Vancomycin

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Ph.D CLINICAL PHARMACY

❶ Clinical uses

✓ is a glycopeptide antibiotic used to treat severe gram-positive infections due to organisms that are resistant to other antibiotics such as methicillin-resistant staphylococci and ampicillin-resistant enterococci.

✓ Vancomycin is bactericidal and exhibits:

❶ Time-dependent killing or concentration independent i.e kill bacteria most effectively if serum conc. 3-5 > MIC of bacteria.

❷ Mechanism of action

✓ inhibition of cell wall synthesis.

❸ Method of administration

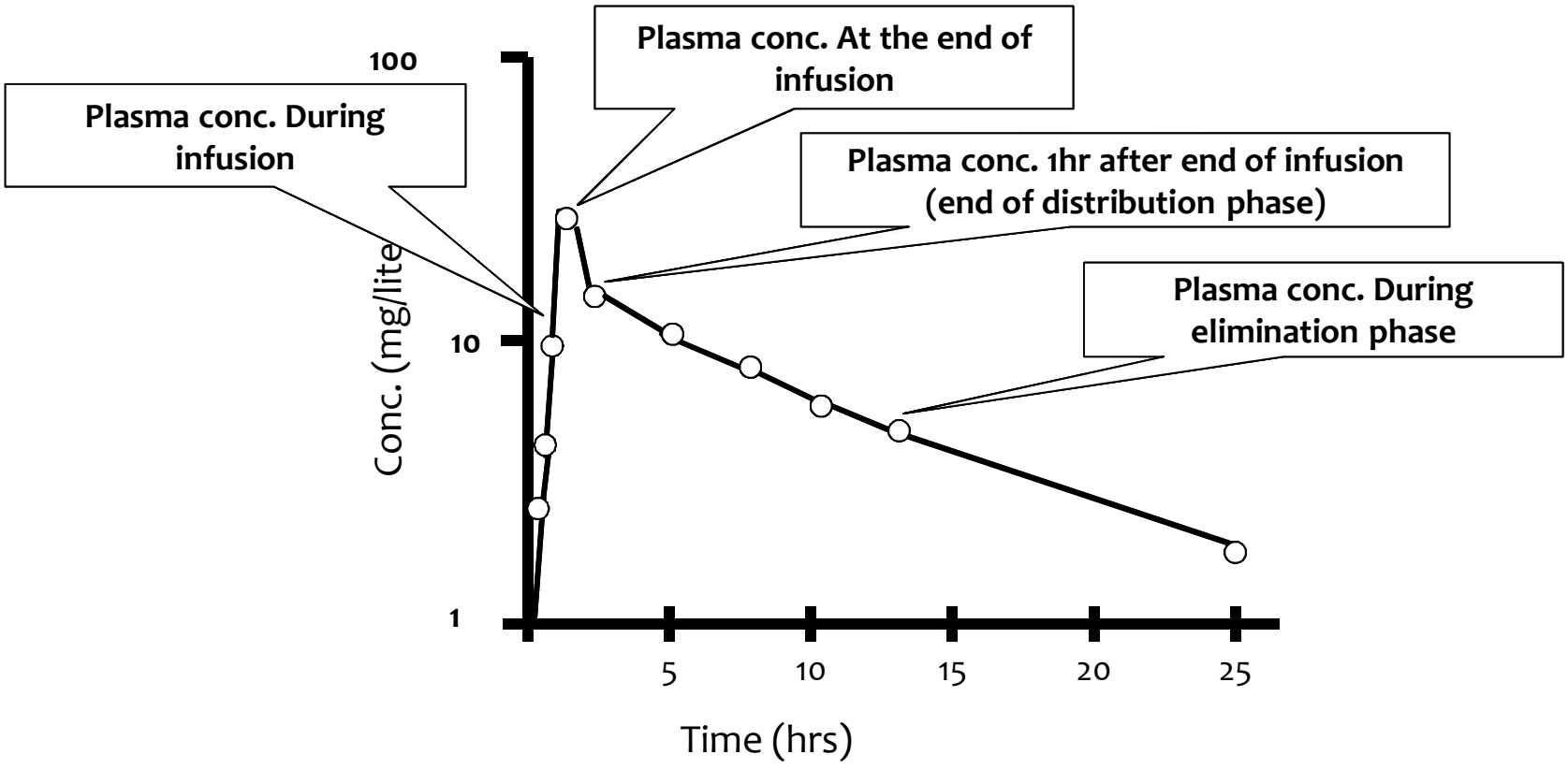
✓ By intermittent IV infusion during 1hr (at least) to reduce incidence of adverse effects like anaphylactic like reaction, ototoxicity, nephrotoxicity.

❹ Summary of kinetic parameters

Bioavailability (F)	IV = 100%, orally <5% but used to treat P.M.C
Volume of Distribution (Vd)	0.7L/Kg - Penetrate only into inflamed meninges - Penetrate poorly into lung (serum : lung conc.)=(6:1)
Fraction unbound (Fu)	≈45% (Bind to albumin)
Elimination	Renally by GFR as unchanged
Clearance (Cl)	0.695*CrCl+0.05
Elimination half life ($t_{0.5}$)	4- 6 hrs at normal renal function
Dosing (iv only)	L.D = 25-30 mg/kg (based on ABW) given at rate 1g/hr 2 or 4 dose/day
Compartmental model	Two compartmental model with distribution phase

❺ When to sample

- ✓ 1 hr after the end of infusion to get Cmax
- ✓ 0.5 hr before next infusion to get Cmin
- ✓ 1hr after infusion end is required to allow the distribution phase to complete



❻ Infusion rate related adverse effects

- ✓ Urticarial or erythematous reactions,
- ✓ intense flushing (known as the "red-man" or "red-neck" syndrome),
- ✓ tachycardia, and hypotension
- ✓ All can be reduced by slowing the rate of infusion

❼ Concentration related adverse effects

① Nephrotoxicity

- ✓ ↑ if Trough cpss > 15 µg/mL
- ✓ is reversible if antibiotic is drawn or dose adjusted if renal function was declined

① Ototoxicity

- ✓ ↑ if serum conc. Is high like 80 mg/liter

❽ Conditions alter its pharmacokinetics parameters

TABLE 5-1 Disease States and Conditions That Alter Vancomycin Pharmacokinetics

DISEASE STATE/CONDITION	HALF-LIFE	VOLUME OF DISTRIBUTION	COMMENT
Adult, normal renal function	8 hours (range: 7–9 hours)	0.7 L/kg (range: 0.5–1.0 L/kg)	Usual dose 30 mg/kg/d in 2 divided doses
Adult, renal failure	130 hours (range: 120–140 hours)	0.7 L/kg (range: 0.5–1.0 L/kg)	Underhydration or overhydration does not effect the volume of distribution as much as with aminoglycosides
Burns **(Inc rate of metabolism leads to increase GFR)**	4 hour	0.7 L/kg	Because of shorter half-life, some patients may need every 6–8-hour dosage interval to maintain therapeutic trough concentrations
Obesity (>30% over IBW) with normal renal function **Inc GFR**	3–4 hours	V = 0.7 IBW*	Total daily doses are based on TBW*, V estimates based on IBW*. Because of shorter half-life, some patients may require every 8-hour dosage interval to maintain therapeutic trough concentrations

*IBW = ideal body weight,
TBW = total body weight

❽ Conditions alter its pharmacokinetics parameters

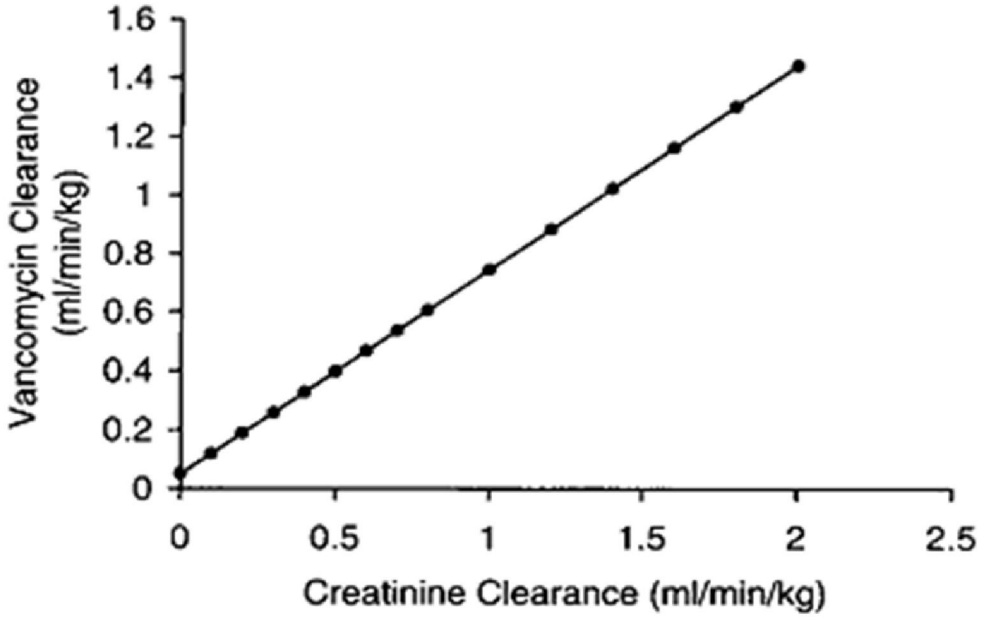


FIGURE 5-2 The clearance rate for vancomycin increases in proportion with creatinine clearance (CrCl). The equation for this relationship is Cl (in mL/min/kg) = 0.695(CrCl in mL/min/kg) + 0.05. This equation is used to estimate vancomycin clearance in patients for initial dosing purposes.

❽ Other Conditions alter its pharmacokinetics parameters

① Age

✓ Volume of distribution not significantly changed,

✓ Clearance is changed with age according to creatinine clearance and maturation of kidneys

Age	Creatinine clearance	Half life
Premature infant	15ml/min	10hr
Full term baby	30ml/min	7hr
3months	50ml/min	4hr
4-8years	130-150ml/min	2-3hr
12>=years	130-150ml/min	2-3hr

❽ Other Conditions alter its pharmacokinetics parameters

① Age

✓ for new babies the dose is depended on neonatal age & body weight

✓ Magnitude of single dose per Kg is not changed but the frequency is changed

Weight	dose	Frequency	
		Age <7days	Age > 7days
<1.2kg	15mg/kg	Every 24hrs	Every 24hrs
1.2 -2kg	10 -15mg/kg	12-18hr	8-12hr
>2kg	10 -15mg/kg	8-12hr	6-8hr

❽ Other Conditions alter its pharmacokinetics parameters

① Age

✓ for Children, Magnitude of single dose per Kg is changed & the frequency is changed

✓ Changes depends majorly on severity of infection

Infection type	dose	Frequency
Meningitis	60mg/kg	Every 6hrs
Sever Systemic infection	40 -60mg/kg	Every 6 hours
Other infections	40mg/kg	Every 6-8hours

✓ Changes depends majorly on severity of infection

❽ Other Conditions alter its pharmacokinetics parameters

② Hemodialysis

- ✓ for low flux dialysis, (<10%) of the total vancomycin body stores is removed during a 3- to 4-hour dialysis period
- ✓ high-flux" filter, serum concentrations decrease by 1/3 during the dialysis period
- ✓ then slowly increase or "rebound" for the next 10–12 hours reaching nearly 90% of pre-dialysis values. So it need to measure plasma conc. after high flux dialysis

③ Peritoneal dialysis

- ✓ removes only a negligible amount of vancomycin
- ✓ Patient that has peritonitis during peritoneal dialysis:
- ✓ 90% of vancomycin is removed from peritoneal dialysate containing vancomycin during 6 hr
- ✓ 50% of vancomycin is removed from peritoneal dialysate containing vancomycin during 6 hr if patient has renal failure

❽ Other Conditions alter its pharmacokinetics parameters

④ HemoFilteration

- ✓ will remove Vancomycin from the body
- ✓ The hemofiltration sieving coefficient for vancomycin is 0.80
- ✓ Recommended initial doses for critically ill patients with acute renal failure undergoing
- ✓ continuous venous hemofiltration (CVVH) are :
- ✓ loading dose of 15–20 mg/kg followed by 250–500 mg every 12 hours
- ✓ continuous ateriovenous hemofiltration (CAVH) are:
- ✓ Initial dose is 500 mg every 24–48 hours
- ✓ Because of pharmacokinetic variability, vancomycin concentrations should be measured in hemofiltration patients

❾ Drug interactions

① With aminoglycosides

✓ will increase incidence of nephrotoxicity

② With warfarin

✓ 45% increase in prothrombin time over baseline values

❿ Initial dose determination methods

① Pharmacokinetic dosing method

✓ **Example 1** JM is a 50-year-old, 70-kg (5 ft 10 in) male with a methicillin-resistant S. aureus (MRSA) wound infection. His current serum creatinine is 0.9 mg/dL, and it has been stable over the last 5 days since admission. Compute a vancomycin dose for this patient.

✓ **Answer 1** Generally vancomycin is given as loading dose initially or given as intermittent infusion with determined frequency.

✓ If we need to calculate loading dose the equation will be

✓ $LD = Cssmax * Vd.$

LD= 980 mg ≈ 1000mg

20 mg/liter

0.7Liter * 70kg =49 liters

⑩ Initial dose determination methods

① Pharmacokinetic dosing method

✓ If we need to calculate daily dose the equation will be

✓ $D = Cssmax * Vd.(1- e^{kT})$

20 mg/liter

0.7L/kg *70 kg= 49 Liters

K=CL/vd

τ= (ln Cssmax – ln Cssmin)/ke

Cmin= 7mg/L according to infection

Cl= 0.695CrCl +0.05

✓ So it is better to solve it step by step

❿ Initial dose determination methods

① Pharmacokinetic dosing method

✓ **Estimate creatinine clearance**

✓ Patient is not obese and serum creatinine is stable. The Cockcroft-Gault equ. Is used

✓ $[(\mathbf{140} - \boldsymbol{Age})\boldsymbol{BW}] / (\mathbf{72} \cdot \boldsymbol{SCr})$

CrCl= 97 ml/min

50 years

70kg

0.9mg/ dl

✓ **Estimate Vancomycin clearance**

✓ Cl= 71.05 ml/min = 4.263 L/hr

97 ml/min

❿ Initial dose determination methods

① Pharmacokinetic dosing method

- ✓ **Estimate Vd**
- ✓ **Vd $= 0.7L/Kg * 70kg = 49L$**
- ✓ **Estimate Ke & T0.5**
- ✓ Ke= 0.087/hr, Vd = 49L, Cl= 4.263 l/hr
- ✓ **T0.5= 0.693 /Ke**

T0.5 = 8 hr, Ke= 0.087/hr

- ✓ **Select Cmin & Cmax**
- ✓ Cmax usually 20 mg/L while Cmin For Staph . aureus Infection is 7mg/L

❿ Initial dose determination methods

① Pharmacokinetic dosing method

✓ **Estimate *T* (*taw*)**

✓ **[illegible]ln Cssmin)/k**

T= 12.1hr

C_{max} =20mg/L

C_{min}= 7mg/L

K=0.087/hr

✓ Dosage intervals should be rounded to clinically acceptable intervals of 12 hours,18 hours, 24 hours, 36 hours, 48 hours, 72 hours, and multiples of 24 hours

✓ **Estimate *daily dose***

✓ Dose= 635mg **[illegible]/(1– e $^{-k\ \tau}$)** [illegible]7/hr

T= 12.1hr

C_{max} =20mg/L

Vd=49L

T= 12.1hr

✓ Vancomycin doses should be rounded to the nearest 100–250 mg. This dose would berounded to 750 mg.

✓ For Obese patient use Salazar and Corcoran. Equ to estimate creatinine clearance

❿ Initial dose determination methods

Estimation of creatinine clearance methods

- ✓ **For obese patient .** use Salazar and Corcoran

$$CrCl_{est(males)} = \frac{(137 - age)[(0.285 \cdot Wt) + (12.1 \cdot Ht^2)]}{(51 \cdot S_{Cr})}$$

$$CrCl_{est(females)} = \frac{(146 - age)[(0.287 \cdot Wt) + (9.74 \cdot Ht^2)]}{(60 \cdot S_{Cr})}$$

- ✓ **to**
- ✓ ag
- ✓ ag

TABLE 5-2B Pharmacokinetic Constant Computations Utilizing a One-compartment Model Used with Vancomycin

ROUTE OF ADMINISTRATION	SINGLE DOSE	MULTIPLE DOSE	STEADY STATE
Intravenous bolus	$k_e = -(\ln C_1 - \ln C_2)/(t_1 - t_2)$ $t_{1/2} = 0.693/k_e$ $V = D/C_{max}$ $Cl = k_e V$	$k_e = -(\ln C_1 - \ln C_2)/(t_1 - t_2)$ $t_{1/2} = 0.693/k_e$ $V = D/(C_{max} - C_{min})$ $Cl = k_e V$	$k_e = -(\ln C_1 - \ln C_2)/(t_1 - t_2)$ $t_{1/2} = 0.693/k_e$ $V = D/(Css_{max} - Css_{min})$ $Cl = k_e V$

Symbol key: C_1 is drug serum concentration at time = t_1, C_2 is drug serum concentration at time = t_2, k_e is the elimination rate constant, $t_{1/2}$ is the half-life, V is the volume of distribution, D is dose, C_0 is the concentration at time = 0, Cl is drug clearance, C_{min} is the predose trough concentration, C_{max} is the postdose peak concentration.

❿ Initial dose determination methods

② Moellering Nomogram Method

- ✓ The stated goal of the nomogram is to provide average steady-state vancomycin concentrations equal to 15 µg/mL (or 15 mg/L).
- ✓ the patient's creatinine clearance is computed and divided by their body weight so that the units for creatinine clearance are mL/min/kg**.**
- ✓ A modification of the vancomycin clearance/creatinine clearance equation can be made that provides a direct calculation of the vancomycin maintenance dose.
- ✓ $\boldsymbol{MD = Cl_{*} Cssave}$
- ✓ Cl (in mL/min/kg) = 0.695(CrCl in mL/min/kg) + 0.05
- ✓ D (in mg/h/kg) = [(15 mg/L · 60 min/h) /1000 mL/L][0.695(CrCl in mL/min/kg) + 0.05]
- ✓ D (in mg/h/kg) = 0.626(CrCl in mL/min/kg) + 0.05

❿ Initial dose determination methods

② Moellering Nomogram Method

✓ **Example 1** JM is a 50-year-old, 70-kg (5 ft 10 in) male with a methicillin-resistant S. aureus (MRSA) wound infection. His current serum creatinine is 0.9 mg/dL, and it has been stable over the last 5 days since admission. Compute a vancomycin dose for this patient.

✓ Answer Estimate Creatinine clearance

✓ $(\mathbf{72} \cdot \boldsymbol{SCr})$

CrCl= 97 ml/min

50 years

70kg

0.9mg/ dl

✓ Determine dosage interval and maintenance dose.

✓ D (in mg/h/kg) = 0.626(CrCl in mL/min/kg) + 0.05

0.918mg/kg/hr

97ml/min/70kg=1.386

✓ 0.918mg/kg/hr .70kg

Dose is suggested by the Moellering nomogram

✓ Loading dose =15mg/kg * 70kg =1050 mg ===1000mg

⑩ Initial dose determination methods

② Moellering Nomogram Method

TABLE 5-3 Moellering Nomogram Vancomycin Dosage Chart

1. Compute patient's creatinine clearance (CrCl) using Cockcroft–Gault method for normal weight or Salazar-Corcoran method for obese patients.
2. Divide CrCl by patient's weight.
3. Compute 24-hour maintenance dose for CrCl value.
4. Loading dose of 15 mg/kg should be given in patients with significant renal function impairment.

CREATININE CLEARANCE (mL/min/kg)*	VANCOMYCIN DOSE (mg/kg/24 h)
2	30.9
1.9	29.3
1.8	27.8
1.7	26.3
1.6	24.7
1.5	23.2
1.4	21.6

* Dose for functionally anephric patients is 1.9 mg/kg/24 h

❿ Initial dose determination methods

③ Matzke nomogram method

✓ This method has been shown to provide precise and unbiased dosage recommendations,

TABLE 5-4 Matzke Nomogram Vancomycin Dosage Chart

1. Compute patient's creatinine clearance (CrCl) using Cockcroft–Gault method: CrCl = [(140 – age)BW] / (Scr × 72). Multiply by 0.85 for females.
2. Nomogram not verified in obese individuals.
3. Dosage chart is designed to achieve peak serum concentrations of 30 µg/mL and trough concentrations of 7.5 µg/mL.
4. Compute loading dose of 25 mg/kg.
5. Compute maintenance dose of 19 mg/kg given at the dosage interval listed in the following chart for the patient's CrCl:

CrCl (mL/min)	DOSAGE INTERVAL (DAYS)
≥120	0.5
100	0.6
80	0.75
60	1.0
40	1.5
30	2.0
20	2.5
10	4.0
5	6.0
0	12.0

❿ Initial dose determination methods

③ Matzke nomogram method

✓ **Example 1** JM is a 50-year-old, 70-kg (5 ft 10 in) male with a methicillin-resistant S. aureus (MRSA) wound infection. His current serum creatinine is 0.9 mg/dL, and it has been stable over the last 5 days since admission. Compute a vancomycin dose for this patient.

✓ Answer Estimate Creatinine clearance

✓ $[(\mathbf{137} - \mathbf{Age})\boldsymbol{BW}] / (\mathbf{72} \cdot \boldsymbol{SCr})$

CrCl= 97 ml/min

50 years

70kg

0.9mg/ dl

✓ Determine dosage interval and maintenance dose.

✓ Dose= 19mg/kg * 70kg =1330 mg

✓ The dose rounded to nearest 250 or 100mg so 1250 mg is suggested

✓ The dose is given ev

Dose is suggested by the matzke nomogram

✓ Loading dose =25mg/kg * 70kg =1750 mg

❿ Initial dose determination methods

④ literature based method

- ✓ Due to variability in vancomycin pharmacokinetics; clinicians preferred to use standard vancomycin doses for pediatric patients is warranted.

- ✓ **Example 1** MM is a 3-day-old, 1015-g male with suspected methicillin-resistant S. aureus (MRSA) sepsis. His serum creatinine has not been measured, but it is assumed that it is typical for his age and weight. Compute an initial vancomycin dose for this patient.

- ✓ a patient in this age and weight category should receive vancomycin 15 mg/kg every 24 hours. (see slide 9)

- ✓ Dose= 15mg/kg * 1.015kg =15 mg given every 24 hr

⓫ Use vancomycin conc to alter the Dose

① Linear Pharmacokinetics Method

✓ use Dnew/Css,new = Dold/Css,old or Dnew = (Css,new/Css,old)Dold

✓ **Example 1** JM is a 50-year-old, 70-kg (5 ft 10 in) male with a methicillin-resistant S. aureus (MRSA) pneumonia. His current serum creatinine is 0.9 mg/dL, and it has been stable over the last 5 days since admission. A vancomycin dose of 1000 mg every 12 hours was prescribed and expected to achieve steady-state peak and trough concentrations equal to 35 µg/mL and 15 µg/mL, respectively. After the 3rd dose, steady-state peak and trough concentrations were measured and equaled 22 µg/mL and 10 µg/mL, respectively. Calculate a new vancomycin dose that would provide a steady-state trough of 15 µg/mL.

✓ Dose new = (15 / 10)*1000 =1500mg every 12hr

✓ Check the new dose by using cmax css new = (1500 / 1000)*22 =33mg /L

⓫ Use vancomycin conc to alter the Dose

② Trough only Method

✓ use $\tau new = (Css,old/Css,new)\tau old$

✓ **Example 1** UI is a 55-year-old, 78-kg (height = 6 ft 1 in) male with a methicillin-resistant S. aureus (MRSA) pneumonia. His current serum creatinine is 1.5 mg/dL, and ithas been stable over the last 3 days since admission. A vancomycin dose of 1000 mgevery 24 hours was prescribed and expected to achieve a steady-state trough concentra-tion equal to 15 µg/mL. After the second dose, the steady-state trough concentration equaled 7 µg/mL. Calculate a new vancomycin dose that would provide a steady-state trough of 15 µg/mL.

✓ $\tau new = (Css,old/Css,new)\tau old$ = (7 µg/mL / 15 µg/mL) 24 h = 11 h, round to 12 h

✓ The dose will be 1000mg every 12 hrs

⓫ Use vancomycin conc to alter the Dose

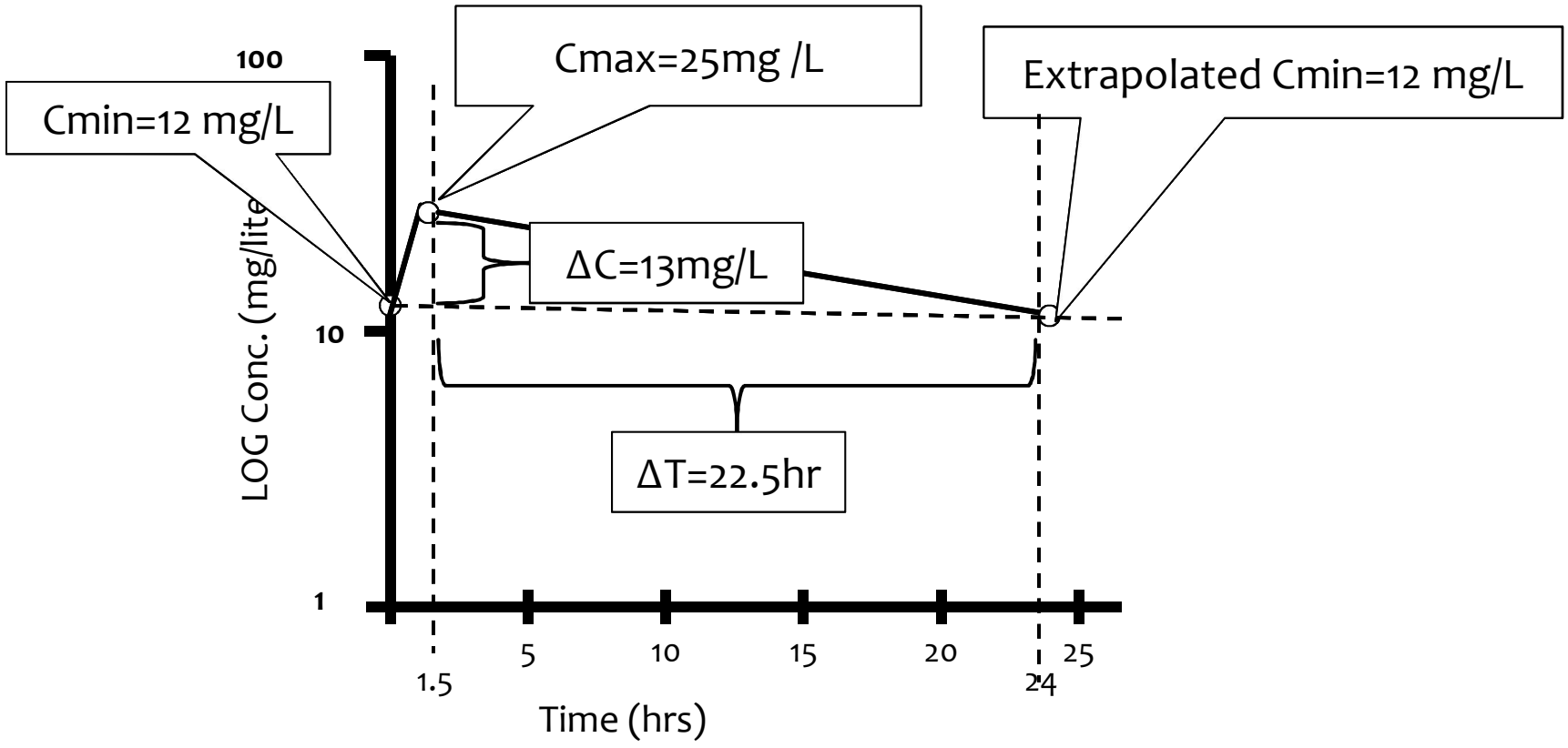
③ Pharmacokinetic Concepts Method

- ✓ By estimating actual pharmacokinetic parameters or surrogates for pharmacokinetic parameters
- ✓ The only requirement is a steady-state peak and trough vancomycin serum concentration pair obtained before and after a dose
- ✓ **Example 1** JM is a 50-year-old, 70-kg (height = 5 ft 10 in) male with a methicillin-resistant S. aureus (MRSA) wound infection. His current serum creatinine is 3.5 mg/dL, and it has been stable over the last 5 days since admission. A vancomycin dose of 800 mg every 24 hours was prescribed and expected to achieve steady-state peak and trough conc. equal to 20 μg/mL and 5 μg/mL, respectively. After the fourth dose, steady-state peak and trough concentrations were measured and equaled 25 μg/mL and 12 μg/mL, respectively. Calculate a new vancomycin dose that would provide a steady-state peak of 20 μg/mL and a trough of 5 μg/mL.
- ✓ use graph method to estimate no of half life present with dosing interval then find out half life by dividing Taw on number of half life
- ✓ Then estimate new dose by using $D_{new} = (\Delta C_{new}/\Delta C_{old})D_{old}$
- ✓ Then estimate Taw by estimate no of T0.5 required to change from Cmax to Cmin

⓫ Use vancomycin conc to alter the Dose

③ Pharmacokinetic Concepts Method

Same thing if we draw new cMax plot line to Cmin and find out no of half lives



⓫ Use vancomycin conc to alter the Dose

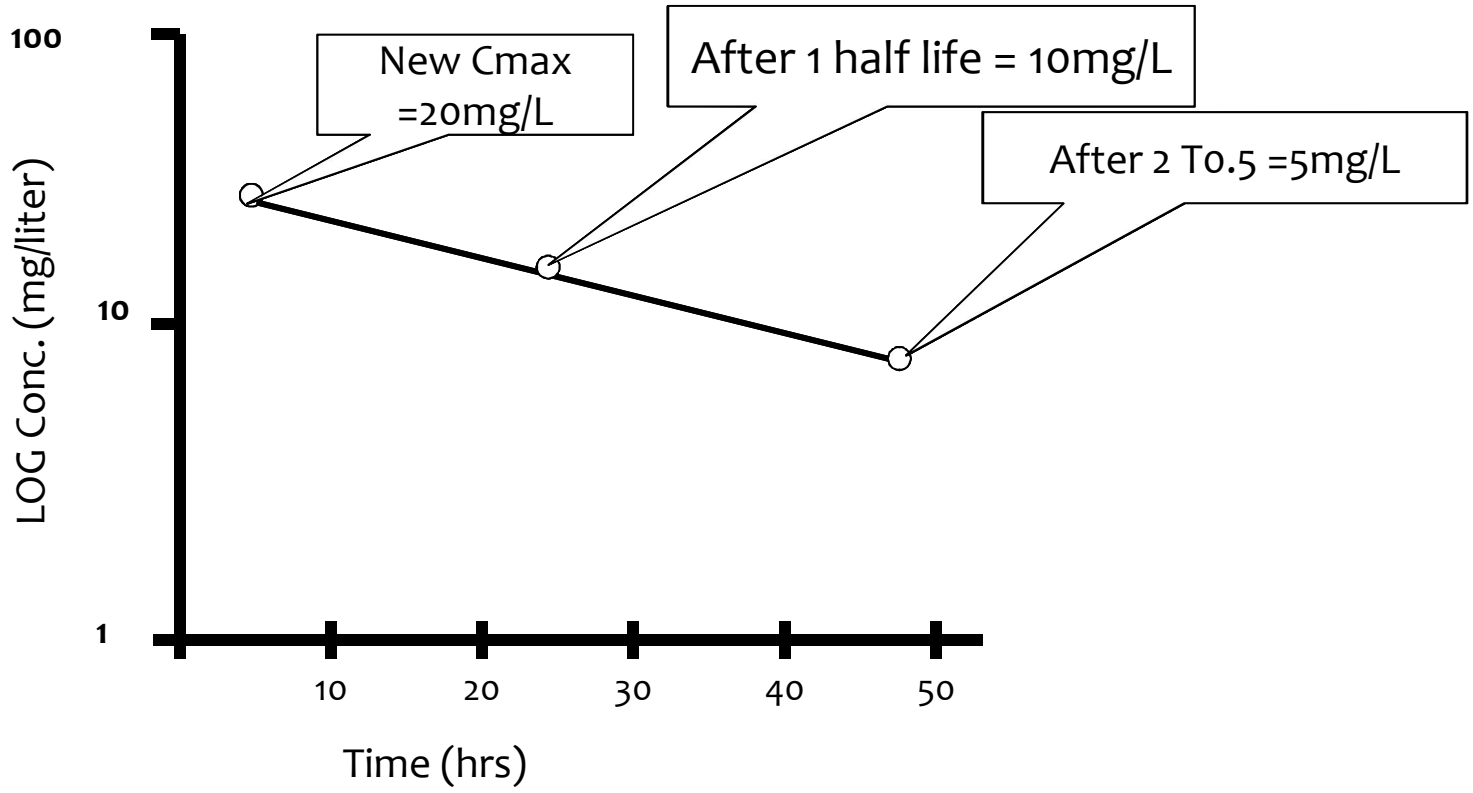
③ Pharmacokinetic Concepts Method

- ✓ Then 12/25 ≈ ½ ie Cmax change to cmin required 1half life
- ✓ Since change from Cmax to next Cmin required 22.5 hr
- ✓ So Half life will be 22.5 hr
- ✓ Estimate the new dose
- ✓ $D_{new} = (\Delta C_{new}/\Delta C_{old})D_{old}$
- ✓ Dose New =[(20 -5)/(25-12)]*800= 923 mg ≈ 1000mg
- ✓ Estimate the new Taw
- ✓ Then 5/20= 1/4 if we use $(1/2)^n$ ie n=2 half lives required to change from new Cmax to new Cmin
- ✓ Since founded to.5 was 22.5 so the new taw will be 2*22.5 =45 hr ≈48hr
- ✓ So the new estimated dose will be 1000mg given every 48 hrs

⓫ Use vancomycin conc to alter the Dose

③ Pharmacokinetic Concepts Method

Same thing if we draw new cMax plot line to Cmin and find out no of half lives



⓫ Use vancomycin conc to alter the Dose

④ Standard one compartment model parameters method

- ✓ It does not require steady-state concentrations. Just trough & max Concentration peri infusion process
- ✓ and 1–2 additional post dose serum vancomycin concentrations are obtained ideally with one half life apart
- ✓ The postdose serum concentrations are used to calculate the vancomycin elimination rate constant and half-life The
- ✓ STEADY-STATE ONE-COMPARTMENT MODEL PARAMETER METHOD
- ✓ If Cssmax and Css Min are known then use same method above to find K eleimination, Half life
- ✓ ke = (ln Cssmax – ln Cssmin)/ (τ– t′); where (τ– t′)= Taw – infusion time
- ✓ Vd =Dose/ (CssMax-Cssmin)
- ✓ In this method the patient's real pharmacokinetic parameters are used in
- ✓ the equations instead of population pharmacokinetic estimates.

⓫ Use vancomycin conc to alter the Dose

④ Standard one compartment model parameters method

- ✓ **Example 1** JM is a 50-year-old, 70-kg (height = 5 ft 10 in) male with a methicillin-resistant S. aureus (MRSA) wound infection. His current serum creatinine is 3.5 mg/dL, and it has been stable over the last 5 days since admission. A vancomycin dose of 800 mg every 24 hours was prescribed and expected to achieve steady-state peak and trough conc. equal to 20 µg/mL and 5 µg/mL, respectively. After the fourth dose, steady-state peak and trough concentrations were measured and equaled 25 µg/mL and 12 µg/mL, respectively. Calculate a new vancomycin dose that would provide a steady-state peak of 20 µg/mL and a trough of 5 µg/mL.
- ✓ ke = (ln Cssmax – ln Cssmin)/ (τ– t′); where (τ– t′)= Taw – infusion time
- ✓ =(ln25-ln12)/(24-1.5) == ke =0.0326/hr
- ✓ Vd =Dose/ (CssMax-Cssmin)
- ✓ Vd =800mg /(25-12) =61.5 L
- ✓ Determine Taw =τ= (ln Cssmax – ln Cssmin)/ke = (ln 20 µg/mL – ln 5 µg/mL)/0.0326 h–1
- ✓ new Taw =τ= 42 hr rounded to 48 hr
- ✓ D =Cssmax V(1 – e–keτ) = 20 mg/L · 61.5 L [1 – e–(0.0326 h–1)(48 h)]= 974 mg, rounded to 1000 mg

THANKS