Drug induced nephrotoxicity on Nephron Damage and Protection

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ABSTRACT: -

Drug-induced nephrotoxicity (DIN) is a leading cause of acute kidney injury (AKI) and contributes significantly to chronic kidney disease (CKD), particularly in hospitalized, critically ill, immunocompromised, polypharmacy, and elderly patients. The kidneys are uniquely vulnerable to xenobiotic exposure due to their high blood supply, active tubular transport mechanisms, and concentration ability. DIN may present with various clinical patterns including acute tubular necrosis, interstitial nephritis, glomerular injury, papillary necrosis, and obstructive crystal nephropathy. This systematic review aims to summarize epidemiology, risk factors, pathophysiology, clinical manifestations, diagnostic modalities, classification of nephrotoxic drugs, and evidence-based prevention strategies. Analysis revealed that major nephrotoxic drug categories include antimicrobials, chemotherapeutic agents, radiocontrast media, immunosuppressants, NSAIDs, and antiviral drugs. Key pathophysiological changes occur through oxidative stress, mitochondrial damage, hemodynamic alterations, inflammation, and tubular toxicity. Preventive strategies focus on dose adjustment, hydration, therapeutic drug monitoring, and early biomarker-based detection. Drug-induced nephrotoxicity remains a preventable global concern and requires multidisciplinary collaboration, pharmacovigilance, and rational prescribing.

Keywords: nephrotoxicity, renal injury, drug safety, acute kidney injury, biomarkers, renal pharmacology, toxicity prevention

1.INTRODUCTION: -

Drugs are widely used in modern medical practice for disease treatment, prevention, symptom control, and life-saving interventions. However, certain medications may adversely affect renal function either directly through nephrotoxic chemical actions or indirectly through pharmacodynamic and hemodynamic alterations. Drug-induced nephrotoxicity is defined as renal dysfunction that develops as a result of drug exposure and can manifest as structural or functional impairment. It contributes to increased morbidity, prolonged hospitalization, dialysis dependency, and worsened patient prognosis in both developed and developing nations.

The kidneys regulate homeostasis by filtering blood, removing waste products, maintaining electrolyte balance, controlling blood pressure, and contributing to endocrine functions such as erythropoietin and vitamin D activation.

Approximately 20–25% of cardiac output perfuses the kidneys, exposing renal tissues to high concentrations of drugs and metabolites. This, along with transporter-rich tubular cells and metabolic activities, makes the kidneys especially susceptible to toxicity.

Despite advances in clinical pharmacology, DIN remains underdiagnosed, primarily due to delayed biomarkers and difficulty recognizing early sub-clinical damage. An improved understanding of mechanisms, early diagnosis, and prevention strategies is crucial for reducing the clinical burden.

2.Background and Importance: -

Drug toxicity accounts for up to 20–60% of AKI cases in hospitalized patients and is among the top contributors to ICU morbidity. The severity ranges from mild, reversible renal impairment to irreversible end-stage renal disease (ESRD). DIN has gained clinical relevance due to:

1. Increased use of high-dose therapies
2. Longer survival of patients with chronic conditions
3. Polypharmacy in elderly populations
4. Self-prescription and OTC drug misuse

3. Renal Physiology and Susceptibility: -

The kidneys are highly vascular organs with complex filtration and tubular reabsorption systems. Major factors leading to renal vulnerability include:

1. High blood flow: Exposes renal tissues to concentrated toxins

2. Concentration gradient: Increases accumulation of drugs in nephron segments

3. Transporter-rich epithelial cells: OCT, OAT, P-gp, and megalin receptors facilitate entry of nephrotoxins

4. Enzymatic metabolism: Generates reactive metabolites

The proximal tubule is the most commonly affected site due to active reabsorption, metabolism, and transporter activity.

4.Research suggests varying incidence patterns depending on patient groups:

Populations	Estimated Occurance
General Hospitals adults	14-26%
ICU Patients	30-60%
Cancer/ Chemotherapy patients	Up to 50%
Polypharmacy elderly	>70%

Post-contrast imaging patients	2-25%
Transplant patients on immunosuppressants	Common

Transplant patients on immunosuppressants commonly on Male gender, dehydration, and comorbidities increase the risk.

5. Synopsis of current theories on Drug- induced Nephrotoxicity:

Drug-induced nephrotoxicity is a major complication of modern pharmacotherapy. Although medications are essential for treating diseases, many of them can unintentionally damage the kidneys—the main organs responsible for eliminating drugs and xenobiotics. Because the renal cortex receives a very large fraction of cardiac output and contains active metabolic and transport systems, the kidneys are particularly susceptible to toxic injury[3,4]. Despite its importance, there is still no universally accepted definition of drug-induced kidney damage, making diagnosis and classification challenging [1].

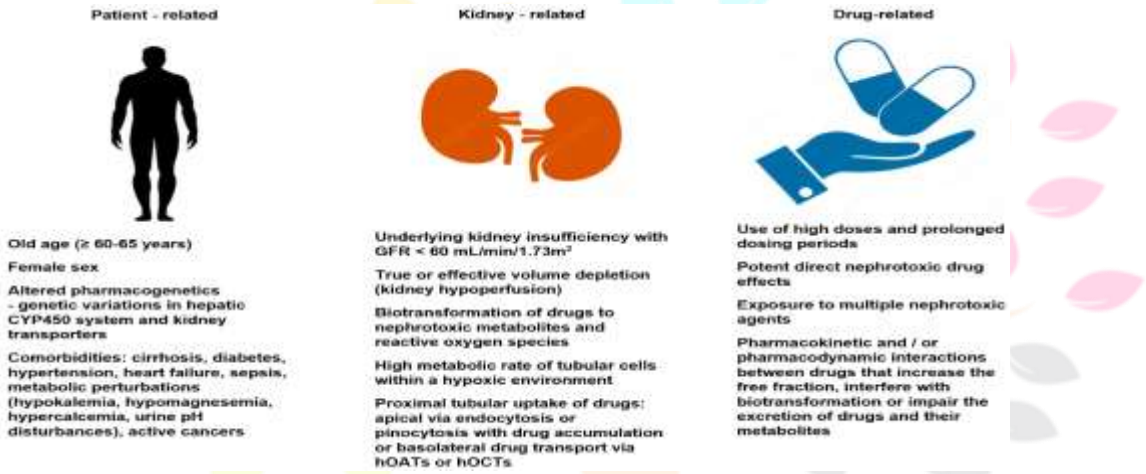
Kidney-related adverse effects occur in many clinical settings, especially among older adults, hospitalized patients, individuals with chronic illnesses, and those exposed to polypharmacy [2]. The injury caused by drugs may range from mild, reversible dysfunction to severe structural damage leading to acute kidney injury (AKI) or chronic kidney disease (CKD). Diagnosis is often difficult because symptoms may appear late or be masked by underlying illnesses. To assist clinicians, a framework known as the "6 Rs" was proposed—risk assessment, recognition, response, renal support, rehabilitation, and research—emphasizing preventive strategies, early identification, and post-treatment monitoring.

Drug-induced nephrotoxicity manifests through several clinical phenotypes: acute kidney injury, glomerular disorders, tubular dysfunction, and nephrolithiasis[8,9]. Each type has characteristic clinical and laboratory features, such as proteinuria, hematuria, metabolic disturbances, or crystal formation. The causes are diverse and often related to either direct cellular toxicity, immune-mediated reactions, hemodynamic alterations, or intratubular crystal deposition. Some widely used drug classes—including nonsteroidal anti-inflammatory drugs (NSAIDs), aminoglycosides, calcineurin inhibitors, radiographic contrast media, and certain antivirals and antineoplastics—are well-known contributors to renal injury[5,6,7].

Several mechanisms underlie these toxic effects. Drugs may provoke inflammatory or allergic reactions in the glomeruli or interstitium, reduce renal blood flow by altering prostaglandin or angiotensin II pathways, directly damage proximal tubular cells, or form crystals that obstruct urine flow. In certain cases, medications trigger rhabdomyolysis or thrombotic microangiopathy, both of which can severely compromise renal function. Oxidative stress, mitochondrial injury, DNA damage, and cytokine-mediated inflammation (particularly involving TNF-α and TGF-β) are common molecular events linking many nephrotoxic agents.

Preventing drug-induced kidney damage relies heavily on identifying high-risk patients, minimizing exposure to nephrotoxic drugs, adjusting doses according to kidney function, and ensuring adequate hydration. Although blood urea nitrogen and serum creatinine remain widely used tests, they are imperfect indicators. Newer biomarkers—including KIM-1, NGAL, cystatin C, and others—offer earlier detection of tubular injury and are increasingly integrated into research and clinical assessment.

Overall, drug-induced nephrotoxicity remains a significant but largely preventable complication. Improved awareness of risk factors, better monitoring strategies, and the development of safer therapeutic alternatives are essential for reducing kidney-related adverse drug reactions. Continued research is needed to clarify underlying mechanisms, refine diagnostic criteria, and enhance patient safety in pharmacological therapy.



6. Drug induced nephrotoxicity: A Mechanistic Approach

Drug-induced nephrotoxicity remains a major clinical challenge because the kidneys are exposed to high concentrations of drugs and their metabolites. Many commonly used medications can harm renal tissue through various mechanisms, often leading to conditions such as acute kidney injury (AKI), chronic kidney disease (CKD), acute tubular necrosis (ATN), or end-stage renal disease[10]. Since the kidneys receive about one-fourth of cardiac output and play a central role in filtration, reabsorption, and secretion, they are particularly vulnerable to toxic injury.

6.1. Hemodynamically medicated kidney injury:

Nephrotoxicity develops through several pathways, including hemodynamic changes, direct tubular cell damage, immune-mediated reactions, and crystal deposition[11]. Drugs may cause apoptosis, necrosis, or autophagy-dependent cell death. Hemodynamic injury typically results from impaired renal blood flow due to changes in prostaglandins, angiotensin II, or nitric oxide[12]. Medications such as ACE inhibitors, ARBs, NSAIDs, and calcineurin inhibitors can disturb vascular tone and reduce glomerular filtration.

A wide range of drugs are associated with structural or functional renal damage. Aminoglycosides, radiographic contrast media, cisplatin, amphotericin B, and other agents can cause acute tubular necrosis by accumulating in

tubular cells, generating reactive oxygen species, and impairing cellular metabolism. Osmotically active drugs like mannitol or sucrose-containing IV solutions may trigger osmotic nephrosis, leading to tubular swelling and vacuolization.

Immune-mediated injury, particularly acute interstitial nephritis (AIN), occurs with β-lactam antibiotics, NSAIDs, diuretics, and gastrointestinal medications. Chronic interstitial nephritis may arise from long-term use of drugs such as lithium or cyclosporine[14]. Other forms of drug-related kidney injury include nephrocalcinosis from oral sodium phosphate preparations, papillary necrosis linked to excessive analgesic use, and drug-induced glomerular diseases such as minimal change disease or focal segmental glomerulosclerosis. Certain medications can also provoke vasculitis or thrombotic microangiopathy, leading to severe renal impairment.[12,13]

In summary, numerous therapeutic agents have the potential to damage the kidneys through diverse molecular and physiological mechanisms. Understanding these pathways is essential for preventing toxicity, identifying high-risk patients, adjusting drug dosages appropriately, and promoting safer pharmacological therapy.

7.Drug induced Kidney disease: Epidemiology, Pathophysiology and Management:

Drug-induced kidney disease (DIKD) is a major contributor to acute kidney injury (AKI), especially among hospitalized patients, the elderly, and those receiving multiple medications. Over recent decades, the incidence of AKI has increased, and drugs now account for an estimated 8–60% of cases depending on patient population. Because the kidneys handle filtration, concentration, and excretion of drugs, they are highly vulnerable to toxic injury.

7.1.Epidemiology:

The true incidence of DIKD is difficult to measure due to varying definitions of AKI and under recognition of drug-related kidney damage. Studies in adults show that 14–26% of AKI episodes are drug-induced, while around 16% of pediatric AKI cases are linked to medications. Antibiotics such as aminoglycosides, chemotherapeutic agents, contrast dyes, and antiviral drugs remain significant contributors. Newer agents, including certain chemotherapeutics and antivirals like tenofovir, are increasingly associated with tubular dysfunction and glomerular injury.

7.2.Mechanisms of Injury:

DIKD develops through multiple pathogenic pathways:

Altered intraglomerular hemodynamics: NSAIDs, ACE inhibitors, ARBs, and calcineurin inhibitors disturb autoregulation, reducing glomerular filtration.

Tubular cell toxicity: Drugs such as aminoglycosides, cisplatin, amphotericin B, and vancomycin accumulate in renal tubular cells, causing apoptosis and necrosis.

Immune-mediated inflammation (AIN): Many drugs—including antibiotics, NSAIDs, PPIs, and diuretics—trigger hypersensitivity reactions leading to interstitial nephritis.

Glomerular injury: Agents like NSAIDs, lithium, and pamidronate may cause proteinuria and glomerular diseases.

Crystal nephropathy: Drugs such as acyclovir, methotrexate, indinavir, and sulfonamides can precipitate in tubules and obstruct urine flow.

Rhabdomyolysis: Statins, some illicit drugs, and toxins release myoglobin, a nephrotoxic protein.

Thrombotic microangiopathy: Chemotherapeutic and anti-VEGF agents may induce endothelial injury.

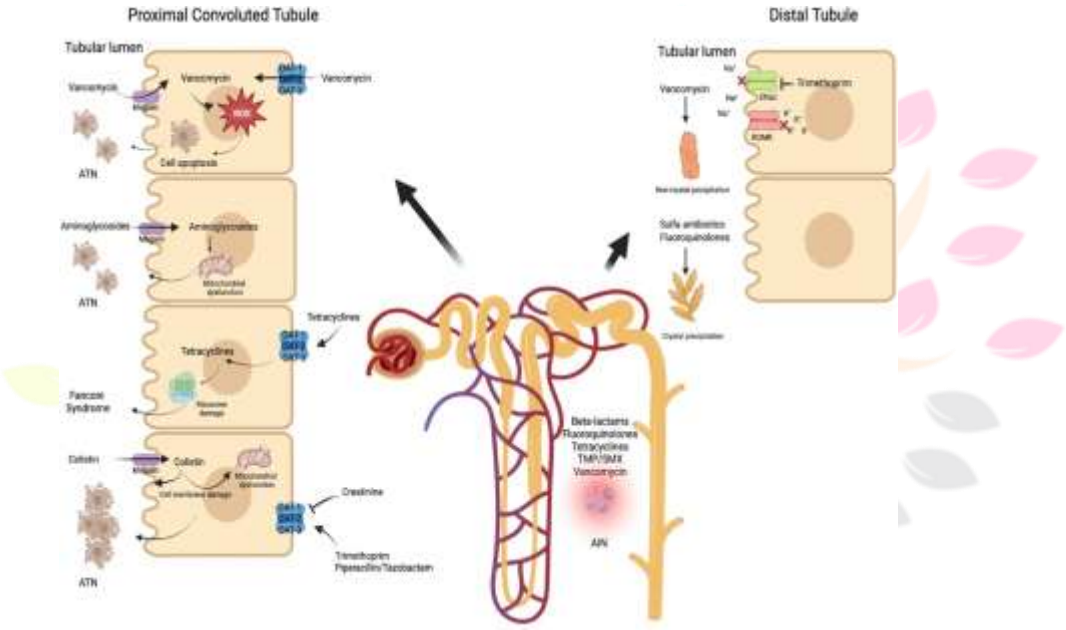


Fig no.2: Risk factors for drug indueced kidney disease development .

7.3. Diagnosis :

Diagnosis is based on rising serum creatinine, reduced urine output, and recent exposure to nephrotoxic drugs, using criteria such as RIFLE, AKIN, and KDIGO. Urine sediment examination aids differentiation: muddy brown casts suggest ATN, WBC casts indicate AIN, and RBC dysmorphism points to glomerular disease. Kidney biopsy is considered when diagnosis is uncertain[16].

7.4.Management and Prevention:

Prevention is the most effective strategy. Key measures include:

- Evaluating baseline kidney function and adjusting drug doses to GFR.
- Avoiding unnecessary nephrotoxic medications.
- Ensuring adequate hydration and stable hemodynamics.
- Monitoring renal parameters closely, especially after initiating high-risk drugs.

- Discontinuing offending agents promptly when renal impairment is detected.
- Supportive care remains the cornerstone of management, and most cases reverse if recognized early. In AIN, corticosteroids may be helpful. Drug-specific strategies—like
- hydration for contrast media and monitoring trough levels for aminoglycosides and vancomycin—reduce risk.

8. Drug induced Kidney Disease: Epidemiology, Pathophysiology and Management :

The kidney is a vital organ responsible for the excretion of metabolic waste and xenobiotics. Dueto its high perfusion rate and active transport processes, it is particularly vulnerable to drug-induced damage. Drug-induced nephrotoxicity contributes to 8–60% of AKI cases, with both community-acquired and hospital-acquired forms recognized. Studies show that 14–26% of AKI cases in adults are linked to drugs, while in pediatric populations, the figure is approximately 16%. Antibiotics, chemotherapeutics, antivirals, and contrast media are major causative agents.

8.1.Epidemiology :

8.2. Epidemiology

The lack of a standardized definition of AKI complicates the accurate estimation of DIKD prevalence. Drug-related nephrotoxicity often goes undiagnosed, especially during short-term exposures. Aminoglycosides, commonly used against Gram-negative bacteria, induce nephrotoxicity in 10–20% of treated patients. Similarly, antivirals such as tenofovir have been associated with tubular injuries in 12–22% of cases[18].

8.3. Pathophysiology of Drug-Induced Kidney Disease

DIKD mechanisms are multifactorial, with most nephrotoxic drugs acting through one or more ofthe following processes:

❖ Altered Intraglomerular Hemodynamics

Drugs that interfere with renal autoregulation—such as NSAIDs, ACE inhibitors, ARBs, and calcineurin inhibitors—can cause vasoconstriction or vasodilation, leading to hemodynamic AKI. NSAIDs inhibit prostaglandin-mediated afferent arteriolar dilation, while ACE inhibitors and ARBs decrease efferent resistance, particularly under hypovolemic conditions.

❖ Tubular Cell Toxicity

Proximal tubular cells, which concentrate drugs and metabolites, are especially susceptible to injury. Aminoglycosides, cisplatin, amphotericin B, and vancomycin cause direct tubular necrosis via oxidative stress and apotosis. Vancomycin, particularly when combined with piperacillin-tazobactum, is linked to cast nephropathy[17].

❖ Interstitial Nephritis

Acute interstitial nephritis (AIN) is an immune-mediated reaction triggered by antibiotics (β-lactams, quinolones), PPIs, NSAIDs, or diuretics. Chronic interstitial nephritis, although less frequent, may result from prolonged exposure to calcineurin inhibitors or analgesics.

❖ Rhabdomyolysis

Statins and illicit drugs such as cocaine and heroin can induce rhabdomyolysis, releasing myoglobin and creatine kinase, which cause tubular obstruction and renal ischemia.

❖ Thrombotic Microangiopathy

Chemotherapeutic agents like gemcitabine and VEGF inhibitors lead to endothelial injury, resulting in microangiopathy, hypertension, and proteinuria.

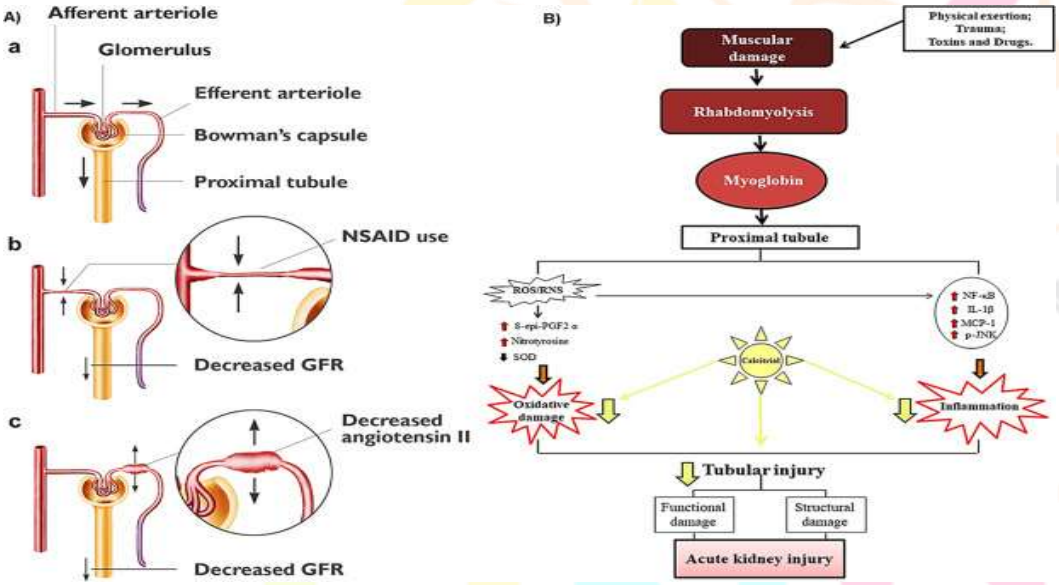


Fig NO. 3: Pathophysiology of drug induced kidney disease

9.Detection, monitoring and monitoring of drug-Induced Nephrotoxicity:

Drug-induced nephrotoxicity (DIN) remains a significant concern in clinical pharmacology and drug development due to the kidneys' critical role in drug metabolism and excretion.

9.1Pathophysiology of Drug-Induced Nephrotoxicity:

DIN manifests as acute kidney injury (AKI) or chronic kidney disease (CKD). The KDIGO criteria (2012) unified previous systems (RIFLE and AKIN) for diagnosing AKI, emphasizing changes in serum creatinine and urine output

as diagnostic markers. However, traditional biomarkers such as serum creatinine and blood urea nitrogen have limitations due to delayed response and low sensitivity. Newer biomarkers, including cystatin C and urinary proteins, offer earlier detection of nephrotoxicity[18].

9.2Risk Factors and Mechanisms:

Risk factors for DIN include advanced age, pre-existing renal impairment, genetic susceptibility, and concurrent use of other nephrotoxic agents. Mechanistically, nephrotoxicity can arise from ischemia, immune-mediated injury, or direct cellular toxicity. Drugs can alter glomerular hemodynamics, disrupt tubular transport, or induce oxidative stress and inflammation.

9.3Biomarkers and Monitoring:

The review highlights the evolution of biomarkers for early kidney injury detection. While serum creatinine remains the standard, its delayed rise limits early diagnosis. Biomarkers such as cystatin C, kidney injury molecule-1 (KIM-1), neutrophil gelatinase-associated lipocalin (NGAL), and β2-microglobulin are more sensitive for early tubular damage detection. Imaging modalities like ultrasound, CT, and MRI complement laboratory testing in diagnosis.

9.4Prevention and Mitigation Strategies:

Preventing DIN involves careful patient selection, dose adjustment, and drug monitoring. Strategies include:

✓ Ensuring adequate hydration before administering nephrotoxic drugs.

✓ Avoiding simultaneous use of multiple nephrotoxic agents.

✓ Employing therapeutic drug monitoring for agents with narrow therapeutic windows.

✓ Using nephroprotective agents (e.g., amifostine for cisplatin-induced toxicity). Clinical trial designs should incorporate renal safety endpoints and monitoring schedules for early detection of DIN.

9.5Special Populations:

Special consideration is needed for children, cancer patients, and the elderly, who have variable renal reserve capacities and altered pharmacokinetics. In pediatric trials, age-adjusted eGFR equations such as the Schwartz formula are recommended. For oncology patients, balancing nephrotoxicity risks against therapeutic benefits is crucial.

10.Nephrotoxicity in Cancer treatment:

Santos et al. (2020) provide a comprehensive overview of anticancer drug-induced nephrotoxicity, highlighting the kidney's vulnerability as a major organ involved in drug elimination. The authors discuss how both traditional cytotoxic agents and molecularly targeted therapies can cause renal injury by affecting different nephron segments

and microvasculature. They emphasize that nephrotoxicity is a growing concern in oncology, as it limits treatment efficacy and contributes to morbidity and mortality.

10.2.Mechanisms and Risk Factors:

The kidneys eliminate most chemotherapeutic agents through glomerular filtration and tubular secretion, making them particularly susceptible to toxic insults. Nephrotoxicity may manifest as acute kidney injury (AKI), glomerulopathy, interstitial nephritis, electrolyte imbalance, and chronic kidney disease (CKD) (Santos et al., 2020). Risk factors include intravascular volume depletion, concomitant use of nephrotoxic drugs (e.g., NSAIDs, antibiotics, proton pump inhibitors), contrast media, radiation therapy, and pre-existing renal disease [19]

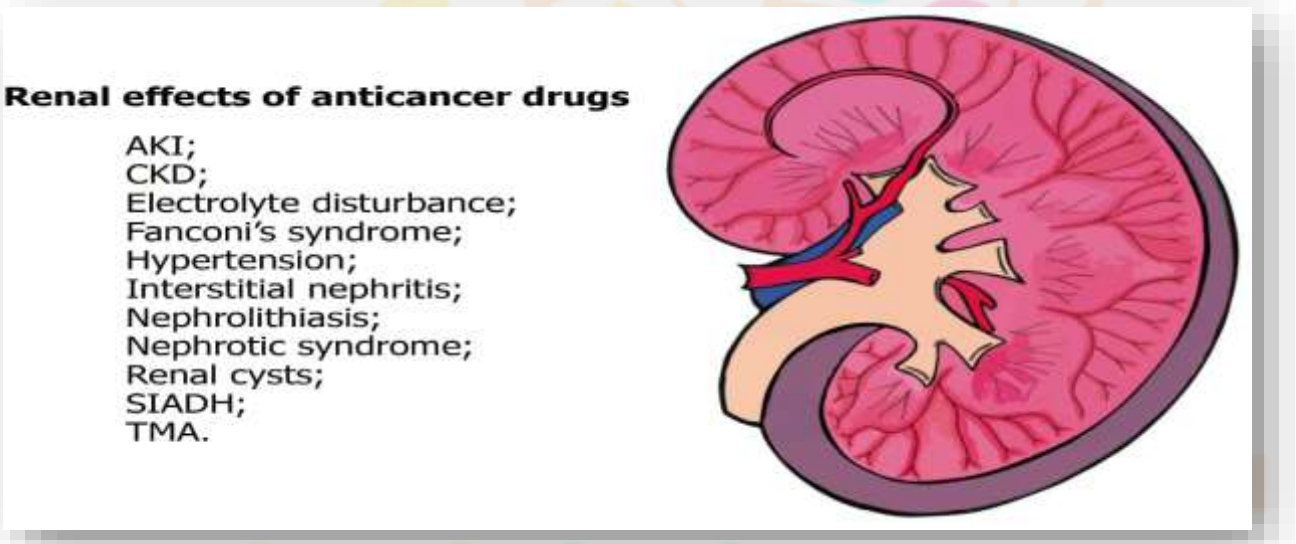


Fig no.4: Renal effect on anticancer drugs

10.3Conventional Cytotoxic Agents:

The review systematically categorizes nephrotoxic effects of major anticancer drugs: Alkylating agents (e.g., cyclophosphamide, ifosfamide, melphalan) cause tubular and interstitial injury through oxidative stress and toxic metabolites. Ifosfamide is particularly nephrotoxic, causing Fanconi syndrome and renal insufficiency (Santos et al., 2020).

Antimetabolites such as methotrexate and pemetrexed induce tubular injury via crystal precipitation and decreased glomerular filtration rate (GFR). Gemcitabine may cause hemolytic uremic syndrome and thrombotic microangiopathy (TMA).

Platinum compounds like cisplatin are among the most nephrotoxic agents, causing dose-dependent AKI, hypomagnesemia, and proximal tubular dysfunction. Preventive strategies such as hydration and dose adjustment are recommended (Santos et al., 2020).

Antitumor antibiotics (e.g., doxorubicin, mitomycin) induce nephrotic syndrome and glomerular sclerosis, often leading to chronic renal damage.

10.4Molecularly Targeted Agents:

The authors also review the newer generation of targeted therapies, noting that these agents, while more specific, are not devoid of nephrotoxic effects.

Epidermal Growth Factor Receptor (EGFR) inhibitors like gefitinib and cetuximab are linked to electrolyte disturbances (e.g., hypomagnesemia, hypokalemia) and proteinuria.

HER2 inhibitors (e.g., trastuzumab, pertuzumab) can cause AKI, proteinuria, and hypertension.

VEGF pathway inhibitors (e.g., bevacizumab, sunitinib) are associated with hypertension, nephrotic syndrome, and TMA, resulting from endothelial dysfunction (Santos et al., 2020).

Immune checkpoint inhibitors (e.g., nivolumab, pembrolizumab, ipilimumab) occasionally cause acute interstitial nephritis and immune-mediated glomerulonephritis, reflecting autoimmune mechanisms.

Proteasome inhibitors such as bortezomib and carfilzomib may cause acute interstitial nephritis and TMA, particularly in multiple myeloma patients.

These findings emphasize the complex interplay between drug action and renal physiology and the need for individualized therapeutic approaches.

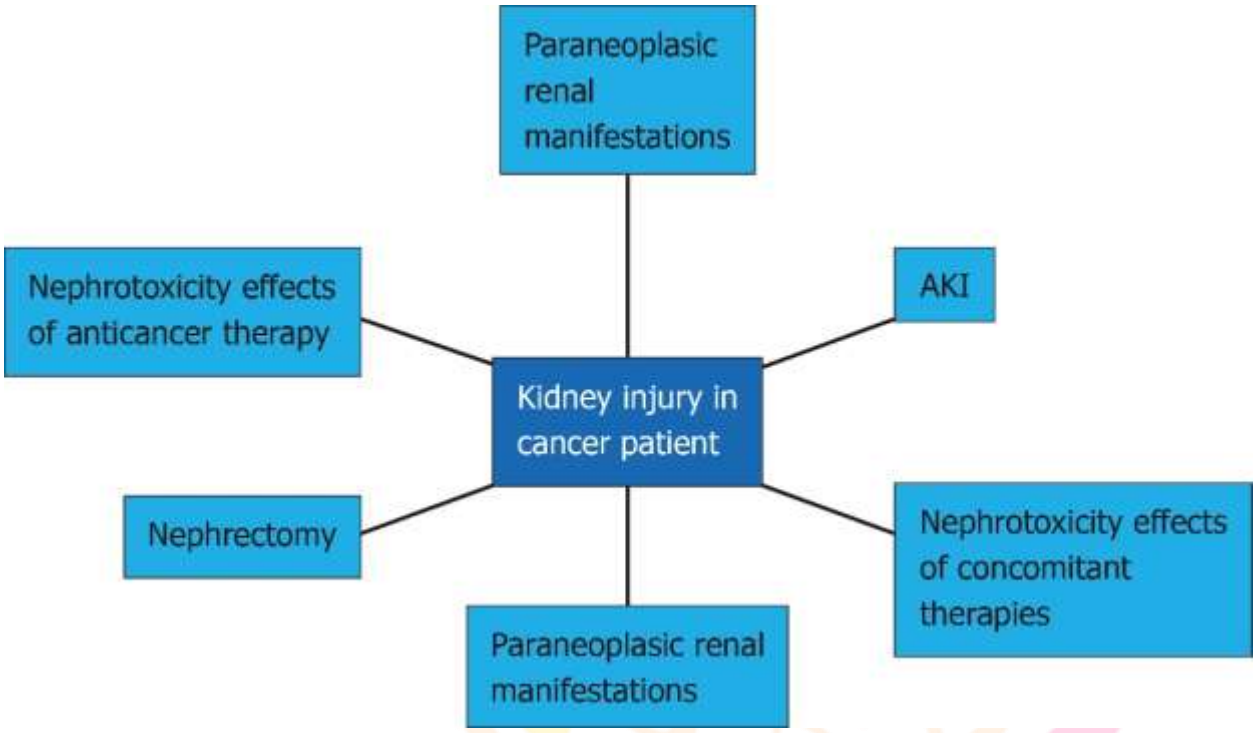


Fig No. 5: kidney injury in cancer Treatment

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