropathy caused by non-steroidal anti-inflammatory drugs. *J Bras Nefrol.* 2019; 41(1): 124–130.
41. Bhandari S, Mehta S, Khwaja A, Cleland JGF, Ives N, Brettell E, Chadburn M, Cockwell P; STOP ACEi Trial Investigators. Renin-Angiotensin System Inhibition in Advanced Chronic Kidney Disease. *N Engl J Med.* 2022;387(22):2021–2032.

42. Jones M., Tomson C. Acute kidney injury and 'nephrotoxins': Mind your language. *Clin. Med.* 2018;18:384–386.
43. Schoolwerth AC, Sica DA, Ballermann BJ, Wilcox CS; Council on the Kidney in Cardiovascular Disease and the Council for High Blood Pressure Research of the American Heart Association. Renal considerations in angiotensin converting enzyme inhibitor therapy: a statement for healthcare professionals from the Council on the Kidney in Cardiovascular Disease and the Council for High Blood Pressure Research of the American Heart Association. *Circulation.* 2001;104(16):1985-1991.
44. Adhiyaman V., Asghar M., Oke A., White A.D., Shah I.U. Nephrotoxicity in the elderly due to co-prescription of angiotensin converting enzyme inhibitors and nonsteroidal anti-inflammatory drugs. *J. R. Soc. Med.* 2001; 94: 512–514.
45. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2024 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. *Kidney Int.* 2024; 105(4S): S117-S314
46. Ahmadiazar F, Rahmanian M, Jalali Z, Joseph A, Foroutan M. Possible nephrotoxic effects of high dose statin therapy; current knowledge. *Nephropharmacol.* 2023; 12(1): e10574.
47. Verdoodt A, Honore PM, Jacobs R, De Waele E, Van Gorp V, De Regt J, Spapen HD. Do Statins Induce or Protect from Acute Kidney Injury and Chronic Kidney Disease: An Update Review in 2018. *J Transl Int Med.* 2018; 6(1): 21-25.
48. Dormuth CR, Hemmelgarn BR, Paterson JM, James MT, Teare GF, Raymond CB, et al.; Canadian Network for Observational Drug Effect Studies. Use of high potency statins and rates of admission for acute kidney injury: multicenter, retrospective observational analysis of administrative databases. *BMJ.* 2013; 346: f880.
49. Annigeri RA, Mani RM. Acute interstitial nephritis due to statin and its class effect. *Indian J Nephrol.* 2015; 25(1): 54-56.
50. Parmar MP, Kaleem S, Samuganathan P, Ishfaq L, Anne T, Patel Y, et al. Impact of Proton Pump Inhibitors on Kidney Function and Chronic Kidney Disease Progression: A Systematic Review. *Cureus.* 2023; 15(12): e49883.
51. Al-Aly Z, Maddukuri G, Xie Y. Proton Pump Inhibitors and the Kidney: Implications of Current Evidence for Clinical Practice and When and How to Deprescribe. *Am J Kidney Dis.* 2020; 75(4): 497-507.
52. Morschel CF, Mafra D, Eduardo JCC. The relationship between proton pump inhibitors and renal disease. *J Bras Nefrol.* 2018; 40(3): 301-306.