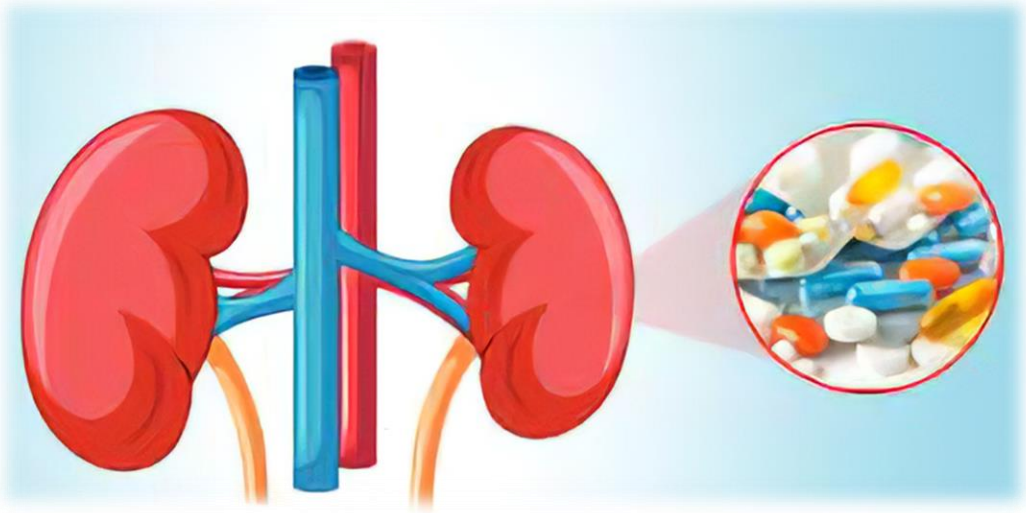

Nephrotoxic Drugs

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2025-2026

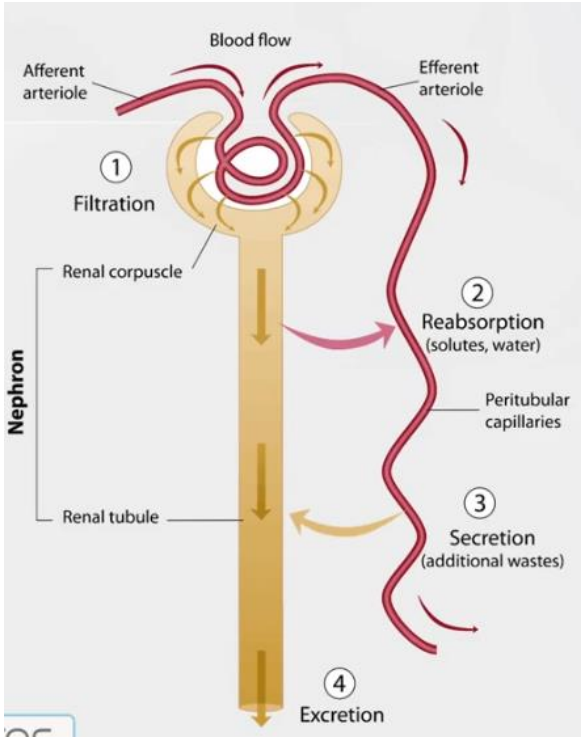
ILOS

- Outline the pharmacology of most drugs implicated in nephrotoxicity.

Outline

1- Nephrotoxicity
2- Mechanisms of drug-induced nephrotoxicity
3- Assessment of renal function
4- drugs

1-Nephrotoxicity



Drug-induced Nephrotoxicity

- Damage to the kidneys from:
  - Decreased blood flow (pre-renal)
  - Direct nephron injury (intrinsic)
  - Obstruction (post-renal)

Nephrotoxicity is an adverse **functional and/or structural change** in the kidney.

- caused **directly or indirectly** by **chemicals**, biological **drugs**, or **metabolites** of these products when systemically absorbed.

the kidneys are **vulnerable to toxic injury** more than any other organ in the body because of:

1- **High blood flow**, the kidneys constitute only 0.4% of the total body weight, yet they receive **20-25%** of the cardiac output.

2- **Large endothelial surface** area more than any other organ.

3- **Metabolic activity** e.g. transformation of paracetamol into highly reactive metabolites.

4- Unique concentrating ability that **exposes** the tubular lumen to **high chemical concentrations.**

Risk Factors

❑ Patient related factors:

- Age
- sex
- race
- Pre-existent renal disease
- Specific disease (DM)
- Dehydration

❑ Drug-related factors :

- Inherent
- Dose
- Duration
- frequency of administration

❑ Drug interactions

Clinical Presentation

General

- Most common manifestation is a decline in glomerular filtration leading to a rise in serum creatinine and blood urea nitrogen.

Symptom

- Malaise, anorexia, vomiting, shortness of breath or edema.

Signs

- Decreased urine output

Mechanism

1-Change in glomerular hemodynamics

2-Tubular Cell Toxicity

3-Crystal Nephropathy

4-Diabetes Insipidus

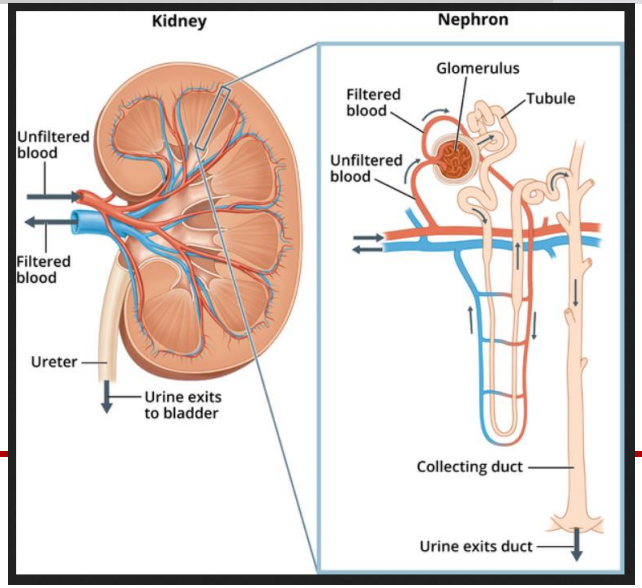
5-Others

1-Change in glomerular hemodynamics

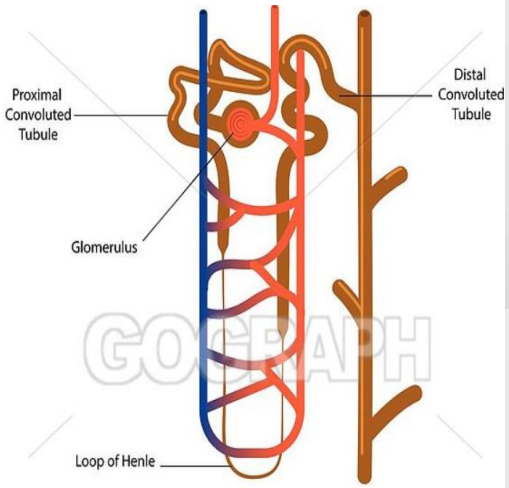
- Kidneys can keep a constant **GFR (120 ml/min)** by regulation of blood flow in **afferent and efferent** arteries through renal **Prostaglandins (PGs) and angiotensin II(AGII)**.

- **Anti-prostaglandin drugs** (as non steroidal anti-inflammatory drugs NSAIDs)

drugs having anti-angiotensin activity (as Angiotensin converting enzyme inhibitors ACEIS and angiotensin receptor blockers ARBS) induce nephrotoxicity by **decreasing GFR**.



2-Tubular Cell Toxicity



Cytotoxicity occurs due to **mitochondrial damage** of renal tubular cells, disturbed tubular transport system and ↑ oxidative stress by **free radical generation**.

EX:

- **A**minoglycosides, **a**mphotericin B, **a**nticancer drugs as cisplatin.

- Heavy metals e.g. mercury, **gold, iron** and lead.

- Radiocontrast media.

- Glomerulonephritis: e.g. **gold** salts and penicillamine

- Acute interstitial nephritis: e.g. NSAIDs and rifampicin.

- Chronic interstitial nephritis: e.g. long-term use of **cyclosporin**, lithium.

Early diagnosis is essential to preserve kidney function

3-Crystal Nephropathy

- Formation of **insoluble crystals** in human urine. It depends on **acidity** of urine and solute **concentration.**

EX: fonamides, cytotoxic and uricosuric drugs

4-Diabetes Insipidus

e.g. **Lithium**, demeclocycline decrease the adenyl cyclase response to ADH.

5-Others

e.g. **Calciferol** (Vit. D) →→ Renal calcifications in

hypervitaminosis D.

Assessment of renal function

Creatinine clearance (Cr. CL) (**75-125** ml/min).

1- It represents the **GFR**

2- it is **better than estimating serum creatinine** (Sr. Cr) (0.6-1.2 mg/dl).

3- Sr. Cr. does not reflect **acute changes** in renal function and may increase in face of improved GFR.

Urine analysis:

1- **albumin** in urine suggests defect in the glomeruli

2- **RBC cast** suggests glomerular lesion,

3- while **WBC casts** suggest tubular or **interstitial damage**.

3- Tubular function:

PCT: if it is damaged by e.g. heavy metals, salicylates or sugar and amino acids will appear in urine although normal serum levels. aminoglycosides,

DCT: damaged by drug like amphotricin B leading to inability to acidify urine to pH 5.5 or less after 0.1 g/kg of ammonium chloride.

Drugs-induced Nephrotoxicity

- Antibiotics (Aminoglycoside . Vancomycin)
- Antifungal (Amphotericin B)
- Antidepressants (Amitriptyline . fluoxetine).
- Antiviral (Acyclovir)
- Antihypertensive (ACE inhibitor. ARBs. Diuretics)
- NSAIDs/ COX2 inhibitor
- Cocaine, Heroin & Ketamine
- Statins
- Antihistamines: (Diphenhydramine)

Drug	Mechanism	Disease
NSAIDs	-↓ renal perfusion - Direct toxicity. - Immune reactions.	-Renal papillary necrosis -Acute kidney injury(AKI) Chronic renal disease(CRD) -Interstitial nephritis
Captopril	-↓ renal perfusion -Immune reaction	-Nephrotic syndrome -Glomerulonephritis -Acute tubular necrosis (ATN) & (AKI). - Interstitial nephritis
Radio-contrast media	- Direct tubular toxicity - tubular obstruction	-Renal ischemia -renal failure with risk factors
Aminoglycosides	-Direct tubular toxicity	-Non-oliguric AKI

Cyclosporin	-Direct toxicity	-Interstitial nephritis
Cisplatin	-Direct toxicity	-ATN
Cyclophosphamide	-Direct toxicity	-Hemorrhagic cystitis ATN & AKI
Rifampicin	-Hypersensitivity reaction primarily with irregular therapy	-Interstitial nephritis & AKI
Cimetidine	-Delayed reversible hypersensitivity	-Interstitial nephritis
Lithium	-B-locks activation of adenyl cyclase in response to ADH	-Nephrogenic diabetes Insipidus (DI)

Measures to prevent drugs-induced Nephrotoxicity

- Adjust medication dosages
- Avoid nephrotoxic combination.
- Correct risk factors for nephrotoxicity before initiation of drug therapy.
- Ensure adequate hydration before and during therapy.
- Use equally effective non-nephrotoxic drugs whenever possible.


thank you