EXTRACORPOREAL NEPHROLOGY GROUP [ECNG]

ACYCLOVIR NEPHROTOXICITY

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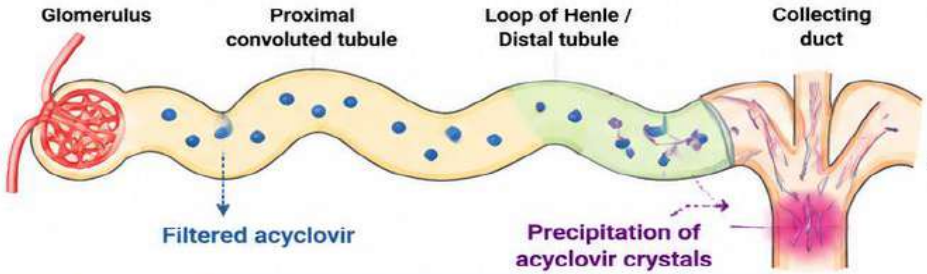
ACYCLOVIR NEPHROTOXICITY

MECHANISM (Crystal–Induced Acute Kidney Injury)

IV acyclovir (high dose) + dehydration /rapid infusion →



→
- Crystal deposition in tubular lumen (mainly distal tubule & collecting duct)
- Tubular obstruction
- ↑ Tubular pressure
- Decreased GFR
- Tubular epithelial injury
- Interstitial inflammation

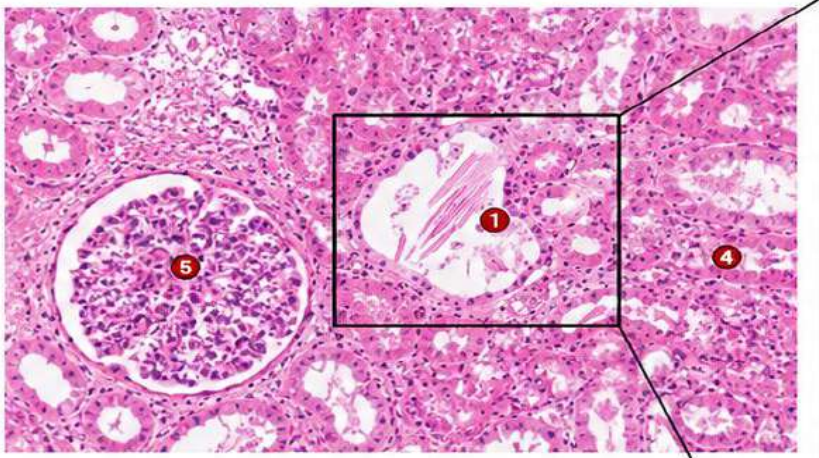
↓

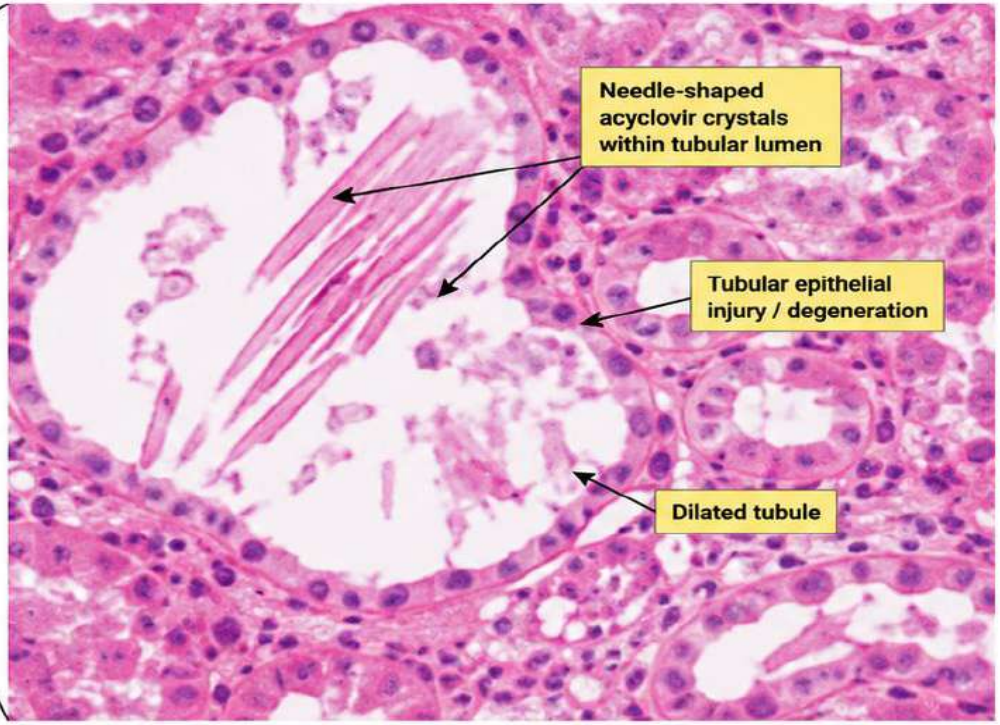
Acute Kidney Injury

Risk factors
- High dose IV acyclovir
- Dehydration / volume depletion
- Pre-existing CKD
- Rapid infusion
- Concomitant nephrotoxins

Management
- Adequate IV hydration
- Slow infusion
- Dose adjustment in renal impairment
- Discontinue / reduce dose if possible
- Hemodialysis in severe cases (acyclovir is dialyzable)

HISTOLOGY (HEMATOXYLIN & EOSIN)





1. Intratubular eosinophilic needle–shaped crystal casts
2. Dilated tubules with flattened/degenerating epithelium
3. Tubular epithelial injury – vacuolization, sloughing, necrosis
4. Interstitial edema with inflammatory cell infiltrate
5. Relative sparing of glomerulus

ACYCLOVIR DOSE ADJUSTMENT

1 STANDARD ADULT DOSING (NORMAL RENAL FUNCTION

IV: 5–10 mg/kg every 8 h (based o ideal body weight)

- **Oral:** 800 mg five times daily for HSV/VZV

2 RENAL DOSE ADJUSTMENT (CrCl)

Creatinine Clearance (mL/min)	Oral Dose	IV dose Recommendat
≥50	800 mg 8 h	5–10 mg/kg q 12.h
25–49	800 mg 12 h	5–10 mg/kg q24 h
10–24	800 mg 24 h	2.5–5 mg/kg q 24 h
<10	800 mg 24 h	2.5–5 mg/kg q 24 h

- Use actual body weight if obese; monitor serum creatinine and urine output.

3 HEMODIALYSIS / PERITONEAL DIALYSIS

- **Hemodialysis:** Give usual dose after dialysis (removes ~50% drug).
- **Peritoneal Dialiysis:** Follow CrCl < 10 mL/min regimen.

4 KEY MONITORING

- **Renal Function:** SCr. BUN dalsily in acute therapy
- **Neurotoxicity Signs:** confusion, tremor, seizures
- Ensure adequate IV fluids to reduce crystal nephothy risk

CLINICAL PEARLS

- Adjust promptly for acute kidney injury to avoid neurotoxicity.

ACYCLOVIR IS DIALYSABLE

ACYCLOVIR NEPHROTOXICITY – DRUG DOSE ASSOCIATED WITH TOXICITY

⚠ There is **NO absolute "safe" dose.** Nephrotoxicity (crystal-induced AKI) can occur even at standard doses, especially with **dehydration, rapid infusion** or **renal impairment.**

POPULATION / SETTING	USUAL RECOMMENDED IV DOSE	DOSE ASSOCIATED WITH NEPHROTOXICITY (Crystal-induced AKI)	NOTES / COMMENTS
Immunocompetent adults (HSV)	5–10 mg/kg IV every 8 h	• ≥ 10 mg/kg per dose • ≥ 30 mg/kg/day (total daily dose) Risk increases markedly > 30–45 mg/kg/day	• Most cases reported with total daily dose > 30–45 mg/kg/day • Risk higher with rapid infusion & dehydration
Immunocompromised adults (HSV)	10 mg/kg IV every 8 h	• ≥ 15 mg/kg per dose • ≥ 45 mg/kg/day (total daily dose) High risk > 45–60 mg/kg/day	• Increased risk with renal impairment, concomitant nephrotoxins
Severe infections (e.g., HSV encephalitis)	10–15 mg/kg IV every 8 h	• ≥ 15 mg/kg per dose • ≥ 45–60 mg/kg/day (total daily dose) Reports of AKI even at 30–45 mg/kg/day in high-risk patients	• Higher doses often required, but toxicity risk higher • Ensure slow infusion & hydration
Pediatrics (general)	10 mg/kg IV every 8 h	• ≥ 15 mg/kg per dose • ≥ 500 mg/m² per dose Increased risk when total daily dose > 30–45 mg/kg/day	• Pediatric studies show increased risk above 15 mg/kg/dose or 500 mg/m²/dose • Dose adjust in renal dysfunction
Patients with renal impairment	Dose adjust as per eGFR/CrCl	Toxicity can occur even at standard doses if dose is not adjusted for renal function	• Reduced clearance → drug accumulation • Strict dose adjustment essential

KEY POINTS

- No universal toxic threshold; risk relates to dose, concentration, hydration status, infusion rate and renal function.
- Total daily dose > 30–45 mg/kg/day is a major risk threshold in adults.
- Single dose ≥ 15 mg/kg (or ≥ 500 mg/m² in children) increases risk.
- AKI has been reported with even standard doses in high-risk situations (dehydration, CKD, rapid infusion).

FACTORS THAT INCREASE RISK AT ANY DOSE


Dehydration / volume depletion


Rapid infusion (< 1 hr)


Pre-existing CKD or reduced GFR


Concomitant nephrotoxic drugs


Acidic urine (pH < 6.5)

PREVENTION (DOSE-DEPENDENT)

- ✓ Adequate IV hydration (2–3 L/day)
- ✓ Slow infusion over 1–2 hours
- ✓ Dose adjustment as per renal function
- ✓ Avoid other nephrotoxins
- ✓ Maintain urine pH 7–7.5 (if needed)

ACYCLOVIR CRYSTALS

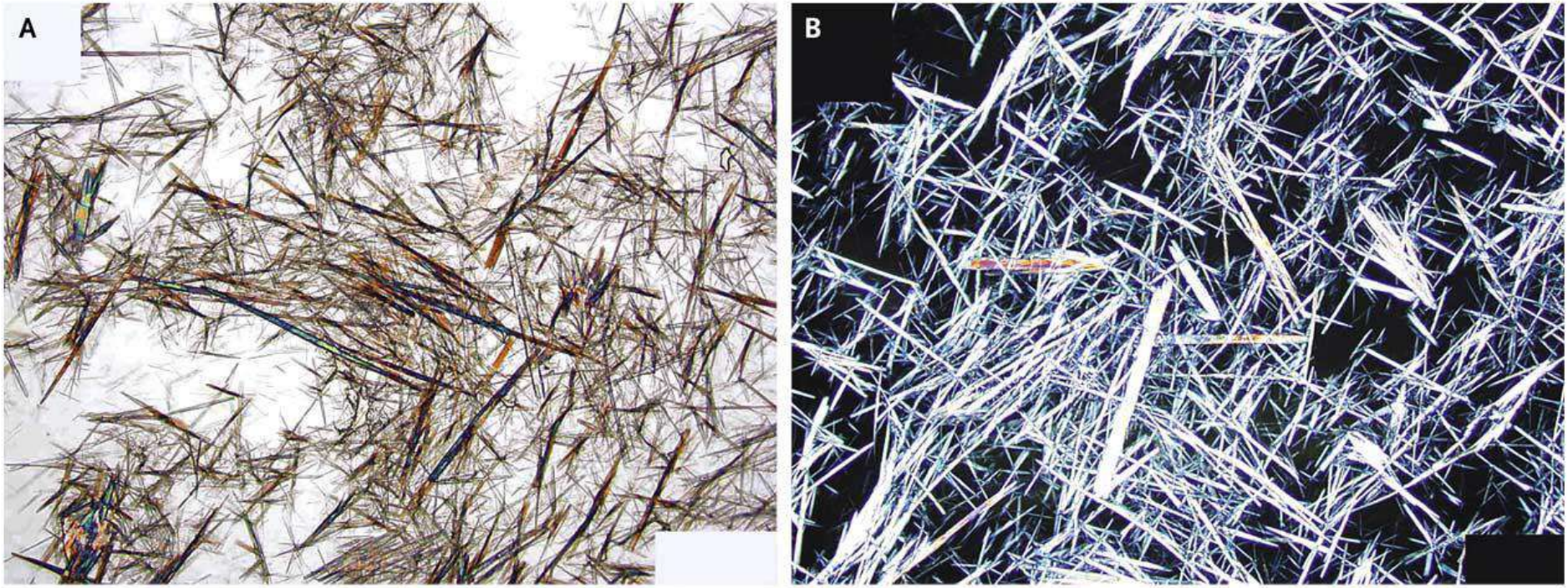


Image A: bright-field microscopy
Image B: polarized microscopy demonstrating birefringence.

Long, slender needle-like crystals Often form **bundles, sheaves, fans, or rosettes** .
Strongly birefringent under polarized light.
Can be colorless or appear refractile /white.
Usually occur with **high-dose IV acyclovir**, particularly with dehydration or renal impairment.

KEY CLINICAL STUDIES / TRIALS ON ACYCLOVIR-INDUCED NEPHROTOXICITY

STUDY (YEAR)	DESIGN / POPULATION	ACYCLOVIR DOSE / EXPOSURE	KEY FINDINGS	COMMENTS / SIGNIFICANCE
Kristensen et al., 1986 (New Engl J Med)	Prospective study 20 patients with herpesvirus infections receiving high-dose IV acyclovir	20–30 mg/kg IV every 8 h (high-dose regimen)	• 36% (7/20) developed increased serum creatinine • Crystalluria present in all 7 patients • All cases were reversible with hydration and/or dose reduction	First prospective study to document high incidence of AKI with high-dose acyclovir and association with crystalluria.
Perazella et al., 1991 (Ann Intern Med)	Case series 13 patients with acyclovir-induced AKI	10–40 mg/kg/day (median 30 mg/kg/day) IV	• All patients developed crystal-induced AKI • Improvement after stopping drug and hydration • Some required hemodialysis	One of the largest early case series establishing crystalluria and AKI causality.
Miller et al., 1991 (Antimicrob Agents Chemother)	Pharmacokinetic study in volunteers with normal vs impaired renal function	Single dose 5 mg/kg IV	• Impaired renal function → higher peak acyclovir levels and prolonged half-life • Increased risk of crystalluria and AKI	Demonstrated the importance of renal function and dose adjustment in preventing toxicity.
LaRosa et al., 2016 (Clin Infect Dis)	Retrospective cohort 987 hospitalized patients receiving IV acyclovir	Median 10 mg/kg IV every 8 h	• Incidence of AKI: 10.9% • Independent risk factors: daily dose >30 mg/kg/day, fast infusion, dehydration, CKD	Large cohort study identifying independent predictors of developing AKI.
Hawkins et al., 2013 (Pharmacotherapy)	Retrospective study 75 patients on high-dose IV acyclovir	Various (5–15 mg/kg per dose)	• AKI incidence: 20% • 85% were at least partly preventable (inadequate hydration or dose issues)	Highlights that most cases are preventable with appropriate measures.
Pai et al., 2006 (Indian J Nephrol)	Case series 10 patients with acyclovir nephrotoxicity	10–15 mg/kg IV every 8 h	• All had crystalluria and AKI • Recovery with hydration, drug withdrawal and supportive care	Indian data supporting crystal-induced mechanism and reversibility.
Pannu et al., 1999 (Pharmacotherapy)	Case report + review severe acyclovir nephrotoxicity	High-dose IV (>30 mg/kg/day)	• Some patients required dialysis • Acyclovir is dialyzable • Recovery after drug cessation	Emphasizes dialyzability of acyclovir and need for early recognition.

OVERALL EVIDENCE: Most data are from prospective studies, case series, cohort studies and pharmacokinetic analyses. No large randomized controlled trials exist (ethical and practical constraints). Evidence consistently shows dose-, concentration- and hydration-dependent risk, with reversibility of AKI after prevention measures.