

# Clinical Applications: Vancomycin

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# Introduction

- Renewed interest in 1980's due to MRSA  
-->Increased understanding of the PK/PD
- Routine monitoring? Trough only?
- Nomogram or PK model?

# Nephrotoxicity

- Related to trough  $> 10\text{mg/L}$ ,
- Duration of therapy  $> 21$  days,
- Concurrent nephrotoxic agents
- Older patient...

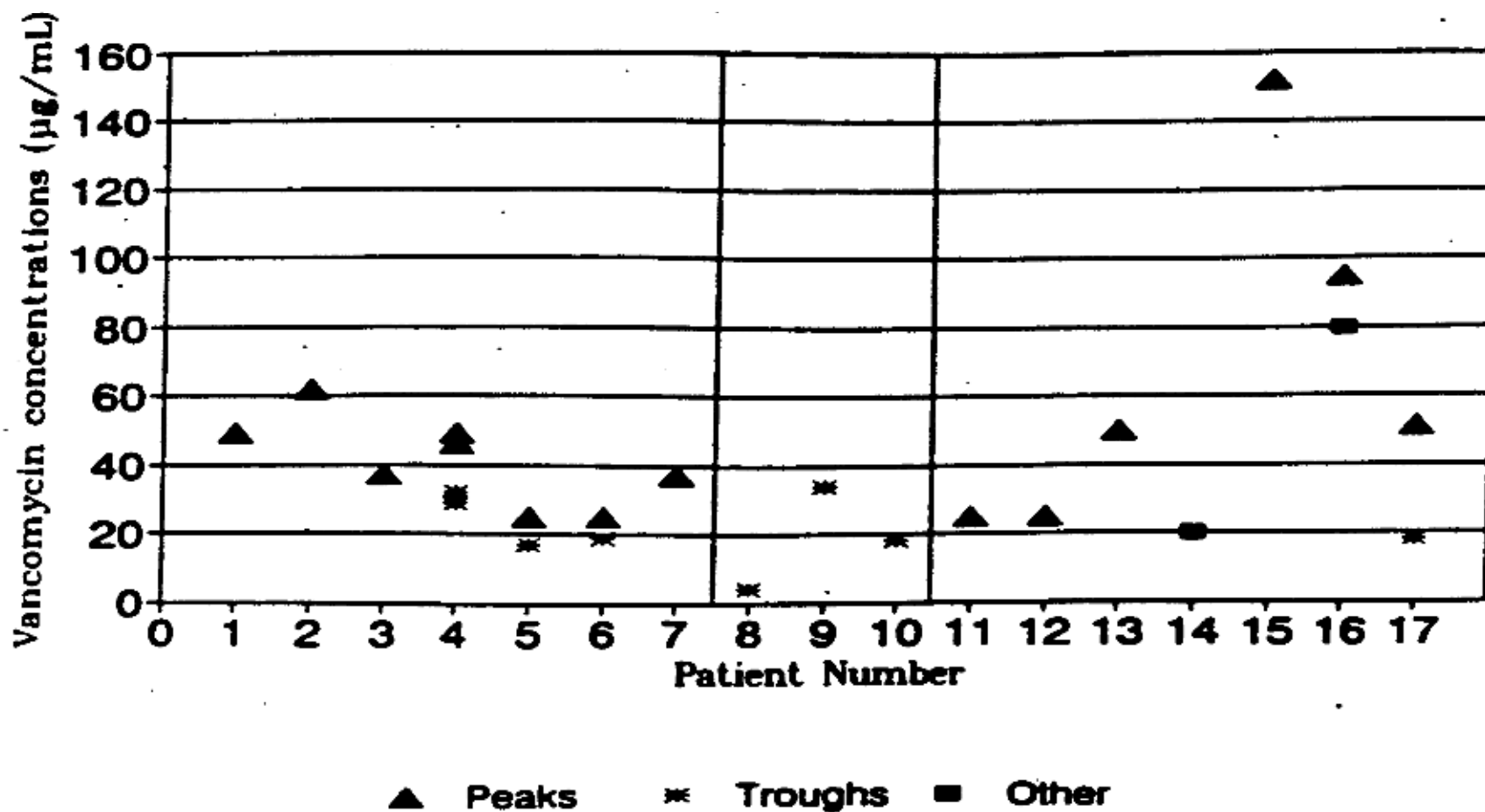
# Nephrotoxicity

- Vancomycin alone  
5% (n=60)
- Vancomycin + aminoglycoside  
22% (n=63)

Rybak et al. JAC 1990;679-87

# Ototoxicity

- Peaks > 80 mg/l?
- Concurrent ototoxic agents
- Duration of therapy > 21 days
- Older patient...



**Figure 1.** Serum vancomycin concentrations in patients in whom ototoxicity was noted. Patients 1 through 7 either did not use other ototoxic drugs or their use was not reported. Patients 8 through 10 were being treated for meningitis, and patients 11 through 17 received aminoglycosides and/or erythromycin in conjunction with vancomycin. Other = a level that is not a peak or trough.

# Pharmacodynamics

- “Concentration-independent killing”
- Maximal activity at 5 x MIC [i.e. 10 mg/L]
- Higher concentrations for deep tissue infections
  - endocarditis, meningitis, osteomyelitis
- Continuous infusion?

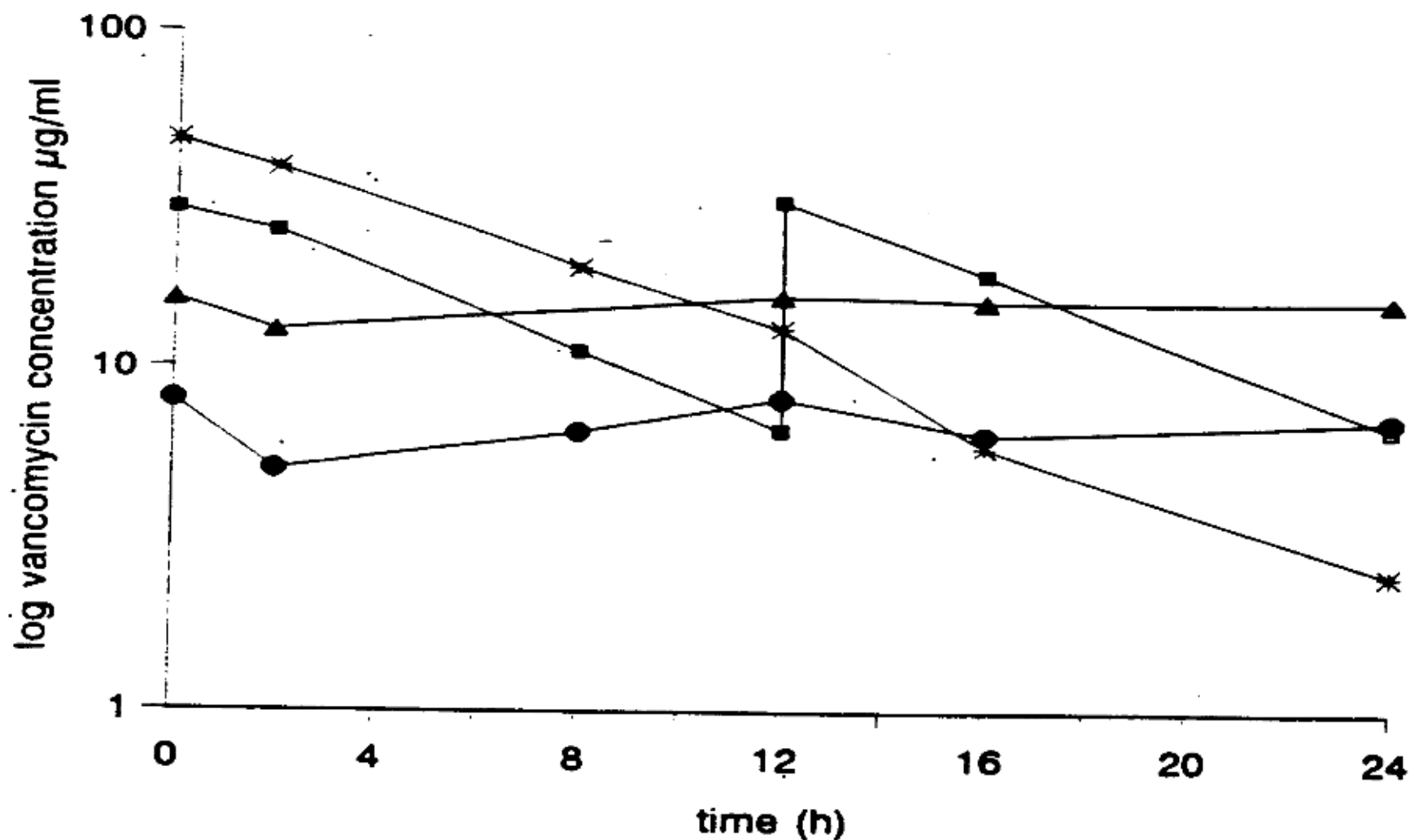


FIG. 1. Concentration-versus-time profile of vancomycin. \*, dosing regimen achieving a single peak of 48  $\mu\text{g/ml}$ ; ■, dosing regimen to achieve a peak of 30  $\mu\text{g/ml}$  dosed again at 12 h; ▲, dosing regimen achieving a constant concentration of 16.2  $\mu\text{g/ml}$ ; ●, dosing regimen achieving a constant concentration of 8  $\mu\text{g/ml}$ .

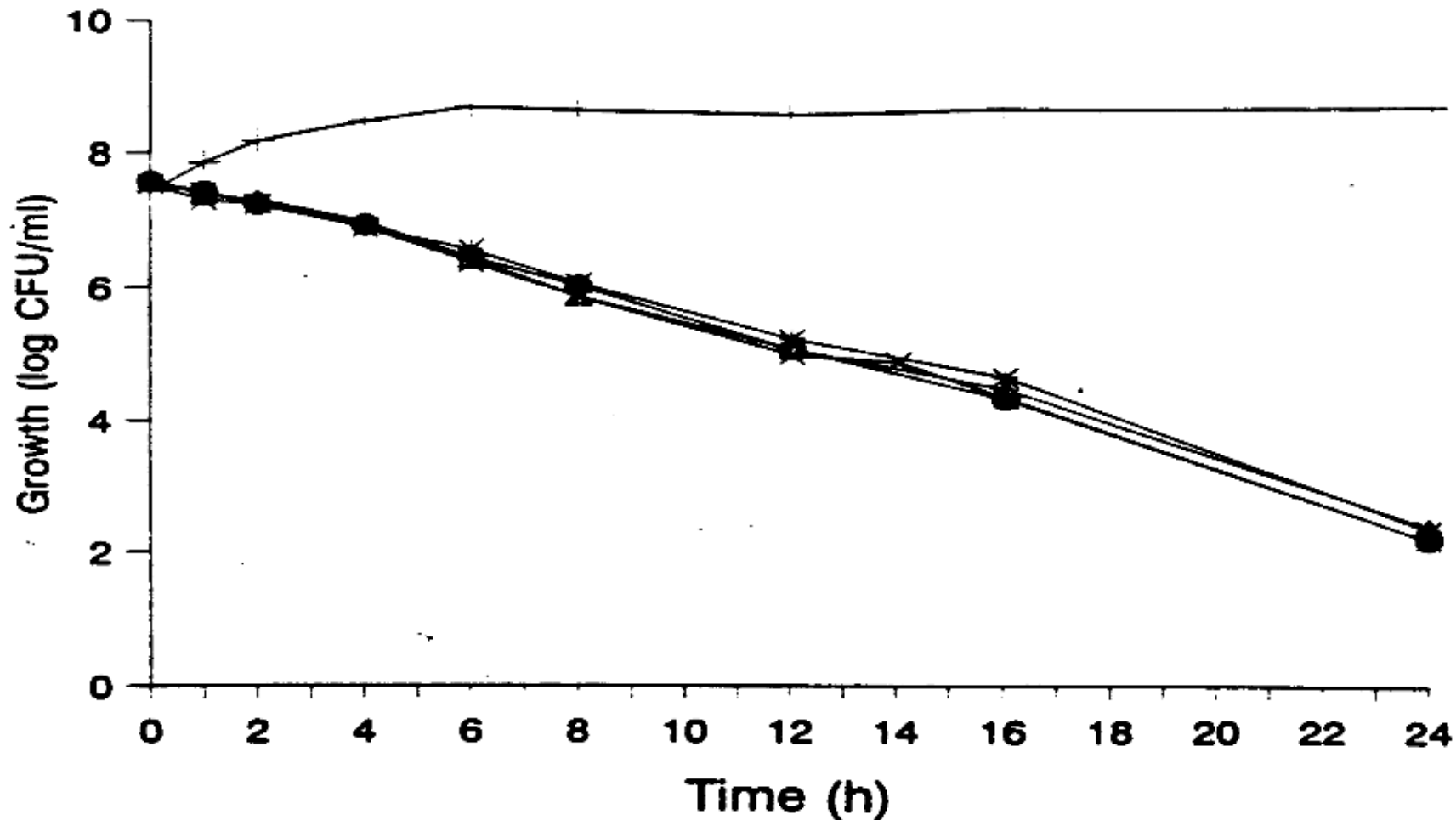


FIG. 2. Antibacterial effects of vancomycin, with different dosing regimens, against *S. aureus* ATCC 29213. +, control bacterial count in the absence of vancomycin; \*, dosing regimen achieving a peak of 48  $\mu\text{g/ml}$ ;  $\times$ , dosing regimen achieving peaks of 30  $\mu\text{g/ml}$  dosed again at 12 h;  $\Delta$ , dosing regimen achieving a constant concentration of 16.2  $\mu\text{g/ml}$ ;  $\bullet$ , dosing regimen achieving a constant concentration of 8  $\mu\text{g/ml}$ .

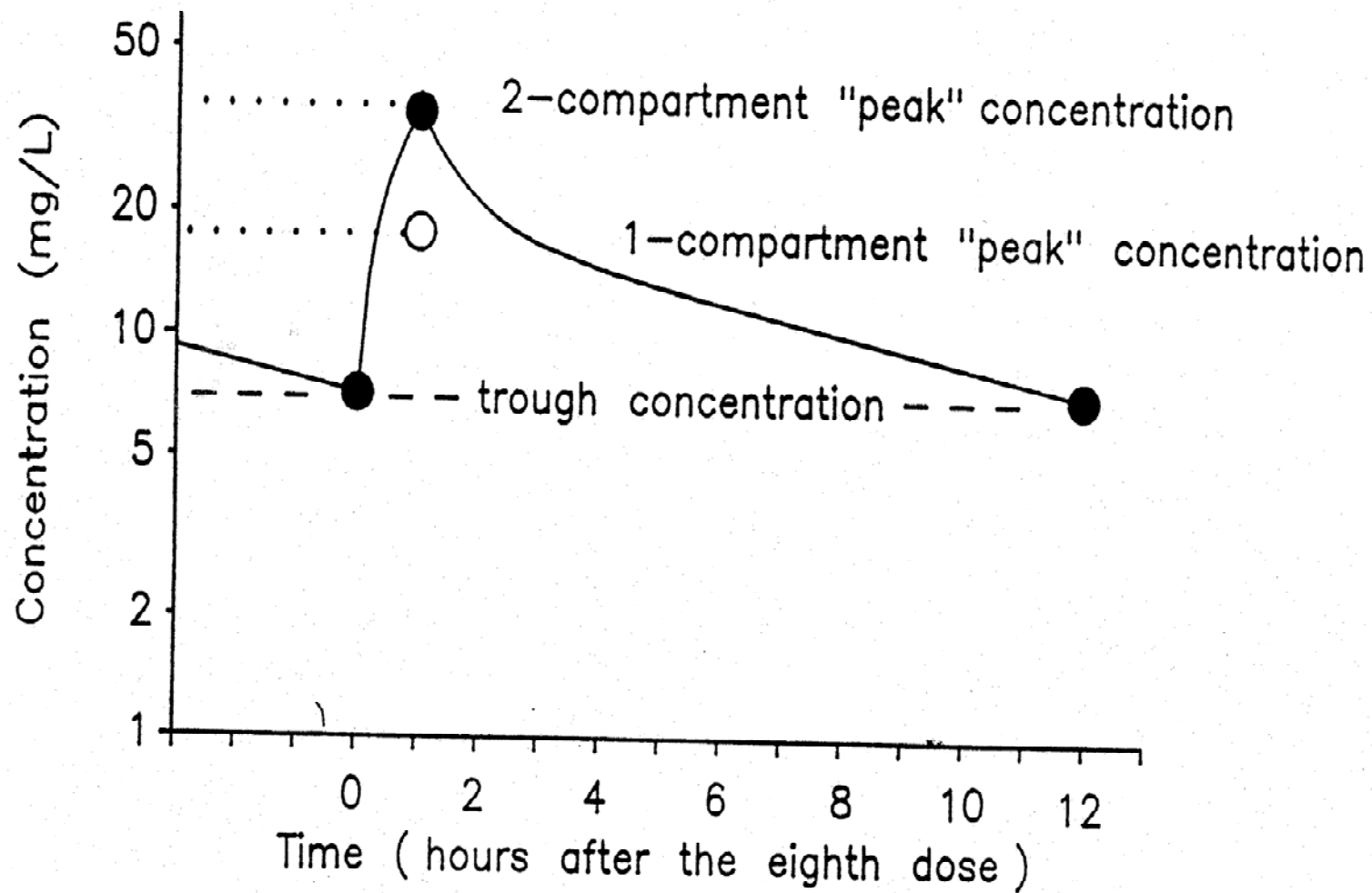
# Dosing Methods

- Predictive performance:  
Nomograms vs. PK methods
  - 1 vs 2-compartments
  - Steady state vs non steady state

# Predictive Performance

| Methods           | Peak  |      | Trough |      |
|-------------------|-------|------|--------|------|
|                   | ME    | MAE  | ME     | MAE  |
| Moellering        | -5.35 | 8.21 | 2.26   | 5.43 |
| Matzke            | -5.95 | 10.5 | 1.67   | 5.76 |
| Sawchuk-<br>Zaske | -2.53 | 4.61 | -2.16  | 2.69 |
| Bayesian          | 1.73  | 4.93 | -0.67  | 2.73 |

Garrelts et al. Clin Pharm 1987;6:795-9



**Figure 19-4.** Serum concentration-time profile of vancomycin at steady state. Difference between the peak concentrations at the end of infusion for two-compartment model (●) and one-compartment model (○).

# Prediction Error (1-compartment model)

| Timing   | $C_{\max}$   | $Vd_{ss}$    | $T_{1/2}$   |
|----------|--------------|--------------|-------------|
| 0.25, 11 | 29.5 (-18)   | 0.44 (-37.7) | 4.9 (-35.6) |
| 0.5, 11  | 25.2 (-29.9) | 0.54 (-23.3) | 5.4 (-28.4) |
| 1, 11    | 20.5 (-43)   | 0.72 (2.3)   | 6.4 (-16.1) |
| 1.5, 11  | 18.5 (-48.6) | 0.84 (19.4)  | 7.0 (-8.0)  |
| 3, 11    | 17.1 (-52.6) | 0.95 (35.1)  | 7.5 (-0.8)  |

Two compartment parameters:  $C_{\max}$  36 mg/L,  $Vd_{ss}$  0.7 L/Kg,  $T_{1/2}$  7.6 h

## 2-Compartment Model

|          | ME          | MAE       |
|----------|-------------|-----------|
| LR       | -3.2 (16.8) | 12.1 (12) |
| Bayesian | 0.0 (4.6)   | 3.6 (2.7) |

Hurst et al. AAC 1990;34:1165-71.

# Summary

- Routine Monitoring?
- Target trough
- 2-compartment Bayesian model
  - Peak/Trough required