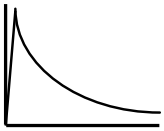
Clinical Vancomycin and Aminoglycoside PK/PD



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Clinical Vancomycin and Aminoglycoside PK/PD
Lecture Objectives and Readings

Objectives

1. Understand the pharmacokinetic and pharmacodynamic (PK/PD) principles of vancomycin and aminoglycosides
2. Apply the principles of PK/PD to a given patient case as it relates to choice and dosage design
3. Understand PK/PD factors associated with efficacy, toxicity, and antibiotic resistance

Readings

1. Rybak MJ et al. Vancomycin therapeutic guidelines: a summary of consensus recommendations from the infectious diseases Society of America, the American Society of Health-System Pharmacists, and the Society of Infectious Diseases Pharmacists. American Journal of Health-System Pharmacy January 1, 2009 vol. 66 no. 1 82-98.
   - Summary of recommendations provided in Table 2.
2. Pharmacotherapy: Chapter e4

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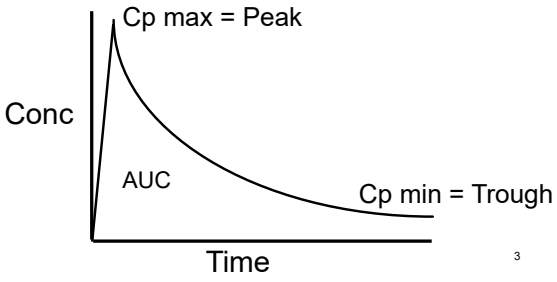
Pharmacokinetics: Concentration vs. Time Profile Single Dose



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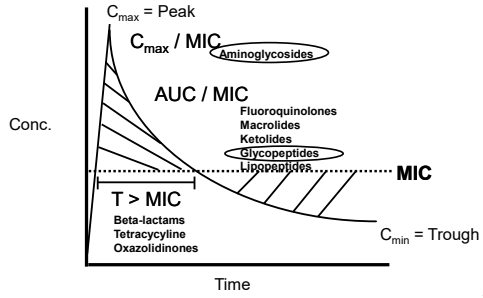
Pharmacodynamic Parameters & Outcome



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Aminoglycosides

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Aminoglycosides

- Aminoglycosides
  - Gentamicin, tobramycin, amikacin
- Standard Dosing - normal renal function
  - Gentamicin/tobramycin - 2 mg/kg every 8-12 h
  - Amikacin 7.5 mg/kg every 12 h
- Used in serious Gram-negative and gram-positive infections
- **Concentration dependent antibiotics**
- Narrow therapeutic window
- Associated with renal (5-15%) and ototoxicity
  - Increased risk with high troughs and long duration

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Application of Pharmacodynamic Principles: Aminoglycosides

- Rationale for single-dose aminoglycosides
  - Higher peak concentrations should increase efficacy
  - Significant PAE allows for longer dosing intervals
  - Lower trough concentrations should improve safety
  - Longer dosing intervals may decrease resistance

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Aminoglycoside Key Parameters

Therapeutic plasma concentration		
Gentamicin and Tobramycin	Peak Trough	4-12 mcg/ml < 2 mcg/ml
Amikacin	Peak Trough	20-30 mcg/ml <10 mcg/ml
Volume of distribution (Vd)	0.25 L/kg	
Clearance (Cl)		
Normal renal function	CrCl	
Functionally Anephric	0.0043 L/kg/hr	
Surgically Anephric	0.0021 L/kg/hr	
Hemodialysis	1.8 L/hr	
Half-life		
Normal renal function	2-3 hr	
Functionally Anephric	30-60 hr	
Protein binding	20-30%	

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AG weight and renal function estimates

- Recent studies display improved PK estimates for AG in obese and underweight patients
  - Lean body weight better estimates Vd

$$LBW_{2005}\text{-male} = (9{,}270 \times TBW)/(6{,}680 + 216 \times BMI)$$

$$LBW_{2005}\text{-female} = (9{,}270 \times TBW)/(8{,}780 + 244 \times BMI)$$

- Estimated glomerular filtration rate (eGFR) more accurately predicts AG CL than CrCl
- For this lecture IBW and CrCL will be used as examples

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Pai MP. Antimicrob Agents Chemother 2011;55(9): 4006-4011

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Aminoglycoside therapeutic C_{max} targets

- Traditional dosing
  - Tobramycin and Gentamicin
    - Severe infections – 8-10 mg/L
    - Moderate infections – 6-8 mg/L
    - Mild infections – 3-5 mg/L
  - Amikacin
    - Severe infections – 25-30 mg/L
    - Moderate infections – 22-25 mg/L
    - Mild infections – 20-22 mg/L
- Extended interval or once-daily dosing
  - C_{max} not determined, doses based on levels 6-14 hours after dose

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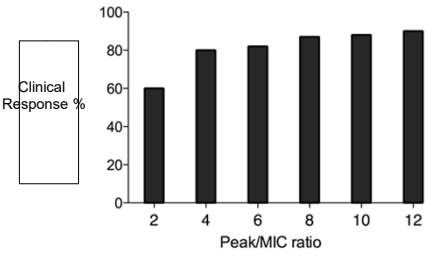
Aminoglycoside Peak/MIC Ratio



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Adapted from Moore RD et al. *J Infect Dis.* 1987;155:93-99.

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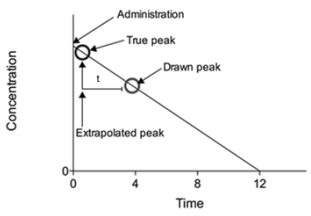
Extrapolating True Peaks and Troughs

$$\text{True peak } (C_{EOI}) = \frac{(Cmax)}{e^{-kt}}$$

$$\text{True trough} = (Cmin) \times e^{-kt}$$



t = time between actual draw time and administered dose

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Initiating a dosing regimen

- Specific patient information
  - Height/Weight
  - Age
  - Gender
  - Serum creatinine
  - Infection type
  - Pathogen
  - Coexisting conditions

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Dose initiation

i.e. "Patient has not received aminoglycosides before and we have no patient-specific values to work with"

- To estimate k (in hr^{-1})

$$k = [0.00293 \times (CrCl)] + 0.014$$

- Initial dosing interval

$$\tau = \left[\frac{(\ln C_{max}) - \ln C_{min}}{k}\right] + T$$

Target values, not measured values

- Initial dosing

$$\text{Dose} = T \times (k) \times (Vd) \times (C_{ss}) \times \left[\frac{(1 - e^{-k\tau})}{(1 - e^{-kT})}\right]$$

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Aminoglycoside Case #1

- 45 year old male with *P. aeruginosa* intra-abdominal infection sensitive only to gentamicin
  - Height 75 inches
  - Weight 84.5 kg
  - SCr = 1.2 ml/min
  - Targeted parameters: C_{max} 10; C_{min} 1
  - Infusion time 0.5 h
- Calculate starting dose and interval

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Aminoglycoside Case #2 - adjusting doses

A 33 year old male is admitted with significant burn injuries. Along with fluid supplementation, he is started on tobramycin to treat an extensive infection contracted during his stay. Height 70 inches; Weight 82 kg; SCr 0.7 mg/dL

Tobramycin was dosed at 150 mg every 8 hours. On the third dose the following levels were obtained: C_{max} 6 (@ 0900) and C_{min} 1.8 (@1600).

- Calculate tobramycin k and Vd in this patient

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Once-Daily Aminoglycosides

- Over 10,000 patients receiving once-daily aminoglycosides have been evaluated.
- Infections studied include: bacteremia, intra-abdominal infections, urinary tract infections, pneumonia and febrile neutropenic patients.
- No difference in efficacy has been reported to date.
- Some investigations have reported less nephrotoxicity for patients receiving once-daily aminoglycosides.

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Extended Interval Dosing

- Concept
  - Increase peak/MIC ratio with larger doses
  - Longer interval between doses (ex. from 8h to 24 h)
- Rationale
  - Utilize the concentration dependent effect for increased efficacy
  - Minimize toxicity with lower trough concentration between doses

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Extended Interval Dosing

- Dose
  - Gentamicin or tobramycin 5-7 mg/kg
  - Amikacin 15 mg/kg
- Interval

CrCl	Interval
> 60 ml/min	q24h
40-59 ml/min	q36h
20-39 ml/min	q48h
< 20 ml/min	N/A

- Level obtained 6-14 hr after start of infusion
- Dose adjust and recheck level every 7 days

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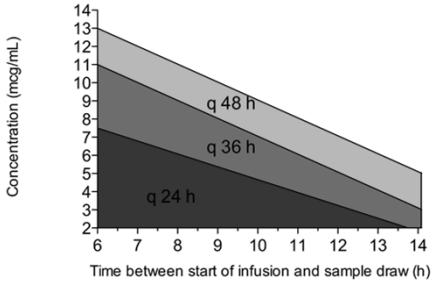
Extended Interval Dosing (Hartford Nomogram)



Nicolau et al. AAC 1995;39:650-655

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Limitations of extended interval dosing

- Populations not studied and therefore should not be used!
  - Pediatrics
  - Pregnancy
  - Burn patients
  - Ascites
  - CrCl < 20 ml/min
  - Dialysis

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Vancomycin

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Vancomycin Key Parameters

Therapeutic plasma concentration	
~~Peak~~	~~35-50 mcg/ml~~
Trough	10-20 mcg/ml
Bioavailability (F)	<5%
Volume of distribution (Vd)	0.7 L/kg
Clearance (L/hr)	$[(0.695)(\mathrm{CrCl}) + 0.05] \times 0.06$
Clearance adjusted for TBW (L/h)	$[(0.695)(\mathrm{CrCl} \times \mathrm{TBW/IBW}) + 0.05] \times 0.06$
elimination rate constant (k)	Cl/Vd in hr^{-1}
Half-life	6-8 hr
Protein binding	45-55%
AUC (mg/L*h)	Dose/Cl

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Vancomycin Use and Monitoring Guidelines

- **Daily doses of 15-20 mg/kg (actual weight) every 8-12 h recommended for most patients with normal renal function**
  - Loading doses of 25-30 mg/kg may be used
  - Vancomycin AUC/MIC ≥ 400 not attainable if MIC ≥ 2 mg/L
  - Continuous infusion unlikely to improve outcome
- **Monitoring trough concentrations**
  - Maintain ≥ 10 mg/L
  - For MIC≥1 mg/L concentrations ≥ 15 mg/L for target AUC/MIC 400
  - Troughs 15-20 mg/L may improve penetration
- **Nephrotoxicity = 2-3 consecutive increases in SCr** (increase of 0.5 mg/dL or a >50% increase from baseline, whichever is greater)

Rybak MJ et al. Am J Health Syst Pharm. 2009 Jan 1;66(1):82-98.

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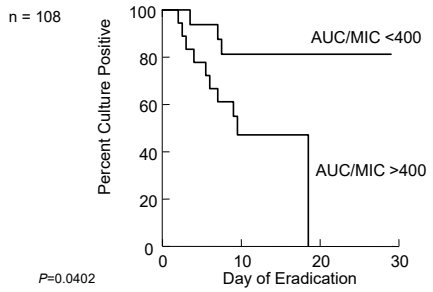
Comparison of Vancomycin days to eradication for MRSA pneumonia



Moise-Broader PA et al. *Clin Pharmacokinet* 2004;43:925-42.

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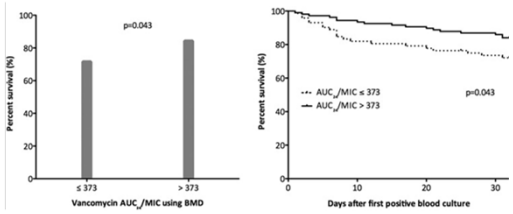
AUC/MIC target in bacteremia



AUC_{24}/MIC > 373 was a greater predictor of MRSA bacteremia mortality than AUC_{24}/MIC>400

Holmes NE, et al. Antimicrob Agents Chemother. 2013 Apr;57(4):1654-63.

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Vancomycin population derived doses

Vancomycin dose	Creatinine Clearance	Interval	Monitoring
15 mg/kg	>50 ml/min	q8-12h	trough*
15 mg/kg	50-30 ml/min	q24h	trough*
15 mg/kg	30-10 ml/min	x 1	random
15 mg/kg	< 10ml/min; HD/PD	x 1	random

*obtained at steady state -- usually after third dose

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Estimated Parameters Nomogram Dosing

Weight (kg) / Cl_{cr} (ml/min)	30	40	50	60	70	80	90	100	≥ 110
50	500 q24h	500 q24h	500 q12h	500 q12h	500 q12h	500 q12h	500 q12h	500 q8h	500 q8h
55	500 q24h	500 q24h	500 q12h	500 q12h	500 q12h	500 q12h	500 q12h	500 q8h	500 q8h
60	500 q24h	500 q24h	500 q12h	500 q12h	1000 q12h	1000 q12h	1000 q12h	500 q8h	500 q8h
65	1000 q24h	1000 q24h	1000 q24h	1000 q12h	1000 q12h	1000 q12h	1000 q12h	1000 q12h	1000 q8h
70	1000 q24h	1000 q24h	1000 q24h	1000 q12h	1000 q12h	1000 q12h	1000 q12h	1000 q8h	1000 q8h
75	1000 q24h	1000 q24h	1000 q24h	1000 q12h	1000 q12h	1000 q12h	1000 q12h	1000 q8h	1000 q8h
80	1000 q24h	1000 q24h	1000 q24h	1000 q12h	1000 q12h	1000 q12h	1000 q12h	1000 q8h	1000 q8h
85	1000 q24h	1000 q24h	1000 q24h	1000 q12h	1000 q12h	1000 q12h	1000 q8h	1000 q8h	1000 q8h
90	1000 q24	1000 q24h	1000 q12h	1000 q12h	1000 q12h	1000 q8h	1000 q8h	1000 q8h	1000 q8h
95	1000 q24h	1000 q24h	1000 q12h	1000 q12h	1000 q12h	1000 q8h	1000 q8h	1000 q8h	1000 q8h
100	1000 q24h	1000 q24h	1000 q12h	1000 q12h	1000 q12h	1000 q8h	1000 q8h	1000 q8h	1000 q8h
105	1000 q24h	1000 q24h	1000 q12h	1000 q12h	1000 q12h	1000 q8h	1000 q8h	1000 q8h	1000 q8h
≥ 110	1000 q24h	1000 q24h	1000 q12h	1000 q12h	1000 q12h	1000 q8h	1000 q8h	1000 q8h	1000 q8h

Table 5. Comparison of Predicted versus Actual Trough Concentrations

	Cl_{cr} (ml/min)			
Variable	30–59 (n=20)	60–89 (n=23)	>90 (n=34)	Totals (n=77)
No. (%) concentrations in target range	17 (85)	21 (91)	34 (100)	72 (94)
No. (%) concentrations > target range	2 (10)	2 (6)	0	4 (5)
No. (%) concentrations < target range	1 (5)	0	0	1 (1)
Mean ± SD avg. predicted trough (µg/ml)	10.5 ± 2.4	10.2 ± 2.1	9.0 ± 1.8	9.7 ± 2.1
Mean ± SD avg. achieved trough (µg/ml)	13.9 ± 6.2	13.5 ± 7.1	9.7 ± 3.2	11.9 ± 5.7

Karam et al. Pharmacotherapy. 1999 Mar;19(3):257-66.

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Always use caution with vancomycin nomograms

Weight (kg) / Creatinine Clearance (ml/minute)	40–49	50–59	60–69	70–79	80–89	90–99	≥ 100
50–54	500 mg q12h	750 mg q12h	1000 mg q12h	750 mg q8h	1000 mg q8h	1000 mg q8h	1250 mg q8h
55–59	750 mg q12h	1000 mg q12h	1250 mg q12h	750 mg q8h	1000 mg q8h	1000 mg q8h	1250 mg q8h
60–64	750 mg q12h	1000 mg q12h	1250 mg q12h	750 mg q8h	1000 mg q8h	1250 mg q8h	1500 mg q8h
65–69	750 mg q12h	1000 mg q12h	1250 mg q12h	1000 mg q8h	1000 mg q8h	1250 mg q8h	1500 mg q8h
70–74	750 mg q12h	1250 mg q12h	750 mg q8h	1000 mg q8h	1250 mg q8h	1500 mg q8h	1500 mg q8h
75–79	1000 mg q12h	1250 mg q12h	750 mg q8h	1000 mg q8h	1250 mg q8h	1500 mg q8h	1750 mg q8h
80–84	1000 mg q12h	1250 mg q12h	1000 mg q8h	1250 mg q8h	1250 mg q8h	1500 mg q8h	1750 mg q8h
85–89	1000 mg q12h	1250 mg q12h	1000 mg q8h	1250 mg q8h	1500 mg q8h	1750 mg q8h	2000 mg q8h
90–94	1000 mg q12h	1500 mg q12h	1000 mg q8h	1250 mg q8h	1500 mg q8h	1750 mg q8h	2000 mg q8h
95–99	1250 mg q12h	1500 mg q12h	1000 mg q8h	1250 mg q8h	1500 mg q8h	1750 mg q8h	2000 mg q8h
100–104	1250 mg q12h	1500 mg q12h	1250 mg q8h	1500 mg q8h	1750 mg q8h	2000 mg q8h	2000 mg q8h
105–109	1250 mg q12h	1500 mg q12h	1250 mg q8h	1500 mg q8h	1750 mg q8h	2000 mg q8h	2250 mg q8h
≥ 110	1250 mg q12h	1500 mg q12h	1250 mg q8h	1500 mg q8h	1750 mg q8h	2000 mg q8h	2250 mg q8h

In 200 patients, 58 % achieved trough goals within 15-20 mg/L

Kullar R. Pharmacotherapy. 2011 May;31(5):441-8.

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Should we monitor vancomycin routinely?

- Historically a standard of practice
- No definitive studies (i.e. prospective, randomized) to demonstrate benefit
- Can we extrapolate study findings to all patients?
- What about dosing adjustments and therapeutic goals?

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When to Monitor

- Criteria
  - No peak concentrations necessary
  - Trough monitoring in patients with
    - aggressive dosing
    - high risk of nephrotoxicity
    - Unstable renal function
    - Prolonged courses of therapy
- Frequency
  - > 1 trough prior to 4th dose not recommended for in short course/low intensity
  - Prolonged course: at least 1 steady state trough
  - Aggressive dosing: once weekly if stable, more frequent otherwise

Rybak MJ et al. Am J Health Syst Pharm. 2009 Jan 1;66(1):82-98.

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Adjusting the dose after levels

Two types of "general" scenarios	Adjustment	
	Dose	Interval
1. C_{min} excessively low/high *excessive = ≤ 0.5 or ≥1.5 x target*		X
2. C_{min} slightly low/high *slightly = within 0.5-1.5 x target*	X	

- Linear PK principles

$$\frac{D_{new}}{\tau_{new}} = \left(\frac{D_{old}}{\tau_{old}}\right)\left(\frac{C_{ss,new}}{C_{ss,old}}\right)$$

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Case #1

A 62 year old female in respiratory failure is on a ventilator for the past week and develops MRSA VAP. Weight 65 kg, height 62 inches, BUN/SCr 26/1.2 The MIC of the pathogen to vancomycin is 1 mg/L.

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Case #2

A 55 year old male with MRSA osteomyelitis is given vancomycin 1 g every 12 hours with a goal trough of 20 mg/L. He weighs 105 kg and has a CrCl 75 ml/min. The vancomycin trough at C_{ss} is 8 mg/L. The physician treating this patient turns to you for recommendations

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Case 2 update

A week later, the patient receives IV contrast which results in minor renal impairment CrCl 40 ml/min. The new trough with your recommended dose is now 26 mg/L. Again you are consulted for your recommendations.

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Application of AG/VA kinetics

- Lecture exercises will discuss cases presented in the slides above

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