Chapter 4

REFERENCE: APPLIED CLINICAL PHARMACOKINETICS

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THE AMINOGLYCOSIDE ANTIBIOTICS

ABOUT AMINOGLYCOSIDE

Concentration-efficacy relationships

The pharmacodynamic properties of aminoglycosides are:

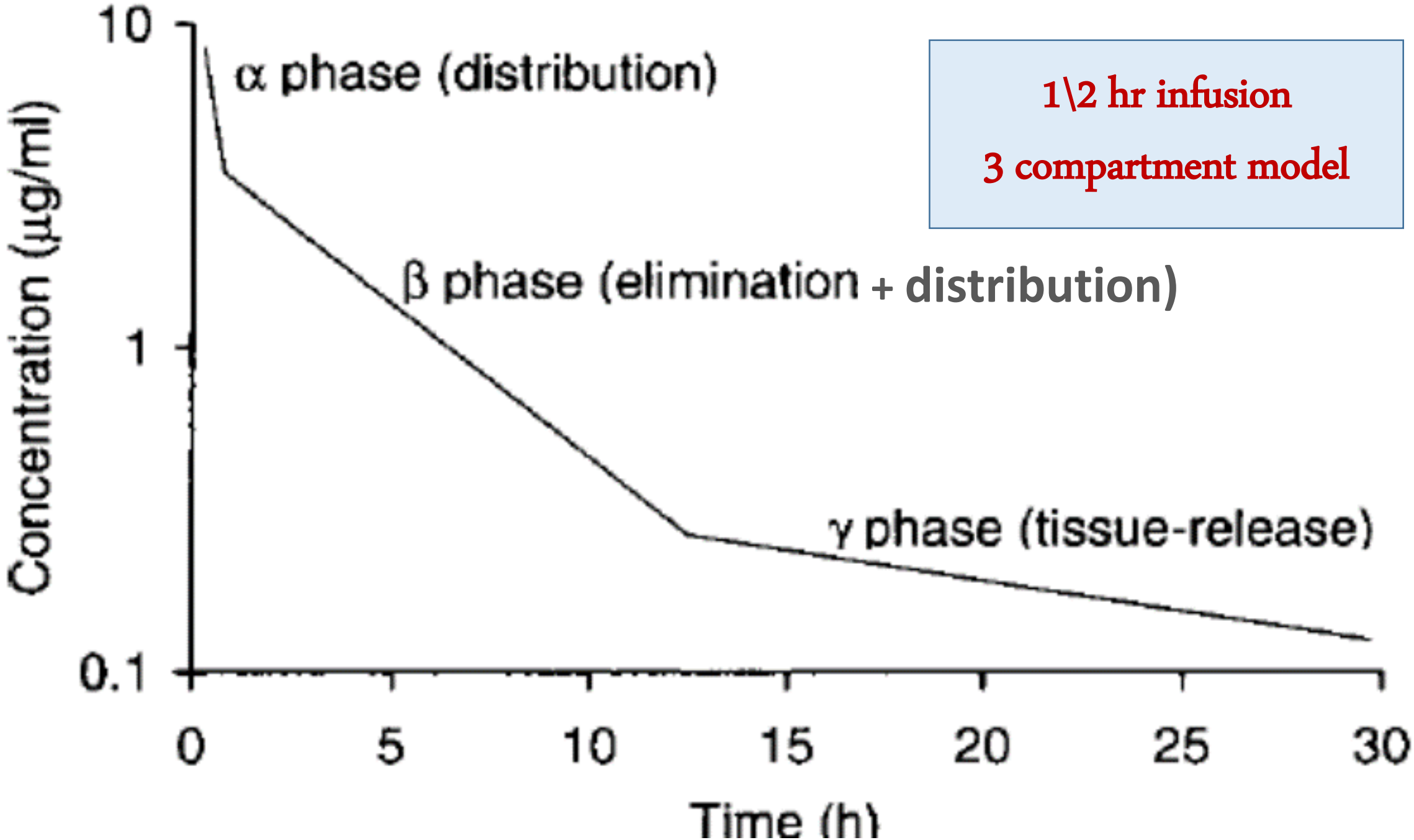
- Concentration–dependent killing
- Significant post–antibiotic effect

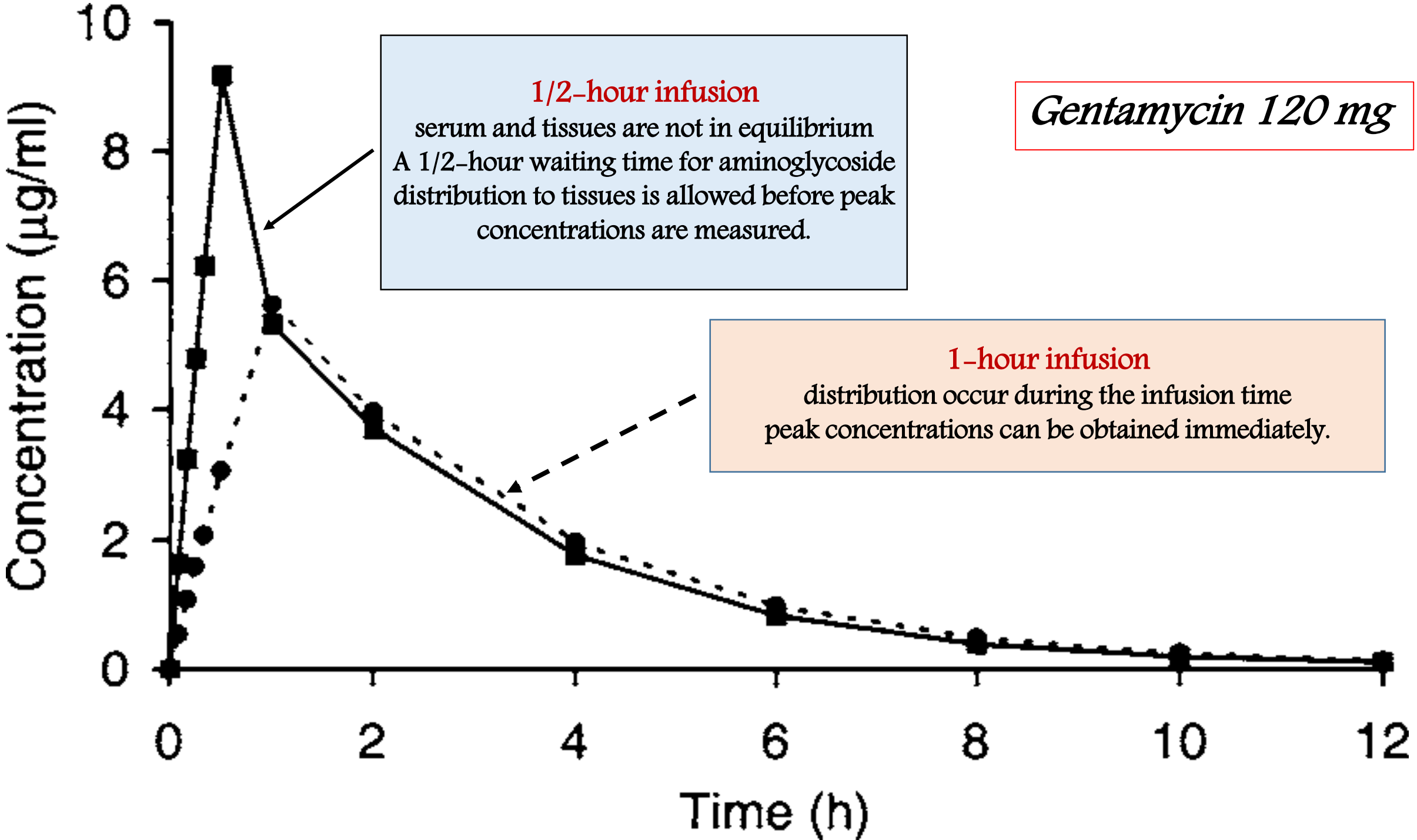
Post-antibiotic effect

- The post antibiotic effect is the phenomenon of continued bacterial killing even though serum concentrations have fallen below the minimum inhibitory concentration (MIC).
- Because the post antibiotic effect is concentration-dependent for the aminoglycosides, higher drug concentrations lead to a longer post antibiotic effect.

Administration

- **Aminoglycoside antibiotics are given as short-term infusions (over 30 min):**
- Follow a 3-compartment model
- Distribution phase not observed and ɣ-phase begins ~16 hrs post infusion.


1\2 hr infusion
3 compartment model
α phase (distribution)
β phase (elimination + distribution)
γ phase (tissue-release)
Concentration (µg/ml)
10
1
0.1
0
5
10
15
20
25
30
Time (h)


1/2-hour infusion
serum and tissues are not in equilibrium
A 1/2-hour waiting time for aminoglycoside distribution to tissues is allowed before peak concentrations are measured.
Gentamycin 120 mg
1-hour infusion
distribution occur during the infusion time
peak concentrations can be obtained immediately.
Concentration (µg/ml)
10
8
6
4
2
0
0
2
4
6
8
10
12
Time (h)

Peak steady-state concentrations (Css max)

- **Peak steady-state concentration always measured after 1 hr**
- **Peak steady-state concentration of aminoglycosides determined according to:تعطى في السؤال**

- **the type of infection (severe, moderate, ….)**
- **the type of AB (Gentamycin, Amikacin, …)**

Trough steady-state concentrations (Css min)

- Predose or minimum concentrations usually obtained within 30 minutes of the next dose.
- Trough steady-state concentration of aminoglycosides determined according to: تعطى في السؤال

- the type of infection (severe, moderate, ...)
- the type of AB (Gentamycin, Amikacin, ...)

Aminoglycoside antibiotics are given by two methods:

- **The conventional method**
- **Extended-interval dosing**

The conventional method

- **The conventional method** is to administer multiple daily doses **(usually every 8 hours)**

➢ ***Steady-state peak concentration***:

- **5–10 µg/mL** for gentamicin, tobramycin, or netilmicin
- **15–30 µg/mL** for amikacin

➢ ***Steady-state trough concentration:***

- **< 2 µg/mL** for gentamicin, tobramycin or netilmicin.
- **< 5 µg/mL** for amikacin

Toxicity of Aminoglycoside

- PEAK steady-state concentrations (>12–14 µg/mL for gentamicin and others) and (>35–40 µg/mL for Amikacin) leads to an increased risk of OTOTOXICITY.

- TROUGH steady-state concentrations (>2–3 µg/mL gentamicin and others) and (>10 µg/mL for Amikacin) predispose patients to an increased risk of NEPHROTOXICITY.

Extended-interval dosing

- Extended-interval dosing (usually the total daily dose given once per day)
- Take advantage of concentration-dependent bacterial killing and the post antibiotic effect.

➢ ***Steady-state*** **peak concentration:**

- **20–30 µg/mL** for gentamicin, tobramycin, or netilmicin

➢ **Steady-state trough concentration**

- **< 1 µg/mL**

Toxicity does not increase in patients with extended-interval dosing of aminoglycosides!?

1-The dosage interval is prolonged, so aminoglycoside concentrations are low for a long period of time and may allow for diffusion of drug out of tissue and into the blood which avoids drug accumulation in the ear and kidney.

2-The uptake mechanisms into the ear and kidney may be saturable, so that high peak serum concentrations of aminoglycosides may not result in high renal or ear tissue concentrations.

EFFECTS OF DISEASE STATES AND CONDITIONS ON AMINOGLYCOSIDE PHARMACOKINETICS AND DOSING

DISEASE STATE/ CONDITION	HALF-LIFE	VOLUME OF DISTRIBUTION	COMMENT
Adult, normal renal function	2 hours (range: 1.5–3 hours)	0.26 L/kg (range: 0.2–0.3 L/kg)	Usual doses 3–5 mg/kg/d for gentamicin, tobramycin, netilmicin, or 15 mg/kg/d for amikacin when using conventional dosing. Usual doses are 5–7 mg/kg/d for gentamicin or tobramycin using extended-interval dosing.
Adult, renal failure	50 hours (range: 36–72 hours)	0.26 L/kg	Renal failure patients commonly have fluid imbalances that may decrease (underhydration) or increase (overhydration) the volume of distribution and secondarily change half-life.
Burns	1.5 hours	0.26 L/kg	Burn patients commonly have fluid imbalances that may decrease (underhydration) or increase (overhydration) the volume of distribution and secondarily change half-life.

Penicillin therapy (patients with creatinine clearance <30 mL/min)	Variable	0.26 L/kg	Some penicillins (penicillin G, ampicillin, nafcillin, carbenicillin, ticarcillin) can bind and inactivate aminoglycosides *in vivo* or *in vitro* (e.g., lab test tubes).
Obesity (>30% over IBW) with normal renal function	2–3 hours	V (in L) = 0.26 [IBW + 0.4 (TBW – IBW)]	Aminoglycosides enter the extracellular fluid contained in adipose tissue requiring a correction factor to estimate volume of distribution.
Cystic fibrosis	1.5 hours	0.35 L/kg	Larger volume of distribution and shorter half-life usually results in larger daily doses.
Acites/overhydration	Variable	V (in L) = (0.26 · DBW) + (TBW − DBW)	Aminoglycosides distribute to excess extracellular fluid; correction equation assumes that weight gain is due to fluid accumulation. Alterations in volume of distribution can cause secondary changes in half-life.

DISEASE STATE/ CONDITION	HALF-LIFE	VOLUME OF DISTRIBUTION	COMMENT
Hemodialysis	3–4 hours	0.26 L/kg	While receiving hemodialysis, aminoglycoside half-life will decreases from ~50 hours to ~4 hours. Renal failure patients commonly have fluid imbalances that may decrease (underhydration) or increase (overhydration) the volume of distribution and secondarily change half-life.
Peritoneal dialysis	36 hours	0.26 L/kg	While receiving peritoneal dialysis, aminoglycoside half-life will decrease from ~50 hours to ~36 hours. Renal failure patients commonly have fluid imbalances that may decrease (underhydration) or increase (overhydration) the volume of distribution and secondarily change half-life.

Methods to initiate aminoglycoside therapy

- The pharmacokinetic dosing method
- The Hull and Sarubbi nomogram
- The Hartford nomogram
- Literature-based recommended dosing

Method 1
The pharmacokinetic dosing method

1- Most flexible. It allows for individualized target serum concentrations to be chosen for a patient.

2- It can be used for both conventional and extended-interval dosing.

To calculate initial dose by pharmacokinetic dosing method

I- calculating the estimated pharmacokinetic parameter

A- Elimination rate constant estimate (Ke)

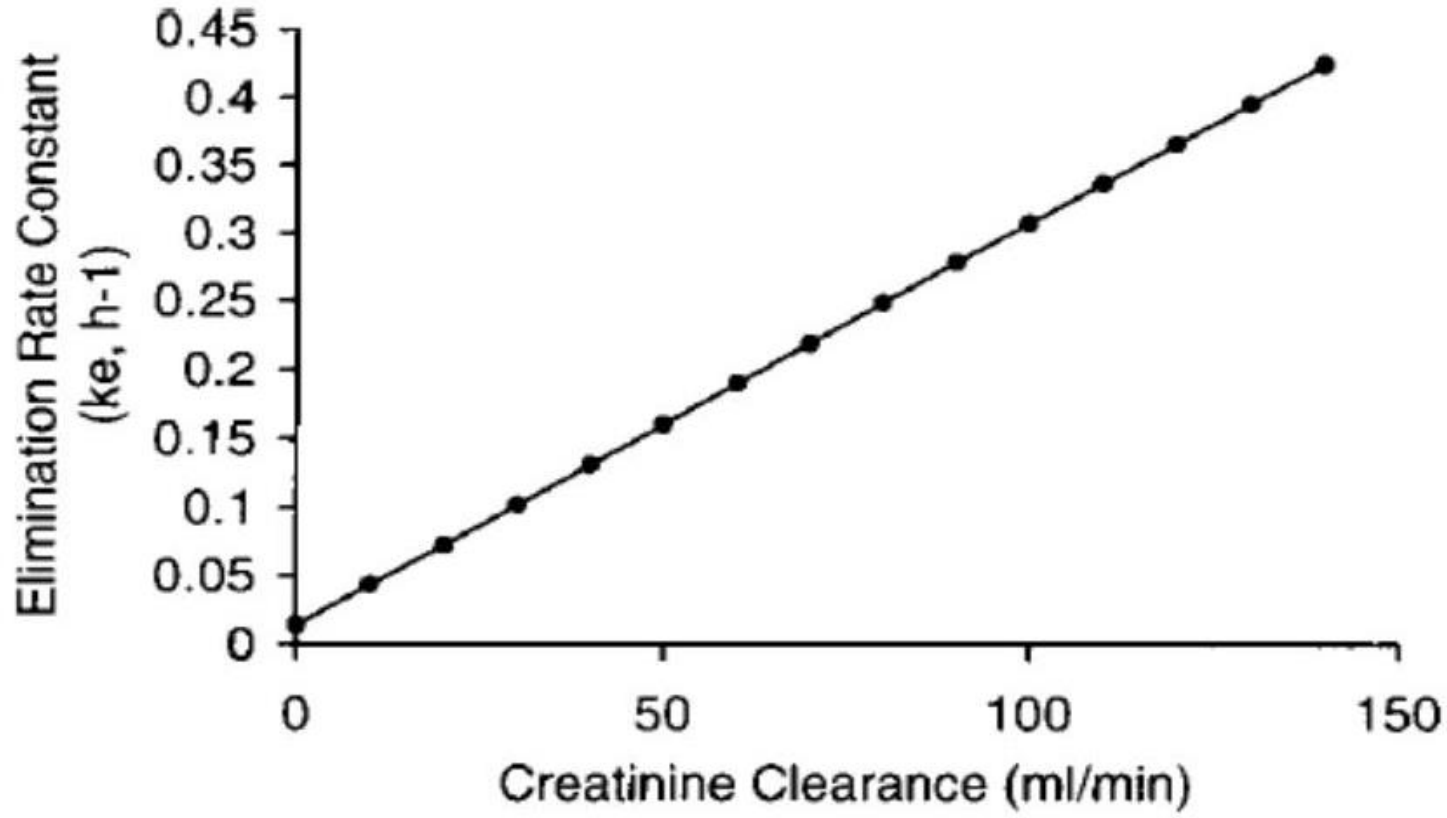
B-Volume of distribution estimate (Vd)

II- Selection of pharmacokinetic model and equations

III-Steady-state concentration selection and dose

A-Elimination rate constant estimate

Ke (in h^{-1}) = 0.00293(CrCl in mL/min) + 0.014



B-Volume of distribution estimate

- ✓ **In normal patient:** $V_d = 0.26$ L/kg
- ✓ **Cystic fibrosis:** $V_d = 0.35$ L/kg
- ✓ **Obese patient (>30% above IBW):** $V_d = 0.26\ [IBW + 0.4(TBW - IBW)]$
- ✓ **Overhydrated or ascites:** $V = (0.26 \cdot DBW) + (TBW - DBW)$

TABLE 4-2C Equations Used to Compute Individualized Dosage Regimens for Various Routes of Administration Used with Aminoglycoside Antibiotics

ROUTE OF ADMINISTRATION	DOSAGE INTERVAL (τ), MAINTENANCE DOSE (D OR K_0), AND LOADING DOSE (LD) EQUATIONS
Intravenous bolus	$\tau = (\ln Css_{max} - \ln Css_{min}) / k_e$ $D = Css_{max}\, V(1 - e^{-k_e\tau})$ $LD = Css_{max}\, V$
Intermittent intravenous infusion	$\tau = [(\ln Css_{max} - \ln Css_{min}) / k_e] + t'$ $k_0 = Css_{max} k_e V[(1 - e^{-k_e\tau}) / (1 - e^{-k_e t'})]$ $LD = k_0 / (1 - e^{-k_e\tau})$

NOTE:

- The choice of equations depend on renal function of the patient so use:
- (intermittent intravenous infusion for creatinine clearances >30 mL/min,
- Intravenous bolus for creatinine clearance ≤ 30 mL/min).
- In general……. Intermittent intravenous infusion equations can be used for all patients regardless of renal function.

III-Steady-state concentration selection

When using conventional dosing:

- **Pneumonia, septicemia, pseudomonas aeruginosa:**

- **Peak steady-state serum concentrations will be:**

- **8–10 µg/mL for gentamicin, tobramycin, or netilmicin**
- **25–30 µg/mL** for amikacin

Steady-state concentration selection

➢ For Moderate infections (intra-abdominal infections):

➢ Peak steady-state serum concentration:

- 5–7 µg/mL (gentamicin, tobramycin, or netilmicin)
- 15–25 µg/mL (Amikacin)

➢ combination with penicillins or other antibiotics for the treatment of gram positive infections such as infective endocarditis:

➢ steady-state peak concentrations:

- 3–5 µg/mL for gentamicin, tobramycin, or netilmicin
- 12–15 µg/mL for amikacin.

Steady-state concentration selection

➢ Steady-state trough concentrations should be maintained: (For conventional dosing)

- **<2 µg/mL** for tobramycin, gentamicin, and netilmicin or
- **<5–7 µg/mL** for amikacin.

➢ Steady-state trough concentrations should be: (For extended-interval dosing)

- **<1 µg/mL** for gentamicin, tobramycin, and netilmicin.

Example 1 JM is a 50-year-old, 70-kg (5 ft 10 in) male with gram-negative pneumonia. His current serum creatinine is 0.9 mg/dL, and it has been stable over the last 5 days since admission. Compute a gentamicin dose for this patient using conventional dosing.

1. *Estimate creatinine clearance*.

- stable serum creatinine + not obese.
- The Cockcroft-Gault equation can be used to estimate CrCl:

- $\text{CrCl}_{\text{est}} = [(140 - \text{age})\text{BW}] / (72 \cdot \text{SCr})$

  $= [(140 - 50\ \text{y})70\ \text{kg}] / (72 \cdot 0.9\ \text{mg/dL})$

  $\text{CrCl}_{\text{est}} = 97\ \text{mL/min}$

2. *Estimate elimination rate constant (ke) and half-life (t1/2).*

- The elimination rate constant versus creatinine clearance relationship is used to estimate the gentamicin elimination rate for this patient:
- **ke** = 0.00293(CrCl) + 0.014

  = 0.00293(97 mL/min) + 0.014

  = 0.298 h^{-1}
- **t1/2** = 0.693/ke

  = 0.693/0.298 h^{-1}

  = 2.3 h

3. *Estimate volume of distribution (V)*

- The patient has no disease states or conditions that would alter the volume of distribution from the normal value of 0.26 L/kg:

- V = 0.26 L/kg (70 kg)

  = 18.2 L

4. *Choose desired steady-state serum concentrations.*

- Gram-negative pneumonia patients treated with aminoglycoside antibiotics require:
- steady-state peak concentrations (C_{ss} max) equal to 8–10 µg/mL;
- steady-state trough (C_{ss} min) concentrations should be <2 µg/mL to avoid toxicity.

- **Set: C_{ss}max = 9 µg/mL and**
- **C_{ss}min = 1 µg/mL.**

5-Use intermittent intravenous infusion equations to compute dose (Table 4-2).

- Calculate required dosage interval (τ) using a 1-hour infusion:
- $\tau = [(\ln Css_{max} - \ln Css_{min}) / k_e] + t'$

  $= [(\ln 9\ \mu g/mL - \ln 1\ \mu g/mL) / 0.298\ h^{-1}] + 1\ h$

  $= 8.4\ h$ ⇒ 8 h

- $k_0 = Css_{max}\, k_e\, V[(1 - e^{-ke\tau}) / (1 - e^{-ket'})]$

  $k_0 = (9 \cdot 0.298\ h^{-1} \cdot 18.2\ L)\{[1 - e^{-(0.298\ h^{-1})(8\ h)}] / [1 - e]\}^{-(0.298\ h^{-1})(1\ h)}$

  $= 172\ mg$ ⇒ 170 mg

So…

- **The prescribed maintenance dose would be 170 mg every 8 hours.**

6. *Compute loading dose (LD), if needed.*

- $LD = k0/(1 - e^{-ke\tau})$

  $= 170\ mg / [1 - e^{-(0.298\ h-1)(8\ h)}]$

  $= 187\ mg$

- As noted, this loading dose is only about 10% greater than the maintenance dose and wouldn't be given to the patient. Since the expected half-life is 2.3 hours, the patient should be at steady state after the second dose is given.

Method 2
The Hull and Sarubbi nomogram

For conventional dosing

- This is a quick and efficient way to apply pharmacokinetic dosing concepts without using complicated pharmacokinetic equations.
- For patients who do not have disease states or conditions that alter volume of distribution, the only two patient-specific factors that change when using the pharmacokinetic dosing method is patient weight and creatinine clearance.

Applied for uncomplicated patients with a standard volume of distribution

With a simple modification, it can also be used for obese patients…

- If the patient is (≥ 30%) above ideal body weight, an adjusted body weight (ABW) can be calculated and used as the weight factor

$$ABW\ (in\ kg) = IBW + 0.4(TBW - IBW)$$

- The Salazar and Corcoran method of estimating creatinine clearance in obese patients should be used to compute renal function in these individuals… other wise use Cockcroft-Gault method.

Calculation method

1. Compute patient's creatinine clearance (CrCl) using Cockcroft-Gault method: $CrCl = [(140 - age)BW] / (SCr \times 72)$.

- Multiply by 0.85 for females.
- Use Salazar-Cocoran method if weight >30% above IBW.

2. Use patient's weight if within 30% of IBW, otherwise use adjusted dosing weight = $IBW + [0.40(TBW - IBW)]$

3. Select loading dose in mg/kg to provide peak serum concentrations in range listed below for the desired aminoglycoside antibiotic:

AMINOGLYCOSIDE	USUAL LOADING DOSES	EXPECTED PEAK SERUM CONCENTRATIONS
Tobramycin Gentamicin Netilmicin	1.5–2.0 mg/kg	4–10 µg/mL
Amikacin Kanamycin	5.0–7.5 mg/kg	15–30 µg/mL

4. Select maintenance dose (as percentage of loading dose) to continue peak serum concentrations indicated above according to desired dosage interval and the patient's creatinine clearance. To maintain usual peak/trough ratio, use dosage intervals in clear areas.

Percentage of Loading Dose Required for Dosage Interval Selected

CrCl (mL/min)	EST. HALF-LIFE (HOURS)	8 HOURS (%)	12 HOURS (%)	24 HOURS (%)
>90	2–3	90	–	–
90	3.1	84	–	–
80	3.4	80	91	–
70	3.9	76	88	–
60	4.5	71	84	–
50	5.3	65	79	–
40	6.5	57	72	92
30	8.4	48	63	86
25	9.9	43	57	81
20	11.9	37	50	75
17	13.6	33	46	70
15	15.1	31	42	67
12	17.9	27	37	61
10*	20.4	24	34	56
7*	25.9	19	28	47
5*	31.5	16	23	41
2*	46.8	11	16	30
0*	69.3	8	11	21

*Dosing for patients with CrCl ≤10 mL/min should be assisted by measuring serum concentrations.

Example 1 JM is a 50-year-old, 70-kg (5 ft 10 in) male with gram-negative pneumonia. His current serum creatinine is 0.9 mg/dL, and it has been stable over the last 5 days since admission. Compute a gentamicin dose for this patient using conventional dosing.

1. *Estimate creatinine clearance.*

2. *Choose desired steady-state serum concentrations.*

3. *Select loading dose (Table 4-3).*

4. *Determine estimated half-life, maintenance dose, and dosage interval.*

1. *Estimate creatinine clearance.*

- **This patient has a stable serum creatinine and is not obese.**
- **The Cockcroft-Gault equation can be used to estimate creatinine clearance:**

CrClest = 97 mL/min

2. *Choose desired steady-state serum concentrations.*

- Gram-negative pneumonia patients treated with aminoglycoside antibiotics require
- steady-state peak concentrations (Cssmax) equal to 8–10 µg/mL.

3. *Select loading dose (Table 4-3).*

- A loading dose (LD) of 2 mg/kg will provide a peak concentration of 8–10 µg/mL.
- LD = 2 mg/kg(70 kg) = 140 mg

4. *Determine estimated half-life, maintenance dose, and dosage interval.*

- From the nomogram:
- the estimated half-life is 2–3 hours,
- the maintenance dose (MD) is 90% of the loading dose

[MD = 0.90(140 mg) = 126 mg], and the dosage interval is 8 hours.

~ 125 mg/ 8 hrs.

Method 3
Hartford Nomogram Method
for Extended-Interval Dosing

- The most widely used extended-interval aminoglycoside dose for patients with renal dysfunction is the Hartford nomogram which uses a 7-mg/kg dose.
- The dosage interval is set according to the patient's creatinine clearance (Table 4-4).

Calculations:

1. Administer 7-mg/kg gentamicin with initial dosage interval:

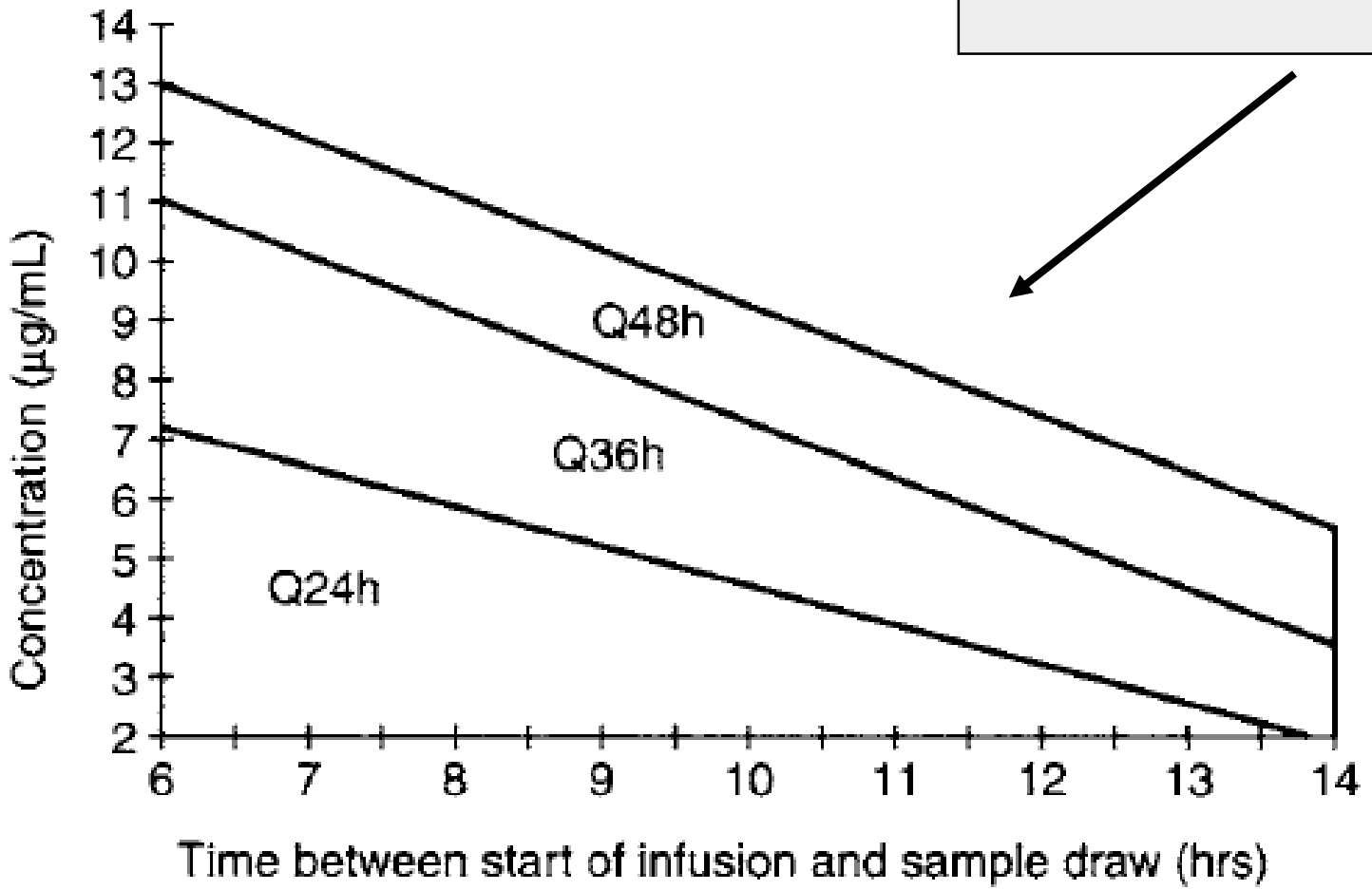
ESTIMATED CrCl	INITIAL DOSAGE INTERVAL
≥60 mL/min	q24 h
40–59 mL/min	q36 h
20–39 mL/min	q48 h
<20 mL/min	monitor serial concentrations and administer next dose when <1 µg/mL

2. Obtain timed serum concentration, 6–14 hours after dose (ideally first dose).

3. Alter dosage interval to that indicated by the nomogram zone.

The nomogram zone:

Above q48 h zone, monitor serial concentrations, and administer next dose when <1 μg/mL



Example 1 JM is a 50-year-old, 70-kg (5 ft 10 in) male with gram-negative pneumonia. His current serum creatinine is 0.9 mg/dL, and it has been stable over the last 5 days since admission. Compute a gentamicin dose for this patient using extended-interval dosing.

1. ***Estimate creatinine clearance.***

To decide the initial dosage interval

CrClest = 97 mL/min --------- i.e. ***initial dosage interval q24 h.***

2. *Compute initial dose and dosage interval*

- D = 7 mg/kg

  D = 7 . 70 kg = 490 mg ~ 500 mg

➢ The prescribed maintenance dose would be 500 mg every 24 hours.

A gentamicin serum concentration measured 10 hours after the dose equals 3 µg/mL.

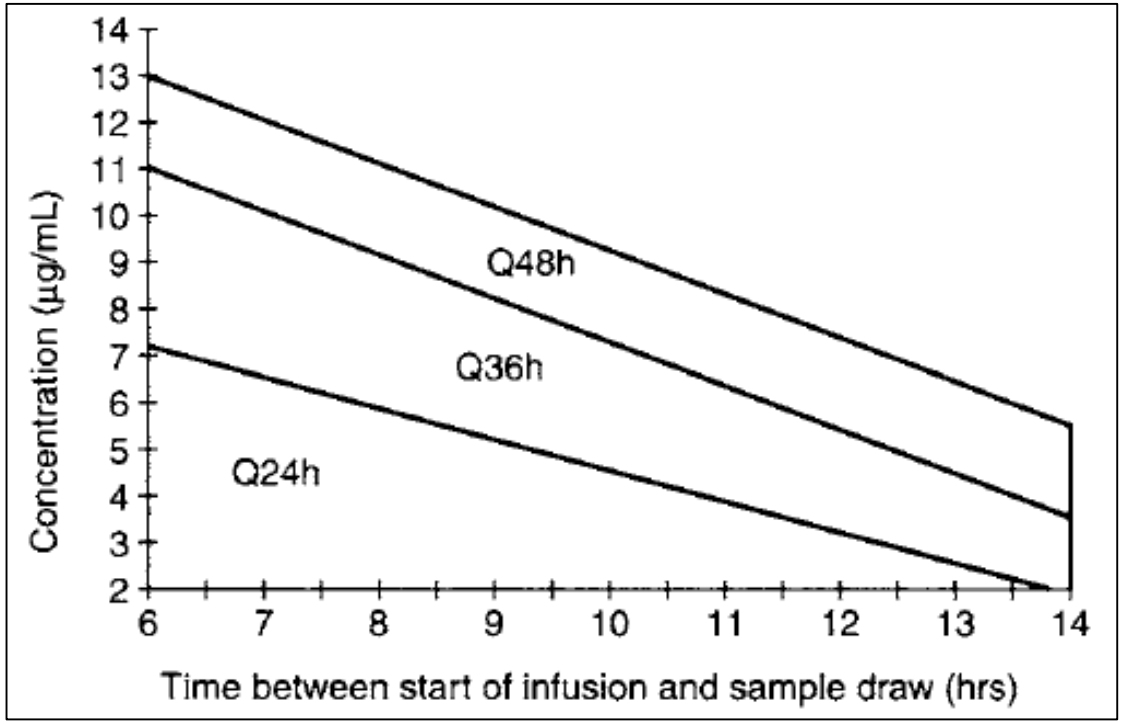
3. Determine the exact dosage interval.

Based on the nomogram,

a dosage interval of 24 hours

is the correct value and does

not need to be altered.



مثال اخر في الكتاب.....

Same patient profile as in example 1, but S.Cr = 3.5 mg/dL indicating renal impairment.

1. **CrClest = 25 mL/min ..... بعد الحساب**
2. **initial dosage interval q48 h.**
3. **The prescribed maintenance dose would be 500 mg every 48 hours.**
4. **If gentamicin serum concentration measured 13 hours after the dose equals 9 µg/mL.**
5. **Based on the nomogram..... a dosage interval of 48 hours is too short and serial concentrations should be monitored.**

How we know when gentamicin serum concentration drop below 1 μg/mL?

- Based on the patient's estimated elimination rate constant:
- ke = 0.00293(CrCl) + 0.014 = 0.00293(25 mL/min) + 0.014 = 0.087 h^{-1};
- t1/2 =0.693/ke = 0.693 / 0.087 h–1 = 8 h,
- it will take approximately 3–4 half-lives or about
- an additional 24–32 hours after the gentamicin serum concentration for the value to drop below 1 μg/mL.

Method 4
Literature-based recommended dosing

✓Conventional dosing

- 3-5 mg/ kg /day for gentamycin,
- 15 mg/ kg /day for amikicin

✓Extended interval dosing

- 4-7 mg/kg/day for gentamycin
- 11-20 mg/kg/ day for amikacin

USE OF AMINOGLYCOSIDE SERUM CONCENTRATIONS TO ALTER DOSAGES

1- Linear pharmacokinetics.

2- Sawchuk-Zaske method

Linear Pharmacokinetics Method

$$D_{new} / C_{ss,new} = D_{old} / C_{ss,old}$$

OR

$$D_{new} = (C_{ss,new} / C_{ss,old}) D_{old}$$

D is the dose, Css is the steady-state peak or trough concentration

Example 1 JM is a 50-year-old, 70-kg (5 ft 10 in) male with gram-negative pneumonia. His current serum creatinine is 0.9 mg/dL, and it has been stable over the last 5 days since admission. A gentamicin dose of 170 mg every 8 hours was prescribed and expected to achieve steady-state peak and trough concentrations equal to 9 μg/mL and 1 μg/mL, respectively. After the third dose, steady-state peak and trough concentrations were measured and were 12 μg/mL and 1.4 μg/mL, respectively. Calculate a new gentamicin dose that would provide a steady-state peak of 9 μg/mL.

1- calculate the new dose:

$D_{new} = (C_{ss,new} / C_{ss,old})D_{old}$

= (9 μg/mL / 12 μg/mL) 170 mg

= 128 mg, round to 130 mg every 8 hrs.

2- Check steady-state trough concentration for new dosage regimen:

$C_{ss,new} = (D_{new} / D_{old})C_{ss,old}$

= (130 mg / 170 mg) 1.4 μg/mL

= 1.1 μg/mL

Sawchuk-Zaske Method

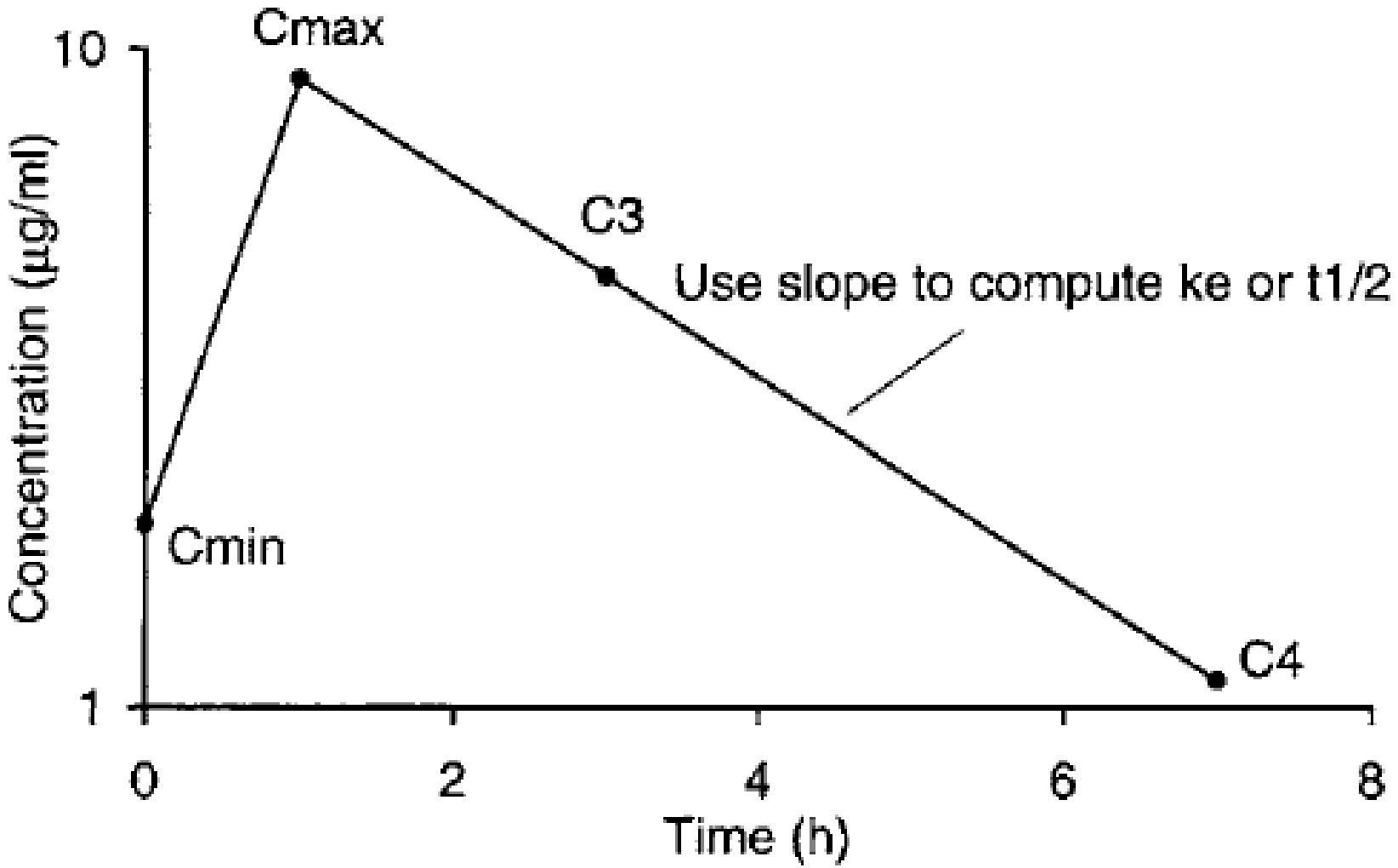
A- The standard Sawchuk-Zaske method

B- The modified Sawchuk-Zaske methods:

I- Peak/Trough Version at steady state

II- Steady-state Sawchuk-Zaske Method: Two Post-dose Concentrations Version

i- The standard Sawchuk-Zaske method



i- The standard Sawchuk-Zaske method

- This version of the Sawchuk-Zaske method does not require steady-state conditions.
- This method uses a trough (C_{min}), peak (C_{max}), and 2 additional post-dose concentrations (C_3, C_4).
- The peak and trough concentrations are used to calculate actual Vd
- The postdose concentrations (C3, C4) are used to compute ke and half-life.
- Vd and $t_{1/2}$ used to compute the exact dose needed to achieve desired aminoglycoside concentrations.

1- Ke = (ln C1 – ln C2) / Δt

2- t1/2 = 0.693 / ke

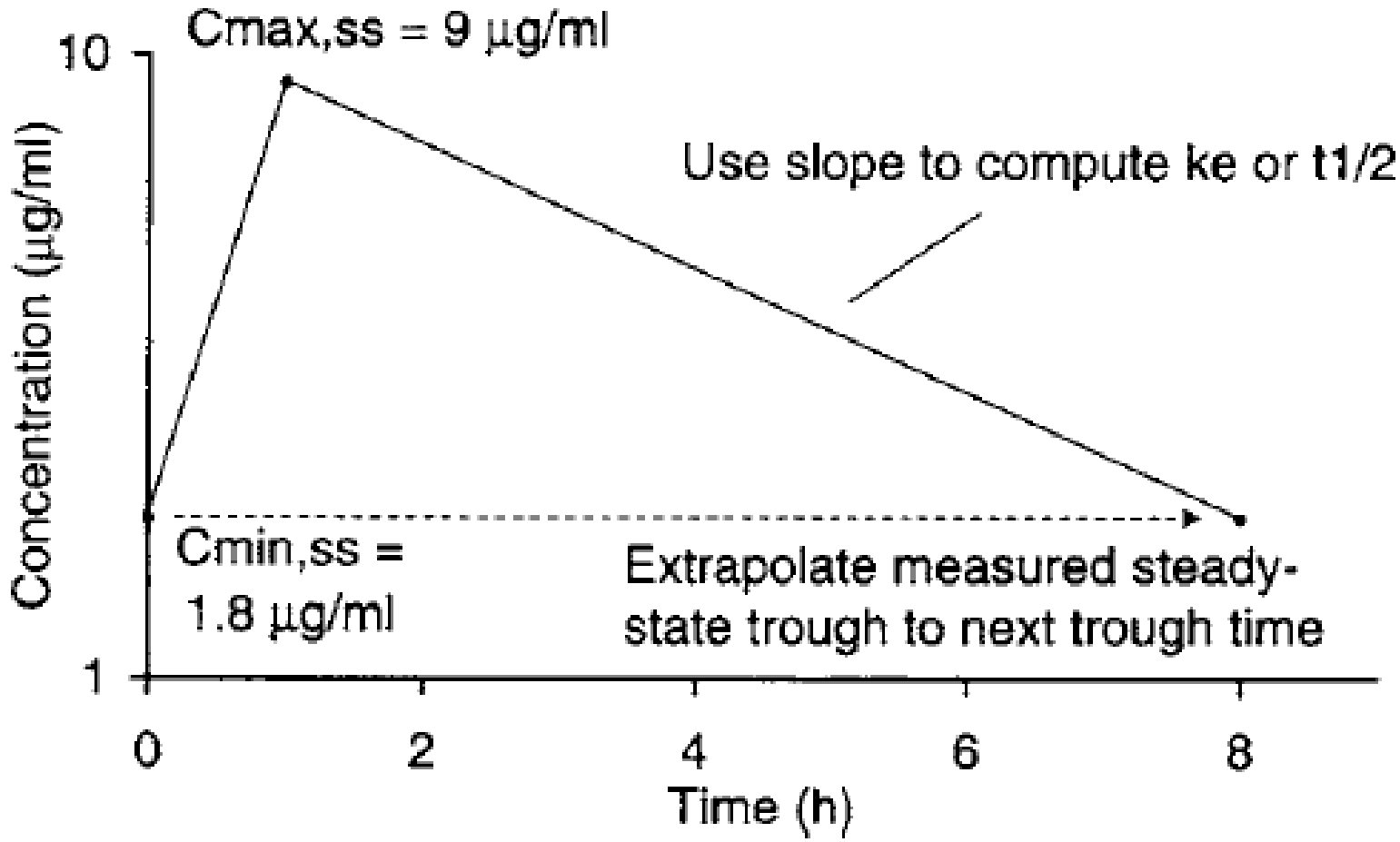
3- actual Vd------>

$$V = \frac{D/t'\,(1 - e^{-k_e t'})}{k_e[C_{max} - (C_{min} e^{-k_e t'})]}$$

4-Use the actual Vd and Ke to calculate new dosage regimen after determination of Cmax and Cmin according to the question.

ROUTE OF ADMINISTRATION	DOSAGE INTERVAL (τ), MAINTENANCE DOSE (D OR K_0), AND LOADING DOSE (LD) EQUATIONS
Intravenous bolus	$\tau = (\ln Css_{max} - \ln Css_{min}) / k_e$ $D = Css_{max}\, V(1 - e^{-k_e \tau})$ $LD = Css_{max}\, V$
Intermittent intravenous infusion	$\tau = [(\ln Css_{max} - \ln Css_{min}) / k_e] + t'$ $k_0 = Css_{max} k_e V[(1 - e^{-k_e \tau}) / (1 - e^{-k_e t'})]$ $LD = k_0 / (1 - e^{-k_e \tau})$

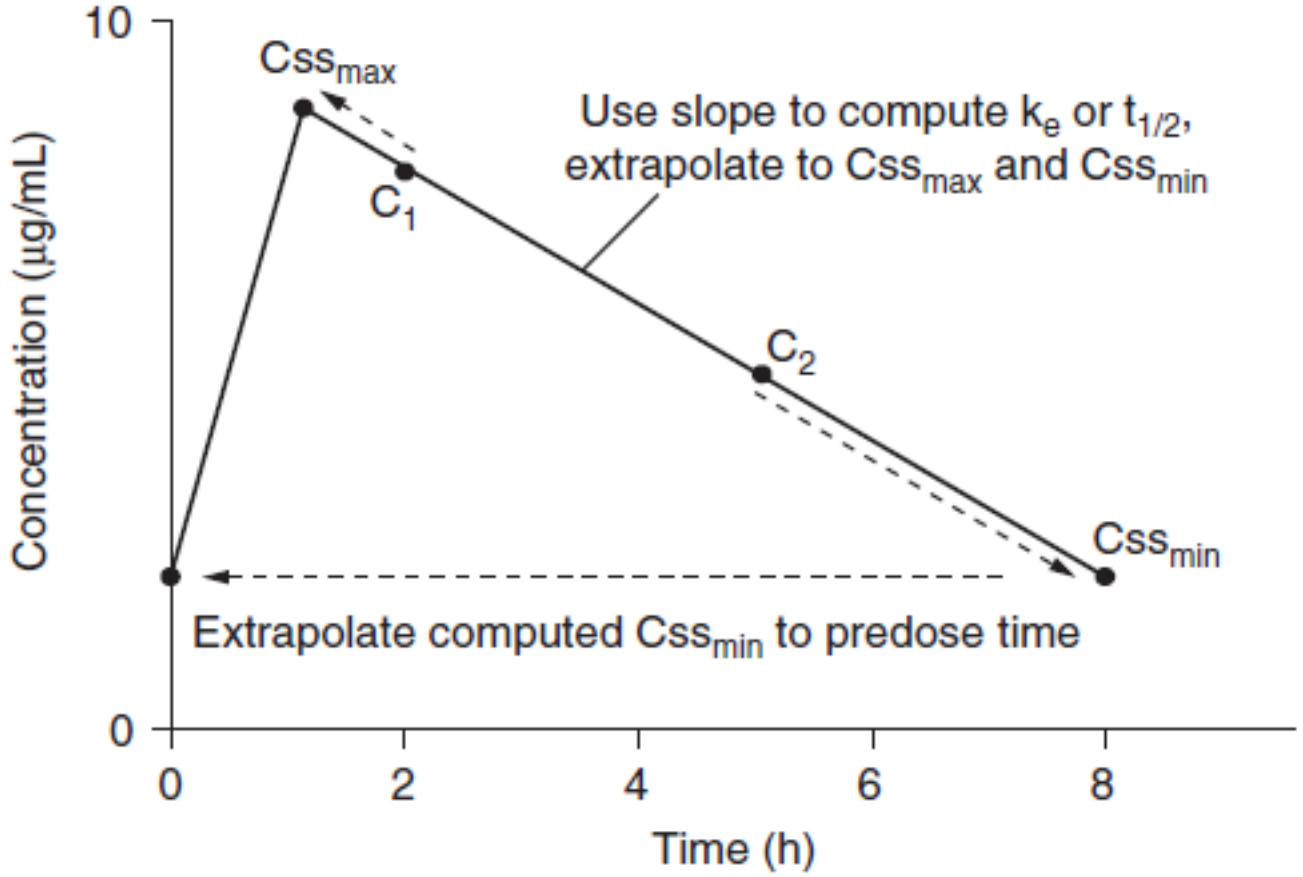
ii- Peak/Trough Version at steady state



Peak/Trough Version at steady state

- This method uses a steady state peak (Cssmax) and trough (Cssmin) concentration pair.
- The patient here is at steady state (may need to calculate t1/2 to ensure reaching the steady state)
- Cssmax and Cssmin are used to calculate Vd, ke and t1/2.
- from Vd and ke compute the exact dose needed to achieve desired aminoglycoside concentrations. وبنفس الطريقة السابقة

iii- Steady-state Sawchuk-Zaske Method: Two Post-dose Concentrations Version



Steady-state Sawchuk-Zaske Method: Two Post-dose Concentrations Version

- This method uses two post-dose concentrations (C_1 and C_2) to individualize aminoglycoside therapy.

1- Use C_1, C_2 to determine Cssmax and Cssmin values

C_{ss} max = C_1 / (e^{-ket}) ------ C_{ss} min = C_2 / e^{-ket}

2- use C_1 nd C_2 to calculate **$k_e = (\ln C_1 - \ln C_2) / \Delta t$**

3- use Cssmax, Cssmin to calculate actual V_d

4- Use the actual V_d and K_e to calculate new dosage regimen

ملاحظة : يجب مراجعة جميع امثلة الكتاب والاسئلة