# Therapeutic Drug Monitoring Workshop

74th Annual CSHP Ontario Branch Conference

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Presenter: Erin Chung, BScPhm, MSc, ACPR, RPh

# Presenter Disclosure

- Presenter's Name: Erin Chung
- I have no current or past relationships with commercial entities.
- Speaking fees for current program:
  - I have received no speaker's fee for this learning activity

# Commercial Support Disclosure

- This learning activity has received no financial or in-kind support from any commercial or other organization.

# Learning Objectives

By the end of this workshop, participants will be able to:

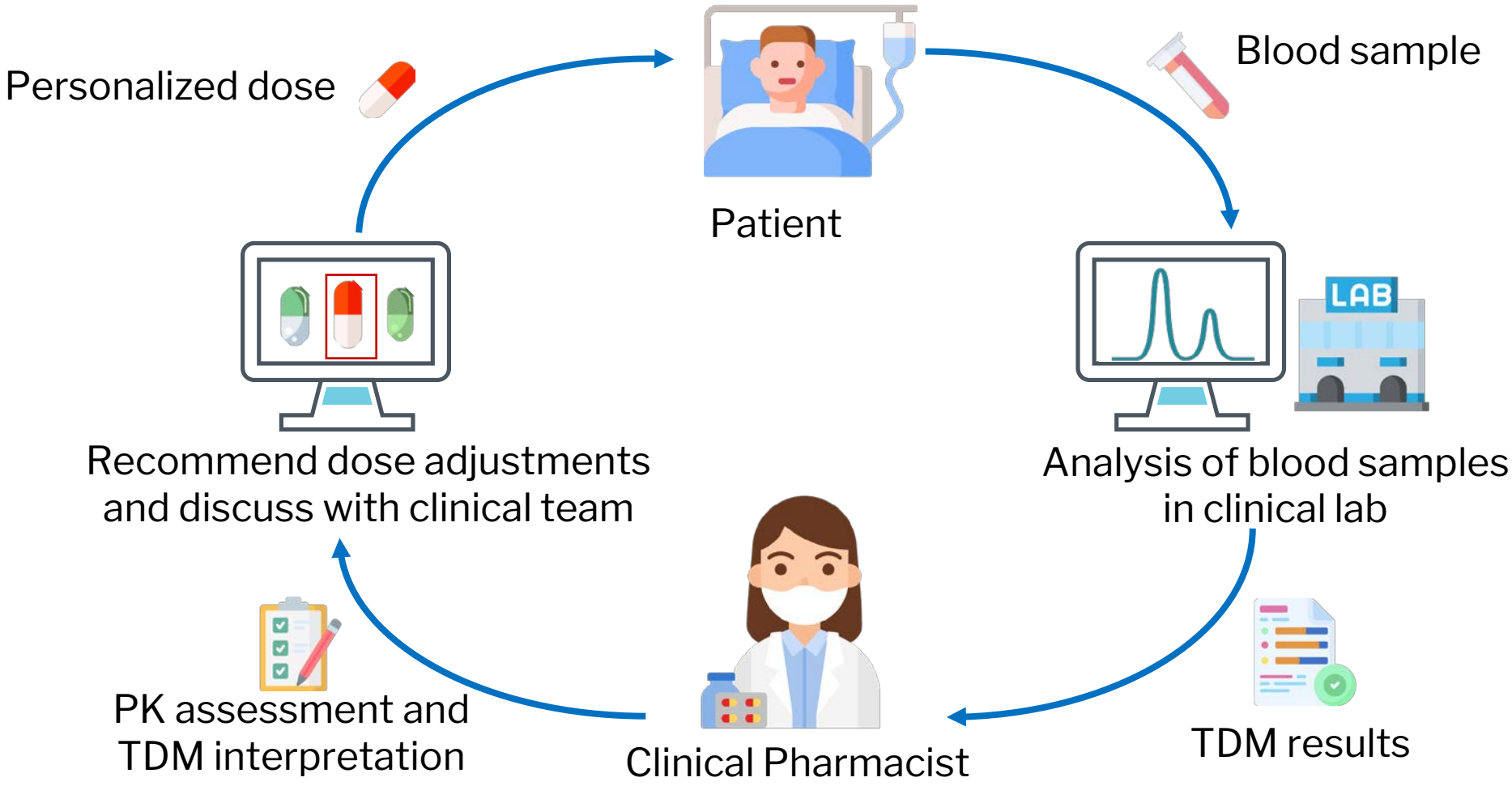
1. Describe concepts for therapeutic drug monitoring (TDM) including indications, and which medications.
2. Describe how to apply pharmacokinetic principles to drug therapy.
3. List practical considerations for TDM of vancomycin, tobramycin, and phenytoin.

What comes to mind when you think of **Therapeutic Drug Monitoring**?

# Concepts of TDM

# TDM Process

Clinical practice of measuring drug concentrations in bodily fluids.




PK, pharmacokinetics; TDM, therapeutic drug monitoring. Images: Flaticon.com. Ates et al. Trends Biotechnol. 2020 Nov;38(11):1262-1277.

# What are **indications** for TDM?

# Criteria for considering TDM

Gross AS. Br J Clin Pharmacol. 2001;52 Suppl 1(Suppl 1):5S-10S
Chung E. Process to Request for TDM Testing at External Laboratory. The Hospital for Sick Children. 2022.

# Common medications with TDM

- amikacin
- gentamicin
- tobramycin
- vancomycin

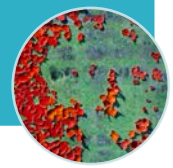
Antibiotics


- phenytoin
- phenobarbital
- carbamazepine
- valproic acid

Antiepileptics

- voriconazole
- itraconazole
- posaconazole

Antifungals



- busulfan
- methotrexate

Chemotherapy

- digoxin

Antiarrhythmics

- cyclosporine
- tacrolimus
- sirolimus
- mycophenolate

Immunosuppressants

- lithium

Mood stabilizers


- enoxaparin
- heparin
- tinzaparin
- warfarin

Anticoagulants

Images: Stock/Online Images in PowerPoint.

# Other TDM may be useful in certain scenarios or have emerging evidence

- Amiodarone
- Amitriptyline & Nortriptyline
- Antiretrovirals
- Beta lactams
- Caffeine
- Clobazam
- Clonazepam
- Clomipramine
- Cycloserine
- Ethambutol
- Ethionamide
- Everolimus
- Flucytosine
- Doxepin & Desmethyldoxepin
- Flecainide
- Fluoxetine (incl. Norfluoxetine)
- Gabapentin
- Ganciclovir
- Haloperidol
- Imipramine & Despiramine
- Infliximab
- Isoniazid
- Leflunomide
- Levetiracetam
- Levofloxacin
- Lidocaine
- Linezolid
- Mitotane
- Oxcarbazepine
- Gabapentin
- Moxifloxacin
- Para-aminosalicylic acid
- Procainamide (and NAPA)
- Pyrazinamide
- Rifampin
- Streptomycin
- Thiocyanate
- Thiopurine Metabolites (6-TG, 6-MMP)
- Topiramate

**Challenges:**

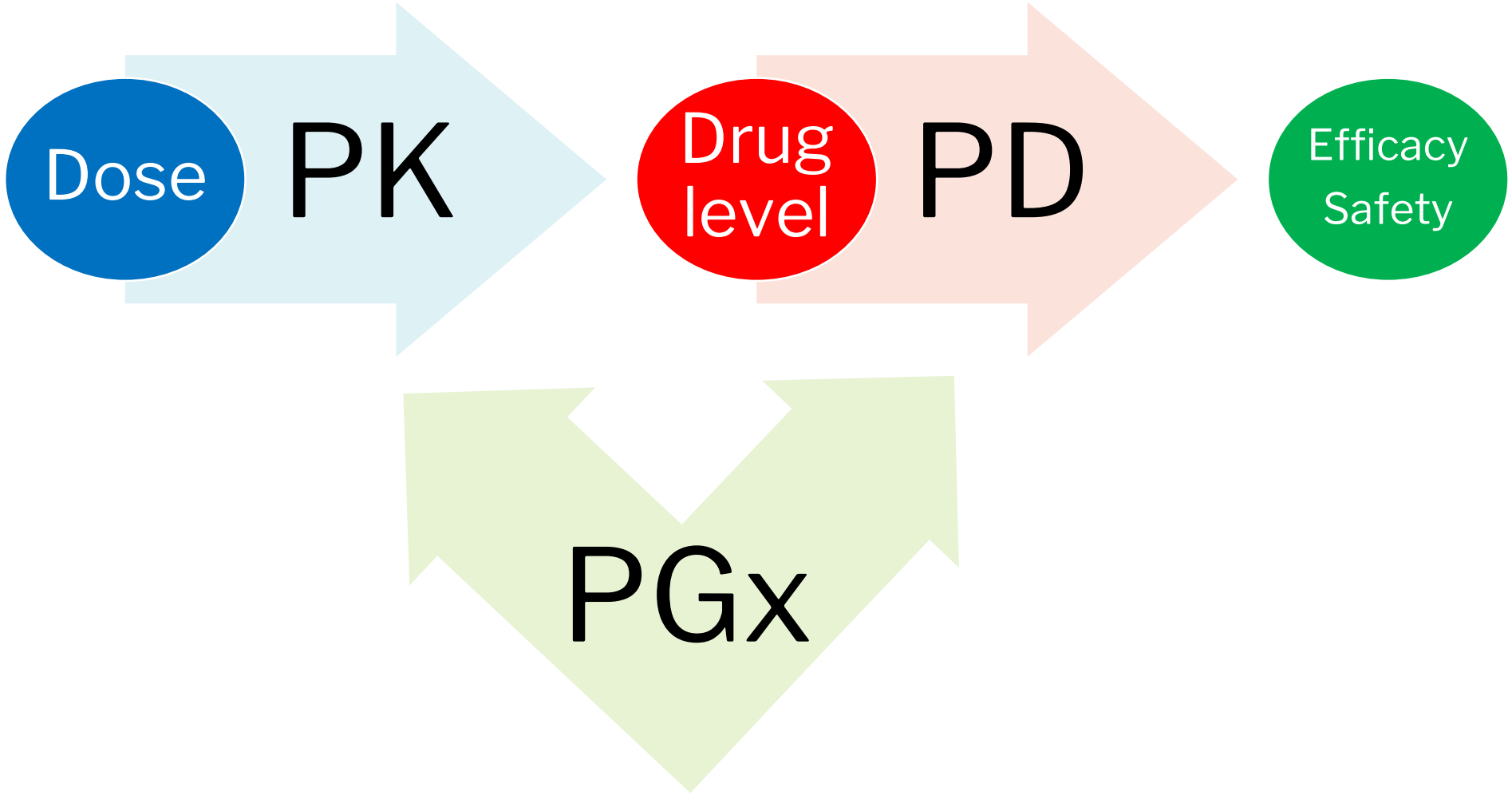
- Access to assay (some not available in Canada), costs and turn-around-time
- Some with unclear association between TDM and clinical outcomes
- Require appropriate assessment for clinical need and approvals, i.e. from clinical biochemist

# Clinical laboratory examples with TDM tests

| | |
|---|---|
| Local hospitals | London Health Sciences Centre Pathology and Laboratory Medicine: https://www.lhsc.on.ca/lab-test-info-guide/laboratory-test-information-guide<br>SickKids Department of Paediatric Laboratory Medicine: https://www.sickkids.ca/en/care-services/for-health-care-providers/lab-tests/lab-test-catalogue/<br>St. Michael's Hospital Laboratory Medicine: https://stmichaelshospital.com/mirror-hosts/stmichaelshospital.com/programs/labs/tests/<br>Sunnybrook Laboratory Medicine and Molecular Diagnostics: http://www.sunnybrook.ca/labmedicine<br>UHN Laboratory Medicine Program: https://www.uhn.ca/Labs/Pages/lab_reference_guide.aspx |
| Out-of-province | CHU Sainte-Justine: https://chusj.omni-assistant.net/labo/MasterSearch.aspx<br>McGill University Health Centre Antiretroviral TDM Program: https://muhc.ca/therapeutic-drug-monitoring<br>Providence Pathology and Laboratory Medicine: https://www.providencelaboratory.com/test_catalog.php?fkCatID=2#catSearch |
| Out-of-country | Mayo Clinic Laboratories: https://www.mayocliniclabs.com/test-catalog<br>University of Florida Health Infectious Disease Pharmacokinetics Laboratory: https://idpl.pharmacy.ufl.edu/<br>University of Texas Health San Antonio Fungus Testing Laboratory: https://lsom.uthscsa.edu/pathology/reference-labs/fungus-testing-laboratory/antifungal-drug-levels/ |
| Laboratory referral network | In-Common Laboratory https://iclabs.ca/ (sources requests across Canada and internationally) |

# Pharmacokinetic principles

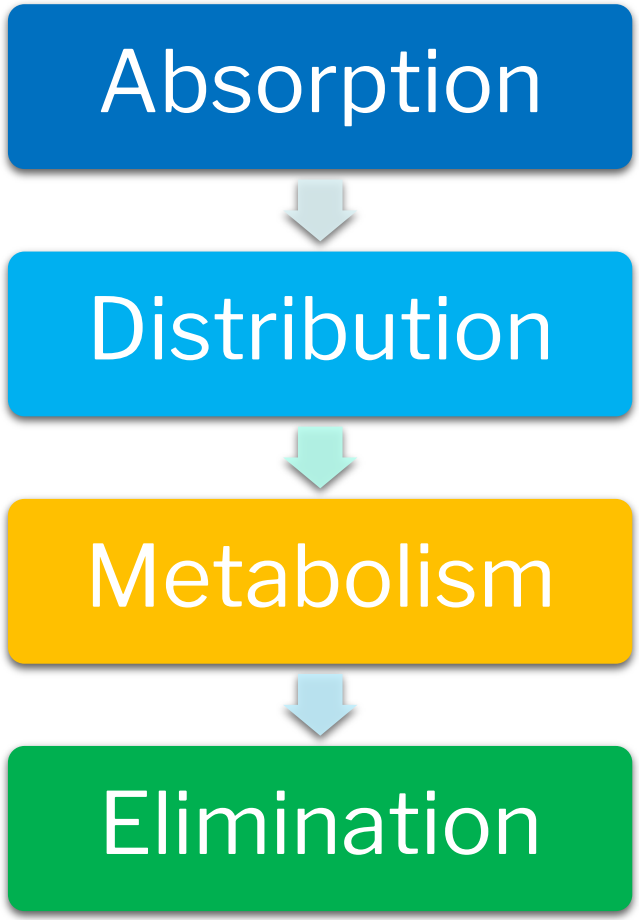
# Drug dose-response relationships are complex.




PD, pharmacodynamics; PK, pharmacokinetics; PGx, pharmacogenomics

# Clinical Pharmacokinetics

- Application of ADME to patients' drug therapy.




ADME, absorption, distribution, metabolism, and elimination; PK, pharmacokinetics.

# PK terminology review

## 1. What is one-compartment model?

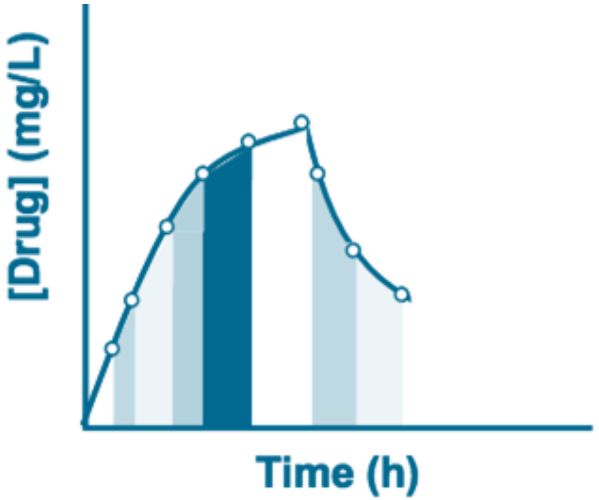
## 2. What is two-compartment model?

Bauer. Applied Clinical Pharmacokinetics,3rd Ed. 2014.

# PK terminology review

## 3. What is elimination constant ($k_e$)?

## 4. What is area-under-the concentration-time curve (AUC)?




DiPiro. Concepts in Clinical Pharmacokinetics. 6th Edition. 2010. Basic Pharmacokinetics. Page 26.
Persky. Pharmacokinetic Tools. Foundations in Pharmacokinetics. 2013. Page 21-22.

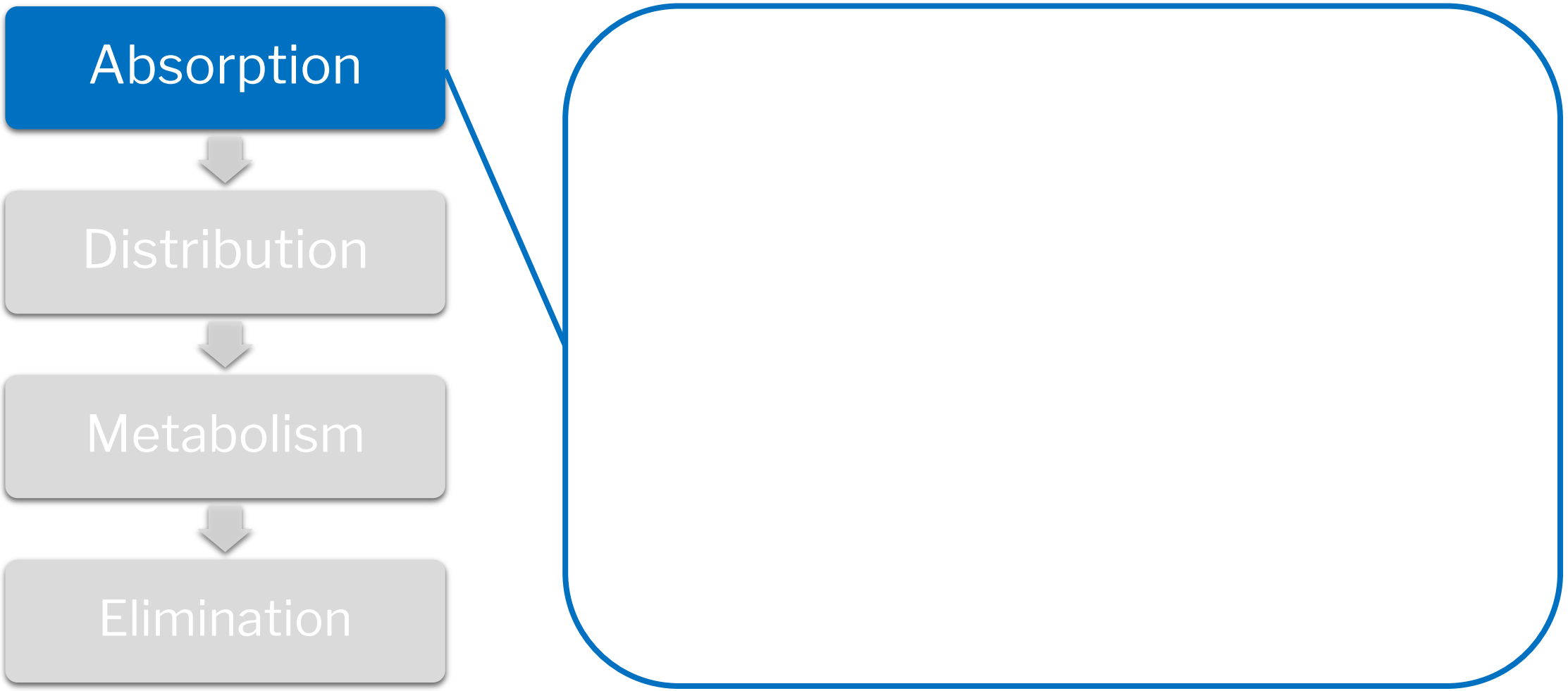
# PK terminology review

## 5. What is volume of distribution ($V_d$)?

## 6. What is clearance (CL)?

AUC, area-under-the-concentration-time curve; $k_e$, elimination constant.
DiPiro. Concepts in Clinical Pharmacokinetics. 6th Edition. 2010. Basic Pharmacokinetics. Page 24.

# What are factors influencing oral absorption?




Meltzer EO et al. Clin Pediatr (Phila). 2006 Oct;45(8):725-33.
Lawless H. J Am Diet Assoc. 1985 May;85(5):577-82, 585.
Cowart BJ. 1981 Jul;90(1):43-73.
Ladebo et al. Scand J Gastroenterol. 2021 Sep;56(9):1023-1029.
Omari et al. J Pediatr. 1999 Oct;135(4):517-21.
Welling et al. J Clin Hosp Pharm. 1984 Sep;9(3):163-79.
Hamaguchi et al. Int J Clin Pharmacol Ther Toxicol. 1993 Jul;31(7):326-30.
Johnson et al. Clin Pharmacol Ther. 1984 Dec;36(6):724-30.
Hong et al. Eur J Drug Metab Pharmacokinet. 2021 Jul;46(4):465-478.
Buchman et al. Dig Dis Sci 2005; 12: 2312–2315.
Asano et al. Transplant Proc. 2004 Sep;36(7):2096-7.
Kearns et al, N Engl J Med 2003;349:1157-67.
Hämmerlein et al. Clin Pharmacokinet. 1998 Jul;35(1):49-64.
Palmer et al. Am Fam Physician. 2000 Apr 15;61(8):2453-62.

# What are factors influencing distribution?

Absorption

Distribution

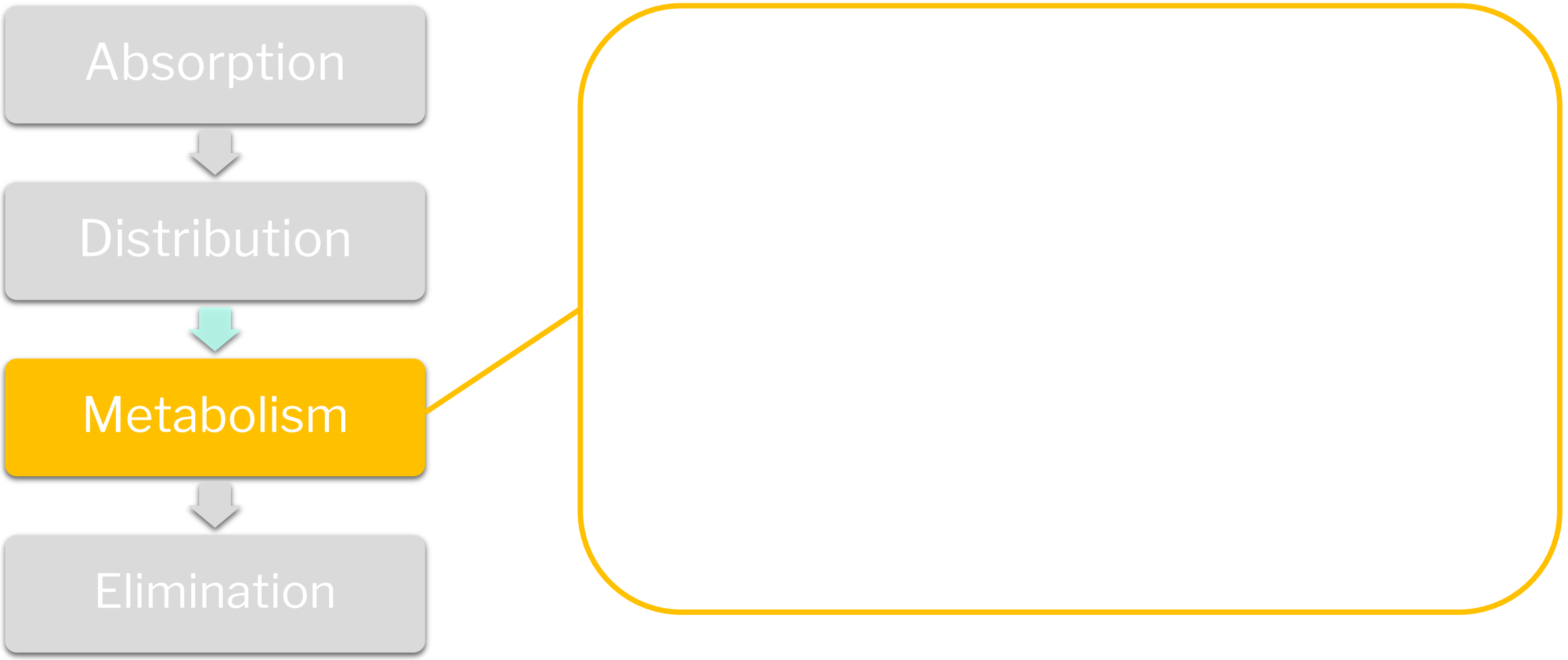
Metabolism

Elimination

Vd, volume of distribution
Image from Shepherd et al. Presentation – Good Hydration to Support Physical and Mental Wellbeing. Sept 2018.

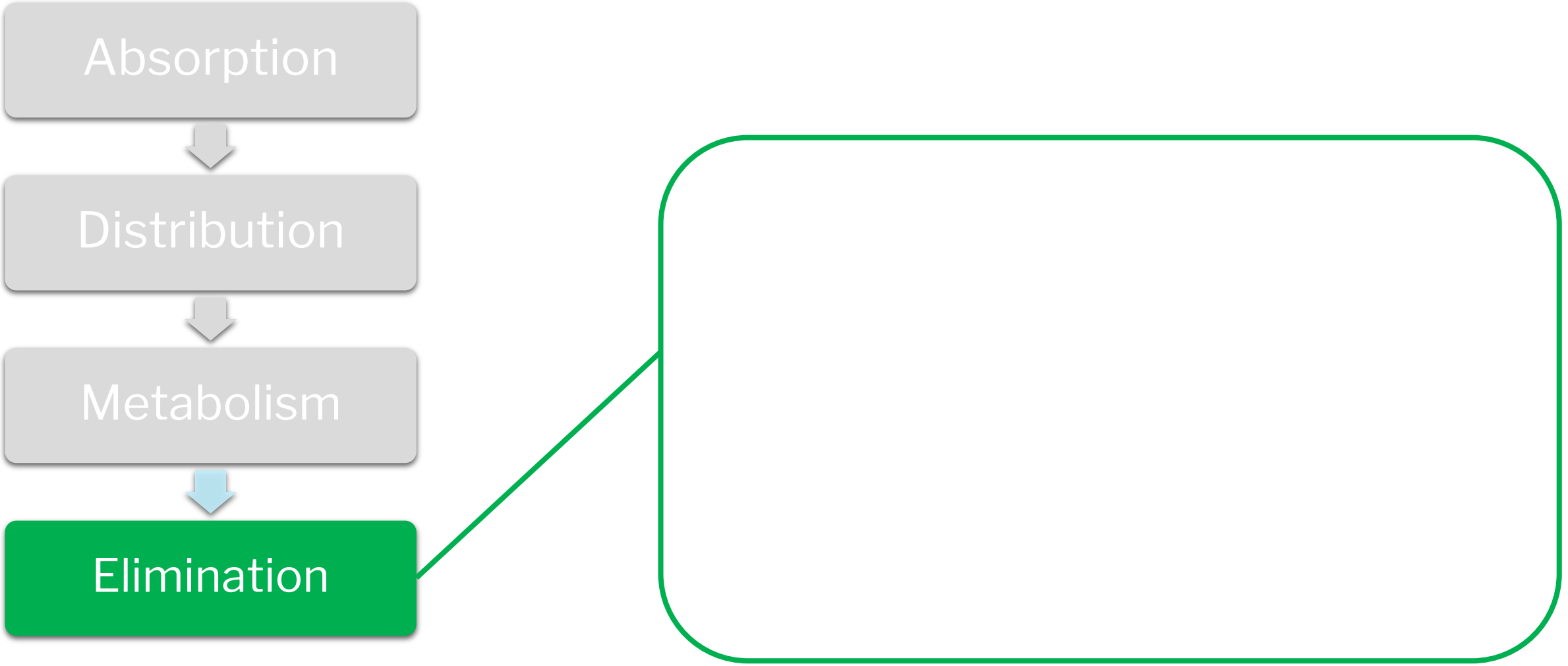
Blanchet et al. Clin Pharmacokinet. 2008;47(10):635-54.
Blot et al. Adv Drug Deliv Rev. 2014 Nov 20;77:3-11.
Lam et al. J Antimicrob Chemother. 2007 Jun;59(6):1135-40.

# What are factors influencing metabolism?




Chevalier et al; ASCPT 2021.
Krekels et al. Drug Metabolism in Diseases. 2017.
Batchelor et al. Br J Clin Pharmacol. 2015 Mar;79(3):395-404.
Kearns et al, N Engl J Med 2003;349:1157-67.
Klotz U. Drug Metab Rev. 2009;41(2):67-76.
Tanaka E. J Clin Pharm Ther. 1999 Oct;24(5):339-46.

# What are factors influencing elimination?




Garza et al. Drug Elimination. [Updated 2021 Oct 10]. In: StatPearls [Internet].
Le J. Pharmacokinetics. Merck Manual. 2020.
Schumacher GE. Am J Hosp Pharm. 1980 Apr;37(4):559-62.

Batchelor et al. Br J Clin Pharmacol. 2015 Mar;79(3):395-404.
Kearns et al, N Engl J Med 2003;349:1157-67.

# Practical considerations for TDM

Clinical cases of vancomycin, tobramycin, and phenytoin

# Case 1 – Vancomycin in an elderly patient

# Case 1 (Vancomycin)

George is a 91-year-old man (Weight = 67 kg; Height = 172 cm) admitted to the general medicine ward with a *Staphylococcus aureus*-infected hip arthroplasty. His baseline serum creatinine was 78 μmol/L. Vancomycin 1000 mg IV q12h was started at 06:00 2 days ago.

Today, serum vancomycin and serum creatinine were collected:

- Serum creatinine = 110 μmol/L
- Serum vancomycin trough = 28.1 mg/L

**What is your TDM interpretation?**
**Please recommend any dose adjustments for vancomycin.**

# Pharmacokinetic considerations of vancomycin in the elderly

## Distribution

- $V_d$ may be ↑ in elderly compared to younger adults (0.9 vs. 0.6 L/kg)
- Protein binding ~55% in normal healthy adult, but 25% in ≥ 60 years old
- Affected by malnutrition, lower total body weight, and lower obesity rates in very elderly population

## Elimination

- Primarily glomerular filtration (75-90%), other: tubular secretion, bile
- $t_{½}$ ↑ in elderly (12-17 hours) compared to younger adults (4-7 hours)
- Affected by declining renal function in elderly
- Caution with using eGFR equations in elderly population.
  - Most eGFR equations were derived in young adults (e.g. CKD-EPI: 88% <65 years old).
  - Factors in elderly that reduce accuracy of eGFR:
    - Increased comorbidities and physiological changes in kidney
    - Decreased nutritional status
    - Lower muscle mass

eGFR, estimated glomerular filtration rate; $t_{1/2}$, half-life; $V_d$, volume of distribution

Barber et al. 2016 Dec;33(12):845-854
Sánchez et al. Int J Clin Pharmacol Ther. 2010 Aug;48(8):525-33.
Bourguignon et al. Antimicrob Agents Chemother. 2016 Jul 22;60(8):4563-7.
Glassock et al. JAMA. 2015 Aug 11;314(6):559-60.

# How do you routinely monitor vancomycin in your practice?

**A.** Trough
**B.** AUC
**C.** Trough or AUC (case by case basis)
**D.** No experience yet

AUC, area under the concentration-time curve

# Vancomycin AUC vs. trough monitoring

## Varying TDM practices needing ongoing evaluation to determine best strategy

| AUC | Trough |
| --- | --- |
| • 24-hr AUC = 400-600 mg·h/L assuming MIC=1 mg/L<br>• Estimated using trapezoid rule and 1st-order PK equations from at least 2 blood samples or from Bayesian software programs with a validated population PK model with 1-2 blood samples<br>• Best predictor of bacterial eradication based on *in vitro* and *in vivo* data<br>• Modest predictive performance for efficacy based on meta-analysis (Dalton 2020).<br>• Above 600 mg*h/L had >2 times higher risk of AKI (Tsutsuura 2021) | • 10-20 mg/L in adults (vary based on infection, severity, and MIC)<br>• 6-10 mg/L in paediatric patients was associated with $AUC_{24h}$ at least 400 mg*h/L<br>• Simpler strategy, fewer blood samples without calculations or software<br>• Above 15 mg/L associated with over 2 times higher risk of AKI<br>Most Canadian institutions use trough monitoring routinely. |

Rybak et al. Am J Health Syst Pharm. 2020 May 19;77(11):835-864.
Tongsai et al. BMC Res Notes. 2016 Sep 29;9(1):455.
Tkachuk et al. Pediatr Drugs. 2018; 20: 153-164.
Tsutsuura et al. BMC Infect Dis. 2021 Feb 6;21(1):153.

MIC, minimum inhibitory concentration.

# Vancomycin TDM

| Time to first TDM | Target range for intermittent IV dosing |
|---|---|
| Prior to 4th-5th dose<br>Earlier for renal impairment, prematurity, or suspected toxicity. | **Trough target:** 10-20 mg/L* |

*Depends on type of infection, pathogen, MIC at different institutions.

## How does the vancomycin trough compare to target?


Bugs and Drugs. https://www.bugsanddrugs.org/4DF64652-4B80-4FEE-A258-8AF087C06C5D
Rybak et al. Am J Health Syst Pharm. 2020 May 19;77(11):835-864.
Culello et al. Ottawa: CADTH; 2020.
Stewart et al. JAMMI. 2021: 6(1): 3-9.

What **other information** do you need to interpret this vancomycin trough result?

# Other information

**Dose times:**

| Vancomycin Dose | Day 0 | Day 1 | Day 2 |
|---|---|---|---|
| 1000 mg IV q12h | 06:00 -given<br>18:00 –given | 06:00 -given<br>18:00 -given | 06:00 - HELD |

**Sampling time:**

| TDM | Result | Time | Timing in relation to doses given |
|---|---|---|---|
| Vancomycin trough | 28.1 mg/L | 5:30 | 11.5 hours post-4$^{th}$ dose |

**Sampling site:** Venipuncture

**Dosing reference:**

Monograph | Images | Adult Patient Education | Pediatric Patient Education

**Prosthetic joint infection**

**Prosthetic joint infection (off-label use): IV:**

*Pathogen-specific therapy for methicillin-resistant or susceptible S. aureus (alternative agent in beta-lactam intolerance):* 15 to 20 mg/kg/dose every 8 to 12 hours initially (Berbari 2022; IDSA [Liu 2011]; IDSA [Osmon 2013]); adjust based on therapeutic monitoring. A loading dose may be considered in seriously ill patients (ASHP/IDSA/PIDS/SIDP [Rybak 2020]). Duration ranges from 2 to 6 weeks depending on prosthesis management, use of rifampin, and other patient-specific factors (IDSA [Osmon 2013]).

*Pathogen-specific therapy for Enterococcus spp (penicillin susceptible [alternative agent] or penicillin resistant):* 15 mg/kg/dose every 12 hours initially; adjust based on therapeutic monitoring. Duration: 4 to 6 weeks (Berbari 2022; IDSA [Osmon 2013]).

**Note:** In select cases (eg, debridement and retention of prosthesis or one-stage arthroplasty), give oral suppressive antibiotic therapy with an appropriate regimen following completion of initial treatment (Berbari 2022; IDSA [Osmon 2013]).

Lexi-Drugs. 2022.

# Other information (Continued)

| | |
|---|---|
| Age | • 91 years |
| Actual body weight | • 67 kg |
| Height | • 172 cm |
| Ideal body weight | • 50 + (2.3 x height in inches over 5 feet) (male)<br>https://www.mdcalc.com/ideal-body-weight-adjusted-body-weight |
| Adjusted body weight | • IBW (kg) + 0.4(total body weight - IBW)<br>https://www.mdcalc.com/ideal-body-weight-adjusted-body-weight |
| Body mass index | • (Weight) / (Height)$^2$<br>https://www.nhlbi.nih.gov/health/educational/lose_wt/BMI/bmi-m.htm |

## Other information (Continued)

### Kidney function:

- Day 0: Serum creatinine = 78 µmol/L, eGFR = 81 mL/min/1.73m$^2$
- Day 2: Serum creatinine = 110 µmol/L, eGFR = 55 mL/min/1.73m$^2$
- Based on CKD-EPI Creatinine Equation (2021)

What is your next **vancomycin TDM plan**?

## What is the most appropriate vancomycin TDM plan?

| | |
|---|---|
| Current dose | • Vancomycin 1000 mg IV q12h (15 mg/kg/dose) |
| TDM | • Vancomycin trough 28.1 mg/L (Target 10-20 mg/L) |

**Recommendation:**

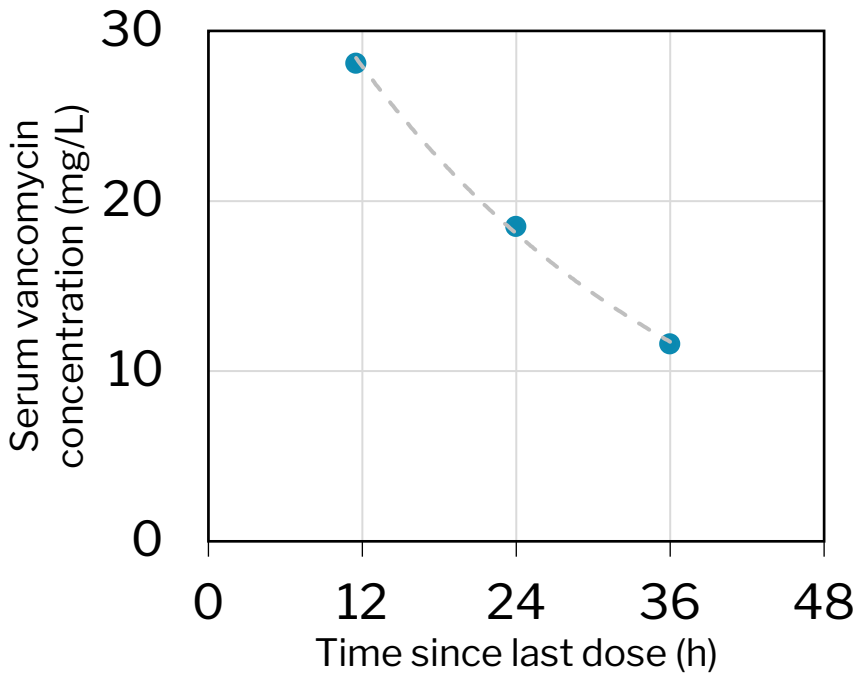
**1.**

**2.**

# Next day

| Serum vancomycin (mg/L) | Serum creatinine (μmol/L) | Date & Time of collection | Time since last dose (h) |
|---|---|---|---|
| 28.1 | 110 | Day 2 5:30 | 11.5 |
| 18.5 | 95 | Day 2 18:00 | 24 |
| 11.6 | 87 | Day 3 6:00 | 36 |

$$k_e = -\frac{\ln C_2 - \ln C_1}{t_2 - t_1} \qquad t_{1/2} = \frac{\ln(2)}{k_e}$$



What is your **dosing recommendation** for vancomycin?

# Suggest a dosing recommendation based on PK

**Calculate $C_{max}$ and $C_{min}$ with your dose prediction:**

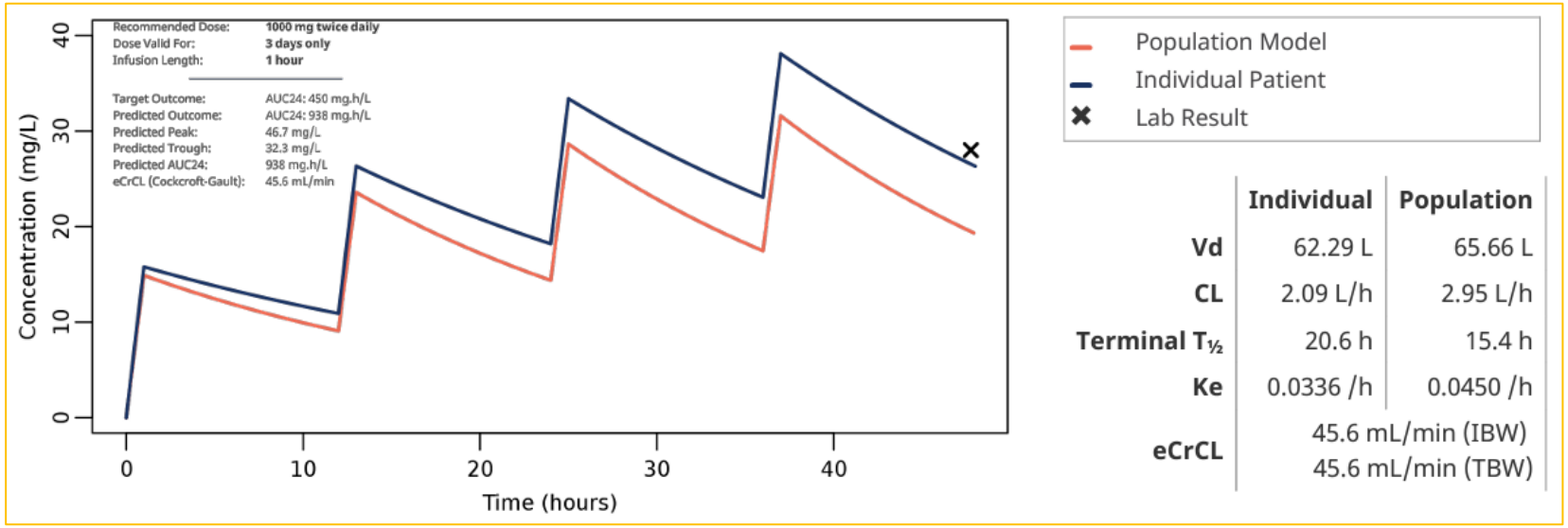
- Predicted steady-state $C_{max} = \frac{k_o*(1-e^{-k_e t'})}{V(k_e)(1-e^{-k_e T})}$
- Predicted steady-state $C_{min} = C_{max} e^{-k_e(T-t')}$

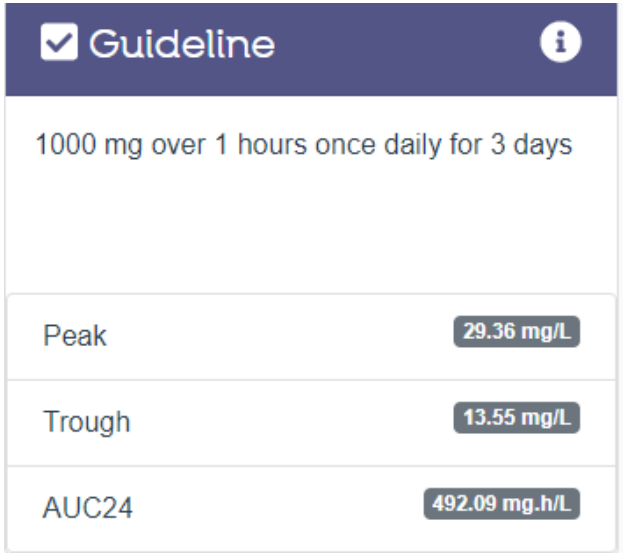
**Vancomycin ____ mg ( ____ mg/kg/dose) IV q __ h** is predicted to achieve steady state trough ___ mg/L, assuming V = 0.9 L/kg, and calculated $t_{1/2}$ = ____hours.

$C_{max}$ = maximum concentration; $C_{min}$ = minimum concentration; $K_0$ = dose/infusion time; $K_e$ = elimination constant; t' = infusion time; T = dosing interval; V = volume of distribution

# Bayesian forecasting software with population PK modelling

- Precision dosing tools for clinical practice
- Do not require sampling at steady-state
- Improve % and shorten time to reach target
- Limitations:
  - Costs
  - Require validation of popPK models especially in special populations (e.g., critically ill, elderly)
  - Need accurate physiological and clinical input data




Broeker et al. Clin Microbiol Infect. 2019 Oct;25(10):1286.e1-1286.e7.
Gastmans et al. Pharmaceutics. 2022 Jul 13;14(7):1459.

# Case 2 – Tobramycin in an adolescent

# Case 2 (Tobramycin)

Adrianna is a 13-year-old girl (Weight = 40 kg, Height = 145 cm) with cystic fibrosis related-pancreatic insufficiency admitted to the respiratory ward, who had 4-day history of cough and sore throat, fever and vomiting. *Pseudomonas aeruginosa* was identified in her sputum culture. Pulmonary function test (FEV1) decreased by 16%.

The respiratory team started the patient on tobramycin 360 mg IV q24h (9 mg/kg/dose), infused over 30 min at 9:00h.

Serum tobramycin levels were drawn on the next day via venipuncture:

| TDM | Result |
|---|---|
| Tobramycin 3 h post-dose (12:00h) | 6 mg/L |
| Tobramycin 6 h post-dose (15:00h) | 1.5 mg/L |

**The respiratory clinical fellow asks you to interpret the tobramycin levels and suggest any dose adjustments for tobramycin.**

# Pharmacokinetics of Tobramycin

## Distribution

- Mostly into extracellular fluid, concentrates in renal cortex
- $V_d$ = 0.3-0.4 L/kg in children; 0.27 L/kg in males, 0.23 L/kg in females with cystic fibrosis
- Also varies based on age, fluid status (increases with edema, decreases with dehydration), and nutritional status
- Protein binding: <30%

## Elimination

- Primarily renal
- $t_{1/2}$ varies based on age (neonates ≤1 week: 3-11.5 h or >1 week: 3-6h; infants: 4 ± 1h; children: 2 ± 1 h; adolescents: 1.5 ± 1 h; adults: 2 h), and renal function (*renal failure: 41 ± 24 h*)

BW, birthweight; CSF, cerebrospinal fluid; PNA, postnatal age; $t_{1/2}$, half-life; $V_d$, volume of distribution.


Lam et al. J Antimicrob Chemother. 2007 Jun;59(6):1135-40.
Aronoff et al. 5th ed, American College of Physicians; 2007.
Vozeh et al. Clin Pharmacokinetics. 1988;15(4):254-282.
MacDougall et al. 12th ed. McGraw-Hill Global Education Holding; 2011.
Dager et al. Ann Pharmacother. 2006;40:9-14.
Demczar et al. Antimicrob Agents Chemother. 1997;41(5):1115-1119.
Leggett. 8th ed. Philadelphia, PA: Saunders; 2015.
McNamara et al. J Clin Pharmacol. 2001;41(4):374-377.
Regamey et al. Clin Pharmacol Ther. 1973;14(3):396-403.
Wallace et al. Pharmacotherapy. 2002;22(9):1077-1083.
Xuan et al. Int J Antimicrob Agents. 2004;23(3):291-295.

# Pharmacodynamics of Tobramycin

## Concentration-dependent bactericidal action

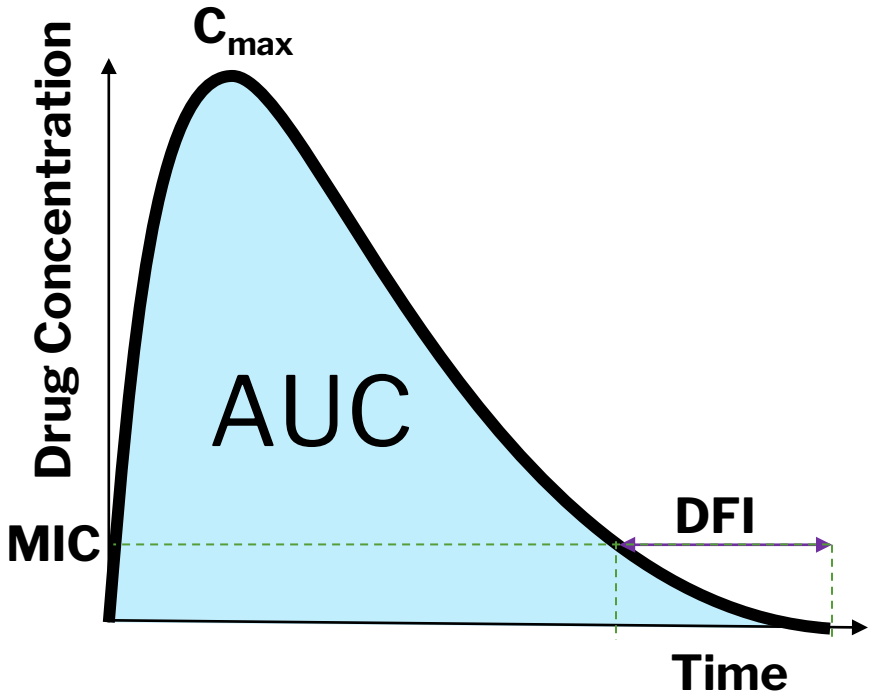
- $C_{max}$/MIC ≥ 8-10
- If MIC is 2 mg/L, $C_{max}$ target: 16-20 mg/L

## Post-antibiotic effect

- Bacterial killing is maintained for a certain period (varies based on organism, $C_{max}$, concomitant therapies) even when concentration < MIC

## Nephrotoxicity, ototoxicity and adaptive resistance

- Trough ≤ 1 mg/L (ideally below limit of quantification)
- Drug Free Interval (DFI): 4-16 hours
- $AUC_{24h}$: 70-100 mg*h/L
- Carriers of *MT-RNR1* variant are at increased risk of aminoglycoside-induced hearing loss




*Supports high dose extended interval vs. multiple daily dosing*

AUC, area under the concentration-time curve; $C_{max}$, maximum concentration; DFI, drug free interval; MIC, minimum inhibitory concentration


Freeman et al. J Antimicrob Chemother. 1997 Jun;39(6):677-86.
Begg et al. Br J Clin Pharmacol. 1995 Jun;39(6):605-9.
Bland et al. Pharmacotherapy. 2018 Dec;38(12):1229-1238.
Chung et al. Open Forum Infectious Diseases. 2015 Dec; 2(S1):792.
Kashuba et al. Antimicrob Agents Chemother. 1999 Mar;43(3):623-9.
Kirkpatrick et al. Br J Clin Pharmacol. 1999 Jun;47(6):637-43.
Zelenitsky et al. J Antimicrob Chemother. 2003 Oct;52(4):668-74.
McDermott et al. Clin Pharmacol Ther. 2022 Feb;111(2):366-372.

# Conventional vs. High dose extended dosing interval?

High dose extended dosing interval is preferred in most cases

Conventional dosing is recommended in the following patient populations:

| | | | | |
|---|---|---|---|---|
| Paediatric patients with renal impairment | Renal replacement therapy | Gram positive infection (synergy) | Endocarditis | Intra-operative prophylaxis |

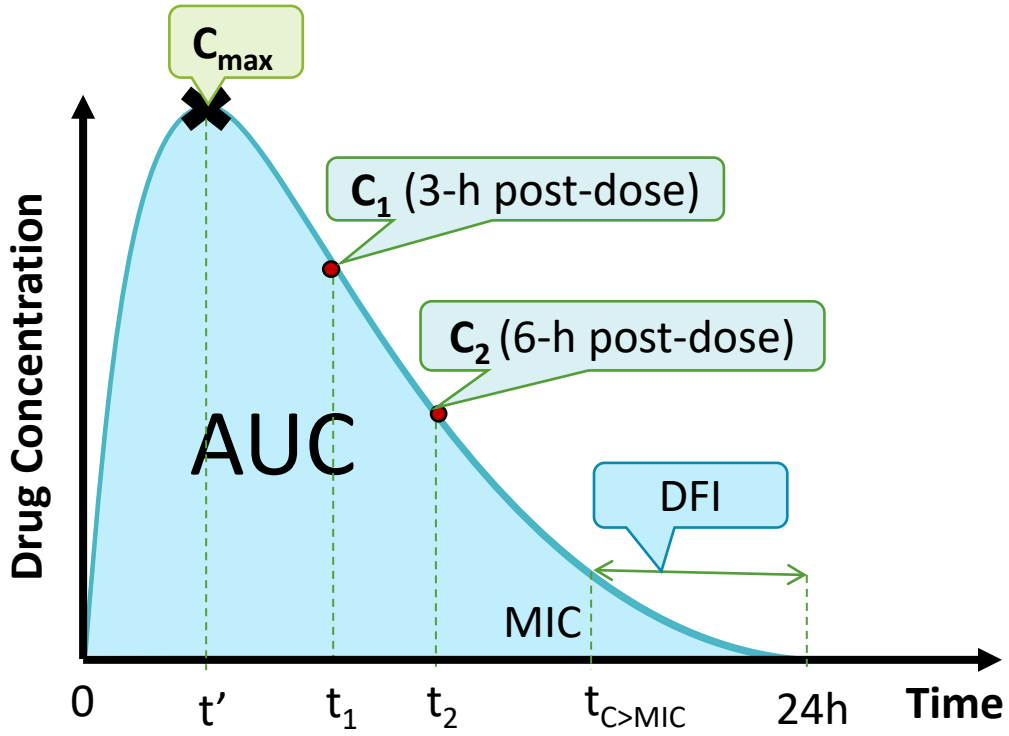
Bugs and Drugs. https://www.bugsanddrugs.org/50D9A3CA-F809-4839-9656-7F415B82A3A0
Roy et al. Can J Hosp Pharm. 2016 Sep-Oct;69(5):367-375.

# Dosing of Tobramycin in Infants & Older Children at SickKids

| Group | SickKids Once Daily Dosing (ODD) | $C_{max}$ target (mg/L) |
|---|---|---|
| Cystic Fibrosis patients | Females:<br><7 yrs: 11 mg/kg/dose IV q24h<br>≥7 yrs: 9 mg/kg/dose IV q24h<br>Males:<br><16 yrs: 11 mg/kg/dose IV q24h<br>≥16 yrs: 9 mg/kg/dose IV q24h | 25-35 |

The Hospital for Sick Children. E-Formulary. 2022.

# Useful PK Equations




$$k_e = -\frac{\ln C_2 - \ln C_1}{t_2 - t_1} = \frac{\ln C_1 - \ln C_2}{t_2 - t_1}$$

$$t_{1/2} = \frac{\ln(2)}{k_e}$$

$$C_{max} = \frac{C_t}{e^{-k_e t}}$$ *where t = time from end of infusion to $C_t$*

$$AUC = \left(\frac{0 + C_{max}}{2}\right)(t') + \left(\frac{C_{max} + C_1}{2}\right)(t_1 - t') + \left(\frac{C_1 + C_2}{2}\right)(t_2 - t_1) + \frac{C_2}{k_e}$$

$$Cl = \frac{Dose}{AUC}$$

$$V_d = \frac{Cl}{k_e}$$

$$DFI = T - t_{C>MIC} = 24 - \left(\frac{\ln(C_{max}) - \ln(MIC)}{k_e} + t'\right)$$

AUC, area under to the concentration time curve; Cl, clearance; $C_{max}$, maximum concentration; DFI, drug-free interval; $k_e$, elimination constant; t', infusion duration; $t_{½}$, half life; MIC, minimum inhibitory concentration; ODD, once daily dosing; $V_d$, volume of distribution; T, Dosing interval; $t_{C>MIC}$, time when concentration is above MIC.

DiPiro et al. Concepts in Clinical Pharmacokinetics (Fourth Edition). 2005.

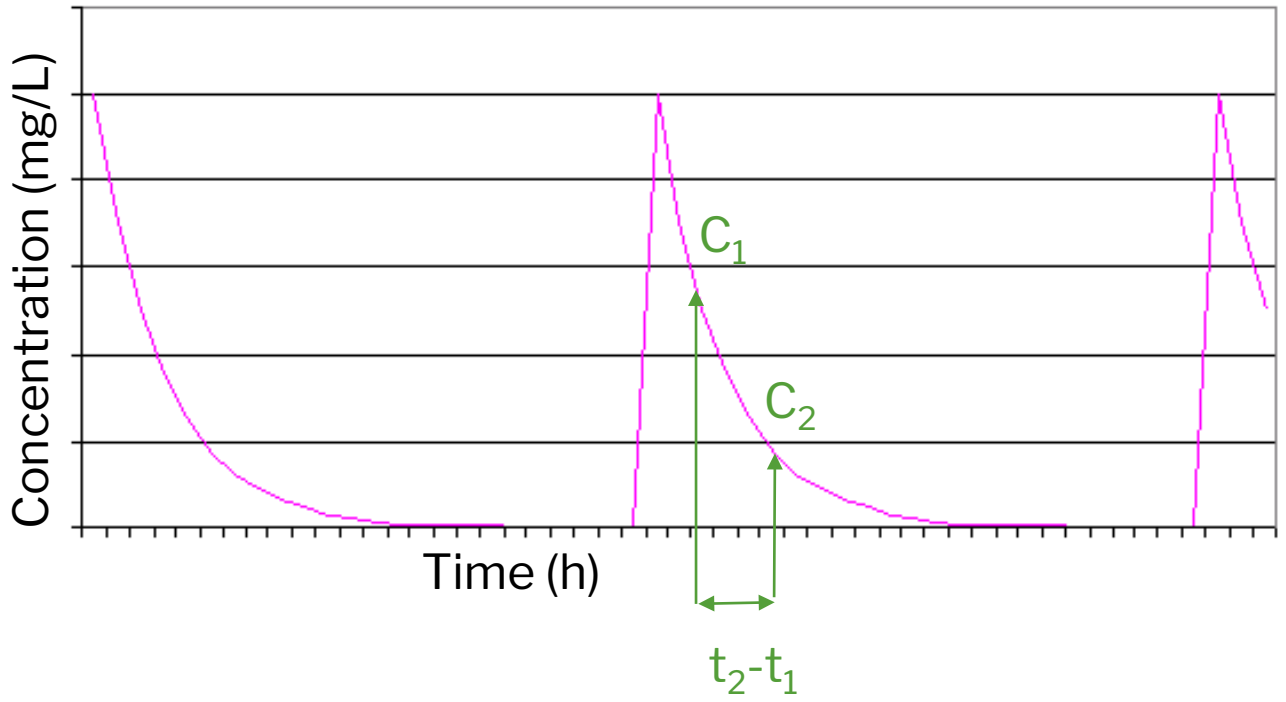
# Estimate PK Parameters using 2-point kinetics

Dose time at 9 am, infused over 30 min
Tobramycin levels @12:00 = 6 mg/L and @15:00 = 1.5 mg/L

## i) What is $k_e$ (elimination constant) and $t_{½}$ (half life)?

$$k_e = -\frac{\ln C_2 - \ln C_1}{t_2 - t_1} = \frac{\ln C_1 - \ln C_2}{t_2 - t_1}$$

$$t_{1/2} = \frac{\ln(2)}{k_e}$$



# Estimate PK Parameters using 2-point kinetics (continued)

## ii) What is the $C_{max}$ (maximum concentration)?

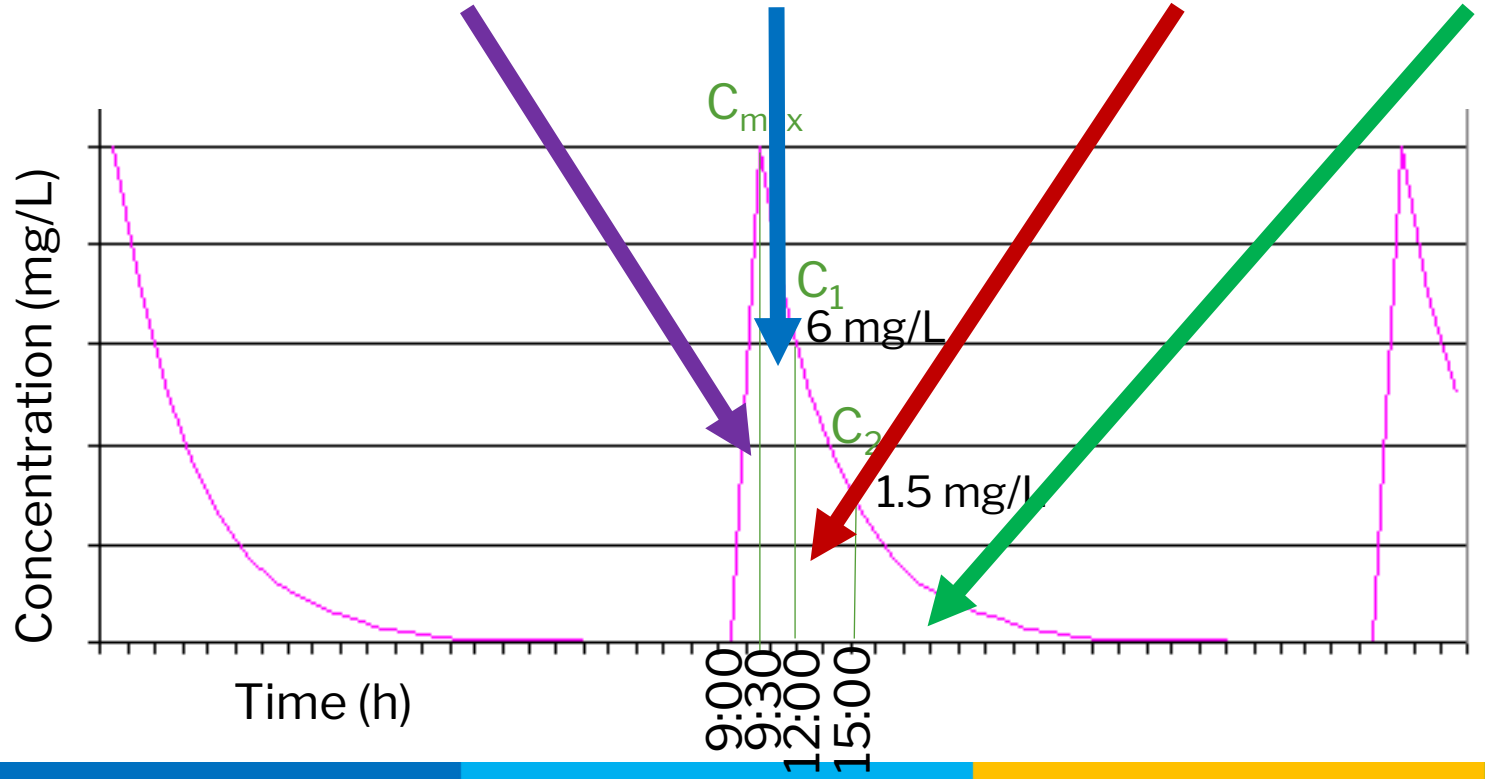
$\boldsymbol{C_{max}} = \frac{C_t}{e^{-k_e t}}$ *where t = time from end of infusion to* $C_t$

(Target: **25-35 mg/L**)

## iii) What is the AUC (area under the concentration-time curve)?

$$\boldsymbol{AUC_{0\rightarrow\infty}} = \left(\frac{0 + C_{max}}{2}\right)(t') + \left(\frac{C_{max} + C_1}{2}\right)(t_1 - t') + \left(\frac{C_1 + C_2}{2}\right)(t_2 - t_1) + \frac{C_2}{k_e}$$

(Target: **70-100 mg*h/L**)



# Estimate PK Parameters using 2-point kinetics (continued)

## iv) What is the clearance?

$$\boldsymbol{Cl} = \frac{Dose}{AUC}$$

## v) What is the $V_d$ (volume of distribution)?

$$\boldsymbol{V_d} = \frac{Cl}{k_e}$$

(Usual 0.3-0.4 L/kg)

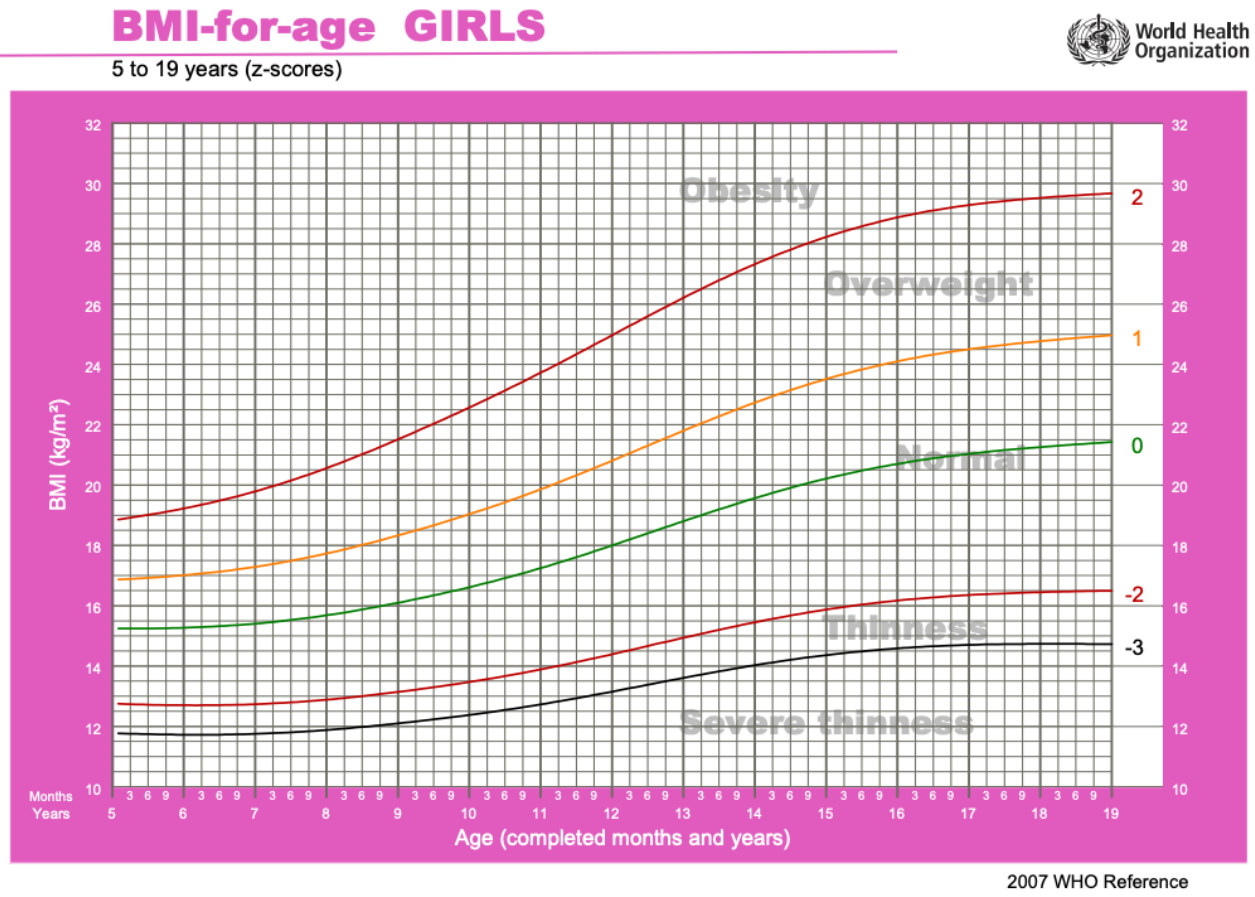
## vi) What is the DFI (drug-free interval)? Assume MIC = 4 mg/L for the pathogen, *Pseudomonas aeruginosa*

**DFI** = 24 h – $t_{C>MIC}$=$24 - (\frac{\ln(C_{max}) - \ln(MIC)}{k_e} + t')$

(Target ≥**4 h**)

# Relevant Patient factors, vitals and labs:

| | |
|---|---|
| Age | • 12 years old |
| Current Weight | • 40 kg |
| Height | • 145 cm |
| BMI | • 40 kg/(1.45 m)$^2$ =<br>Based on WHO growth chart, patient is not overweight or obese |
| Ideal body weight | • $2.396e^{0.01863[Height(cm)]} = 2.396e^{0.01863(145)}$<br>(Traub 1983 for 1-17 years) |
| Adjusted body weight | • IBW (kg) + 0.4(total body weight - IBW) |
| Clinical factors | • $FEV_1$: 64% (vs. 80% at baseline)<br>• WBC within normal range |
| Renal function | • SCr = 38 µmol/L, urea = 2.4 mmol/L<br>• eGFR = 36.5 x height (cm) / SCr (µmol/L) = (Bedside Schwartz equation 2009 for 1-18 years old)<br>• Urine output in last 24 hrs = 2 mL/kg/h |



# What is the most appropriate dose adjustment for tobramycin?

**Calculated PK parameters:**

$C_{max}$ = (Target: **25-35 mg/L**)

$AUC_{0\rightarrow\infty}$ = (Target: **70-100 mg*h/L**)

$k_e$ =

$V_d$ = (Usual **0.3-0.4 L/kg**)

**DFI** = (Target ≥**4 h**)

$$Dose = k_e\, V_d\, C_{max\,target}\left(\frac{1 - e^{-k_e T}}{1 - e^{-k_e t'}}\right) t'$$

## Suggested recommendation:

1.

2.

3.

# Example TDM guideline for ODD Tobramycin in Cystic Fibrosis patients

Therapeutic Drug Monitoring - Once Daily Dosing of Tobramycin in Cystic Fibrosis Patients

Print | Hel

**Inpatient Monitoring Recommendations:**

- Serum tobramycin "special" concentrations are collected at 3 and 6 hours after the first dose has been administered
- Subsequent 3- and 6-hour samples should be collected after each change in dose and at least weekly
- Peripheral venous sampling is done in patients on concurrent inhaled and intravenous tobramycin
- The target maximum concentration ($C_{max}$) is 25-35 mg/L to optimize therapy and minimize toxicity
- Pulmonary function tests ($FEV_1$) at baseline and prior to discharge from hospital to monitor for efficacy
- Baseline and weekly serum creatinine are collected to monitor for nephrotoxicity
- Routine audiograms are conducted to monitor for ototoxicity at baseline and 1 month later. Ensure follow-up audiogram is requested in the discharge summary.

Once therapeutic tobramycin concentrations have been attained as an inpatient, some select patients may qualify to finish their intravenous course as an outpatient. Candidates will be chosen at the discretion of the Respirology team, and must be willing to return to HSC for outpatient tobramycin levels.

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# Case 3 – Phenytoin in a neonate

# Case 3 (Phenytoin)

A 7-day-old baby girl (GA: 31w5d, weight 1.4 kg) was admitted to NICU with status epilepticus secondary to a large right parietal intraparenchymal hematoma after delivery.

She received the following antiepileptic medications:

- Lorazepam 0.1 mg/kg/dose IV x 2 (Day 1 of life)
- Phenobarbital 20 mg/kg/dose IV x 1 then 10 mg/kg/dose IV x 2 (Day 1 of life)
- Midazolam infusion, rate peaked at 20 mcg/kg/min (Day 1-4 of life)
- Fosphenytoin 20 mg PE/kg/dose IV x 1 dose (Day 1 of life) then 2 mg PE/kg/dose IV q12h (Day 2 of life to present)

Seizures stopped on Day 2 of life after fosphenytoin was started.

Today, a phenytoin trough level was collected prior to 9am dose, which was 27 µmol/L (Therapeutic range: 40-80 µmol/L).

**What are your recommendations for phenytoin dosing and TDM?**

What **other information** do you need to interpret this phenytoin trough result?

# Pharmacokinetics of Phenytoin

## Absorption

- Oral: Slow, variable; dependent on product formulation; decreased in neonates
- Time to peak: extended release capsule 4-12 h; immediate-release 1.5-3 h

## Distribution

- $V_d$: premature neonate: 1-1.2 L/kg; full-term: 0.8-0.9 L/kg; children: 0.7 L/kg; adults: 0.6-0.7 L/kg
- Protein binding: neonates: ≥80%; infants: ≥85%; adults: 90-95% (↑ free phenytoin with hypoalbuminemia, renal impairment, hepatic impairment, pregnancy, cystic fibrosis, jaundice, hyperbilirubinemia)

## Metabolism

- Metabolized primarily by CYP2C9 (80%) and CYP2C19 (20%) to an inactive metabolite; saturable
- Follows Michaelis-Menten (nonlinear) PK; best described using parameters such as $V_{max}$ and $K_m$

## Elimination

- Urine <5% unchanged; ↑ $t_{1/2}$ increases with ↑ phenytoin concentrations
- $t_{1/2}$ 7-42 h for capsule or suspension; 7-29 h for chewable tablet
- Newborns <1 week of life have ↑ $t_{1/2}$ (↓ clearance) and then rapidly accelerates by 5 weeks of life

$K_m$, Michaelis-Menten constant; PK, pharmacokinetics; $t_{½}$, half-life; $V_d$, volume of distribution; $V_{max}$, maximum velocity or rate of a reaction.

Cranford et al. Neurology. 1978;28(9 Pt 1):874-880.
Lund et al. Eur J Clin Pharmacol. 1974;7(2):81-86.
Patsalos et al. Ther Drug Monit. 2018 Oct;40(5):526-548.
Richens et al. Clin Pharmacokinet. 1979;4(3):153-169.

# TDM Considerations for Phenytoin

| Time to first TDM | Optimal Sample Timing | Optimal Concentration Range |
|---|---|---|
| Loading dose: no restriction<br><br>Maintenance: within 2-3 days, then at 5-8 days | **After loading dose:**<br>• 2 h post- IV dose<br>• 6-12 h post-oral dose<br><br>**Trough:** 0-60 min before dose<br>(timing not as critical for ER oral doses) | **Total Phenytoin levels:** 40-80 µmol/L<br><br>**Free Phenytoin levels:** 4-8 µmol/L<br>• Recommend in renal or hepatic impairment hypoalbuminemia and/or drug-drug interactions |

Patsalos et al. Ther Drug Monit. 2018 Oct;40(5):526-548.
Soriano et al. Ann Pharmacother. 2017;51(8):669-674.

# Other information

**Total Phenytoin:**
27 µmol/L
(Therapeutic range: 40-80 µmol/L)

**Free phenytoin:**
3 µmol/L
(Therapeutic range: 4-8 µmol/L)

**Bound fraction:**
89%

**Albumin:**
30 g/L

**Conjugated bilirubin:**
0 µmol/L
**Unconjugated bilirubin:**
26 µmol/L

The patient starts seizing today. What **dose** of fosphenytoin do you recommend?

# Fosphenytoin loading dose

If a single phenytoin level is subtherapeutic and seizures are not controlled, consider using a simple pharmacokinetic equation to estimate subsequent loading dose.

$$Loading\ dose\ = \frac{V_d * (C_{desired} - C_{measured})}{(\text{if salt form: } 0.92 \text{ for phenytoin sodium or fosphenytoin})}$$

Tips: Phenytoin ER capsules and injection are expressed as phenytoin sodium salt (equivalent to 92% phenytoin base)
Equations require conversion of phenytoin levels from SI to conventional units (µmol/L ÷ 3.96 = mg/L)

https://clincalc.com/Phenytoin/LoadingDose.aspx

# How should the maintenance dose be adjusted?

Total Phenytoin: 27 µmol/L (Therapeutic range: 40-80 µmol/L)

Free phenytoin: 3 µmol/L (Therapeutic range: 4-8 µmol/L)

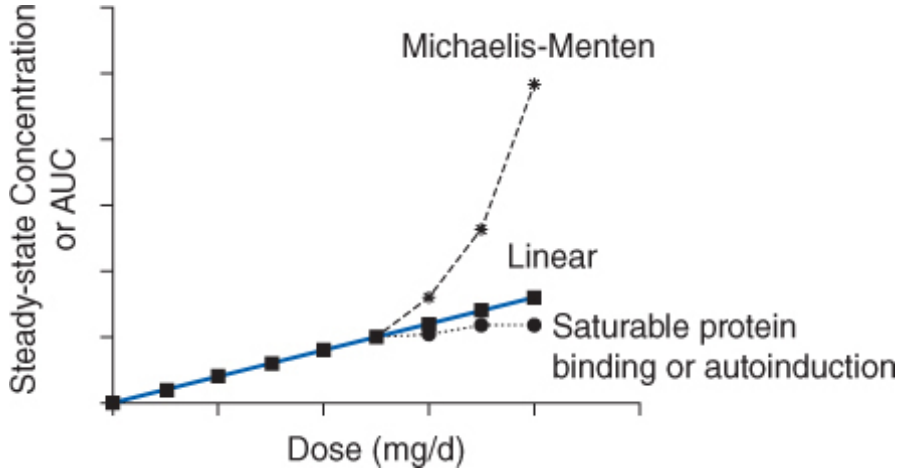
Bound fraction = 89%

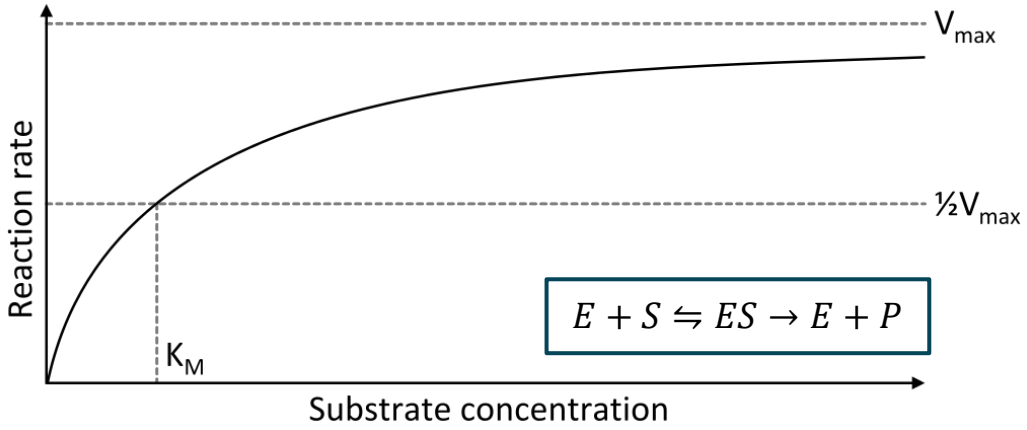
Albumin = 30 g/L

- Adjustments to the maintenance dose of phenytoin should be made in small increments due to nonlinear pharmacokinetics and steady state not achieved yet due to prolonged half-life in neonates.

# Michaelis–Menten Equation

A dose can be estimated to reach desired $C_{ss}$, if patient has two $C_{ss}$ from two dosing rates using Michaelis–Menten equations. Note: v=dose/day and [S]=phenytoin level.




**1.** $V_{max} = \frac{v_1 v_2([S]_2 - [S]_1)}{[S]_2 v_1 - [S]_1 v_2}$

**2.** $K_M = \frac{[S]_1 (V_{max} - v_1)}{v_1} = \frac{[S]_2 (V_{max} - v_2)}{v_2}$

**3.** $v = \frac{V_{max}[S*]}{K_M + [S*]}$

Tips: Phenytoin ER capsules and injection are expressed as phenytoin sodium salt (equivalent to 92% phenytoin base)
Equations require conversion of phenytoin levels from SI to conventional units (µmol/L x 3.96 = mg/L)

E, enzyme; $K_m$, Michaelis-Menten constant; P, product or metabolite; S, substrate or drug; S*, desired drug concentration; v, velocity of reaction (in pharmacokinetics, equivalent to rate of metabolism or at steady state, dosing rate); $V_{max}$, maximum velocity or rate of a reaction.

DiPiro et al. Concepts in Clinical Pharmacokinetics (Fourth Edition). 2005.

# Estimate dose needed to reach desired phenytoin of 50 µmol/L.

7 days after dose adjustment, the phenytoin level before next dose was 37 µmol/L.

| Fosphenytoin dose | Steady state Phenytoin level [S] |
|---|---|
| 2.8 mg PE (2 mg PE/kg/dose) IV q12h ($\mathbf{v_1}$ = 5.6 mg PE/day = 5.2 mg phenytoin base/day) | 27 µmol/L = 6.8 mg/L |
| 3.5 mg PE (2.5 mg PE/kg/dose) IV q12h ($\mathbf{v_2}$ = 7 mg PE/day = 6.4 mg phenytoin base/day) | 37 µmol/L = 9.3 mg/L |

*Note: v=dose/day and [S]=phenytoin level. Phenytoin ER capsules and injection are expressed as phenytoin sodium salt (equivalent to 92% phenytoin base). Conversion of phenytoin from SI to conventional units: µmol/L x 3.96 = mg/L*

**1.** $$V_{max} = \frac{v_1 v_2([S]_2 - [S]_1)}{[S]_2 v_1 - [S]_1 v_2}$$

**2.** $$K_M = \frac{[S]_1\,(V_{max} - v_1)}{v_1} = \frac{[S]_2\,(V_{max} - v_2)}{v_2}$$

**3.** $$v = \frac{V_{max}[S*]}{K_M + [S*]}$$

E, enzyme; $K_m$, Michaelis-Menten constant; P, product or metabolite; PE, phenytoin sodium equivalents; S, substrate or drug; S*, desired drug concentration; v, velocity of reaction (in pharmacokinetics, equivalent to rate of metabolism or at steady state, dosing rate); $V_{max}$, maximum velocity or rate of a reaction.

DiPiro et al. Concepts in Clinical Pharmacokinetics (Fourth Edition). 2005.

# Want to learn more about TDM?

- CSHP Hospital Pharmacy 101 Program – TDM Module
- Paediatric pharmacy practice:
  - SickKids TDM Certificate Program – available for international learners: https://www.sickkidsinternational.ca/courses/therapeutic-drug-monitoring-certificate-program/
  - Future TDM workshop in Paediatrics for Pharmacy Professionals conference

# Summary

**Therapeutic drug monitoring** is an important clinical practice that pharmacists play a major role in personalizing dosing for many medications, improving efficacy while reducing adverse effects.

Many **physiological, drug-related, and environmental factors** influence ADME.

**Prediction of dose selection** for various age groups can be performed with confidence by applying PK principles.

**Model-informed precision dosing or Bayesian approach** have potential to improve precision in dose selection and target attainment.

# **Thank you!**
# Any questions?

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