



When “Therapeutic” Is Not Safe



Pharmacist-led management of sirolimus–voriconazole interaction in a hypoalbuminemic pediatric liver transplant patient: a case report

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Background

- Sirolimus: CYP3A4 substrate used after liver transplantation
- Voriconazole: strong CYP3A4 inhibitor → ↑ sirolimus concentration
- Hypoalbuminemia → ↓ protein binding → ↑ free (active) fraction
- Total trough may underestimate pharmacologically active exposure
- Risk: toxicity despite “therapeutic” levels

! Dual PK Amplification → Hidden Free Drug Toxicity

Aim and objectives

- Identify mechanism of unexpected thrombocytopenia
- Demonstrate pharmacist-led therapeutic drug monitoring (TDM)
- Optimize safety while maintaining effective immunosuppression

Material and methods Results

Patient Profile

- 12-year-old girl (38 kg)
- 8 years post–liver transplant
- Suspected graft rejection
- Albumin: 14.9 g/L (severe hypoalbuminemia)

Treatment

- Tacrolimus: 0.25 mg/day (level 4.8 ng/mL)
- Voriconazole: 100 mg twice daily (level 1.56 mg/L)
- Sirolimus: initiated at 1 mg/day with close TDM

Monitoring Strategy

- TDM every 2–3 days
- Platelet surveillance
- Pharmacist-driven dose adjustment

References

1. Statz CE, Tett SE. Sirolimus PK/PD in transplant. Clin Pharmacokinet 2014;53(10):849–72
2. KDIGO Work Group. Kidney transplant guideline. Am J Transplant 2009;9(Suppl 3):S1–57.
3. PKP-013. Drug interactions with azole antifungals in transplants. Eur J Hosp Pharm 2014;21(Suppl 1):A141.2.

Critical Event – Day 5

- Sirolimus 21.93 ng/mL
- Platelets dropped to $100 \times 10^3/\mu\text{L}$
- Interaction mechanism identified

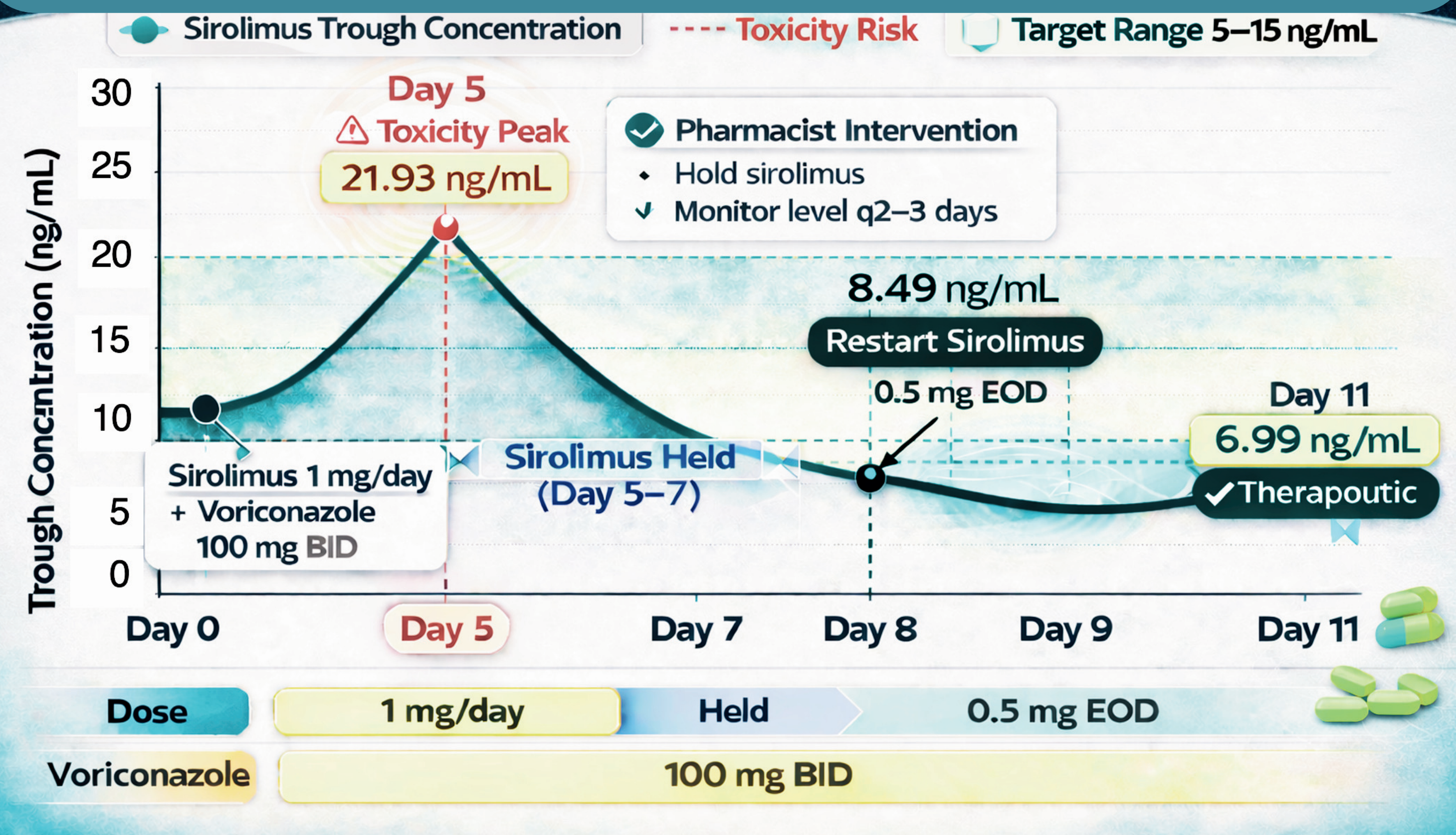
Intervention

- Held sirolimus 7 days
- Structured platelet monitoring
- Reinitiated at 0.5 mg every other day (~75% dose reduction)

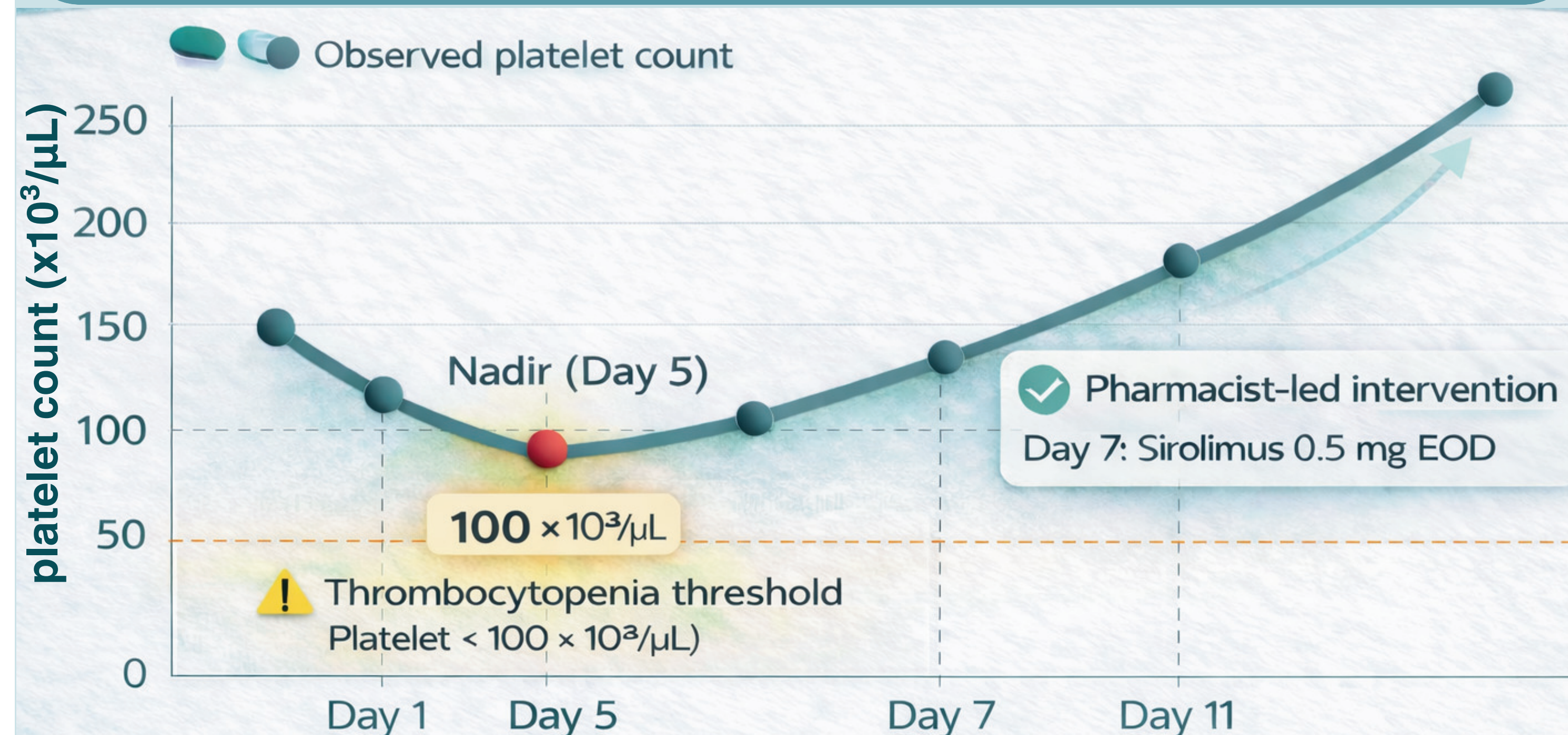
Outcome

- Platelet count recovered
- Trough reduced to 6.99 ng/mL
- No further toxicity

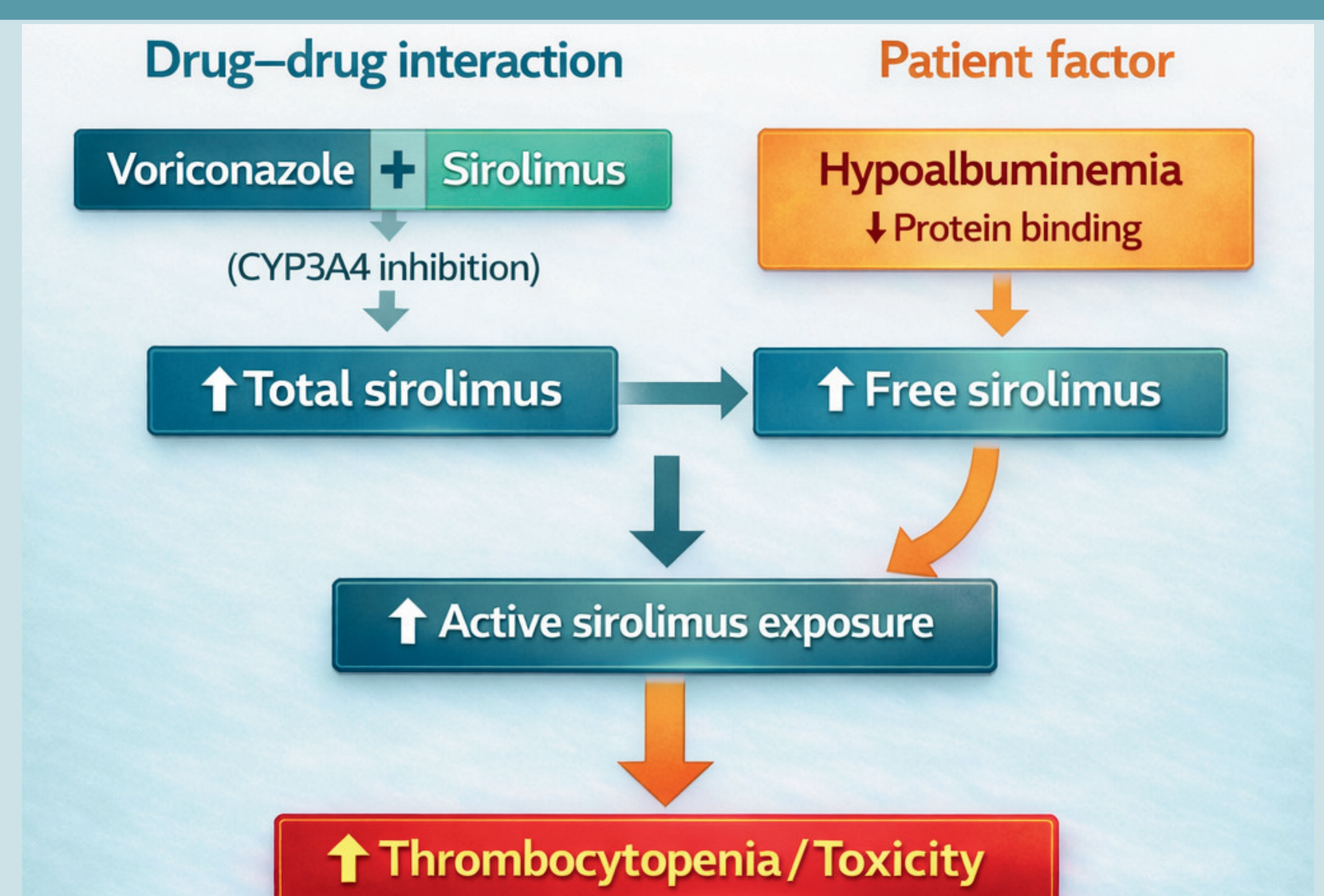
Sirolimus Trough Concentration Over Time



Platelet Recovery After Dose Adjustment



Mechanistic Pathway to Sirolimus Toxicity



Conclusion and relevance

- Hypoalbuminemia magnifies CYP3A4-mediated interactions
- Pharmacist-led TDM is critical in pediatric transplant care
- Consider ~75% dose reduction of sirolimus with voriconazole

