Antiviral Drug–Induced Nephrotoxicity

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Introduction

- Medications are a relatively common cause of AKI in hospitalized patients and those in the intensive care unit.
- Depending on the definition employed, drugs are associated with AKI in 14%–26% of adults in prospective cohort studies and 37.5% in a cross-sectional survey.
- The proximal renal tubule presents a large area for nephrotoxin binding and transport into the renal epithelium.

Risk Factors

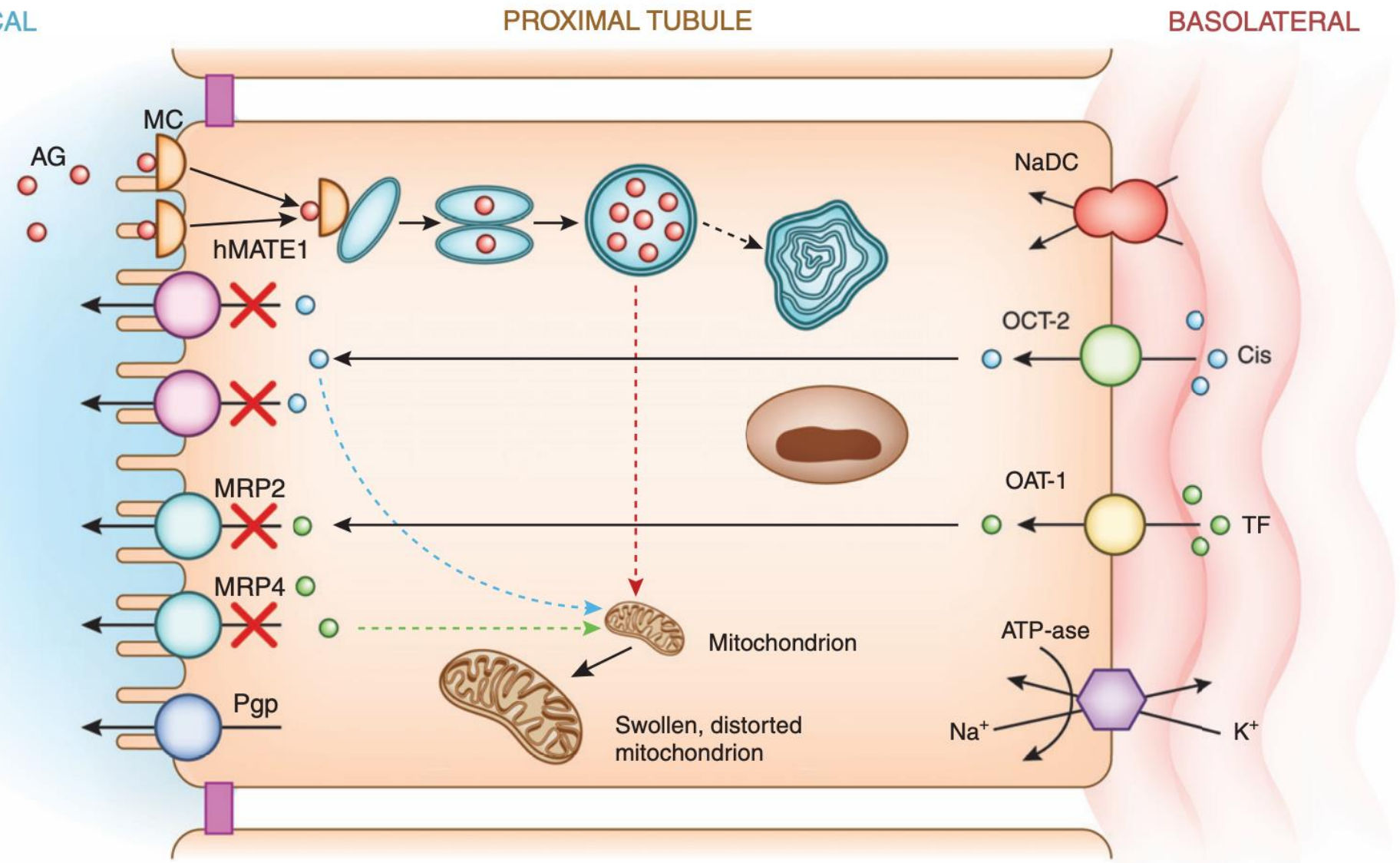
Table 3. Common risk factors for drug-induced acute tubular injury

Modifiable Risks	Nonmodifiable Risks
Volume depletion and/or hypotension	Advanced age especially with concomitant CKD (eGFR<45 ml/min per 1.73 m^2)
Exposure to concomitant nephrotoxins	Comorbid conditions such as liver disease, diabetes mellitus, heart failure, major surgery (especially cardiovascular)
High-level exposure to nephrotoxins (high-dose and long-duration therapy)	High-risk settings such as intensive care unit, burn unit, cardiovascular care unit
Excessive medication dose for underlying GFR	Shock states such as sepsis
	Solid organ transplantation
	Stem cell transplantation
	Genetic vulnerability

Pathogenesis

- Although tubular cell death is a significant component of toxicity associated with several antiviral drugs, others may induce small amount of injury without cell death or apoptosis, resulting in such isolated tubular damages, thereby likely causing Fanconi-like syndrome, distal tubular acidosis and nephrogenic diabetes insipidus (NDI).
- There are 3 mechanisms of antiviral agents that could induce proximal tubule injury:

1. transporter defects
2. apoptosis
3. mitochondrial damage


APICAL
PROXIMAL TUBULE
BASOLATERAL
MC
AG
hMATE1
NaDC
OCT-2
Cis
MRP2
OAT-1
TF
MRP4
Mitochondrion
ATP-ase
Pgp
Swollen, distorted mitochondrion
Na+
K+

Pathogenesis

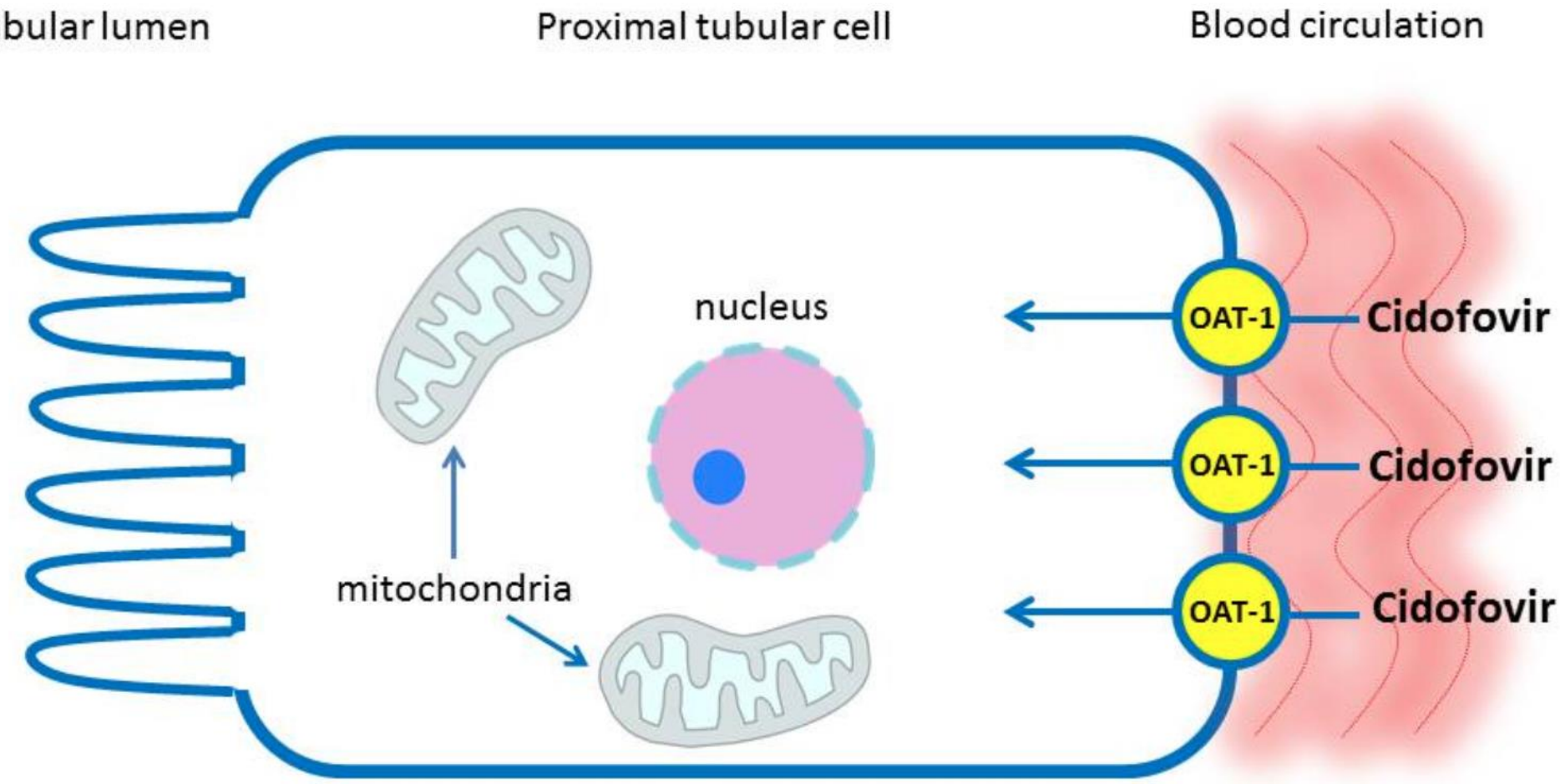
- Genetic defects in transporters, as in human organic anion transporter 1 (hOAT-1), human organic cation transporter (hOCT), or multidrug resistance-associated protein type 2 (MRP-2), may induce renal insufficiency antiviral drugs therapy.
- The pathophysiology is increase in intracellular influx through hOAT-1 and a defect in luminal excretion through MRP-2 or both usually from genetic disorders in transporters.
- Intrarenal obstruction can occur when crystalline deposits form in the renal tubule in response to acyclovir, ganciclovir, and indinavir therapy.
- Finally, the glomerulus can be the target of the drug, resulting in proteinuria and, in some cases, nephrotic syndrome by immune-mediated complex (IFN)7,8 or crystal deposit.

1. ACUTE TUBULAR NECROSIS (ATN) (Cidofovir, tenofovir, adefovir)
2. ALLERGIC INTERSTITIAL NEPHRITIS (AIN)
3. CRYSTAL NEPHROPATHY

Cidofovir

- Cidofovir is a monophosphate NA with inhibitory activity against human herpesvirus, adenovirus, polyomavirus, papillomavirus, and poxvirus. It has also been used for treating acyclovir-resistant mucocutaneous HSV infection, adenovirus infection in transplant recipients.
- Cidofovir is excreted by the kidney via glomerular filtration and tubular secretion.
- Over 90% of the drug is excreted unchanged in the urine.
- Proximal tubular cell injury and AKI are dose dependent cidofovir nephrotoxicity.

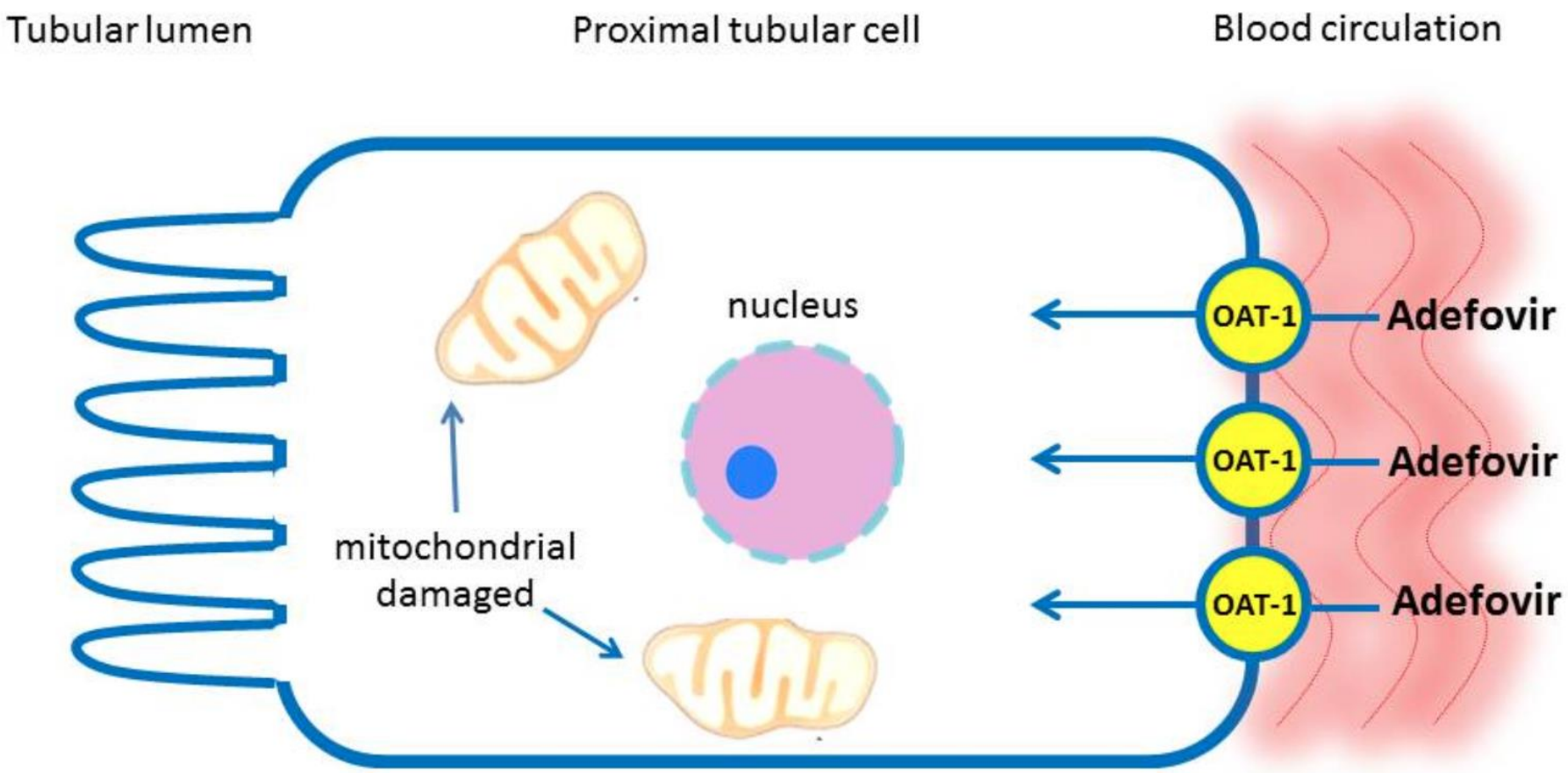
Cidofovir is delivered to the basolateral membrane, transported into the cell via human organic anion transporter-1 (OAT-1), and excreted into the urinary space via multidrug resistance proteins (MRPs).



Adefovir

- Adefovir dipivoxil is a diester prodrug of adefovir, an acyclic phosphonate NA of adenosine monophosphate. It enters cells and is de-esterified to adefovir.
- The adefovir dipovoxil dose is 10 mg once daily but must be reduced for those with renal impairment.
- The drug is excreted unchanged by the kidney through a combination of glomerular filtration and tubular secretion with secretion contributing about 60%.
- Dose reductions are recommended for GFR below 50 mL/min.

Adefovir has a high affinity for substrates of hOAT-1 but is only marginally transported by hOAT-3 (mitochondrial injury, impaired ATP synthesis, and/or interference with ATP-dependent cellular mechanisms)



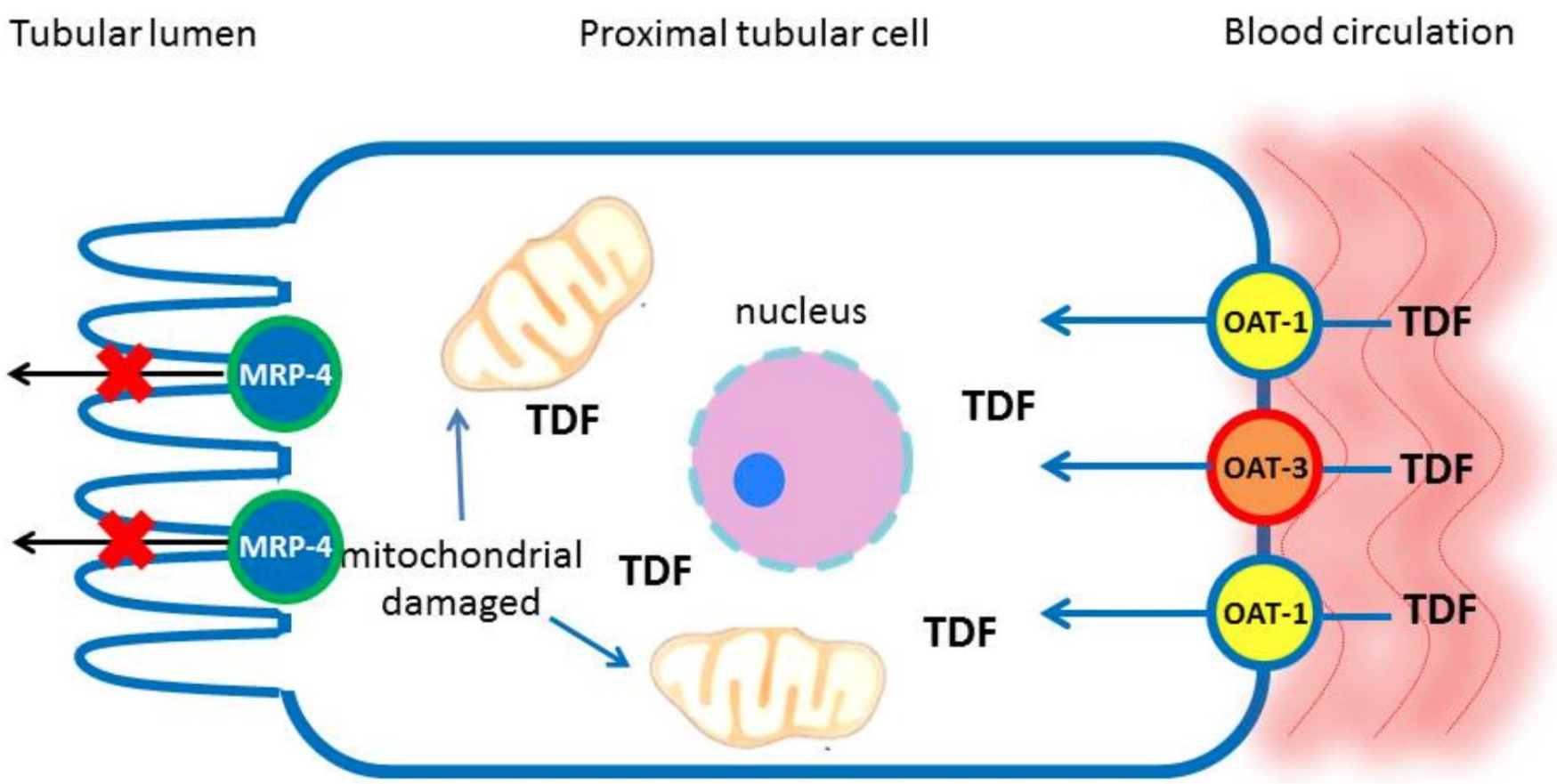
Adefovir

- Adefovir dipivoxil causes dose-related nephrotoxicity and tubular dysfunction, manifested by azotemia, hypophosphatemia, acidosis, glycosuria, and proteinuria, which are reversible after discontinuation.
- Side effects of adefovir lead to discontinuation of treatment in about 2% of the patients.
- After 3 years of treatment, the risk of serum creatinine levels increasing above 0.5 mg/dL is approximately 3-4% but is higher in patients with pre-existing renal insufficiency.

Tenofovir

- Tenofovir disoproxil fumarate (TDF) is a nucleotide analogue reverse-transcriptase inhibitor (NtRTI). It is used to treat chronic hepatitis B and to prevent and treat HIV patients.
- Tenofovir is excreted unchanged in the urine by a combination of glomerular filtration and proximal tubular secretion, and 20 - 30% of the drug is actively transported into the renal proximal tubular cells by hOAT-1.
- Kidney toxicity may lead to AKI, chronic kidney disease (CKD), and proximal tubular injury, including Fanconi syndrome, isolated hypophosphatemia, and decreased bone mineral density.

Tenofovir is taken up by (hOAT)-1 and hOAT-3 and effluxed into urine by (MRP)-4 in proximal tubule cells. MRP-4 transporter mutation or drug competition, inducing accumulation of tenofovir and damaged mitochondria of proximal tubular cells



- Tenofovir alafenamide (versus tenofovir disoproxil) is less nephrotoxic due to its conversion to active drug in lymphocytes, resulting in much lower plasma levels.
- Nucleoside analogues, including zidovudine, stavudine, didanosine, zalcitabine, and lamivudine, also are substrates of OAT1, but these agents have not been associated with tubular dysfunction.

Tenofovir

- Given the importance of proximal tubule transport of these agents, certain drugs that block hOAT1 and cellular uptake (probenecid) may decrease nephrotoxicity.
- In contrast, drugs such as nonsteroidal anti-inflammatory drugs (NSAIDs) that block apical tenofovir efflux through MRP4 increase kidney injury.
- The most effective treatment of tenofovir-related acute tubular injury is early drug discontinuation, which enhances resolution of tubular dysfunction.
- Approximately 50% of patients completely recover kidney function to baseline levels over weeks to months after AKI.

Prevention and Treatment

- There are no specific therapies for acute tubular injury and, thus, therapy is largely conservative and focused on stopping offending agents, avoiding further kidney injury by maximizing kidney perfusion with intravenous fluids, and avoiding nephrotoxins.
- In addition, recognition of clinical scenarios of high risk is critical in alerting clinicians to the need for avoidance of nephrotoxic agents.
- Recognition of the early signs of tubular injury utilizing sensitive biomarkers may also hold future promise to predict early kidney injury and allow cessation of potential nephrotoxins.

1. ACUTE TUBULAR NECROSIS (ATN)
2. ALLERGIC INTERSTITIAL NEPHRITIS (AIN):
3. CRYSTAL NEPHROPATHY

Allergic Interstitial Nephritis

- AIN is an immune-mediated form of kidney injury that is characterized histologically by infiltration of immune cells in the tubulointerstitium.
- The hallmark of classic AIN is rapid onset of AKI after the initiation of a suspect drug.
- kidney injury is usually non-oliguric and severe AKI and dialytic therapy are usually needed.
- The clinical presentation includes, fever, rash and eosinophilia.

Allergic Interstitial Nephritis

- The onset may range from 3 to 20 days and may be accelerated following re-challenge.
- In addition, AIN is often accompanied by low grade proteinuria
- Biopsy findings consistent with interstitial infiltration of immune cells.
- Diagnosis is based on clinical evidence
- Ultrasound or computerized tomography (CT) scanning may show renal enlargement.

Atazanavir

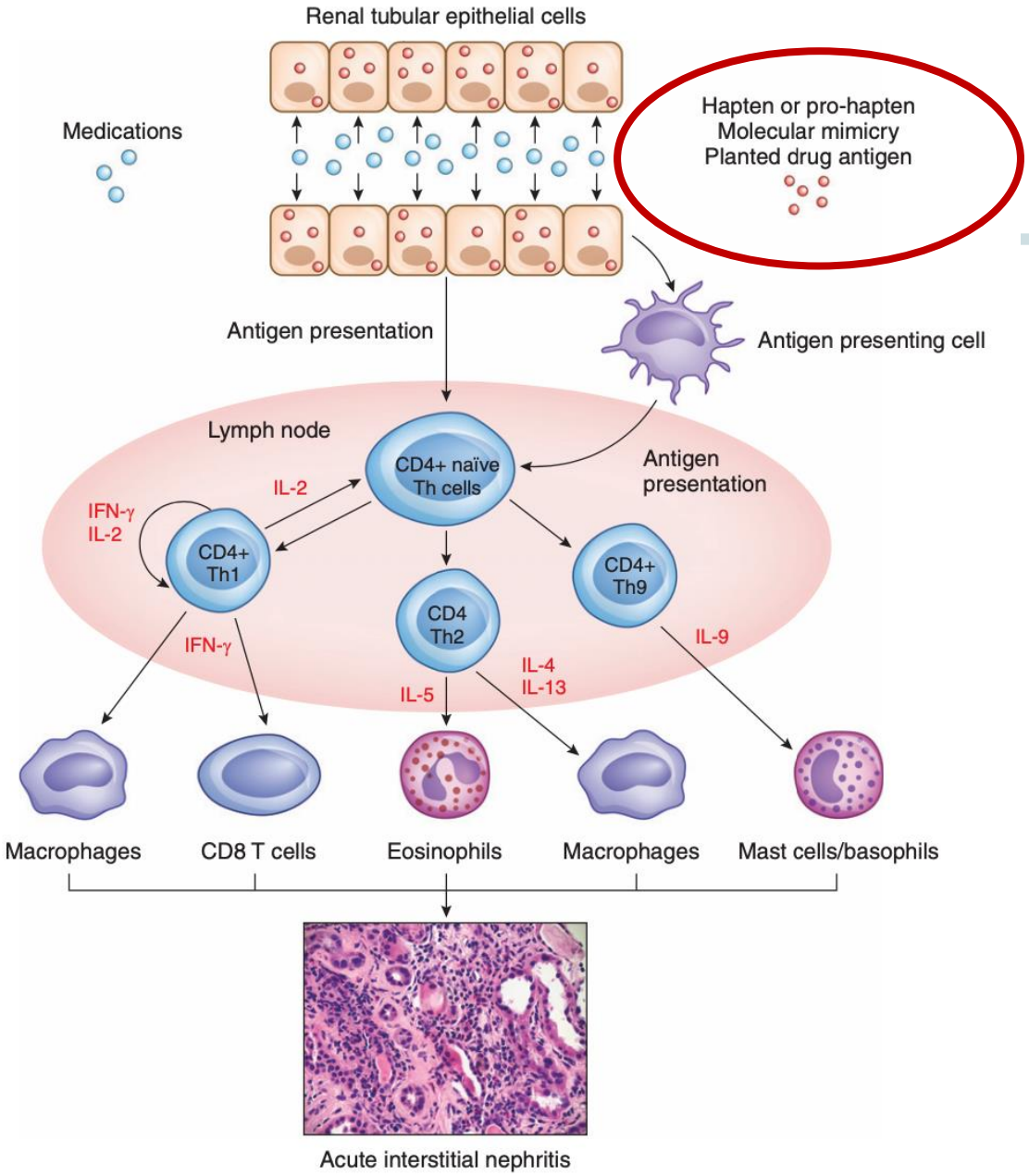
- Atazanavir, an azapeptide protease inhibitor (PI) that is active against both HIV-1 and HIV-2.
- Atazanavir, with or without ritonavir, is approved for the treatment of adults with HIV.
- Atazanavir and its metabolites, which are insoluble in urine, frequently cause renal cell injury.
- In addition to drug characteristics that induce insolubility, factors such as urine pH, slow urine flow rates, and rapid parenteral administration increase the risk for precipitation and crystallization in distal tubular lumens.

pathogenesis

- Drug-induced AIN is considered primarily a T cell–driven process that is often limited to the kidneys.
- High drug concentrations within kidneys
- Local drug metabolism before excretion, or
- Damage caused to tubular epithelial cells are important factors

Medications or their metabolites can incite an immune response through various processes:

- They can bind to TBM and act as haptens or prohaptens, mimic an antigen that is normally present on TBM or interstitium, or deposit within the interstitium, thereby inducing an immune response directed at this antigen.
- Dendritic cells interspersed between tubular cells recognize these drug-related antigens, migrate to local lymph nodes, and initiate adaptive immune responses.
- These cells then produce various cytokines such as ILs and IFNs, which attract a number of cells (macrophages, eosinophils, CD8 T cells, and mast cells/basophils) to the tubulointerstitium.
- These cells can participate in the development of acute interstitial nephritis.


Renal tubular epithelial cells
Medications
Hapten or pro-hapten
Molecular mimicry
Planted drug antigen
Antigen presentation
Antigen presenting cell
Lymph node
CD4+ naïve Th cells
Antigen presentation
IL-2
IFN-γ
IL-2
CD4+ Th1
CD4+ Th9
CD4 Th2
IL-9
IFN-γ
IL-4
IL-13
IL-5
Macrophages
CD8 T cells
Eosinophils
Macrophages
Mast cells/basophils
Acute interstitial nephritis

atazanavir

- Withdrawal of atazanavir does not lead to the recovery of renal function.
- Therefore, periodic careful monitoring of hematuria and renal function tests are the most important in early identification of AIN or GIN.
- Dose reduction should be considered when hematuria is sustained concurrently with crystalluria.

Treatment of Drug Induced AIN

- In patients suspected of having drug-induced AIN, drug discontinuation is critical.
- Given the immune-mediated nature of kidney damage, corticosteroids are often prescribed.
- However, corticosteroid dosing regimens are not standardized and vary widely.
- Outcome data consist of positive and negative effects that are limited to observational studies.
- In some but not all studies, earlier corticosteroid therapy was associated with benefit.
- Furthermore, no differences in kidney function outcomes were derived from high-dose intravenous corticosteroid versus 1 mg/kg oral prednisone.

Table 5. Corticosteroid therapy in acute interstitial nephritis

Author, Year	Sample Size		Peak sCr (mg/dl) or eGFR (ml/min per 1.73 m^2)		Final sCr (mg/dl) or eGFR (ml/min per 1.73 m^2)		Follow-Up (months)	Study Details
	CS	No CS	CS	No CS	CS	No CS		
Clarkson, 2004 (89)	26	16	7.9	6.1	1.6	1.6	12	Patients received CS late after diagnosis (median delay >3 wk).
Gonzalez, 2008 (85)	52	9	5.9	4.9	2.1	3.7	19	CS-treated patients with complete recovery had shorter delay to CS (13 d) as compared with those without complete recovery (34 d).
Raza, 2012 (84)	37	12	6.5	5.2	2.8	3.4	19	Improved GFR with CS versus control ($P<0.05$). No difference in renal outcomes on the basis of CS timing.
Muriithi, 2014 (73)	83	12	3.0	4.5	1.4	1.5	6	CS-treated patients had superior renal outcomes with early versus late CS therapy.
Valluri, 2015 (87)	73	51	4.03	3.16	NR	NR	12	Worse renal function in CS-treated versus control at biopsy (sCr 4.2 versus 3.3 mg/dl). CS-treated patients had complete recovery (48%) versus control group (41%); final sCr not different at 1 yr.
Prendecki, 2016 (86)	158	29	eGFR 20.5	eGFR 25	eGFR 43	eGFR 24	24	CS-treated patient had better eGFR at 2 yr and less dialysis (5.1% versus 24.1%). Dose, duration, and time to CS initiation were variable.
Yun, 2019 (88)	82	20	4.67	4.43	NR	NR	33 (median)	Kidney recovery at 6 mo: CS 58.5% versus 50% (NS); kidney recovery at last F/U: CS 78% versus 65% (NS); kidney failure: CS 14.6% versus 20% (NS).

CS, corticosteroids; NR, not reported; sCr, serum creatinine concentration; NS, not significant; F/U, follow-up.

Treatment

- Identifying patient subgroups that may benefit from corticosteroids is paramount.
- These include those with higher GFR at biopsy and histology with more infiltrate and less fibrosis.
- Patients with brittle diabetes, advanced cancers, and severe infections may not be candidates for corticosteroids due to their associated adverse effects.

Treatment

- Because kidney recovery occurs primarily within the first month after diagnosis, we recommend oral corticosteroids for approximately 4–6 weeks with rapid taper if no response is seen.
- Other than corticosteroids, immunosuppressive agents such as azathioprine and mycophenolate mofetil have been employed on the basis of limited data.

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3. CRYSTAL NEPHROPATHY

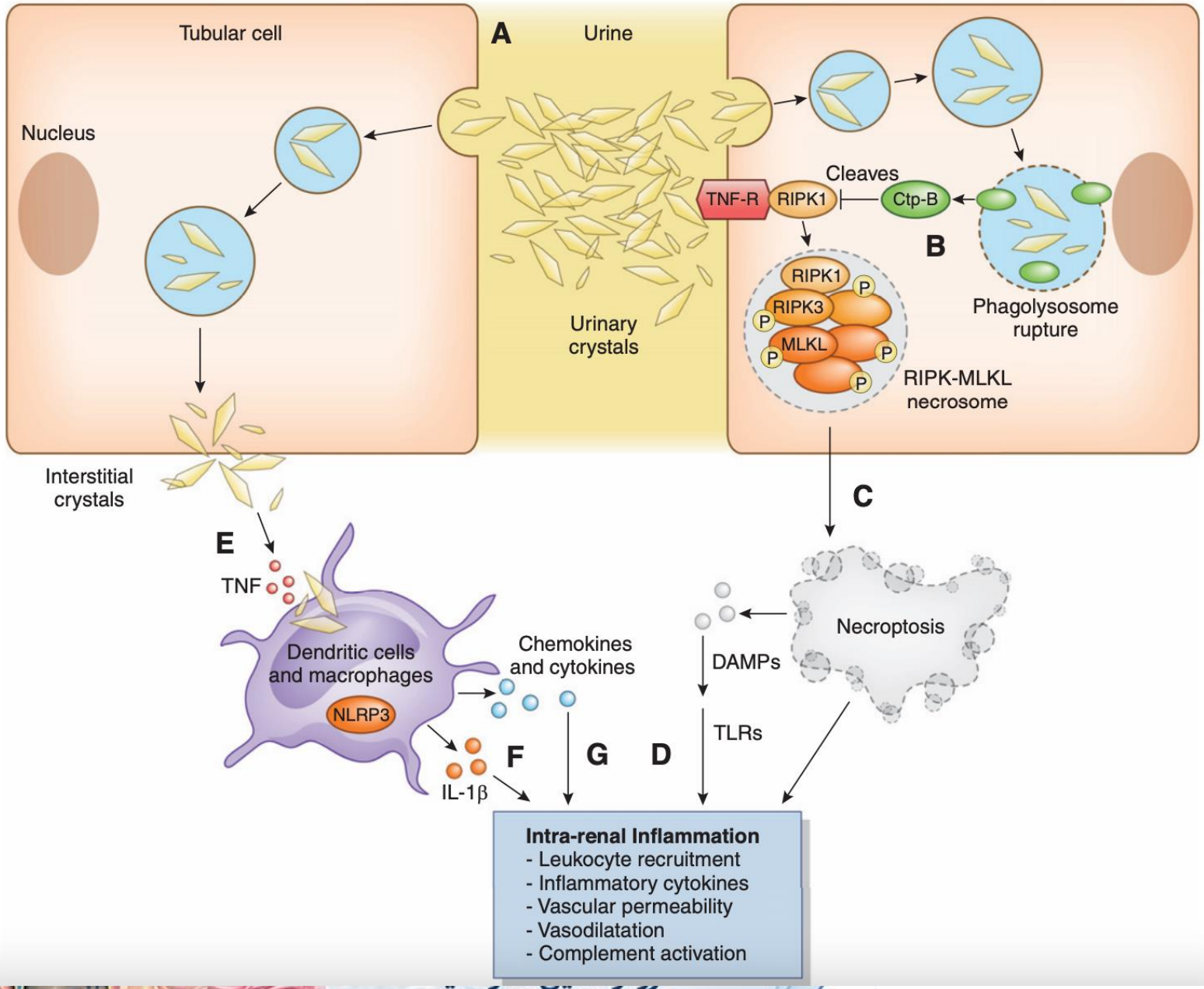
Crystal Neohropathy

- Deposition of crystals within the kidney can promote acute and chronic kidney injury.
- Renal dysfunction usually occurs owing to precipitation of crystals in distal tubular lumens.
- Several routinely prescribed drugs can cause crystal-induced AKI termed "crystal nephropathy".
- Clinical presentation and laboratory findings, in particular urine microscopy, can be helpful for diagnosis of drug-induced crystalline nephropathies.

Crystal Neohropathy

- Intrarenal crystal deposition occurs primarily due to the kidney route of drug/metabolite excretion and enhanced drug supersaturation within urine.
- Supersaturation of drugs with crystal-forming capacity occurs with volume depletion/dehydration, which lowers urinary flow rates.
- Excessive drug dosing, which increases urinary drug concentrations, causes intratubular crystal deposition with several medications.
- Urine pH also influences supersaturation depending on the pK of the drug in question
- The presence of underlying kidney disease may further enhance risk for drug-induced crystalline nephropathy

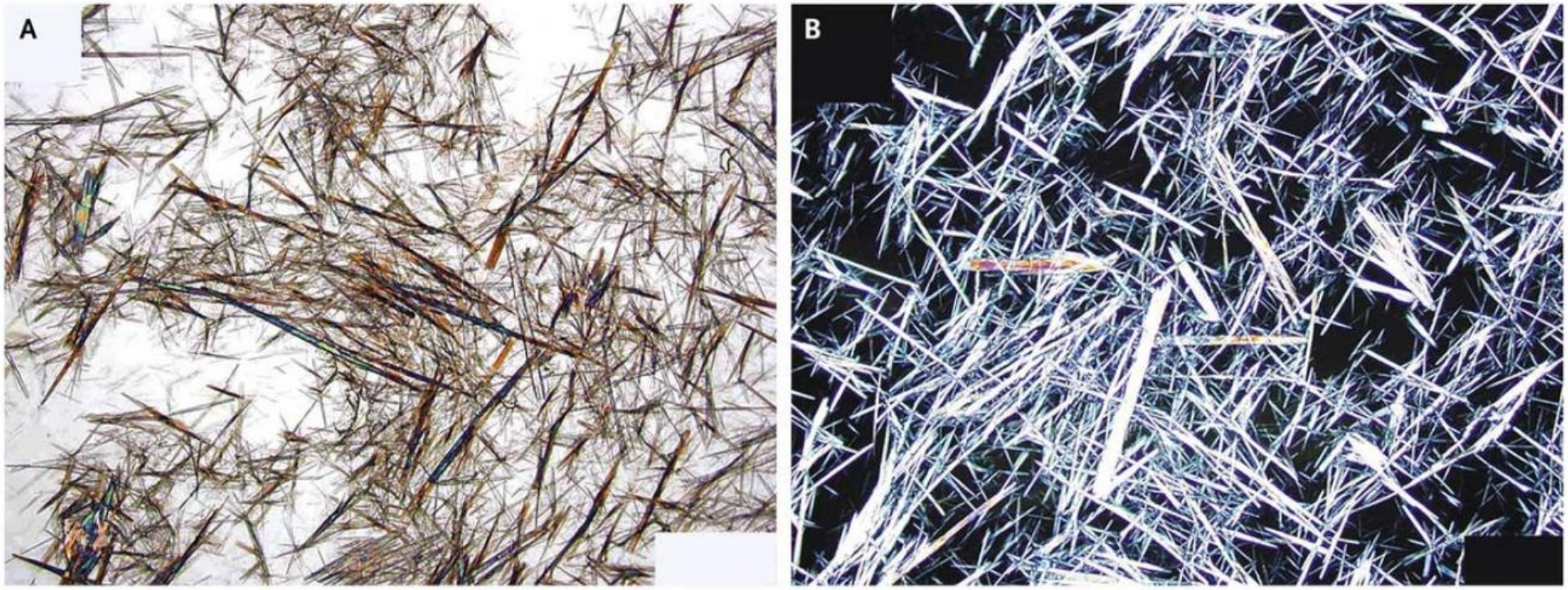
Agent	Mechanism(s) of kidney injury	Proposed approaches to minimize toxicity
Antivirals		
aciclovir[a], valaciclovir	• poor solubility in urine leads to formation of crystal deposits and tubular obstruction • crystal formation more likely with rapid infusions, high-dose therapy and in the setting of volume depletion • crystal formation often occurs early in therapeutic course (first 1–2 days)	• use of slow infusions and optimization of hydration status and urine output prior to administration decreases formation of crystals and reduces toxicity with intravenous aciclovir


Tubular cell
A
Urine
Nucleus
Urinary crystals
Cleaves
TNF-R
RIPK1
Ctp-B
B
RIPK1
RIPK3
MLKL
P
RIPK-MLKL necrosome
Phagolysosome rupture
Interstitial crystals
C
E
TNF
Dendritic cells and macrophages
NLRP3
Chemokines and cytokines
DAMPs
Necroptosis
TLRs
F
G
D
IL-1β
Intra-renal Inflammation
- Leukocyte recruitment
- Inflammatory cytokines
- Vascular permeability
- Vasodilatation
- Complement activation

Acyclovir

- Renal excretions of unchanged drugs are 62 - 91% of acyclovir.
- Acyclovir is relatively insoluble in urine.
- This low urine solubility and low urine output concomitant with volume contraction may induce drug crystallization in distal tubules.
- Intravenous bolus injection of acyclovir contributes to intratubular precipitation of crystals.
- Crystal nephropathy usually develops within 24 to 48 hours of acyclovir administration.

birefringent needle-shaped crystals (Panel A; visualized under polarizing light in Panel B)



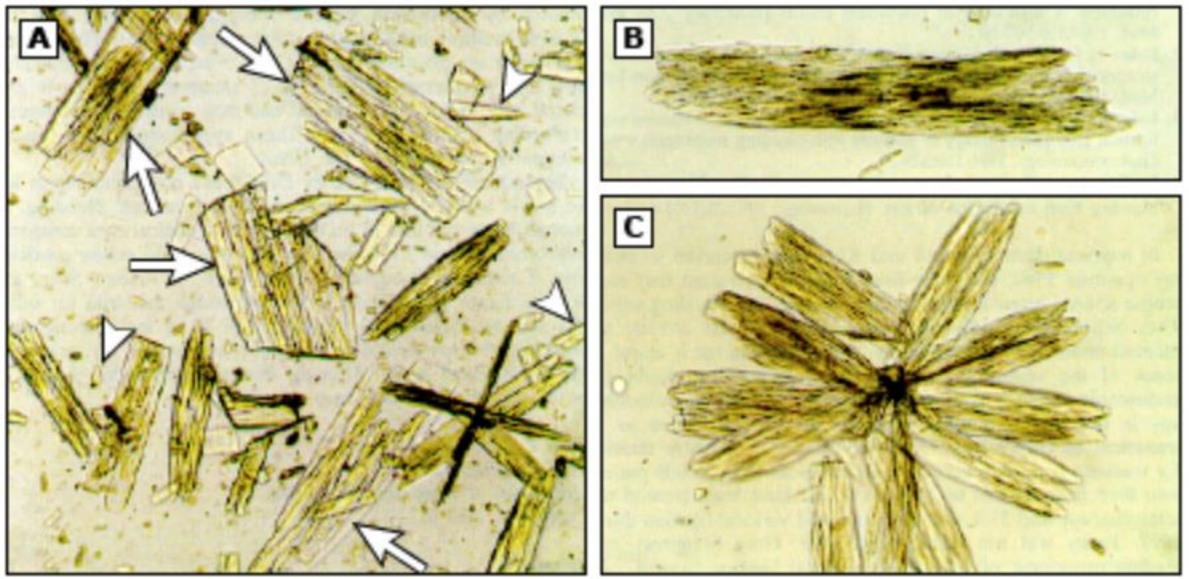
Indinavir

- Indinavir is a protease inhibitor used in the treatment of HIV infection.
- Approximately 20 % of the drug is cleared by kidney.
- Indinavir has low solubility at a pH of 6.0 but is quite soluble at a pH of 3.5.
- This has important clinical implications because precipitation of indinavir crystals occurs within the tubular lumens in human urine at a pH of 5.5 – 7.0.
- Intra-renal tubular obstruction can cause AKI or CKD.
- Interstitial fibrosis and obstructing calculi can lead to renal dysfunction.

Indinavir

- The nephrotoxicity of indinavir has two syndromes, acute nephrolithiasis and chronic indolent renal insufficiency.
- Renal colic, dysuria, back or flank pain, and gross hematuria have been described in HIV-infected patients treated with indinavir.
- In asymptomatic patients, elevated serum creatinine concentrations or abnormal urinalysis may be the only clue to renal injury.
- Microscopy of the urine sediment reveals crystals of varying shapes, including plate-like rectangles, fan-shaped crystals, and star bust forms.

Photomicrographs showing urine sediment of a patient with indinavir sulfate crystalluria



Light microscopic photographs of a fresh unstained preparation of urinary sediment showing three different forms of indinavir sulfate crystals.

(A) Rectangular plates of various sizes containing needle-shaped crystals. The plates have irregular borders with occasional tapering, and internal layering evident in the largest forms (arrows). Small, triangular pieces (arrowheads) represent broken ends of needles.

(B) A sheaf of densely packed indinavir sulfate needles.

(C) Several indinavir crystal groupings are arranged in a rosette.

Foscarnet

- Foscarnet is an inorganic pyrophosphate analog that inhibits herpesvirus DNA polymerase, RNA polymerase, and HIV reverse transcriptase directly.
- Clearance of foscarnet is primarily renal and is directly proportional to creatinine clearance.
- Serum drug concentrations are reduced to 50% by hemodialysis.
- Potential adverse effects of foscarnet include crystal nephropathy, hypo- or hypercalcemia, hypo- or hyperphosphatemia, hypokalemia, and hypomagnesemia.

Prevention and Treatment

- Appropriate drug dosing for level of GFR,
- Correcting any underlying volume depletion,
- Achieving high urinary flow rates, and
- Targeting a urine pH (when applicable) to prevent intratubular crystal precipitation.

Prevention and Treatment

When AKI develops, treatment includes:

- culprit medication discontinuation,
- fluids to restore euvolemia and enhance tubular flow rates, and
- avoidance of concomitant nephrotoxin exposure.

Specific treatment considerations for each form of crystalline nephropathy include:

- modification of urine pH to enhance solubility,
- interventions to reduce plasma and urine drug concentrations, and
- rarely extracorporeal therapy

Thrombotic Microangiopathy

- TMA has been observed in patients treated with IFN for chronic myelogenous leukemia, hairy cell leukemia, and hepatitis C. How
- IFN may enhance cellular immunity and stimulate HLA-DR antigen expression on glomerular and tubular cells with subsequent attack by activated lymphocytes.
- Moreover, IFN-α may induce the production of autoantibodies, and the presence of antiphospholipids also was reported in patients with IFN-associated TMA.
- Finally, a direct nephrotoxic effect has been proposed.
- Only 1 case of TMA associated with ARF has been reported in an immunocompromised patient treated with valacyclovir.