University of Strathclyde Science

How to adapt dosing in critically ill patients

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Challenges in critically ill patients

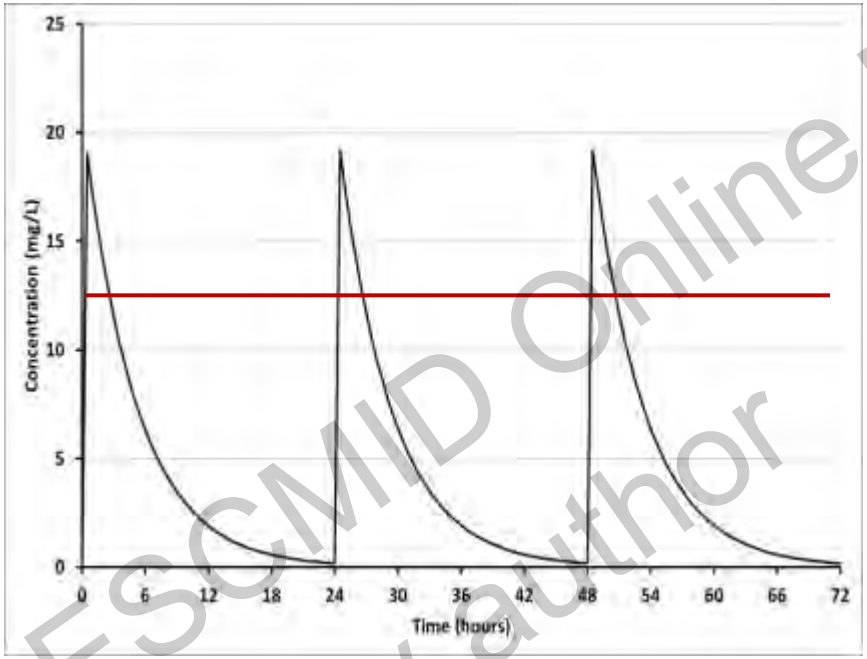
- **Pharmacokinetic variability**
  - Impact of changes in clearance and volume of distribution on concentration-time profiles in plasma and tissue

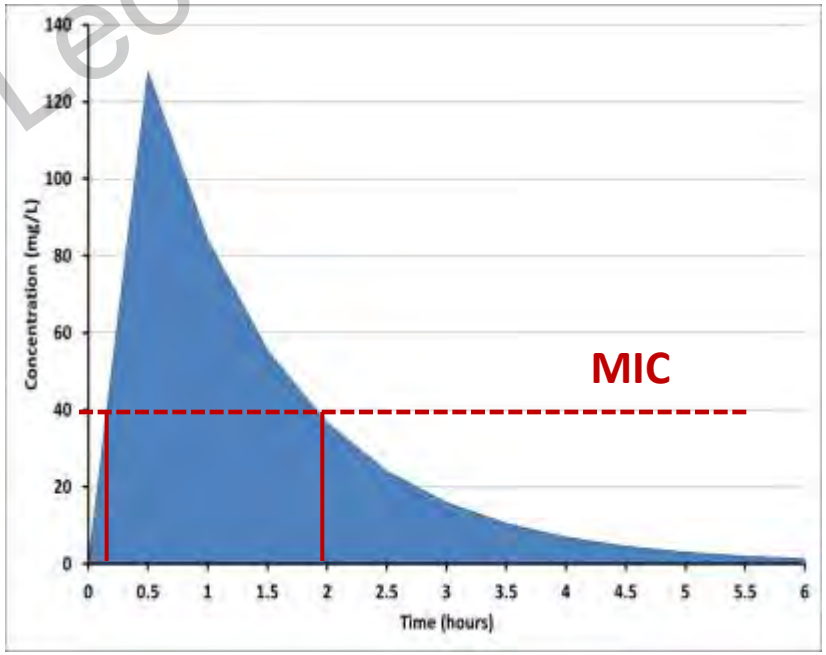
- **Pharmacodynamic variability**
  - PK-PD targets – ideal concentration-time profile?
    - time above MIC, Cmax/MIC ratio, AUC/MIC ratio?
  - Sensitivity of organism(s)
  - Severity of infection
  - Impact of comorbidities on PK and PD
  - Toxicity

Pharmacodynamics - target concentration-time profiles

Cmax/MIC aminoglycosides

Time > MIC
AUC/MIC ratio β-lactams
glycopeptides
fluoroquinolones





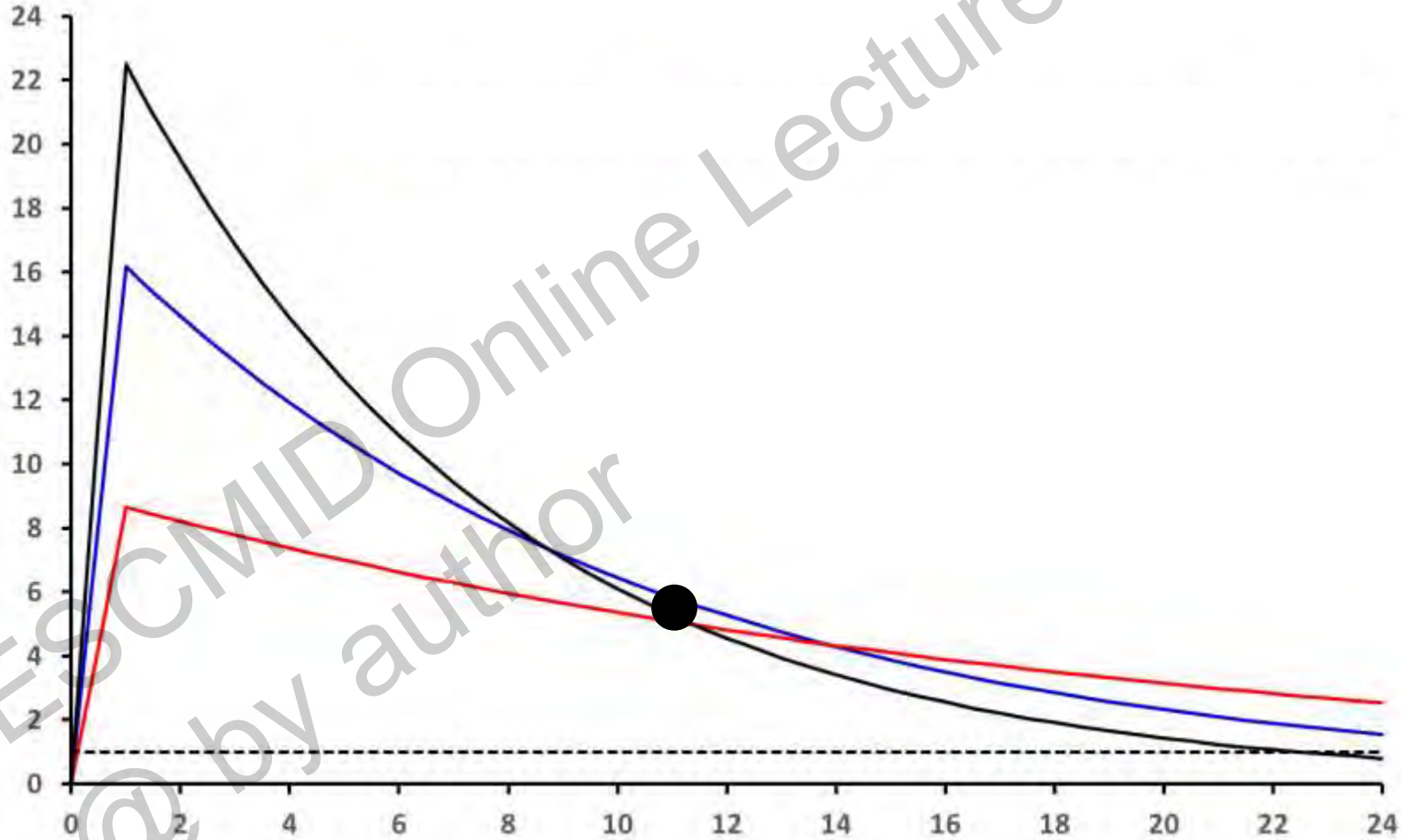
Pharmacokinetic challenges

- Clearance and volume of distribution determine the antibiotic concentration-time profile achieved with any dosage regimen
- Volume of distribution depends on size
  - important if Cmax/MIC is the PK/PD target
- Clearance depends on size and organ function
  - important if %T>MIC or AUC/MIC ratio is the PK/PD target
- Elimination half-life depends on CL and V (0.693 x CL/V)
- How does critical illness alter CL and V?

Confounding factors that influence volume of distribution in critically ill patients

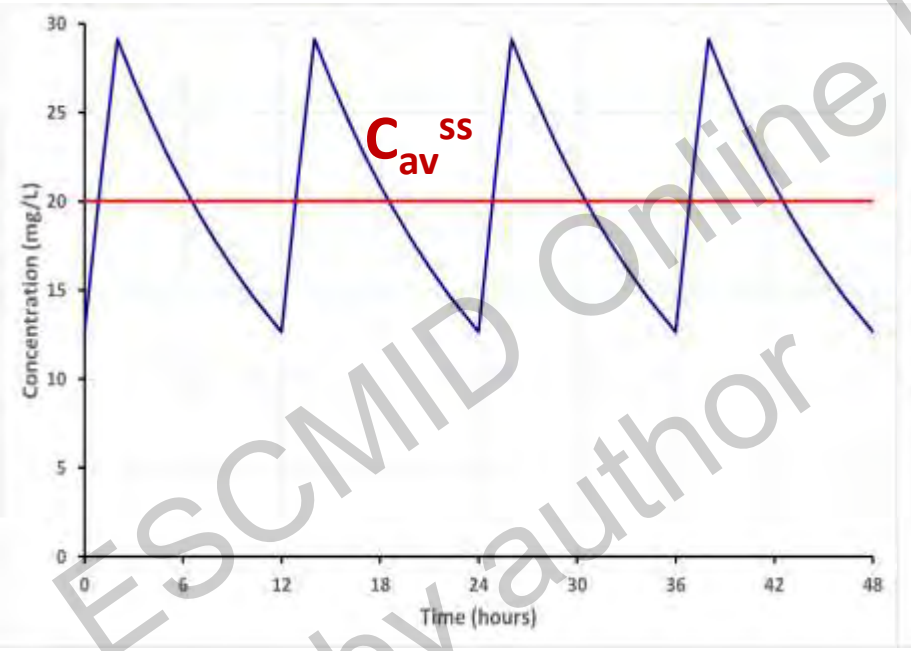
- Altered fluid balance
- “Third space” due to endothelial damage and capillary leakage (systemic inflammatory response syndrome)
- Changes in protein binding
- Shock / impaired tissue distribution
- Sepsis
- Burn injuries
- Obesity
- Renal Replacement Therapy (RRT)
- ExtraCorporeal Membrane Oxygenation (ECMO)

Impact of an increase in volume of distribution on peak concentrations



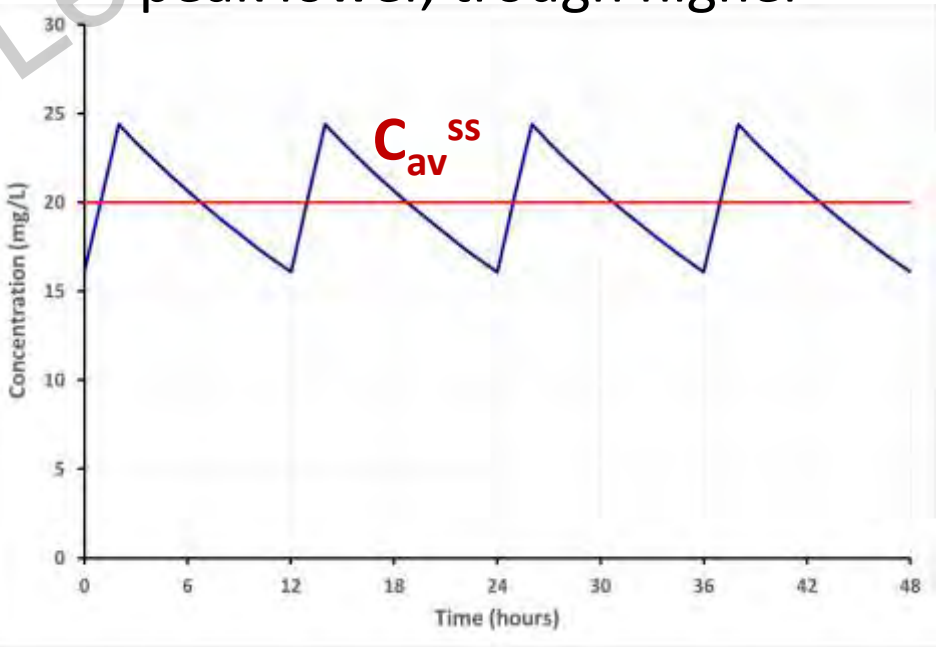
Impact of an increase in volume of distribution on steady state profile

Original Volume



Volume doubled

peak lower, trough higher

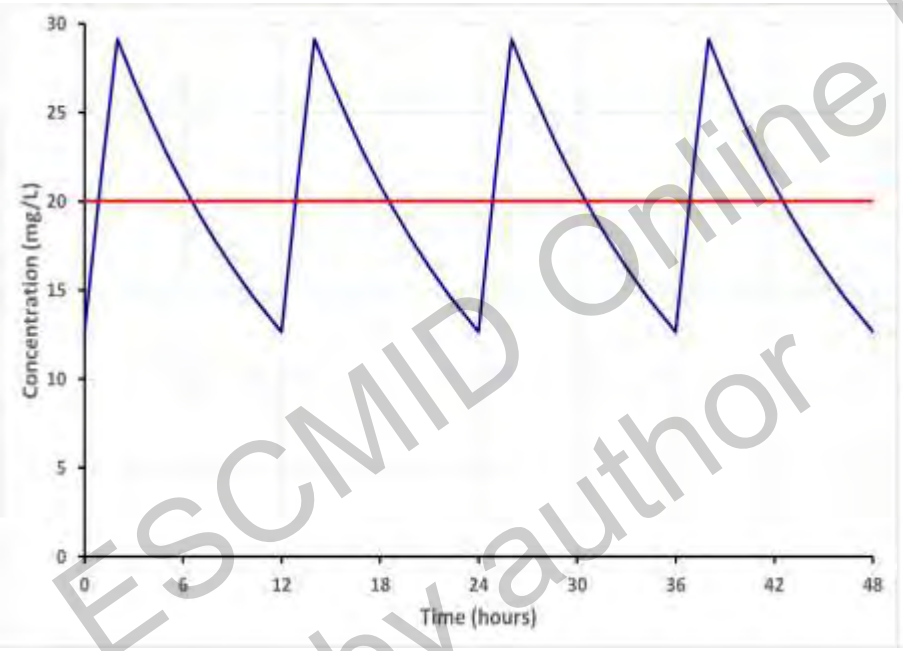


Confounding factors that influence drug clearance in critically ill patients

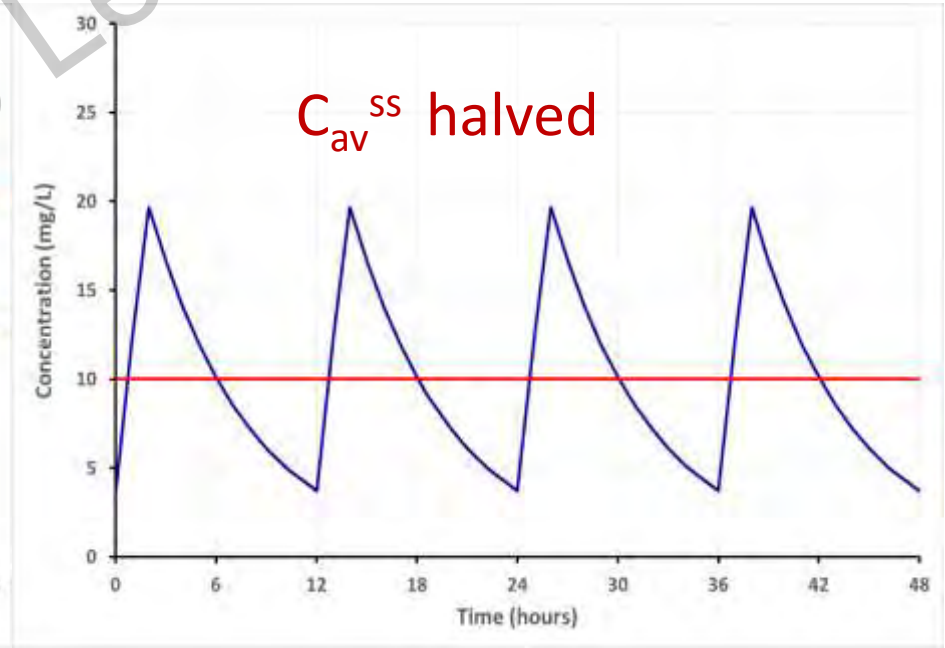
- Hyperdynamic circulation - increased cardiac output and GFR – risk of underdosing (Roberts et al, Clin Inf Dis, 2014)
- Renal impairment
- Hepatic impairment
- Burn injuries
- Sepsis
- Obesity
- RRT and/or ECMO

What happens if clearance increases?

Original clearance and volume of distribution

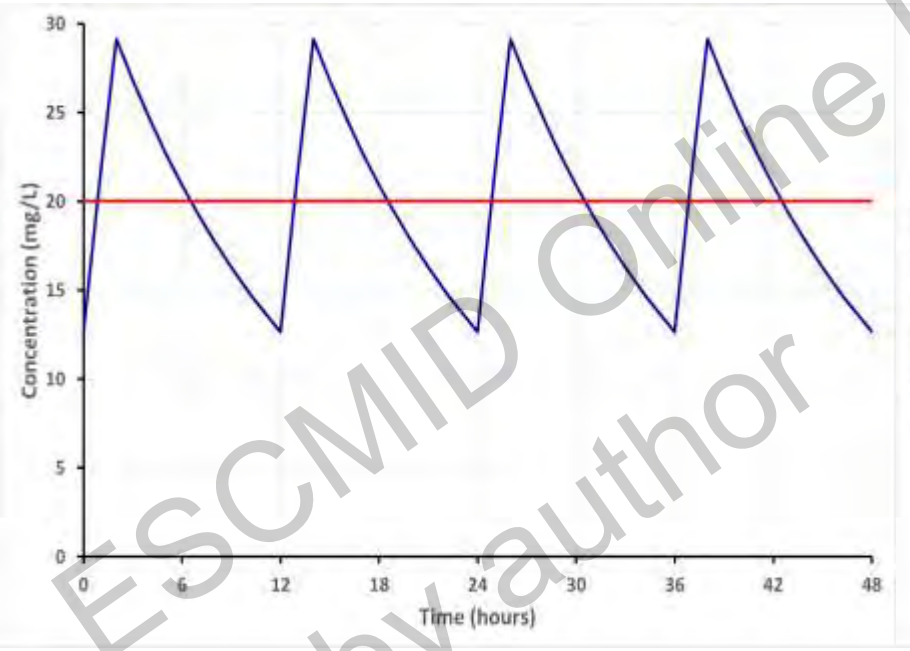


Clearance doubled



What happens if clearance and volume increase?

Original clearance and volume of distribution



Clearance and volume doubled

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What are the options for dose adjustment to avoid underdosing?

- Target C_{max}/MIC
  - Increase the dose

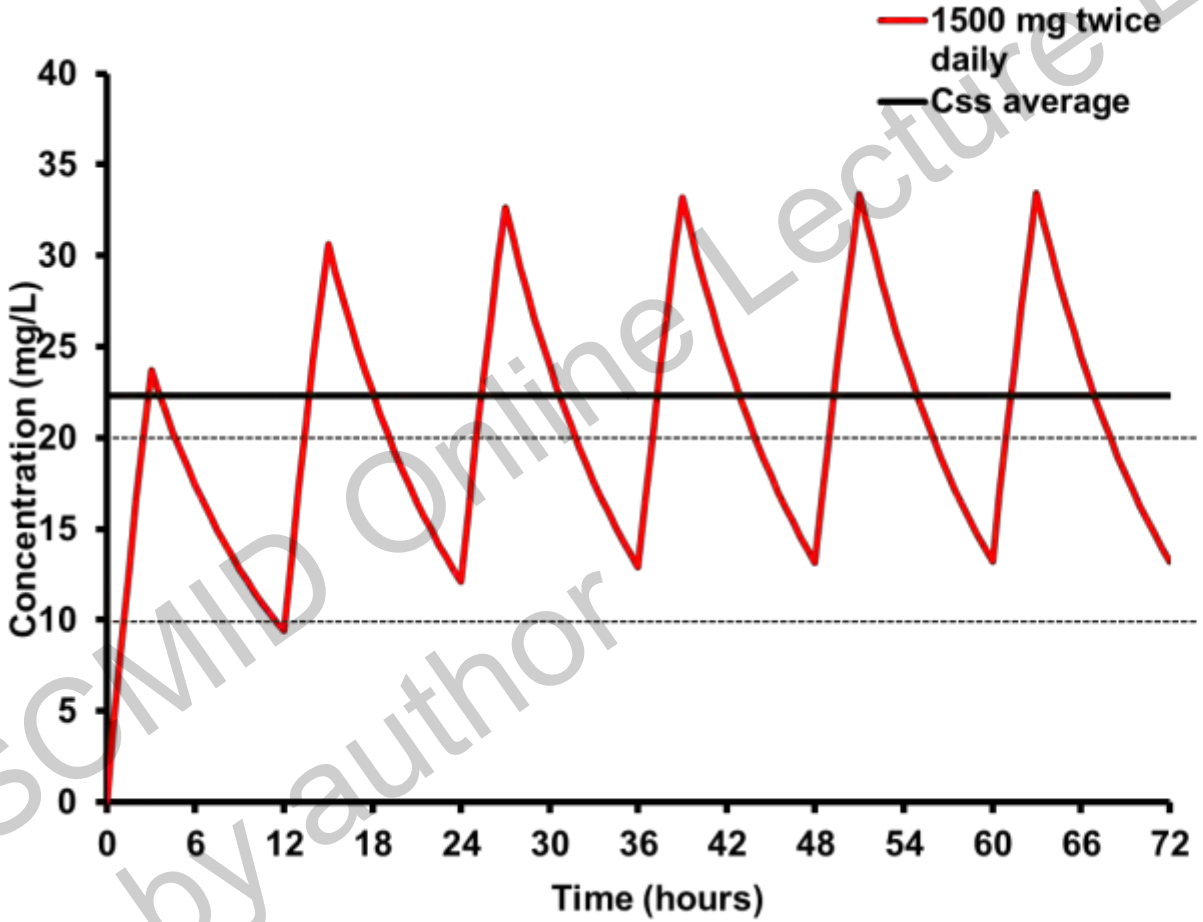
- %Time >MIC, target trough
  - increase the dose
  - increase the duration of infusion (Cataldo et al, JAC 2012, Roberts et al Clin Inf Dis 2014)

- AUC/MIC
  - increase the dose

What are the options for dose adjustment to avoid toxicity?

- Target C_{max}/MIC
  - increase the dosage interval
- %Time >MIC, target trough
  - decrease the dose
- AUC/MIC
  - decrease the dose

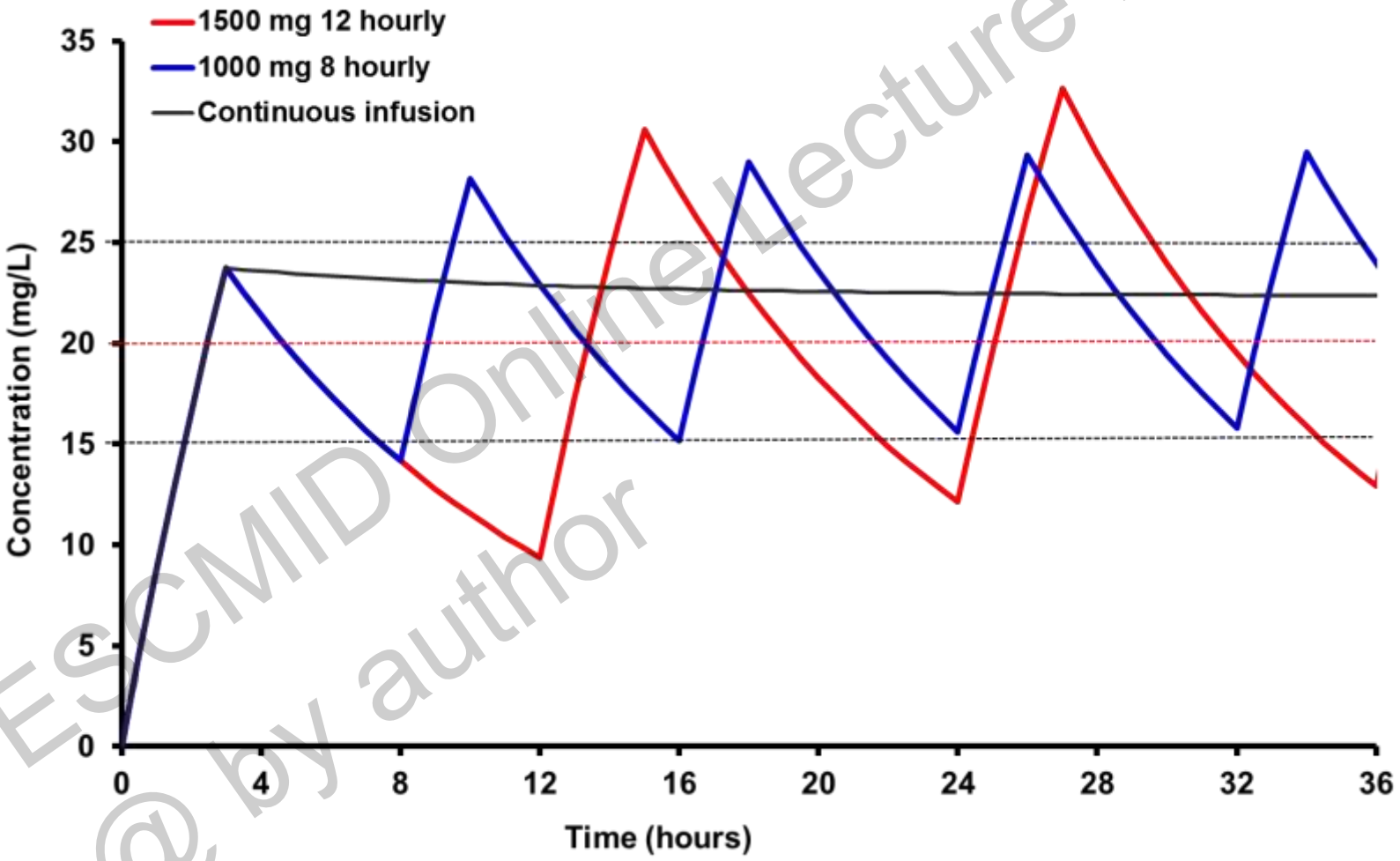
Vancomycin dosing rate 1500 mg twice daily over 3 h



Vancomycin – same dose, different profiles

Daily dose (mg)	Dose (mg)	Duration of Infusion	Dosage Interval (h)	AUC_{24} (mg.h. L^{-1})	$Ctrough_{ss}$ (mg L^{-1})	Css average (mg L^{-1})
3000	1500	12 h	Continuous	535	22.3	22.3
3000	1000	2 h	8	535	16.0	22.3
3000	1500	3 h	12	535	13.2	22.3
3000	3000	6 h	24	535	7.0	22.3

Same daily dose, split 8 hourly or by continuous infusion

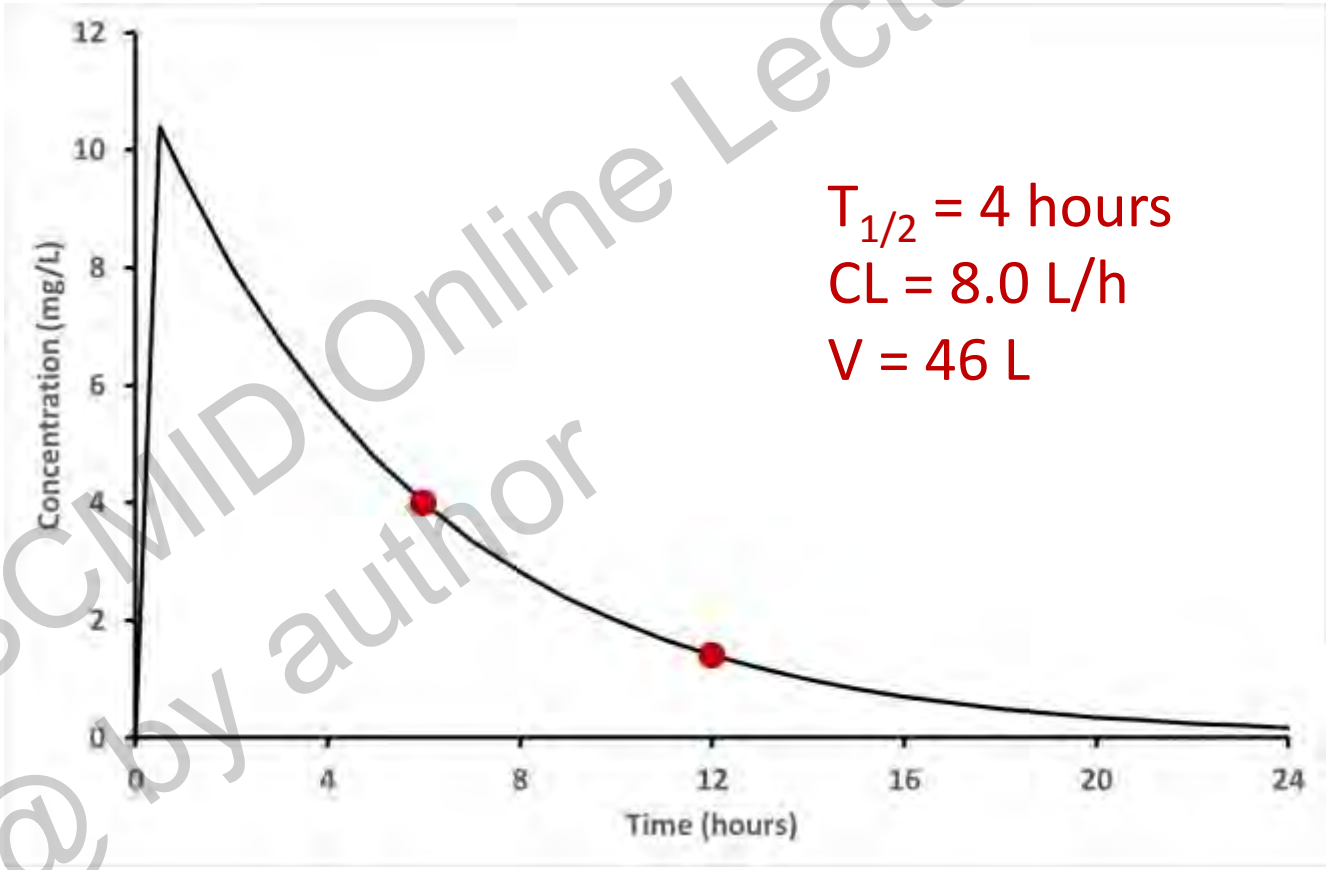


What techniques can we use to determine the appropriate dose adjustment?

- Measure concentrations, estimate pk parameters and design new dosage regimen
  - manually
  - using pk software (Macdonald et al, Ther Drug Monit, 2008)
- Use data from the literature to make an informed guess (Ramon-Lopez et al, JAC 2014)
- Measure renal function directly if the drug is renally cleared
- Measure concentrations of another antibiotic and use the results to estimate dose requirements

Challenges of obesity and critical illness – gentamicin case

48 year old male, TBW 140 kg, IBW 84 kg, creatinine 63 μmol/L, single dose of 500 mg



$T_{1/2}$ = 4 hours
CL = 8.0 L/h
V = 46 L

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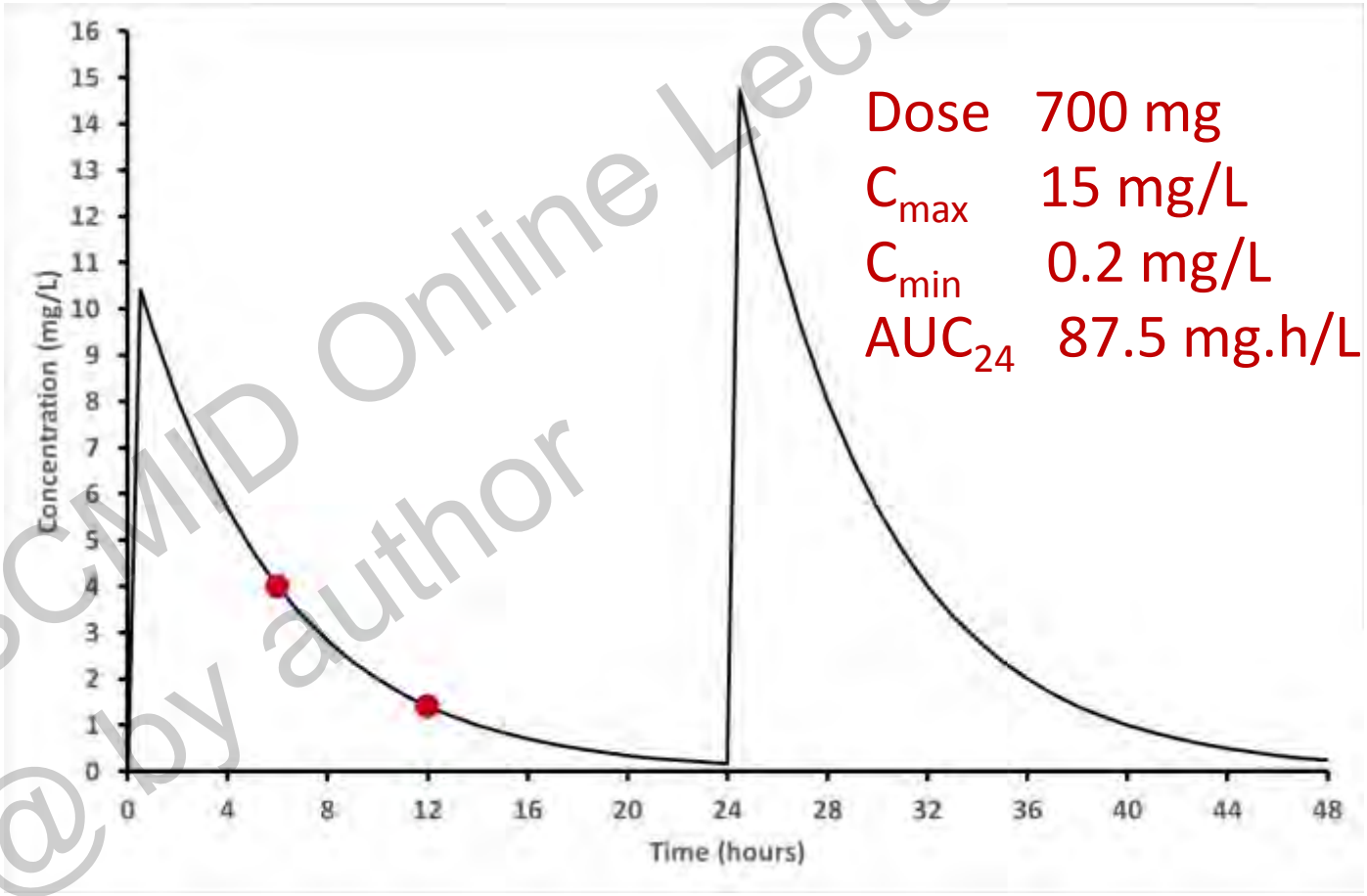

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Measure concentrations of another antibiotic and use the results to estimate dose requirements

- Kirkpatrick *et al*. The use of a change in gentamicin clearance as an early predictor of gentamicin-induced nephrotoxicity. Ther Drug Monit 2003;25:620-3

- Pai *et al*. Using vancomycin concentrations for dosing daptomycin in a morbidly obese patient with renal insufficiency. Ann Pharmacother 2006;40:553-8

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