CLINICAL PHARMACOKINETIC OF VANCOMYCIN

INITIAL DOSAGE DETERMINATION METHODS

1. The pharmacokinetic dosing method

2. Nomograms

- Moellering nomogram
- Matzke nomogram

3. Literature-based

1-Pharmacokinetic Dosing Method

1- CLEARANCE ESTIMATE

$$\mathbf{Cl = 0.695(CrCl) + 0.05}$$

Where

Cl is vancomycin clearance in mL/min/kg

CrCl is creatinine clearance in mL/min/kg

Note : The weight factor that is used for all individuals, including obese patients, is total body weight (TBW).

2- VOLUME OF DISTRIBUTION ESTIMATE

The average volume of distribution of vancomycin is 0.7 L/kg.

The weight factor that is used to calculate vancomycin volume of distribution for obese patients is ideal body weight (IBW).

3-HALF-LIFE AND ELIMINATION RATE CONSTANT ESTIMATE

$$\mathbf{ke = Cl/V}$$

$$\mathbf{t1/2 = 0.693/ke}$$

4-SELECTION OF APPROPRIATE PHARMACOKINETIC MODEL AND EQUATIONS

Intravenously administered vancomycin is given over 1 hour as intermittent continuous infusions. Since the drug has a long half-life relative to the infusion time (1 hour) and waiting time (0.5–1 hour) necessary to allow for distribution to complete before peak concentrations are obtained, little of the drug is eliminated during this 1.5- to 2-hour time period. So, although the antibiotic is given as an intravenous

infusion, intravenous bolus equations accurately predict peak vancomycin concentrations and are mathematically simpler.

TABLE 5-2A One-Compartment Model Equations Used with Vancomycin

ROUTE OF ADMINISTRATION	SINGLE DOSE	MULTIPLE DOSE	STEADY STATE
Intravenous bolus	$C = (D/V)e^{-k_e t}$	$C = (D/V)e^{-k_e t}[(1 - e^{-nk_e \tau})/(1 - e^{-k_e \tau})]$	$C = (D/V)[e^{-k_e t}/(1 - e^{-k_e \tau})]$

Symbol key: C is drug serum concentration at time = t, D is dose, V is volume of distribution, k_e is the elimination rate constant, n is the number of administered doses, τ is the dosage interval.

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.

TABLE 5-2C Equations Used to Compute Individualized Dosage Regimens for Vancomycin

ROUTE OF ADMINISTRATION	DOSAGE INTERVAL (τ), MAINTENANCE DOSE (D), AND LOADING DOSE (LD) EQUATIONS
Intravenous bolus	$\tau = (\ln Css_{max} - \ln Css_{min})/k_e$ $D = Css_{max} V(1 - e^{-k_e \tau})$ $LD = Css_{max} V$

Symbol key: Css_{max} and Css_{min} are the maximum and minimum steady-state concentrations, k_e is the elimination rate constant, V is the volume of distribution, k_0 is the continuous infusion rate.

5. STEADY-STATE CONCENTRATION SELECTION

- **Steady-state trough concentrations (C_{min})** are selected based on site and severity of infection in addition to the infecting organism.

5–15 µg/mL

For selected patients, such as those with hospital acquired pneumonia in institutions with high MICs for methicillin-resistant *S. aureus* (MRSA), trough concentrations as

high as 20 µg/mL may be needed to effect a cure. For patients, with acquired pneumonia in institutions with high MICs for methicillin-resistant S. aureus (MRSA), trough concentrations as high as **20 µg/mL**

- **Steady-state peak (Cmax) concentrations**

20–40 µg/mL

In severe, life-threatening infections of the central nervous system, peak vancomycin serum concentrations as high as **60 µg/mL** may be necessary to facilitate drug penetration.

(**Note:** µg/mL = mg/L and this concentration unit was substituted for Cssmax so that unnecessary unit conversion was not required).

6. DOSAGE COMPUTATION

The equations given in Table 5-2C is used to compute vancomycin doses.

2.Moellering Nomogram Method

(MD = Css .Cl) where MD is maintenance dose

$$\text{Cl (in mL/min/kg)} = 0.695(\text{CrCl in mL/min/kg}) + 0.05$$

$$\text{D (in mg/h/kg)} = [(15\ \text{mg/L} \cdot 60\ \text{min/h}) / 1000\ \text{mL/L}][0.695(\text{CrCl in mL/min/kg}) + 0.05]$$

$$\text{D (in mg/h/kg)} = 0.626(\text{CrCl in mL/min/kg}) + 0.05$$

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
1.3	20.1
1.2	18.5
1.1	17
1.0	15.4
0.9	13.9
0.8	12.4
0.7	10.8
0.6	9.3
0.5	7.7
0.4	6.2
0.3	4.6
0.2	3.1
0.1	1.5

3- Matzke Nomogram Method

- The Matzke dosing nomogram is a quick and efficient way to apply pharmacokinetic dosing concepts without using complicated pharmacokinetic equations (Table 5-4)
- The nomogram has not been tested in obese subjects (>30% over ideal body weight) and **should not** be employed in this patient population.
- Additionally, the authors suggest that the nomogram **should not** be used in patients undergoing peritoneal dialysis.

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

USE OF VANCOMYCIN SERUM CONCENTRATIONS TO ALTER DOSAGES

1. Linear pharmacokinetics & Trough-only Method

2. One-compartment model parameter method

Linear pharmacokinetics

$$D_{new} = (Css_{new}/Css_{old})\, D_{old}$$

- D is the dose
- Css is the steady-state peak or trough concentration
- Old indicates the dose that produced the steady-state concentration that the patient is currently receiving
- New denotes the dose necessary to produce the desired steady-state concentration.

Trough-only Method

$$\tau_{new} = (Css_{,old}/Css_{,new})\tau_{old}$$

- Css,old and Css,new are the original measured and new desired steady-state trough concentrations, respectively
- τ old and τ new are the original and new dosage intervals, respectively.
- New dosage intervals are rounded to clinically acceptable values (12 hours, 18 hours, 24 hours, 36 hours, 48 hours, 72 hours, and multiples of 24 hours thereafter, whenever possible), and the original dose is retained.

One-Compartment Model Parameter Method

1- Standard one-compartment model parameter method

- ❖ Does not require steady-state concentrations.
- ❖ A trough vancomycin concentration is obtained before a dose, a peak vancomycin concentration is obtained after the dose is infused (1/2–1 hour after a 1-hour infusion)
- ❖ 1–2 additional postdose serum vancomycin concentrations are obtained (Figure 5-9).

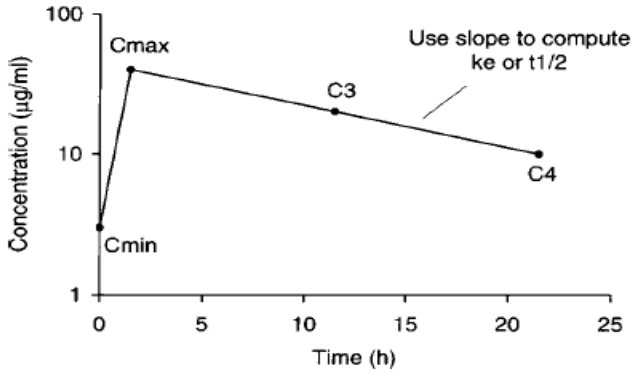

FIGURE 5-9 The one-compartment model parameter method for individualization of vancomycin doses uses a trough (C_{min}), peak (C_{max}), and 1–2 additional postdose concentrations (C_3, C_4) to compute a patient's own, unique pharmacokinetic parameters. This version of the one-compartment model parameter method does not require steady-state conditions. The peak and trough concentrations are used to calculate the volume of distribution, and the postdose concentrations (C_{max}, C_3, C_4) are used to compute half-life. Once volume of distribution and half-life have been measured, they can be used to compute the exact dose needed to achieve desired vancomycin concentrations.

Once the half-life is known, the elimination rate constant (ke) can be computed:

ke = 0.693/t1/2.

Alternatively, the elimination rate constant can be directly calculated using the postdose serum concentrations

ke = (ln C1 − ln C2)/Δt

- C1 and C2 are postdose serum concentrations
- Δt is the time that expired between the times that C1 and C2 were obtained

❖ Half-life can be computed using the elimination rate constant (t1/2 = 0.693/ke).

❖ The volume of distribution (V) is calculated using the following equation:

V = D / (Cmax − Cmin)

❖ Determination the new dosage interval for the desired concentrations.

τ = (ln Cssmax − ln Cssmin)/ke

❖ Determination the new dose for the desired concentrations.

D = Cssmax V(1 − $e^{-ke\tau}$)

2. Steady-state one-compartment model parameter method

If a steady-state peak and trough vancomycin concentration pair is available for a patient, the one-compartment model parameter method can be used to compute patient pharmacokinetic parameters and vancomycin doses **(Figure 5-10).**

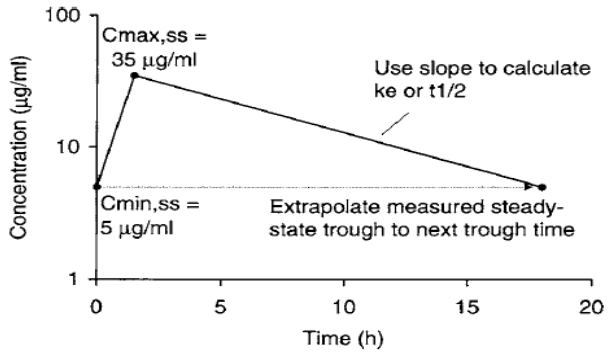

FIGURE 5-10 The steady-state version of the one-compartment model parameter method uses a steady-state peak (Css_{max}) and trough (Css_{min}) concentration pair to individualize vancomycin therapy. Because the patient is at steady state, consecutive trough concentrations will be identical, so the trough concentration can be extrapolated to the next predose time. The steady-state peak and trough concentrations are used to calculate the volume of distribution and half-life. Once volume of distribution and half-life have been measured, they can be used to compute the exact dose needed to achieve desired vancomycin concentrations.

- **ke = (ln Cssmax − ln Cssmin) / τ − t′**
- **t1/2 =0.693/ke**
- **V = D / (Cssmax − Cssmin)**
- **D = Cssmax V(1 − $e^{-ke\tau}$)**

(**Note:** This summery is designed only for the lab; it never designed for any exam)

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