بسم الله الرحمن الرحيم

Drugs and the kidney

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Impact of Kidney diseases on the pharmacological properties of Drugs

- Kidney disease/impairment can cause alteration in the disposition (**pharmacokinetics**) of renally excreted drugs and might increase the toxicity (if the **active drug or metabolites** are renally cleared).

- Doses of renally excreted drug usually should be reduced in renal disease in proportion to the predicted reduction in clearance of the active drug moiety.
- Both patient and drug factors should be considered:

1- Patient factor: the degree of renal impairment and patient size.
2- Drug factors: the **fraction of the drug excreted unchanged in urine** and the drug's **therapeutic index.**

Dose adjustment & therapeutic index (TI)

- For drugs with narrow therapeutic indices (**Aminoglycosides, warfarin, lithium, digoxin, vancomycin, cyclosporine & Phenytoin**), even minimal increase in drug concentration in the plasma (caused by decreased renal clearance) can cause serious toxicity.

- These drugs should be dosed using either robust parameters (e.g. clinical **response**, **INR for warfarin**, **therapeutic drug monitoring (TDM)** , etc.) OR by empirical calculations of doses (however, most calculations are not reliable enough to be safe).

✓ Conversely, drugs with wide therapeutic index (e.g., **Penicillins**), even large changes in drug clearance may have only a modest impact , and therefore dose adjustments are not critical like drugs with narrow TI.

- For drugs with intermediate therapeutic index: an estimate of renal function as an estimate of drug clearance provides useful guidance to dosing and can be used together with clinical and biochemical measures of effects (e.g. **serum uric** acid for the anti-gout drug allopurinol).

Dose adjustment according to renal functions

- For chronic kidney disease, measurements of renal function are used to predict renal disease outcome.

- For drug dosing estimation of renal function are used to estimate the renal clearance of the drug which is used for further calculation of doses.

For dose adjustment:

1- Calculate the drug clearance based on renal functions.

2- Consider oral bioavailability for oral drugs

Both CL and F determine steady state conc.

$$\text{Dose} = \text{Desired plasma conc.} \times \frac{Clearance}{Bioavilability}$$

- Thus, if a drug is 100% renally cleared and renal function is half-normal, the drug dose should be halved, all other things being equal.
- However, many drugs are inactivated by metabolism (in the liver predominantly), and hence doses of metabolized drugs do not usually require changing in renal disease.

Drug-induced nephrotoxicity

❑Drug-induced nephrotoxicity is the presence of any kidney injury (acute or chronic) caused **directly** or **indirectly** by medication.

❑ Drugs can cause acute renal injury, intrarenal obstruction, interstitial nephritis, nephrotic syndrome, acid-base and fluid electrolytes disorders.

Drug induced acute kidney injury (AKI)

1- **Pre-renal AKI**

2-**Intra-renal or renal AKI**:

- ❑Drugs causing **Acute Tubular Necrosis** or **injury**
- ❑Drugs causing **Acute Interstitial Nephritis**
- ❑Drugs causing **Glomerulonephritis**

3- **Post-renal AKI**

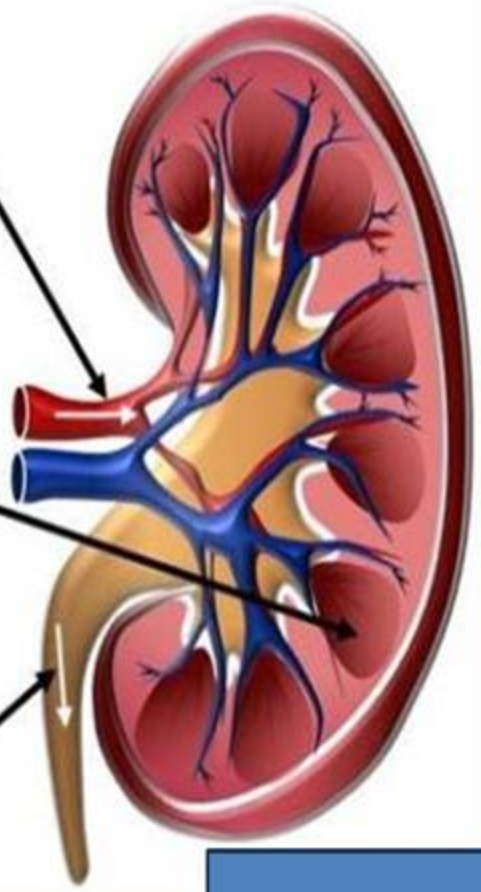
Acute kidney injury (AKI) induced by drugs

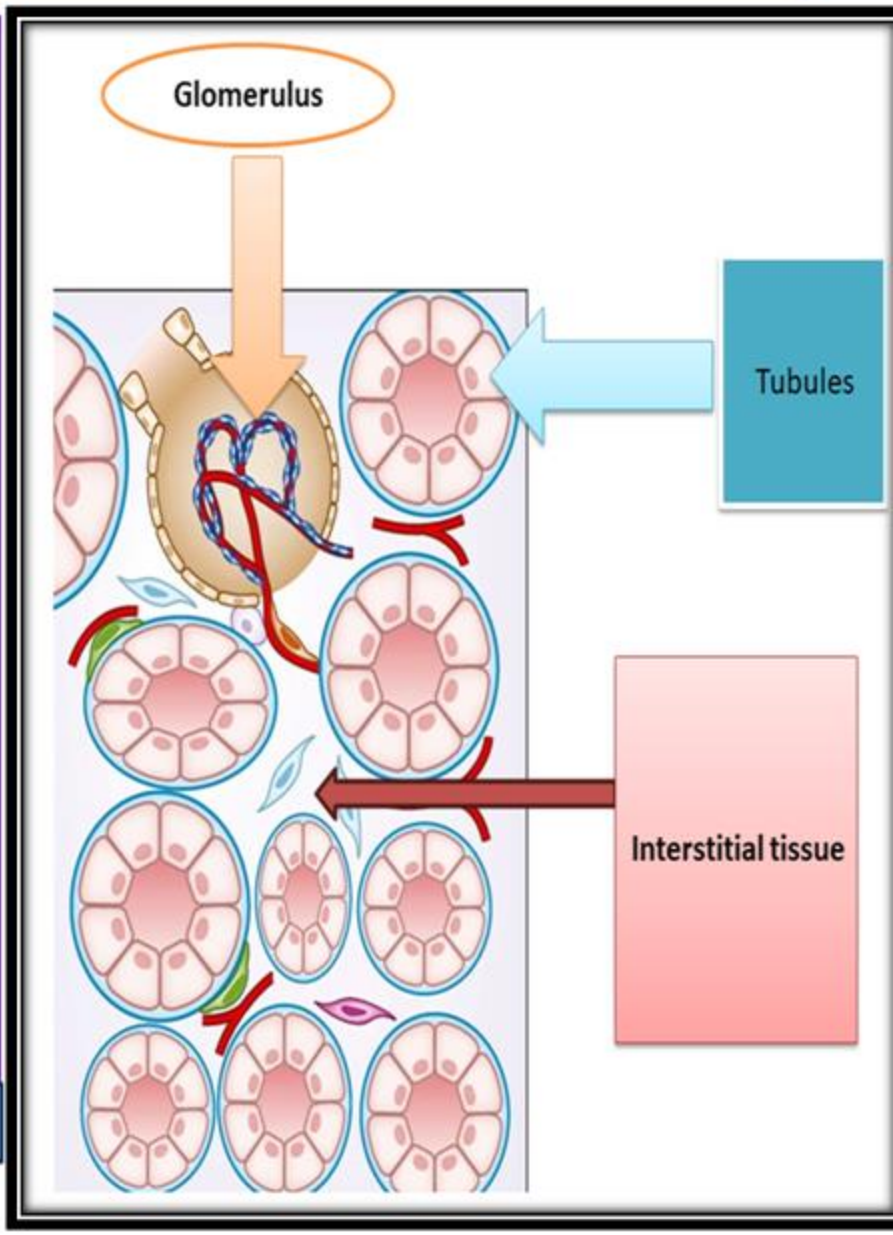
Acute Kidney Injury (AKI)

Prerenal: marked decrease in renal blood flow

Renal: damage within the kidney structures

Postrenal: obstruction of urine outflow





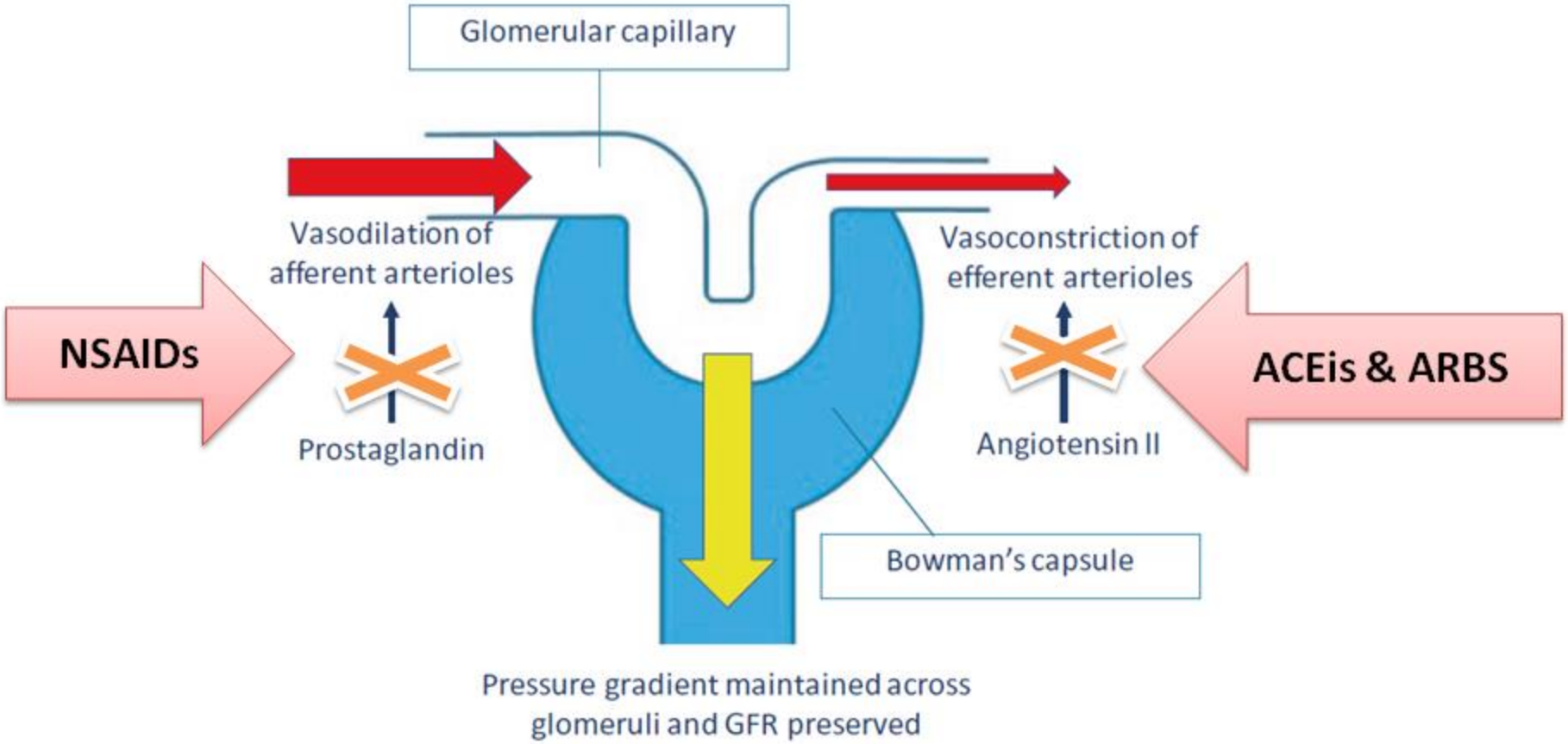
1-Drug induced pre-renal AKI

1- Reduced circulating volume (e.g., Diuretics).

2- Selective reduction in renal perfusion (Drugs that affect glomerular blood flow) like:

- NSAIDs/COX2 inhibitors – inhibit synthesis of vasodilatory prostaglandins.
- ACE inhibitors/ARB – block vasoconstrictor effects of angiotensin II.
- Calcineurin inhibitors (cyclosporin and tacrolimus) which increase vasoconstriction.

- Treatment include **maintain vascular volume**, Using Vasopressors if necessary.


Glomerular capillary
Vasodilation of afferent arterioles
Vasoconstriction of efferent arterioles
NSAIDs
ACEis & ARBS
Prostaglandin
Angiotensin II
Bowman's capsule
Pressure gradient maintained across glomeruli and GFR preserved

2- Intra-renal AKI induced by drugs

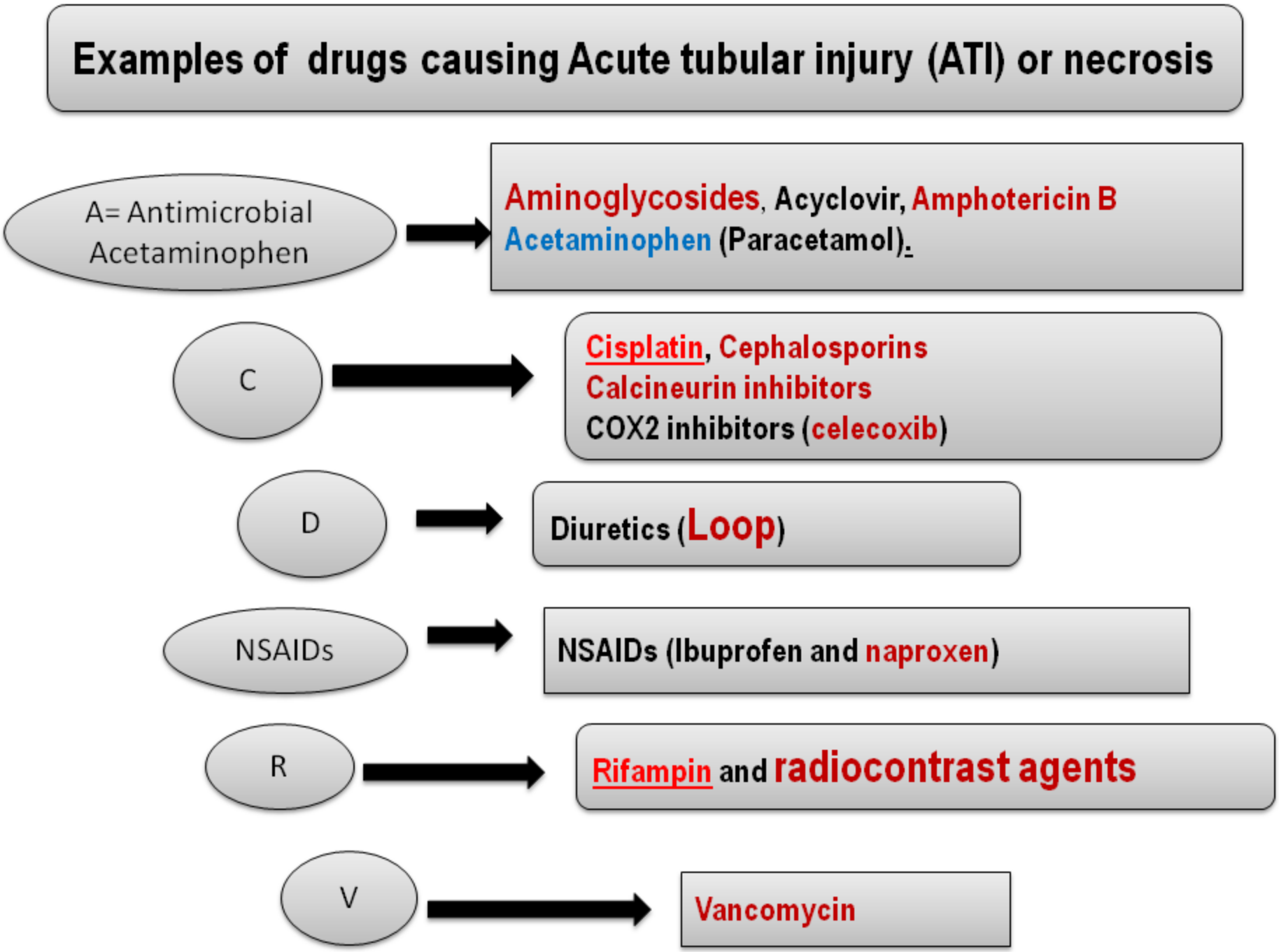
Intra-renal refer to intrinsic damage to the structure of the kidney (apoptosis or necrosis) by ischemia or other cellular mechanisms (e.g. impairing mitochondrial function, interfering with tubular transport or increasing oxidative stress).

A- Acute tubular injury (ATI) or tubular necrosis

❑ **The important risk factors for acute tubular injury:**

1. Exposure to multiple nephrotoxic drugs.
2. High doses (**ATI is dose dependent adverse effect**)
3. A disease that increase the tubular injury (e.g., diabetes, hypertension).
4. Extremes of age (very young or very old age).
5. Pre-existing chronic kidney disease (CKD).
6. Intravascular volume depletion.

Examples of drugs causing Acute tubular injury (ATI) or necrosis



B- Acute interstitial nephritis (AIN)

Acute interstitial nephritis (AIN) is an immune-mediated form of kidney injury (infiltration of immune cells in the tubulo-interstitium) .

- Medications **are the most common cause of AIN**.
- AIN can cause **permanent kidney damage** from fibrosis formation.
- In drug-induced AIN, drug discontinuation is critical.

- Management of AIN: **corticosteroids are usually prescribed** to prevent permanent kidney damage

- Examples of drug induced AIN: Antimicrobials (**β-lactams**, **sulfonamides**, quinolones, vancomycin, Aminoglycosides.), NSAIDs, Proton Pump Inhibitors, **phenytoin**, **carbamazepine**, **allopurinol**, **thiazides**, **Calcium channel blockers** & **lithium**.

chronic interstitial nephritis

- Chronic Interstitial Nephritis is a **long-term**, **progressive** kidney disorder characterized by inflammation and scarring (**fibrosis**) of renal tubules and renal connective tissue.

- Chronic Interstitial Nephritis causes irreversible, permanent damage to the kidneys, often leading to kidney failure.

- Unlike Acute Interstitial Nephritis (AIN), which is often an allergic reaction with a sudden onset, **Chronic Interstitial Nephritis** is a **slow**, **chronic inflammatory process**

- Drugs causing chronic interstitial nephritis: prolonged use of **NSAIDs** and **paracetamol**, **antibiotics**, **lithium** and **diuretics**.

C- Drug induced glomerulonephritis

- Some medications can cause **direct injury** involving the **mesangial, endothelial, or visceral epithelial cells (podocytes)** in glomeruli.

Drug-induced **podocytopathy** can occur in several situations:

1- Interferon (**IFN**) **causes podocyte injury & nephrotic syndrome.**

2- **Pamidronate** in high doses can cause **direct podocyte injury.**

3- Chronic **lithium** exposure.

4- **Minimal change disease** (MCD) is the most common glomerular lesion observed with **NSAIDs**; due to shunting arachidonic acid metabolites into pathways that alter immune function & **promote podocyte injury.**

Drugs that might cause nephrotic syndrome

Tolbutamide, **probenecid**, gold therapy, penicillamine, interferon-alfa, NSAIDs, lithium, and pamidronate

3- Post renal injury by drugs

- Drug induced Crystalline nephropathies are characterized primarily by intra-tubular crystal deposition (crystalluria).
- Urine sediment examination showing **crystal-containing casts** is a helpful non-invasive diagnostic test instead of renal biopsy.

Intra-renal crystal deposition occurs when:

1-The kidney is the major route of a drug/metabolite excretion.

2- Increased excretion of the drug (e.g., excessive drug dosing).

3- Supersaturation of the drug & precipitation within urine due to :

- Circulatory volume depletion/dehydration.
- the pKa of the drug & the Urine pH that favor drug precipitation:
  - Examples acidic pH for methotrexate or sulfadiazine and alkaline pH for ciprofloxacin.

4-The presence of underlying kidney disease may further enhance risk for drug-induced crystalline nephropathy.

Culprit Medication	Disease induced	Prevention &Treatment
Methotrexate	Crystalluria, AKI, & chronic kidney disease (CKD)	IV fluids before/during drug, alkalinize urine, adjust drug dose, **TDM**, folinic acid**, or glucarbidase.**
Sulfadiazine, sulfamethoxazole	Crystalluria, AKI & **nephrolithiasis**	Alkalinize urine, adjust dose for kidney function, assure euvolemia
Acyclovir	Crystalluria, AKI, and CKD	Avoid rapid iv bolus, adjust drug dose, assure euvolemia

- **Glucarpidase** is used for treatment of elevated levels of methotrexate in cancer patients with impaired kidney functions.
- Glucarpidase is an enzyme that inactivates methotrexate rapidly.
- Glucarpidase also degrades folinic acid (e.g. Leucovorin) so the two should not be used together (within two hours of one another).

Culprit Medication	Disease induced	Prevention &Treatment
Ciprofloxacin, levofloxacin	Crystalluria and AKI	Assure euvolemia during drug therapy and **avoid alkaline urine** if possible
Triamterene	Crystalluria, AKI, CKD, and **nephrolithiasis**	Alkalinize urine, assure euvolemia during drug therapy
Cyclophosphamide	Hemorrhagic cystitis	Hydration, continuous bladder irrigation, & prophylactic use of mesna.

- **Mesna** has **antioxidant properties.**
- Mesna concentrates in the bladder and conjugates acrolein.
- This conjugation reaction **inactivates the toxic compound** (acrolein) to harmless metabolites.

Indirect drug induced postrenal AKI

Here, **AKI is NOT caused by precipitation of the drug** itself or its metabolites in urine. Instead, different mechanisms are involved.
Examples:
1- Crystal nephropathy may also result from the use of anticancer chemotherapy due to uric acid and calcium phosphate crystal deposition (due to death of many malignant cells).

2- Drug induced **rhabdomyolysis** and **myoglobnuria** (postrenal AKI). **Statins** , alcohol, **Benzodiazepines, methadone and Methamphetamine** can cause rhabdomyolysis and AKI.

Drug induced renal Acid base disturbances

- **Phenformin** and metformin may cause **lactic acidosis**
- Proximal renal tubular acidosis by acetazolamide

Drug induced renal water imbalance

- **Hyponatremia**, syndrome inappropriate ADH secretion by Chlorpropamide
- Nephrogenic diabetes insipidus by lithium.


Thank you