به نام خدا

فارماکوویژیلانس و عوارض ناخواسته داروها

دی ماه ۱۳۹۳

Drug-induced renal injury

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- Toxic effects on the kidney related to medications are both *common* and *expected*, given the kidney's roles in plasma filtration and maintenance of metabolic homeostasis.

- The renal vascular bed is exposed to a quarter of resting cardiac output.
- Glomerular, tubular and renal interstitial cells frequently encounter significant concentrations of medications and their metabolites, which can induce changes in kidney function and structure.

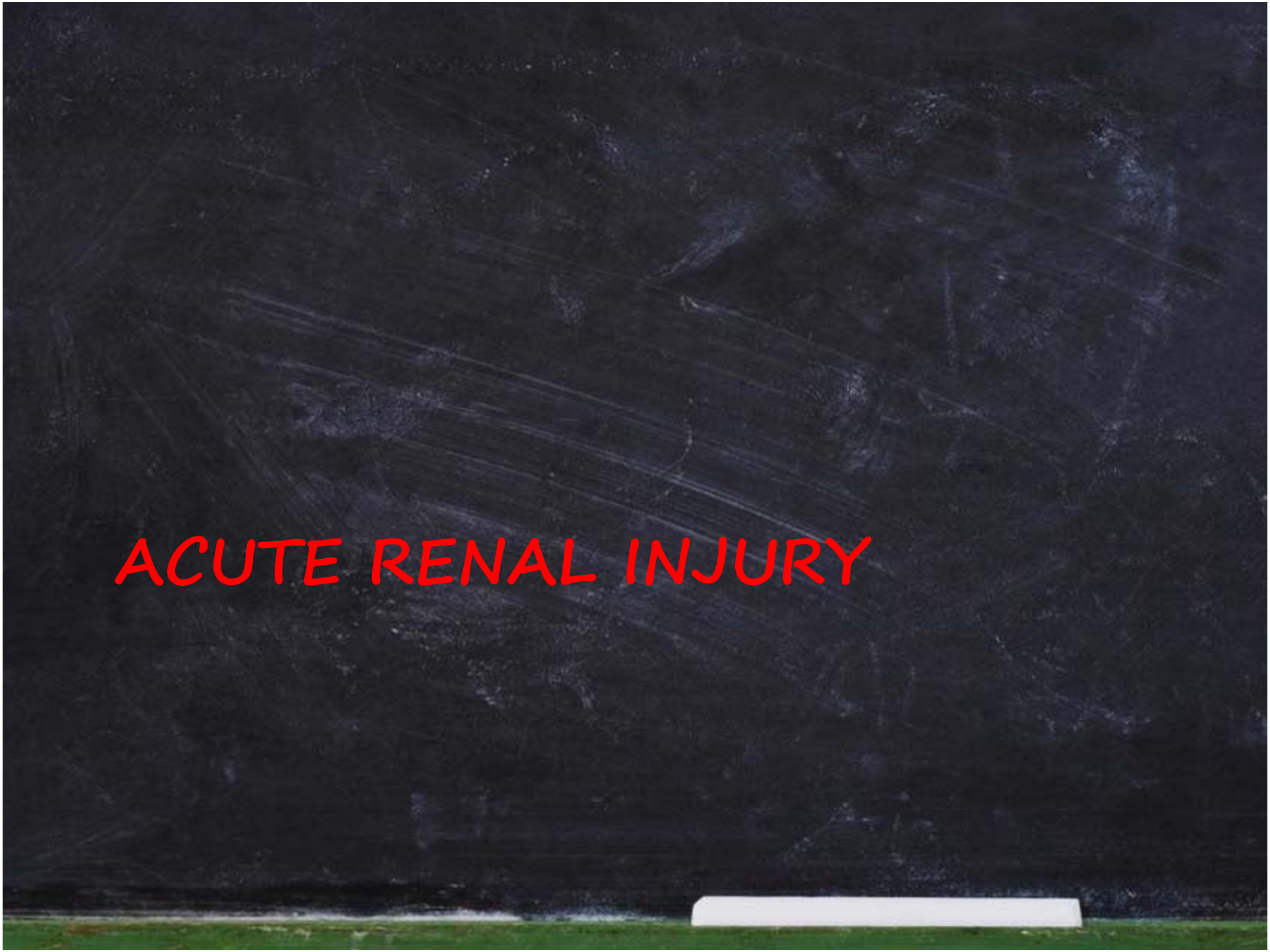
- **Can present as subtle injury and/or overt renal failure**

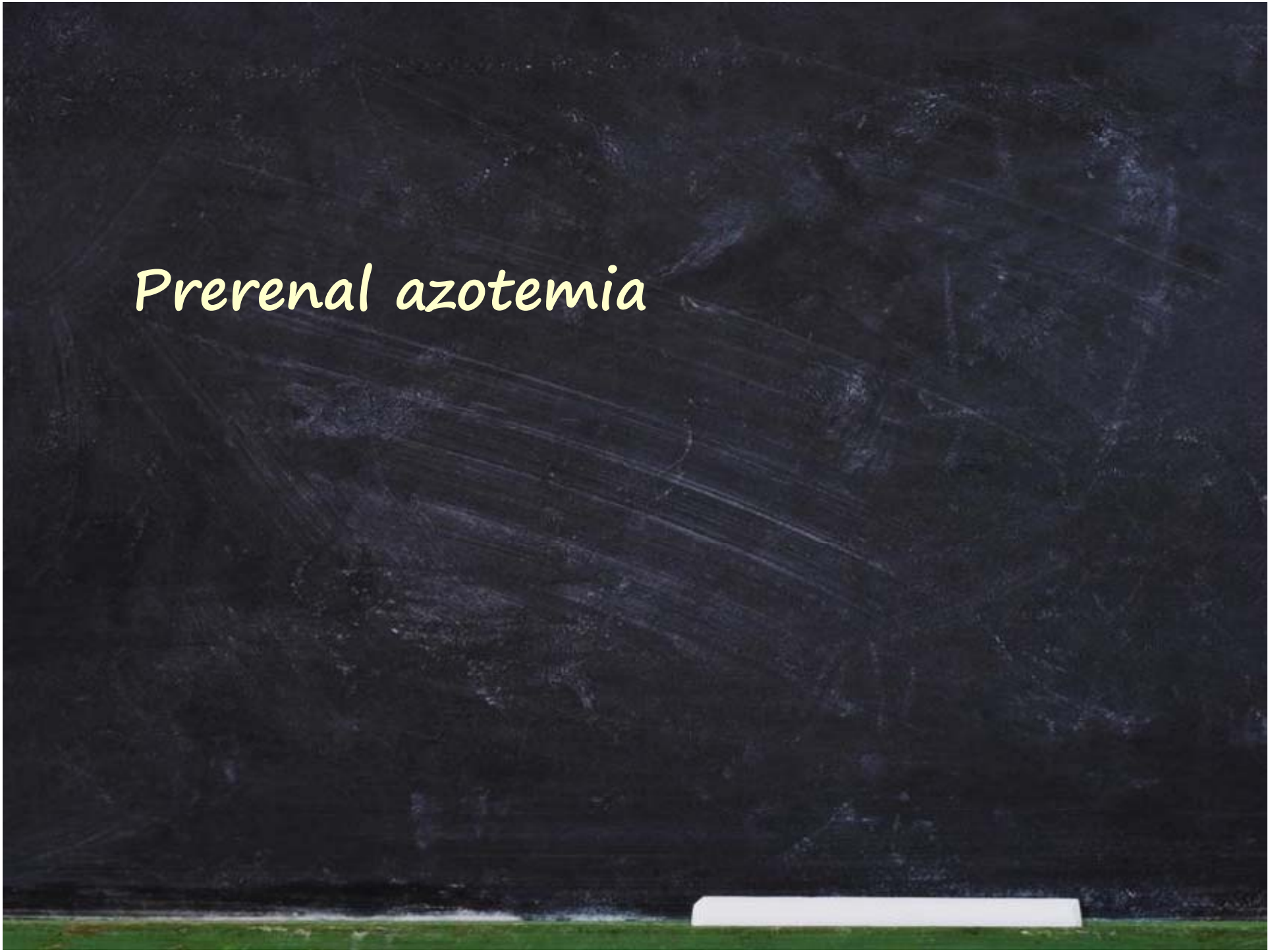
- Renal toxicity can be a result of hemodynamic changes, direct injury to cells and tissue, inflammatory tissue injury, and/or obstruction of renal excretion.

- Some drugs perturb renal perfusion and induce loss of filtration capacity.

- Others directly injure vascular, tubular, glomerular and interstitial cells, such that specific loss of renal function leads to clinical findings, electrolyte abnormalities and chronic renal failure.

- Detection is often delayed until an overt change in renal functional capacity is measured as an increase in serum BUN or creatinine.
- The true incidence of drug-induced nephrotoxicity is therefore difficult to determine.
- Most episodes of drug-induced renal dysfunction are reversible, with function returning to baseline when the medication is discontinued.
- But .....


ACUTE RENAL INJURY


Prerenal azotemia

- **Diuretics** alone or in combination with other antihypertensives

- Natriuresis is the desired outcome of diuretic use, but the kidney is extremely sensitive to maintaining adequate renal perfusion.

- **Significant volume depletion can occur when:**

- Oral or parenteral intake changes suddenly
- During episodes of diarrhea, vomiting, massive sweating or bleeding
- When patients suffer compromised cardiac output, cirrhosis or nephrosis.
- Concomitant administration of drugs from more than one diuretic class

- Large volume losses stimulate renal vasoconstriction with marked tubular avidity for NaCl uptake, and decreased urine output.

- Prolonged vasoconstriction can then lead to tubular dysfunction and tubular necrosis.

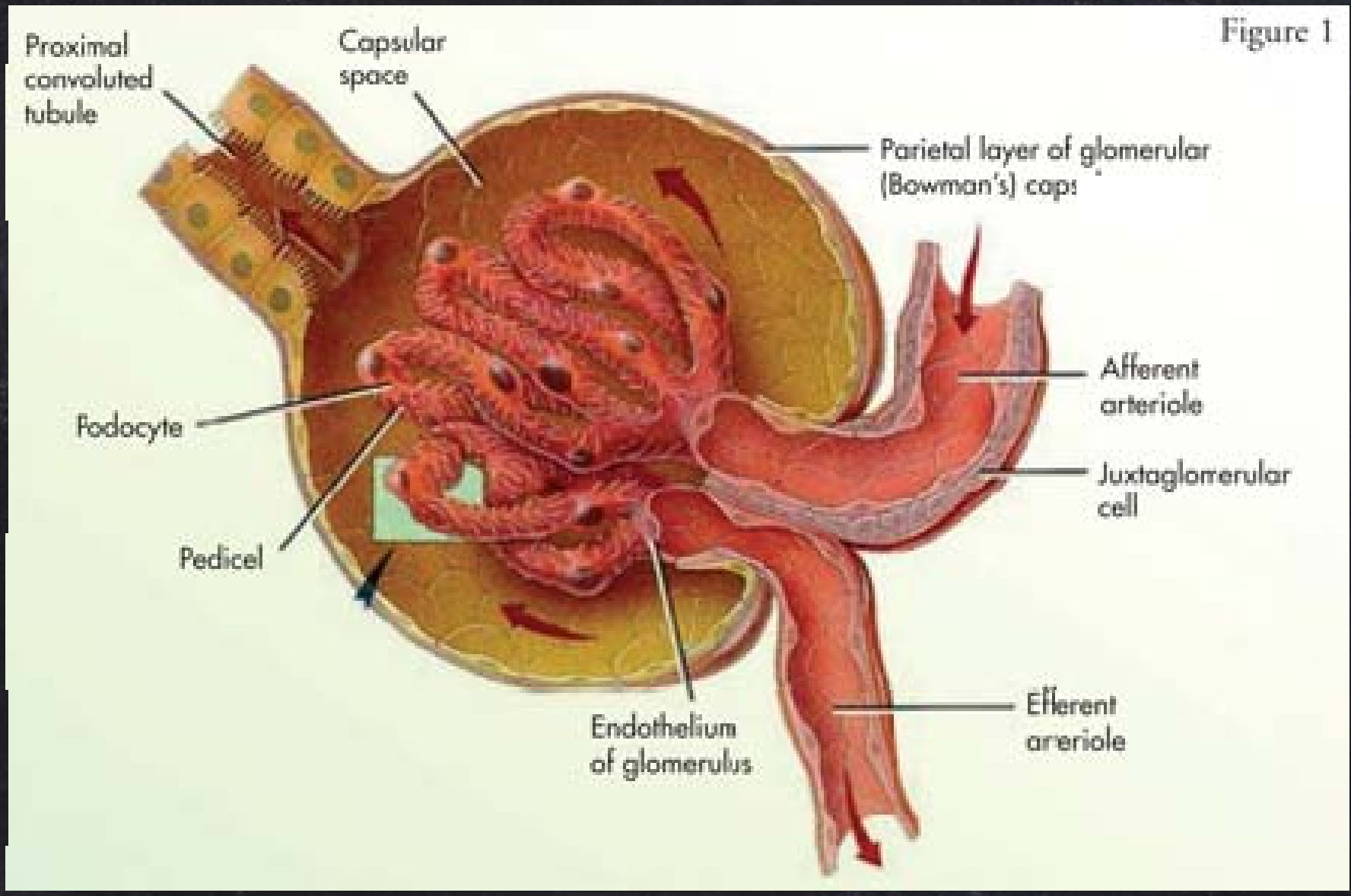


Figure 1
Proximal convoluted tubule
Capsular space
Parietal layer of glomerular (Bowman's) cap
Afferent arteriole
Podocyte
Juxtaglomerular cell
Pedicel
Endothelium of glomerulus
Efferent arteriole

- **Immuno suppressive agent cyclosporin and tacrolimus** → vasoconstriction of both afferent and efferent arterioles can decrease GFR in a dose-dependent and reversible manner

- **Infusion of osmotic contrast dye** can also cause acute vasoconstriction

- **Hydralazine, calcium-channel blockers, minoxidil, diazoxide, ACE inhibitors, ARBs**

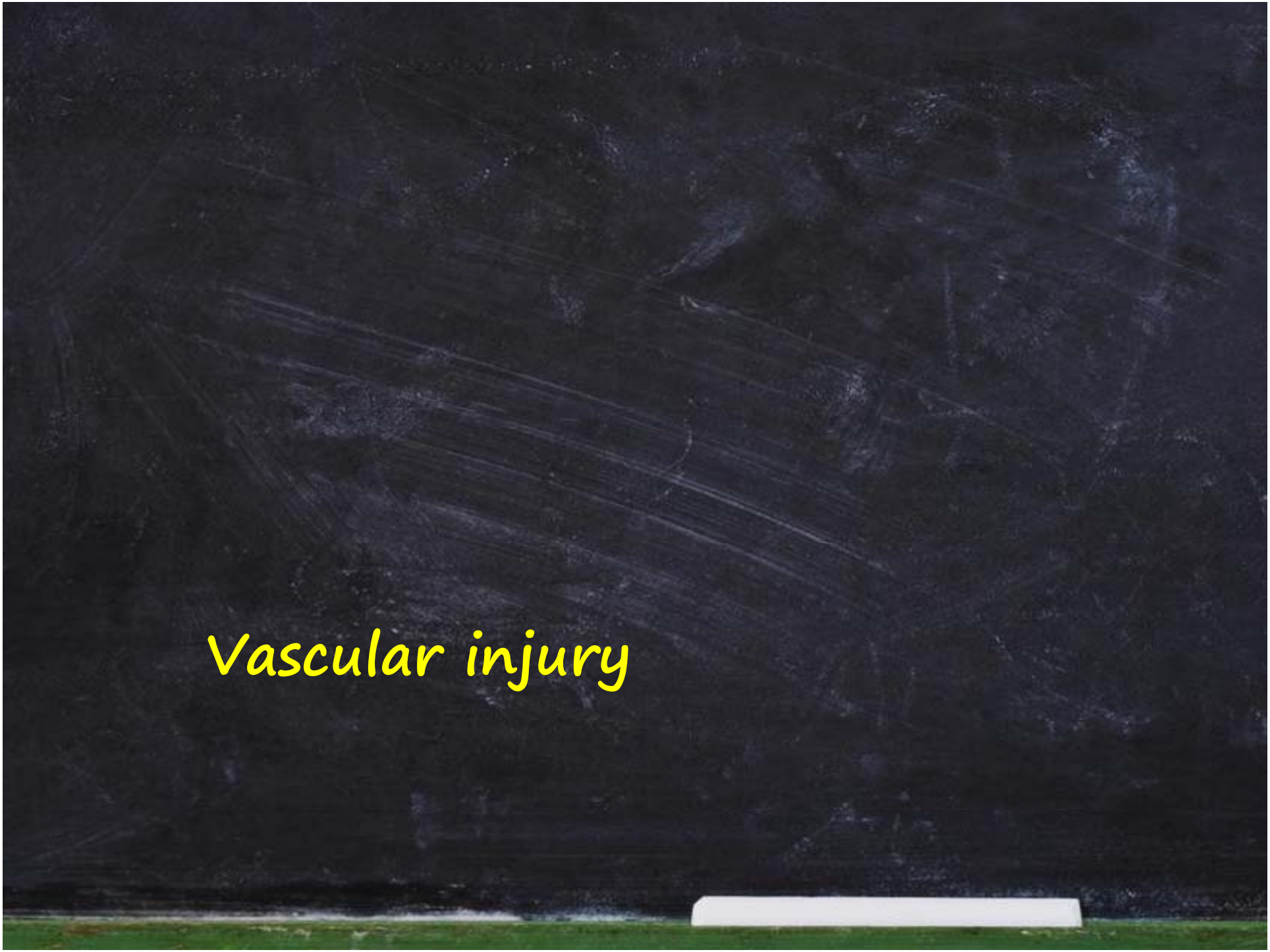
→often administered in combination with diuretics, are particularly prone to induce acute changes in renal function with associated tubular sodium avidity

- Reversal of renal failure and injury is possible if the problem is promptly recognized, the drug discontinued and volume infused to restore blood pressure.

- **Unrecognized prerenal failure can lead to serious tubular injury and tubular necrosis.**

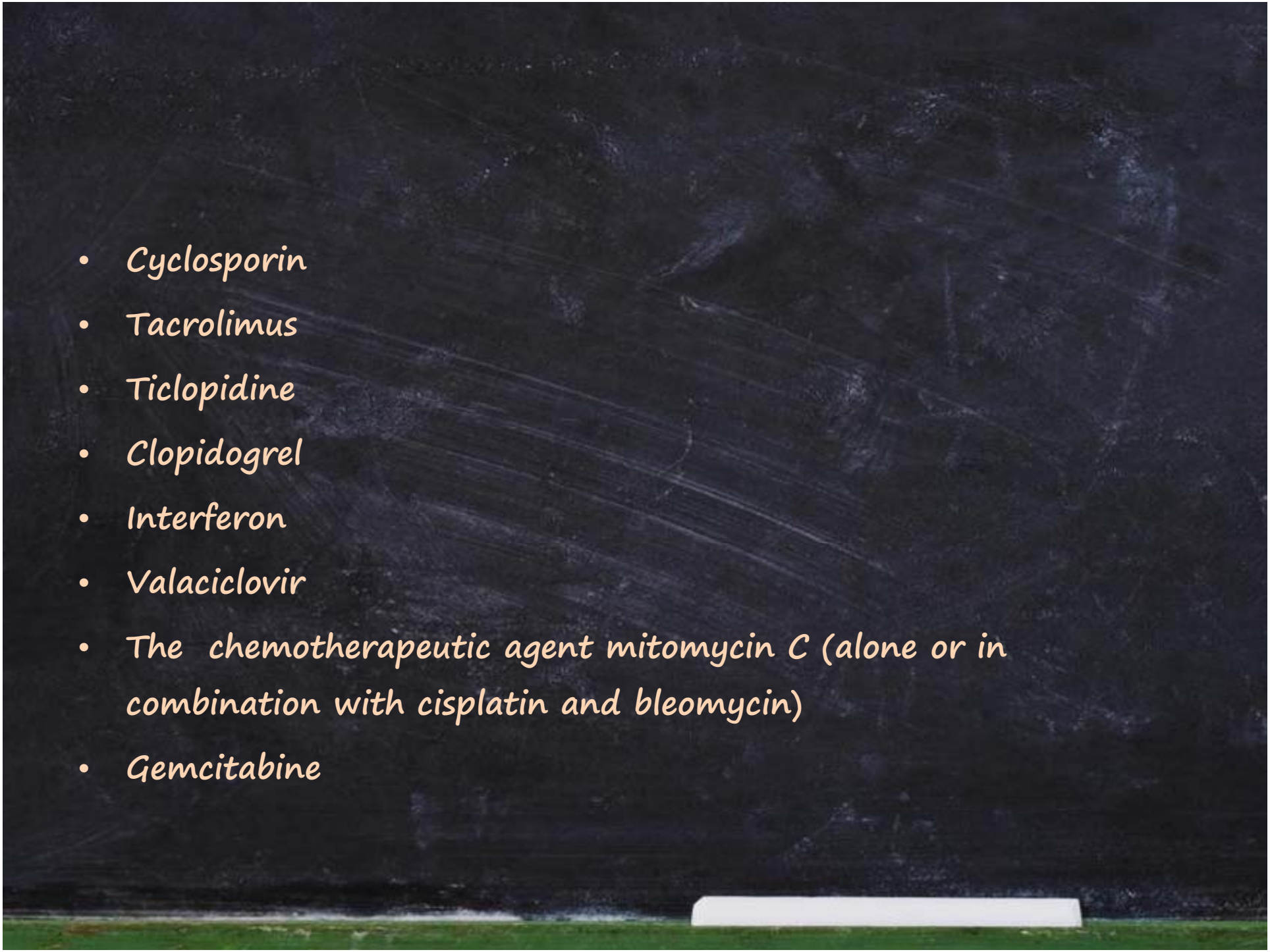

INTRARENAL TOXICITY

- Medications can have direct toxic effects on cells of the renal vasculature, tubules and glomeruli, and/or induce inflammation of the renal interstitium, leading to acute intrinsic renal failure.


Vascular injury

- Primary endothelial damage inducing platelet aggregation and consumption causes thrombotic **microangiopathy** and **renal vascular injury**.

- Mechanisms:
- immune mediated and dose-mediated


Cyclosporin
Tacrolimus
Ticlopidine
Clopidogrel
Interferon
Valaciclovir
The chemotherapeutic agent mitomycin C (alone or in combination with cisplatin and bleomycin)
Gemcitabine

- **Cholesterol embolization with anticoagulation** therapy is sometimes observed weeks or months after initiation of therapy.
- Thrombolytic agents often disrupt or dissolve protective thrombi covering ulcerated plaques, thereby releasing cholesterol plaques into the circulation.
- Embolization becomes evident within hours, days or weeks.
- Treatment is supportive, as renal failure is generally irreversible.


Tubular injury

- Direct injury of tubules is commonly associated with use of
- Antibiotics
- Chemotherapeutics
- Bisphosphonates
- Immunosuppressives
- Radiocontrast agents
- IVIG

- Damage can be toxic, ischemic, inflammatory or obstructive.
- U/A:
- no cells OR
- numerous RBCs, WBCs and/or brown granular casts
- proteinuria
- Crystalluria
- depending on the site and mechanism of injury

- **Aminoglycosides**
- Degree of nephrotoxicity:

Neomycin> gentamicin> tobramycin> amikacin> streptomycin

- Hypomagnesemia, nonoliguric ATN and perturbation of GFR is a late manifestation of aminoglycoside nephrotoxicity.

- Concurrent administration of other nephrotoxins, age, obesity, female gender, hypoperfusion, underlying renal failure or liver disease, hypomagnesemia, hypokalemia and metabolic acidosis, increase the risk of toxicity.

- Decreasing the frequency of aminoglycoside dosing to atleast daily (as dictated by renal clearance) can reduce the risk of toxicity

- Nephrotoxicity can occur within a week of therapy initiation or manifest after cessation of treatment despite all therapeutic monitoring.


Ischemic tubular injury

- Can result from acute vasoconstriction induced by:
  - **calcineurin inhibitors**
  - **radiocontrast agents**
  - **amphotericin B**

- The cyclosporin and tacrolimus can stimulate dose dependent vasoconstriction of both afferent and efferent arterioles, leading to a drop in GFR that can be reversed during the early stages via dose adjustment or drug discontinuation.

- The antifungal **amphotericin B** also decreases renal blood flow via dose-dependent acute renal vasoconstriction.

- At cumulative doses exceeding 2–3 g, causes direct distal tubular injury resulting in nonoliguric renal failure with distal tubular acidosis, concentrating defects and potassium wasting.
- It can cause ATN at higher doses.

- Lipid-based formulations of amphotericin B are less likely to have renal toxic effects

- The osmotic load of **radio-contrast agents** induces acute vasoconstriction, increases medullary oxygen consumption and eventually leads to tubular ischemia.

- Risk factors:
- CKD
- DM
- Prerenal state
- Multiple myeloma
- Age
- Intratubular obstruction

- The use of the **ionic high-osmolar or low-osmolar contrast** products also increases the risk of nephropathy.

- **Nonionic, iso-osmolar, or low-osmolar contrast** appears to be better tolerated.

Nonionic, Iso-osmolality

Nonionic, Low Osmolality

Nonionic, Low Osmolality

Ionic, High Osmolality

Ionic, High Osmolality

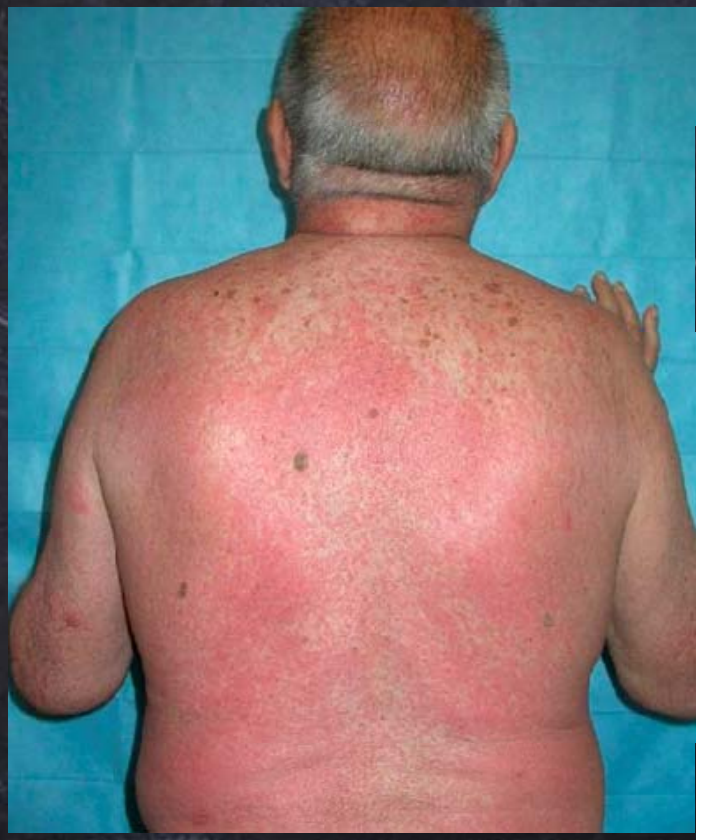
Nonionic, Low Osmolality

Ionic, high osmolality, macrocyclic

- It has been suggested that infusion of saline alone, 0.45% normal saline plus bicarbonate or N-acetylcysteine pre-procedure decreases the likelihood of CIN developing, particularly in high-risk patients.


Interstitial injury

- The common manifestation of medication associated renal interstitial inflammation is:
- Pyuria and/or white blood cell casts
- Eosinophiluria
- Hematuria
- Mild to moderate proteinuria
- Fever
- Rash
- Arthralgias
- Eosinophilia



- Only one-third of patients present with these classic symptoms of hypersensitivity, renal failure occurs in most patients at relatively early stages.

- Medications are thought to bind to, or mimic, renal tubular antigens, or to induce an immune reaction following deposition in the interstitium.

- Numerous medications have been associated with AIN
- Penicillins
- Cephalosporins
- Quinolones
- Sulfa drugs
- Phenytoin
- Thiazide
- Furosemide
- Cimetidine
- Ranitidine
- Rifampin
- Allopurinol
- Interferon
- NSAIDs
- Clarithromycin
- Telithromycin
- Omeprazole
- Pantoprazole

- **Drug discontinuation** and **supportive therapy**, including careful volume monitoring and avoidance of hypotension and other nephrotoxins, should be the mainstays of therapy.

- No controlled trials have justified routine use of **steroids** for drug-induced AIN.

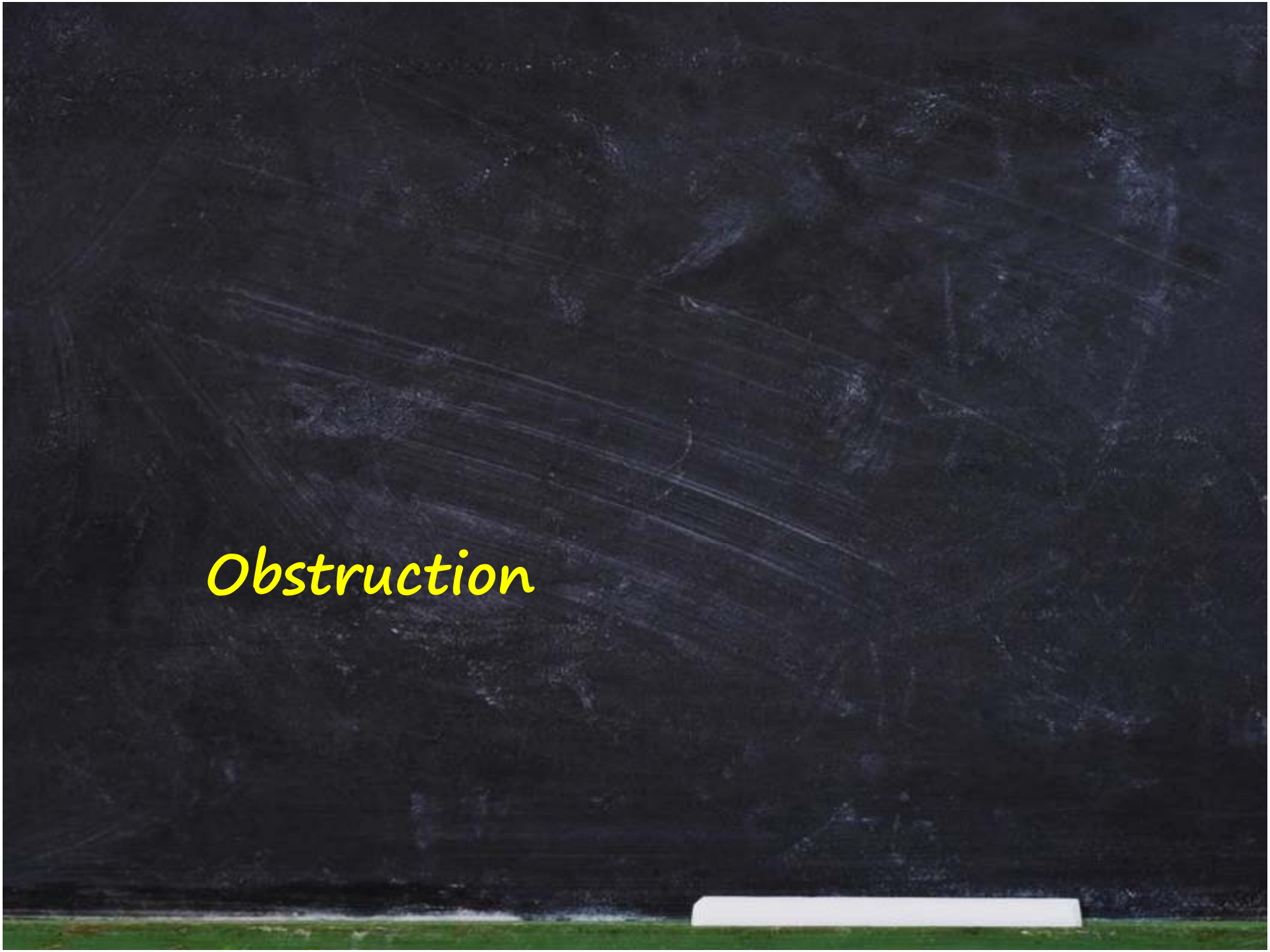

Glomerular injury

- Medications that alter glomerular histology and permeability often cause proteinuria
- NSAID
- Gold
- Penicillamine
- ACE inhibitors
- Interferon-α
- Pamidronate

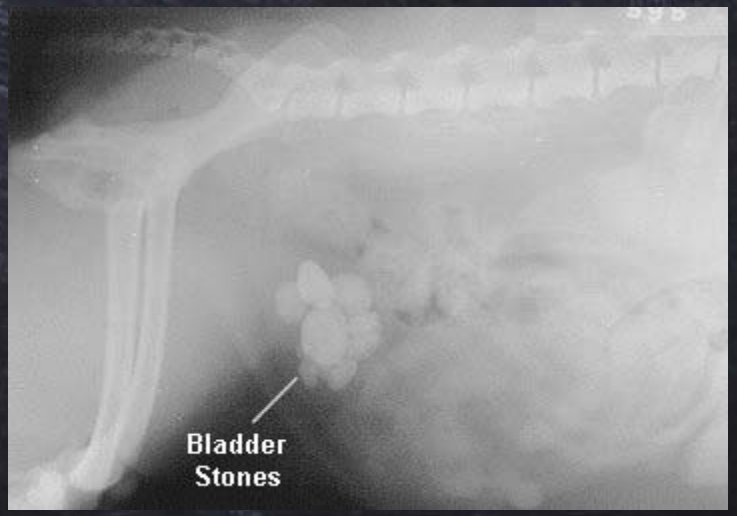
- Discontinuation of medication usually reverses the clinical findings.

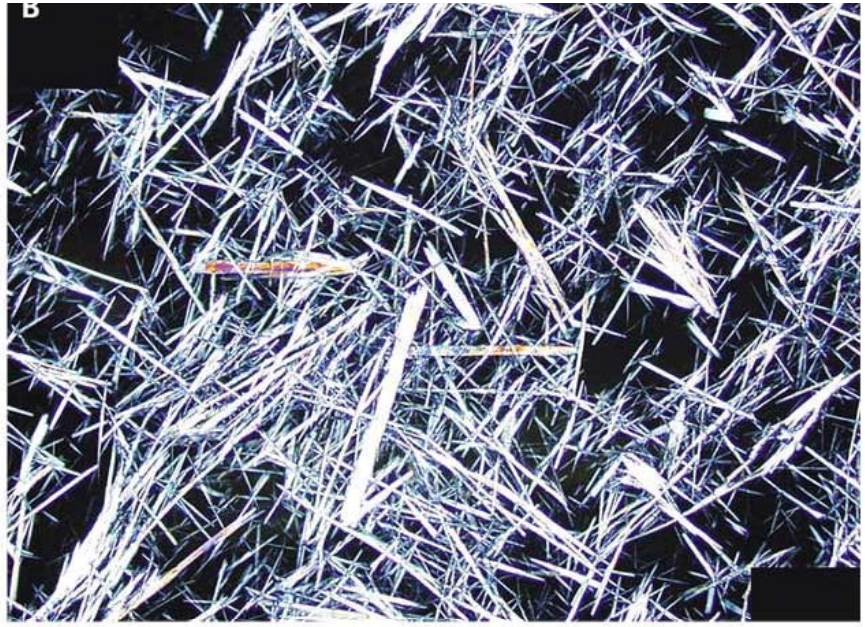
- Resolution can, however, be delayed for months or years, especially that of gold-induced nephropathy.
- Discontinuation of pamidronate does not resolve nephrosis


POSTRENAL TOXICITY


Obstruction

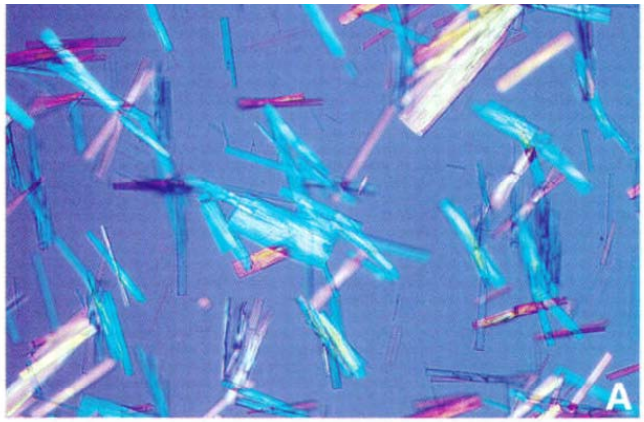
- Crystalluria
- Acyclovir
- Indinavir
- Methotrexate
- Sulfonamides
- Triamterene

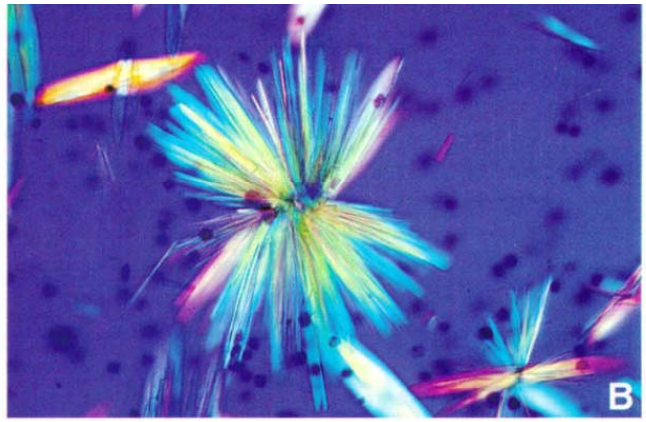


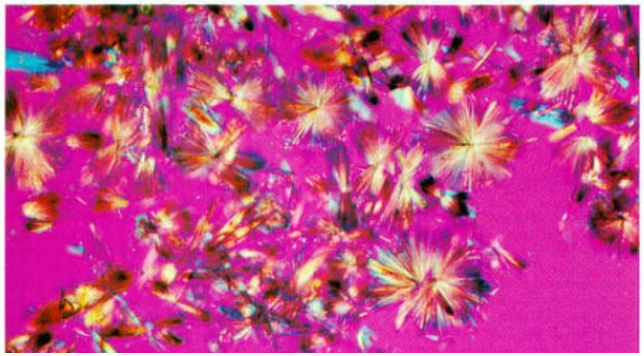


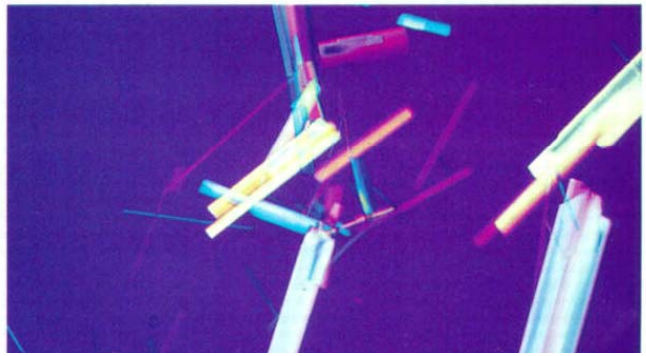
Acyclovir

Indinavir



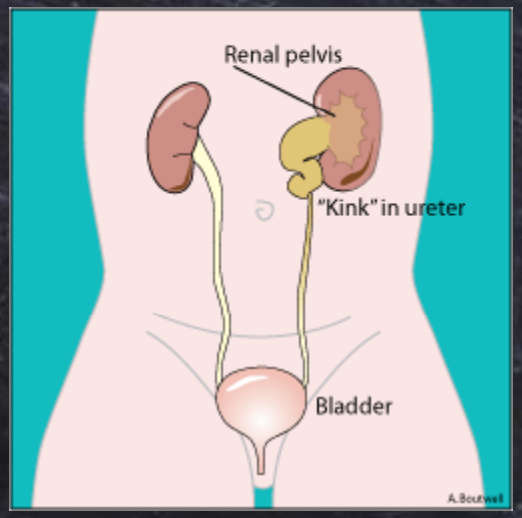


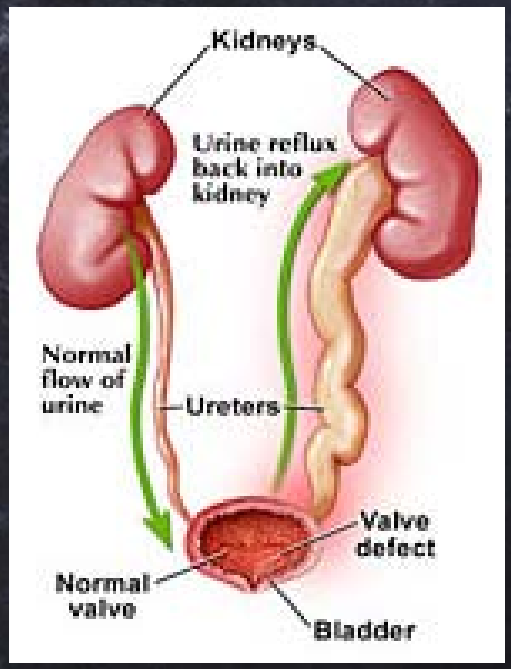




- Nephrolithiasis
- Factors that predispose a patient to drug-induced urinary calculi
- History or presence of renal lithiasis
- Low urine volume
- Abnormally low or high urine pH
- Hypercalciuria
- Hypocitraturia
- Medication-specific factors:
- (high or prolonged dosing regimens, increased urinary drug excretion and poor aqueous drug solubility)

- Anti-cholinergic drugs (affect bladder outlet muscles)

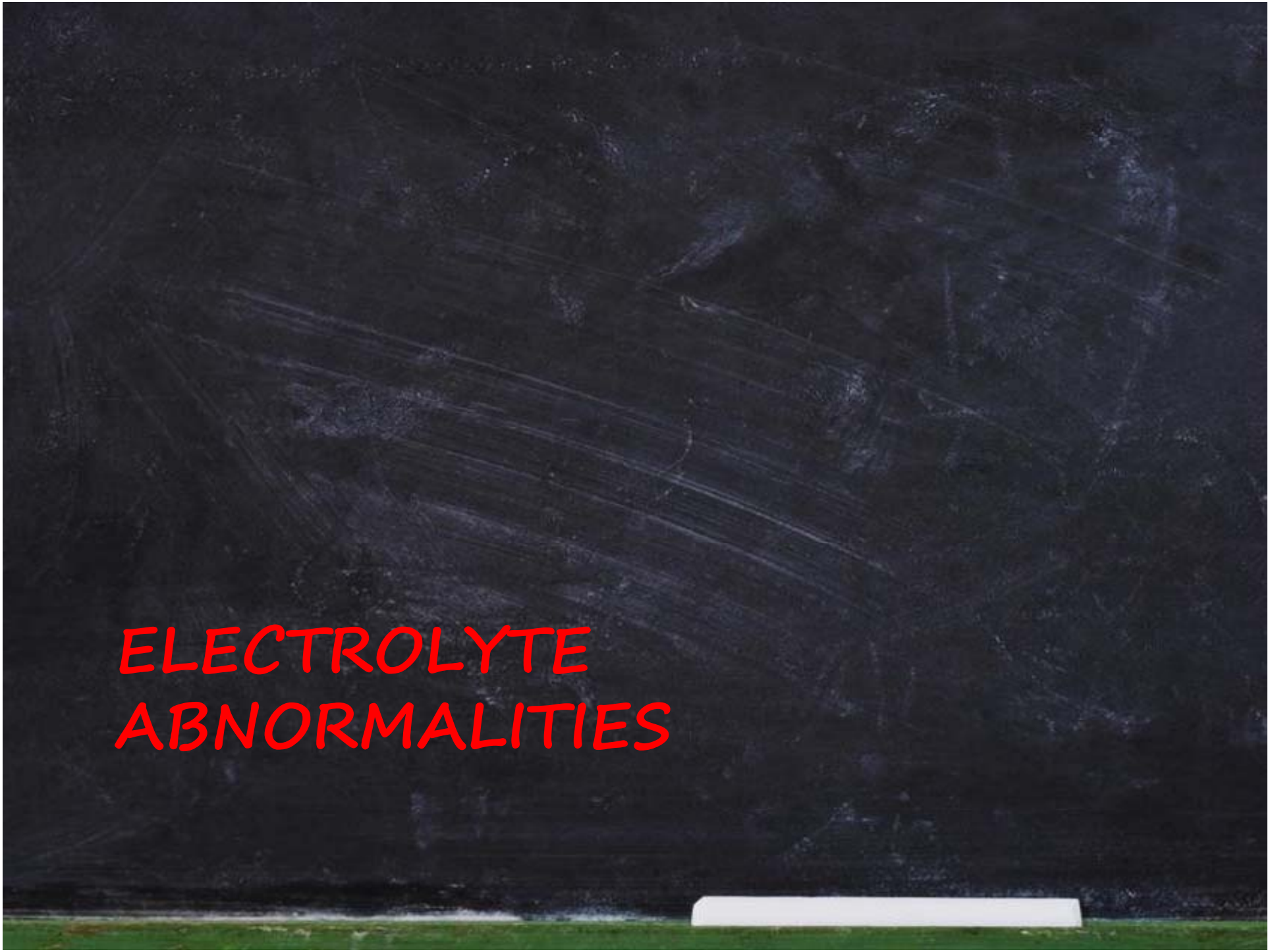





CHRONIC RENAL INJURY

- Prolonged exposure of the kidney to **Analgesics**, **Calcineurin inhibitors** or **Lithium** can cause chronic renal damage

- People taking large cumulative doses of acetaminophen and NSAIDs were at increased risk of developing end-stage renal.
- Urogenital transitional carcinomas and renal cell cancers have also been linked with prolonged analgesic use.


ELECTROLYTE
ABNORMALITIES

- Hypokalemia:
- Diuretic agents
- Gentamicin
- Cisplatin
- Carboplatin

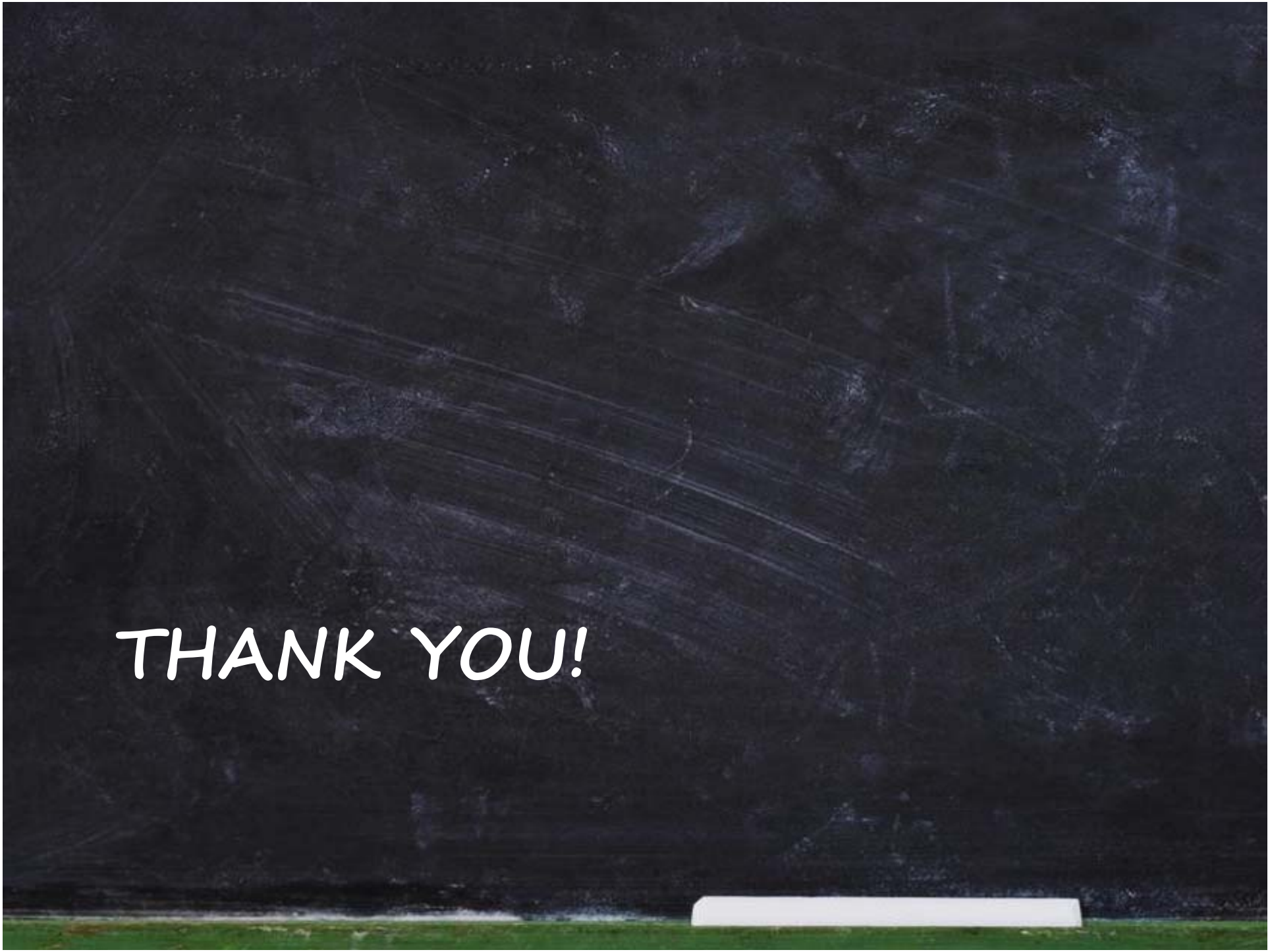
- Hypomagnesemia:
- Amphotericin B
- Aminoglycosides


Hyperkalemia
Potassium-sparing diuretics
ACE inhibitors
ARBs
Heparin
Cyclosporin
NSAIDs
COX-2 inhibitors
β-blockers
Trimethoprim
Hyponatremia
Thiazide diuretics
Cyclophosphamide
Vincristine


PSEUDO-NEPHROTOXICITY

- Mimic renal failure by increasing serum creatinine
- **Trimethoprim**
- **Cimetidine**
- **Steroids**
- **Tetracycline**

- Medications that interfere with laboratory determination of serum creatinine:
- **Ascorbic acid**
- **Levodopa**
- **Methyldopa**


THANK YOU!