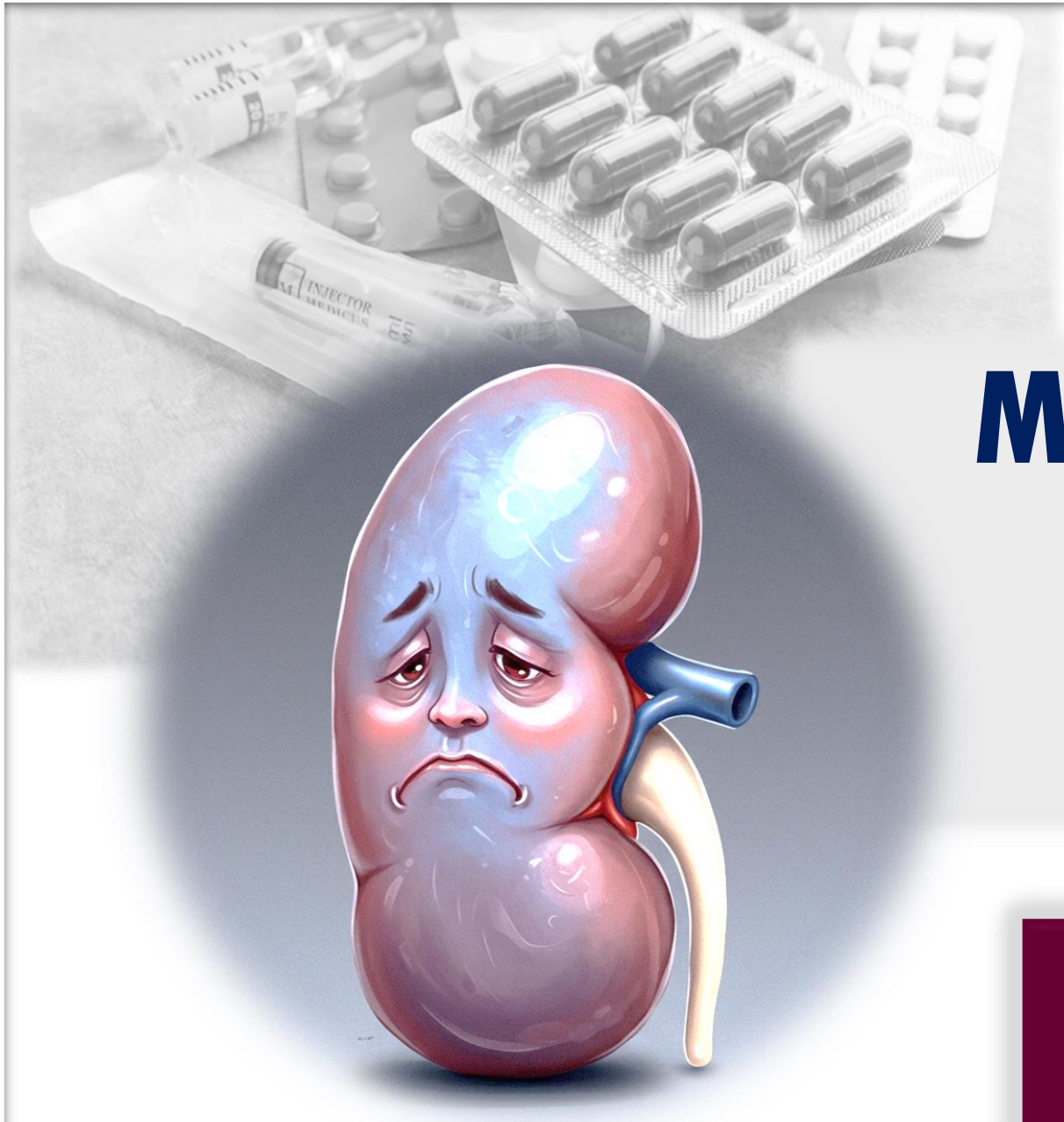


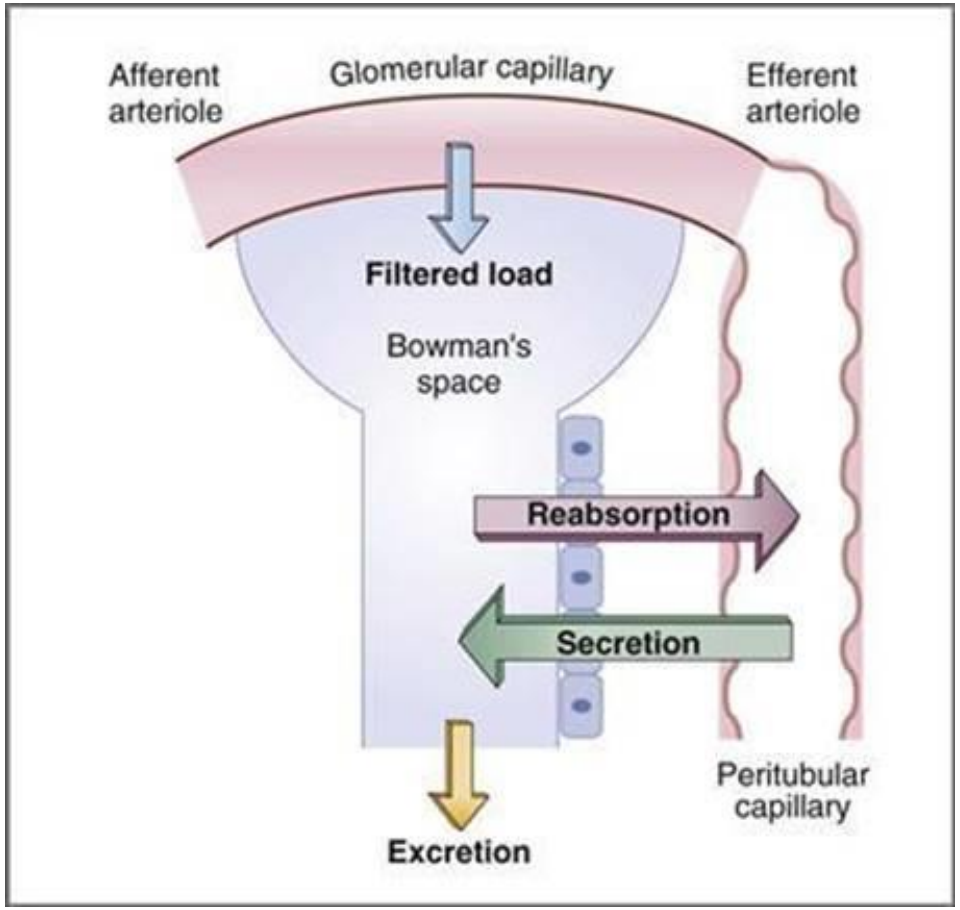
Medication-Induced Nephrotoxicity in Children

Dorna Derakhshan
Pediatric Nephrologist
SUMS

www.farsped.co

Introduction

- The kidney performs many important functions, including the elimination of drugs or their metabolites
- Many medications undergo filtration, secretion, reabsorption, and excretion by the kidney
- Drug-induced nephrotoxicity (DIN) can occur in all age groups and is the most common preventable cause of AKI



Epidemiology:

- Incidence: in hospitalized adults approximately 14–26% (more common in critically ill patients)
- The epidemiology of DIN appears to be lower in children
- Medications are the etiologic factors in 16% of hospitalized non-critically ill pediatric patients and are the second most common cause of AKI in children
- Incidence of AKI in PICU: 2.5 to 4.5%
- **Premature infants are at higher risk** for nephrotoxic AKI and chronic kidney disease (CKD) because of incomplete maturation of the kidney

Factors contributing to Nephrotoxicity

Kidney:

- High RBF
- Large capillary surface area
- Specialization of proximal tubular cells

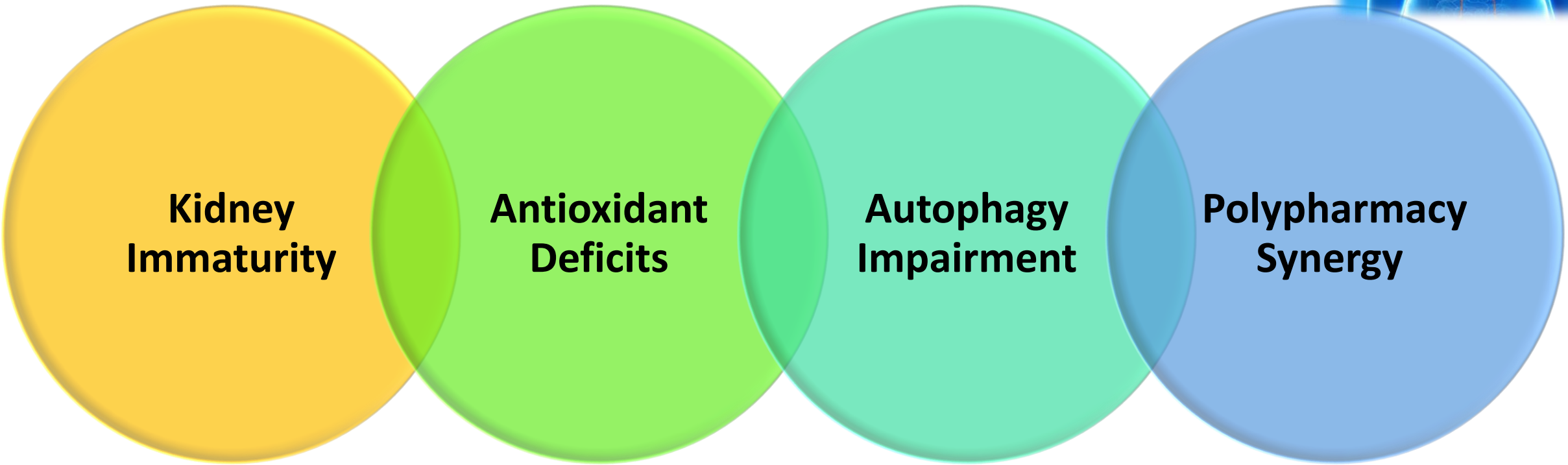
Patient:

- Age
- Underlying AKI and CKD
- Volume depletion
- Genetic mutations of transporters

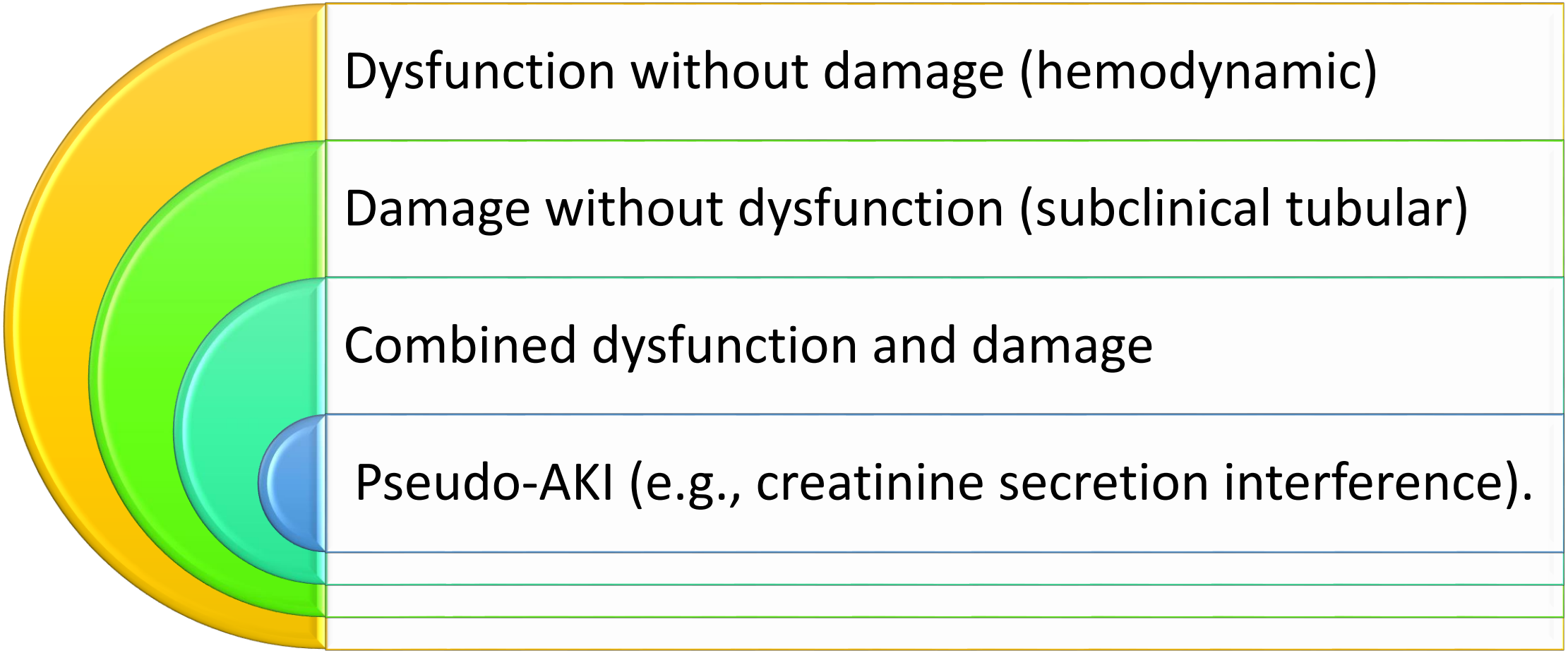
Drug:

- Mechanisms of nephrotoxicity
- Prolonged exposure to nephrotoxin

Kidney vulnerability to nephrotoxicity in children:



The 2023 ADQI classification delineates four drug-induced kidney disease (DIKD) phenotypes, applicable to pediatrics:



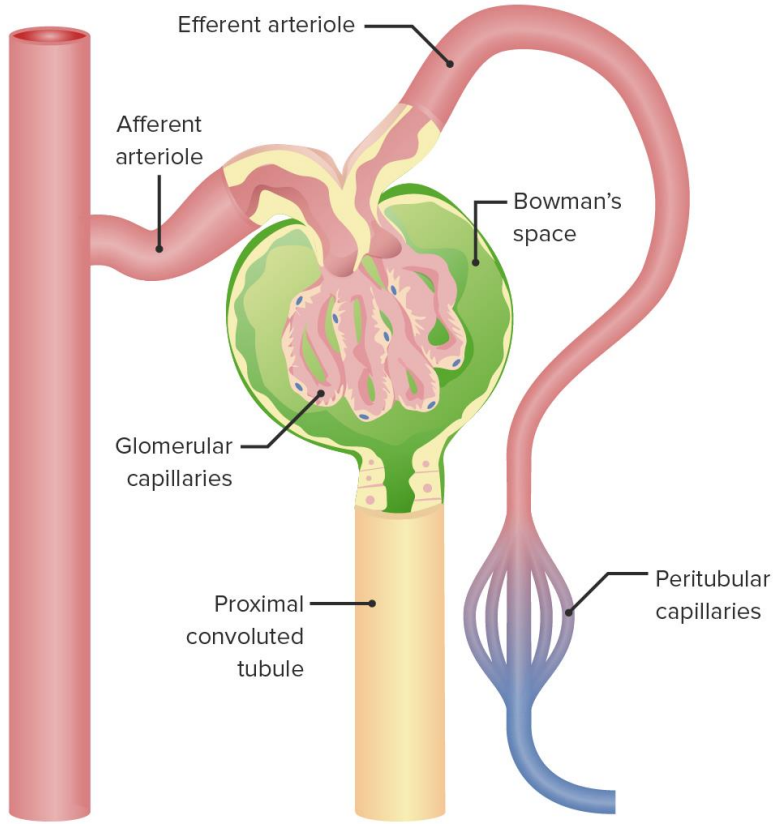
Mechanisms of Nephrotoxicity

- **Altered intraglomerular hemodynamics**
- **Tubular cell toxicity**
- **Inflammation (glomerulonephritis, AIN, CIN)**
- **Crystal Nephropathy**
- **Thrombotic microangiopathy (TMA)**

Glomerular Damage

Altering intraglomerular hemodynamics:

- NSAIDs → Suppress prostaglandin activity → decreasing GFR
- ACEi and ARB
- Calcineurin inhibitors



Immunological effect on the glomerulus :

Minimal change glomerular damage with nephrotic range proteinuria:

- NSAIDs (often with AIN)
- Lithium, Rifampin, Ampicillin, Phenytoin
- Management: cessation of the medication and a course of steroids

Focal Segmental Glomerular Sclerosis:

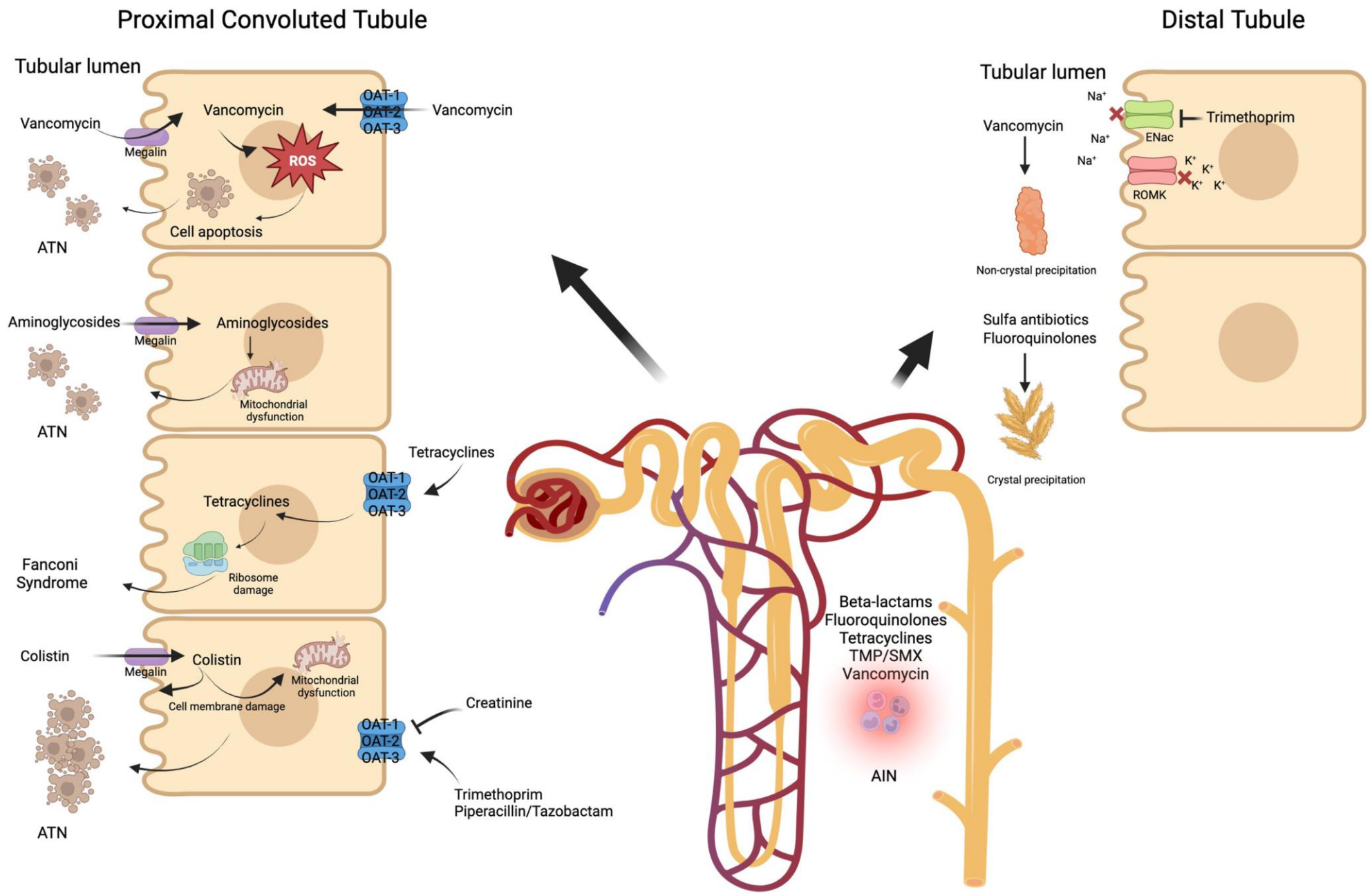
- Heroin: unclear pathophysiology may be direct toxicity from heroin
- Pamidronate: Collapsing FSGS. Patients taking large dosages for longer time are at greater risk
- Alpha interferone

Membranous Nephropathy:

- Penicillamine, Gold, NSAID, Captopril
- Mechanism: Damage to the PCT epithelium may result in antigen release, antibody production, and the creation of glomerular immune complexes.

Tubular cell toxicity

- The most common sites of damage are the proximal and distal tubular epithelium.
- ATN: Cellular deterioration and sloughing from the proximal and distal basement membranes.
- In the inpatient setting, ATN is the most prevalent symptom of DIN.
- **Mechanisms of injury:**
  - Direct cytotoxic effect of the drug
  - Damaged mitochondria
  - Disrupted tubular transport mechanism
  - Oxidative stress damage caused by free radical production
- **Examples:** Aminoglycoside antibiotics, antifungal medications (amphotericin B), antiviral treatments (adefovir), and anticancer drugs like cisplatin and foscarnet



** Overview of Antibiotic-Induced NephrotoxicityCampbell, Ruth E. et al.Kidney International Reports, Volume 8, Issue 11, 2211 - 2225*

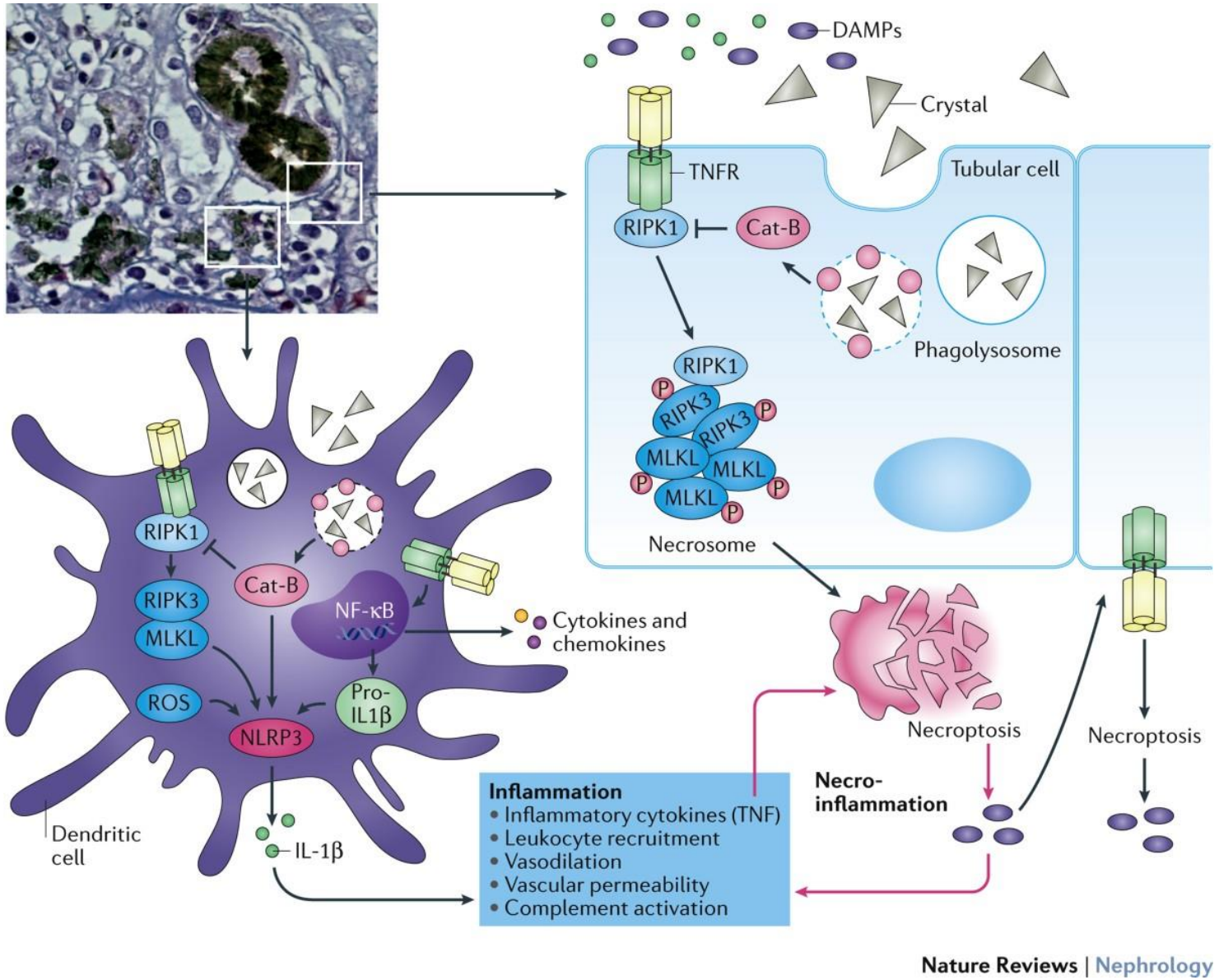
Inflammation (glomerulonephritis, AIN, CIN)

- **Glomerulonephritis**: Minimal change disease, FSGS, MGN
- **Acute Interstitial Nephritis (AIN):** Immune-mediated infiltration of the kidney insterstitium by inflammatory cells
  - The classic triad presentation of AIN usually includes fever, rash, and eosinophiluria, although this is seen in less than 10% of patients
  - The onset: A Few days to several weeks after exposure
  - Examples: β-lactam antibiotics (Penicillins, Cephalosporins), other antibiotics (e.g., rifampin, vancomycin, ciprofloxacin, sulfonamides, macrolides), NSAIDs, diuretics (e.g., thiazides, loop diuretics), anticonvulsants (e.g., phenytoin), antivirals (e.g., acyclovir, indinavir, atazanavir), and proton pump inhibitors (PPIs)
  - Corticosteroid therapy may be beneficial, especially within 1–2 weeks of diagnosis
- **Chronic Interstitial Nephritis(CIN)**
  - Insidious in onset, can lead to irreversible interstitial fibrosis, and is less likely to be drug-induced
  - CNIs, chemotherapeutic agents (carmustine), lithium, and aristolochic acid, a Chinese herbal medicine

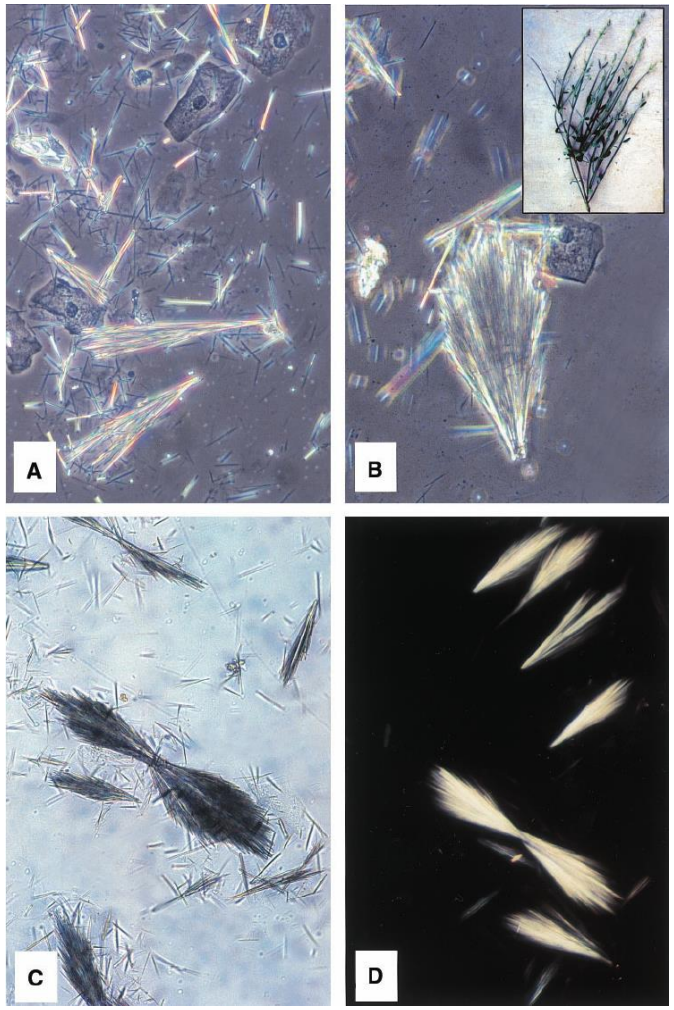
Crystal Nephropathy

- Crystal production is influenced by urine PH, medication concentration and urine crystal inhibitors

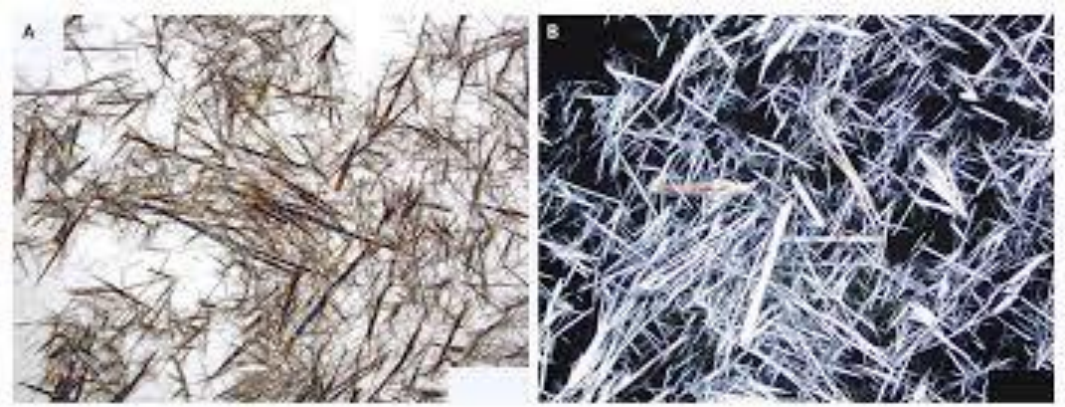
- Examples: Sulfonamides, sulfadiazine, sulfamethoxazole, acyclovir, methotrexate, indinavir, triamterene, aminopenicillins, amoxicillin, ampicillin, quinolones, ciprofloxacin, norfloxacin, and nitrofurantoin are all drugs linked to crystal nephropathy
- Risk factors of drug precipitation:
  - severe volume depletion (Diarrhea, Vomiting, severe diuresis, Pancreatitis, heart failure ,…)



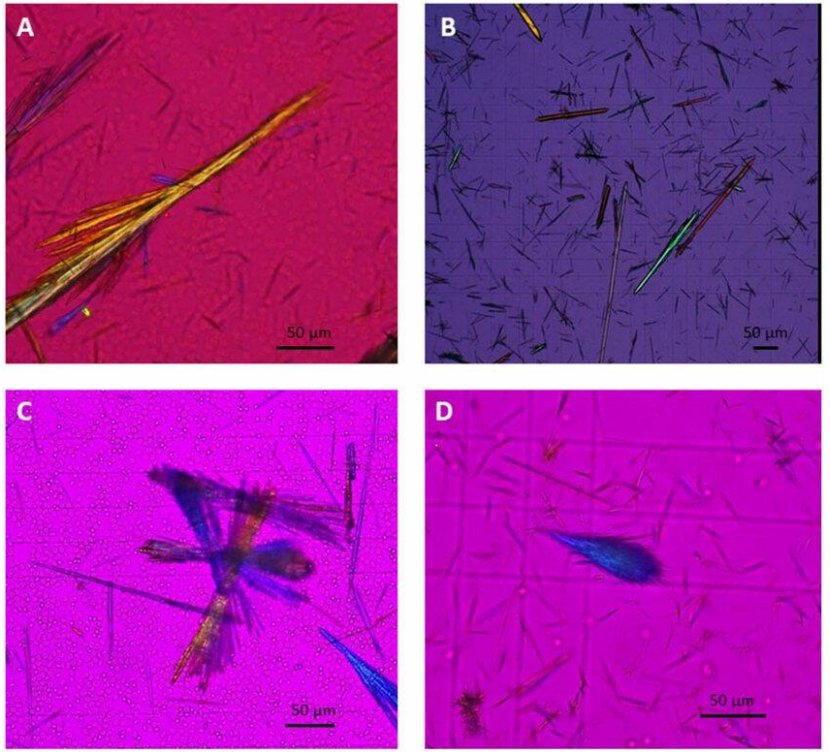
Mulay, S., Anders, HJ. Crystal nephropathies: mechanisms of crystal-induced kidney injury. *Nat Rev Nephrol* 13, 226–240 (2017). https://doi.org/10.1038/nrneph.2017.10



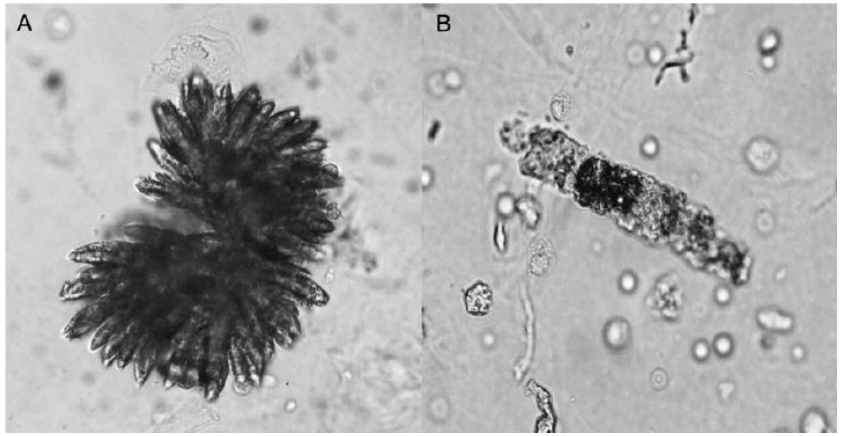
Ciprofloxacin



Acyclovir

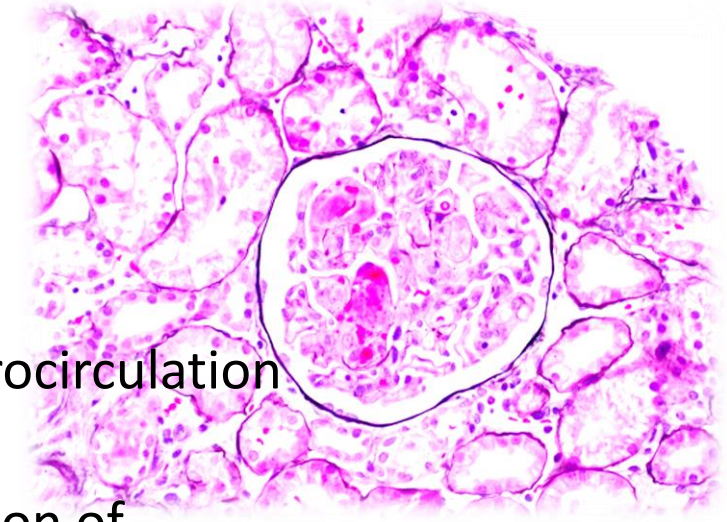


Amoxicillin



Sulfasalazine

Thrombotic microangiopathy (TMA)



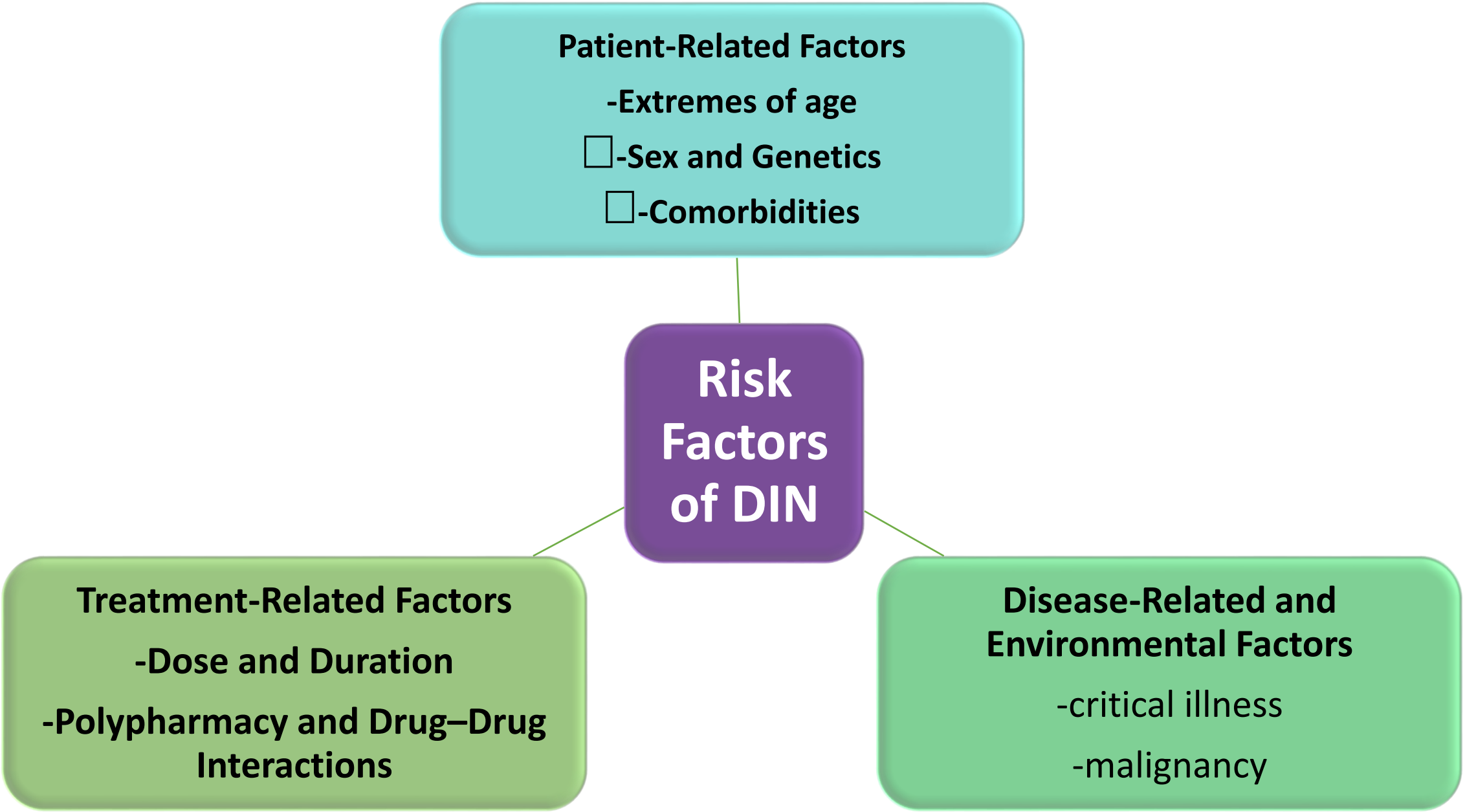
- **TMA**: Microangiopathic hemolytic anemia + thrombocytopenia
- Causing variable end-organ damage caused by platelet thrombi in the microcirculation

- **Mechanism:** Direct endothelial toxicity or immune-related, such as induction of autoantibodies to ADAMTS-13 or antiplatelet antibodies (e.g., quinine)

- **Examples:** Chemotherapeutic agents (e.g., mitomycin-C, gemcitabine), interferon-alfa, CNIs, antiplatelet agents (e.g., ticlopidine, clopidogrel), muromonab-CD3, and quinine

- **Common manifestations**: Hypertension, proteinuria, and AKI (Maybe severe and irreversible)

- **Recommended treatments:** Corticosteroids, Antiplatelet agents, Vincristine, Plasmapheresis, and IVIG are sometimes effective
- Pediatric reports of drug-induced TMA is scarce (a recent report described an adolescent with TMA following valproic acid toxicity)


Patient-Related Factors
-Extremes of age
-Sex and Genetics
-Comorbidities
Risk Factors of DIN
Treatment-Related Factors
-Dose and Duration
-Polypharmacy and Drug–Drug Interactions
Disease-Related and Environmental Factors
-critical illness
-malignancy

Clinical Manifestations and Diagnosis

Clinical features include:

- **AKI**: Oliguria, elevated serum creatinine, and reduced GFR, per KDIGO criteria (≥0.3 mg/dL increase in 48 hours or ≥50% increase in 7 days).

- **Tubular Dysfunction**: Fanconi syndrome (ifosfamide) with glycosuria, aminoaciduria, and electrolyte wasting.

- **Electrolyte Imbalances**: Hypomagnesaemia (cisplatin) and hypokalaemia (aminoglycosides).

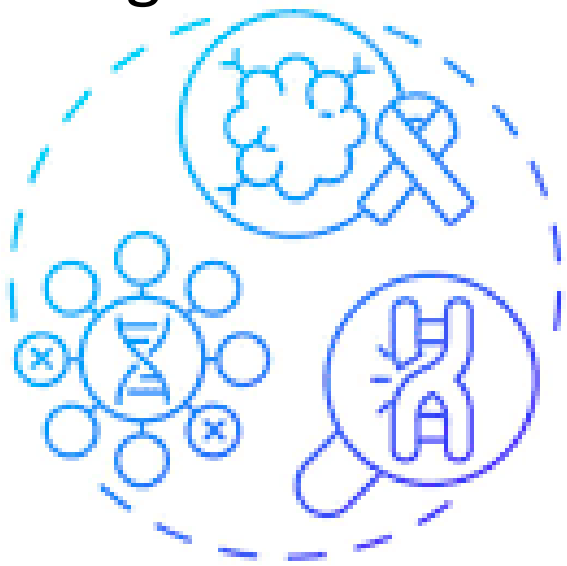
- **AIN**: Fever, rash, eosinophilia (NSAIDs, β-lactams).

Diagnostic Challenges:

- Serum creatinine is unreliable in children due to low muscle mass and rapid renal maturation.
- Neonates have higher baseline creatinine (0.8–1.2 mg/dL) due to maternal transfer.
- Creatinine may double but still be in normal range in pediatric population
- Creatinine rises with delay after AKI

Novel Kidney biomarkers

- Detects kidney damage early before the kidney reserve is depleted and creatinine levels increase.
- Reflects the level of toxicity to describe dose dependence
- Displays similar reliability across different species (including humans).
- Identifies the location of the renal injury.
- Monitors the recovery and progression of the injury



Kidney biomarkers

- **Urinalysis** may reveal glycosuria, proteinuria, or eosinophiluria (AIN)
  - **Proteinuria:**
    - HMW proteins: Albumin and IGG4 , Type IV collagen Glomerular injury
    - LMW proteins (β2-microglobulin, alpha-1 microglobulin, retinol binding proteins and cystatin C (cysteine proteases inhibitor) tubular injury

- **Cytokines:** indicate tissue healing process
  - Interferons, interleukins (IL), (TNF-α), colony-stimulating factors, and numerous growth factors are potentially nephrotoxicity indicators

- **KIM-1 (Kidney injury molecule-1):** Elevated within 24–48 hours, with 85% sensitivity

- **NGAL:** Detected within 6–12 hours, with 80–90% sensitivity.

- **MicroRNAs**: miR-21 and miR-192 (needs more evaluation)

Table 2 List of biomarkers for evaluation of nephrotoxicity [35–42]

Sr. No.	Kidney area	Nephrotoxicity induced by drug	Biomarker
1.	Proximal convoluted tubule	Aminoglycosides, Methamphetamine, Amphotericin-B, Heroin, Adefovir, Cisplatin, Cocaine, Methadone and Foscarnet	α-GST, NAG, Protein in urine, Retinol binding proteins, Albumin, Transferrin, IgG, β2-microglobulin, interferons, α1-microglobulin, Cytokines, TNF, osteopontin, clusterin, KIM-1, NGAL, urinary proteins with enzymatic activity, Cystatin C, interleukins
2.	Distal convoluted tubule	Lithium, Indinavir, Amphotericin-B, Sulfonamides and Acyclovir	Osteopontin, NGAL, Clusterin
3.	Glomerulus	NSAIDs, Quinone, Cyclosporin, ACE inhibitor, Antiplatelet drugs, ARBs and Mitomycin-C	Proteinuria, Cytokines, IgG, TNF, Albumin, Cystatin C, β2-microglobulin, Retinol binding proteins, Interleukins, α1-microglobulin, Interferons, Type IV collagen and transferrin

Prevention

- Consider the risk factors for nephrotoxicity (dehydration, sepsis, DM, CKD)
- Calculation of an appropriate dose
- Correct evaluation of renal function prior to and during treatment
- Early detection of kidney injury

Preventive Measures:

- **Drug related:**
  - **Once daily dose** : aminoglycosides
  - **longer infusion**: amphoB, Cisplatin
  - **Avoiding nephrotoxic combinations**
  - **Correct dosage based on IBW in obese, GFR in CKD,…**
  - **Urinary alkalinization (pH >7) prevents methotrexate precipitation.**
  - **Therapeutic Drug Monitoring**: Vancomycin , CNI
  - **Antioxidants:**
    - N-acetylcysteine reduces ifosfamide toxicity
    - Theophylline reduces cisplatin toxicity

- **Patient related factors :**
  - **Sepsis** : beyond hemodynamic changes , endotoxins has synergistic interactions with potentially toxic substances
  - **Hypoalbuminemia** :increases the risk of nephrotoxicity of cisplatin and aminoglycosides

Contrast-induced Nephropathy (CIN)

- Radio contrast is one of the most common causes of in-hospital AKI.
- The rise in serum creatinine within the first 24–48 h after exposure
- The AKI is usually reversible within 7–10 days

- Mechanism : afferent vasoconstriction shortly after injection, Renal medullary hypoxia, Osmotic nephrosis
- Prevention :NAC + IV hydration

- Indication: children with CKD GFR<60 **and** a history of contrast-induced AKI in the past, or when the patient is already on two nephrotoxins and contrast will be the third nephrotoxin to be used.

- For children with CKD and GFR <60 mL/min/1.73m^2) **and no** history of contrast-induced AKI in the past, we use the IV hydration with D5W and $NaHCO_3$ protocol but do not routinely add NAC.

Protocol IV hydration and NAC to prevent CNI

- **IV hydration with D5W and $NaHCO_3$ (70 meq/L) at 2400 mL/m^2 for 6 hours before and continuing through 2 hours after contrast administration**

- **NAC 12 mg/kg given either IV or orally every 12 hours for four total doses (one dose before and three doses after contrast administration).**

- The efficacy of this approach has not been systematically studied.

Management:

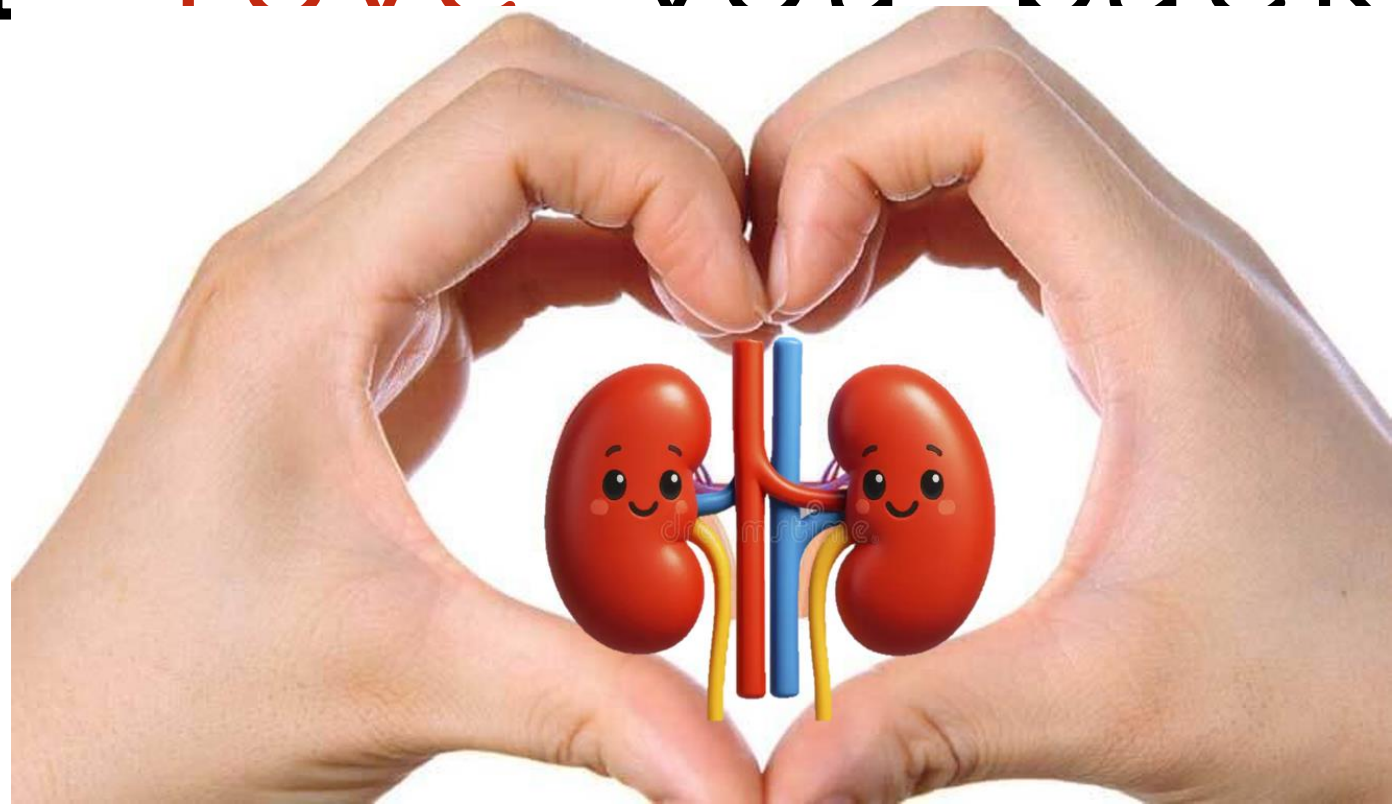
- **Drug Discontinuation**: Immediate cessation of the offending drug.

- **Supportive Care**: Hydration, electrolyte correction (e.g., magnesium, potassium), and nutritional support.

- **AIN Treatment**: Prednisone (1–2 mg/kg/day) for biopsy-confirmed AIN, with 60–80% response rates.

- **Dialysis**: High-flux hemodialysis for severe AKI (e.g., methotrexate, vancomycin).

Love your kidneys they will love you back



Thank You