1. Which of the following are true about aminoglycosides? (1 point)
   a. Approximately 50% of the drugs are excreted in the urine.
   b. Hepatic metabolism is an important factor in their elimination.
   c. For gentamicin and tobramycin, the trough concentration should be below 2 µg/mL.
   d. Clinical peak and trough concentrations can be used to compute the volume of distribution.
   e. Clinical peak and trough concentrations can be used to compute the dosing interval but adjustments are required.

   i. A, B and C are false
   ii. D and E are true
   iii. C and E are true

   Answer: iii

2. Use the following graph to answer the question regarding ceftazidime:

   Explain which parameter(s) you will use to evaluate efficacy of ceftazidime against the infection of *K. pneumonia* in neutropenic mice, based on the graph above. Estimate the value of your selected parameter that is required to achieve a minimum efficacy, if the target is 7.2 Log_{10} CFU/Thigh at 24 hours. Also estimate the minimum value of this parameter that achieves the maximum efficacy. Discuss as to how the drug relates to bactericidal versus bacteriostatic killing of antibiotics. (2 points)

   The effect profile for this drug is a time-dependent one. The graphs above show that the time above MIC provides the tightest relationship with effect characterized by the log_{10} CFU/thigh
at 24 hours. Therefore, the time above MIC is the parameter of choice to evaluate efficacy of ceftazidime against K. pneumonia. The parameter value that achieves the minimum effect is approximately 35 hr, which corresponds to a target of $7.2 \log_{10}$ CFU/Thigh at 24 hours. The value that achieves the maximum effect is about 60 hr, corresponding to $4 \log_{10}$ CFU/Thigh at 24 hours. Bactericidal refers to drugs that kill the organism whereas bacteriostatic drugs only inhibit growth. Increasing the time above MIC, peak drug concentration and AUC/MIC ratio resulted in a decrease in CFU, suggesting that this drug has bactericidal effects.

3. Gentamicin, after IV bolus administration, exhibits a triphasic disposition that is characterized by the following equation:

$$\text{Conc}(t) = A \exp(-\alpha t) + B \exp(-\beta t) + C \exp(-\gamma t)$$

If the $t_{1/2}$ for the $\alpha$-, $\beta$-, and $\gamma$-phases are 10 minutes, 1.5 hours and 125 hours, respectively, estimate the parameter values for $\alpha$, $\beta$, and $\gamma$ in hr$^{-1}$. (2 points)

Using the equation $k = \frac{\ln(2)}{t_{1/2}}$,

- $\alpha = \frac{0.693}{0.167} = 4.15 \text{ hr}^{-1}$
- $\beta = \frac{0.693}{1.5} = 0.462 \text{ hr}^{-1}$
- $\gamma = \frac{0.693}{125} = 0.0055 \text{ hr}^{-1}$
Useful information: 1 kg = 2.2 lbs

4. A female patient, 45 years of age, 5’2” in height and 130 lbs in weight acquired S. pneumonia. Her serum creatinine is 0.75 mg/dL. The MIC of vancomycin against her infection was estimated in the laboratory to be 1.5 µg/mL. Compute both $C_{ss,max}$ and $C_{ss,min}$ based on IV bolus administration. Do you need to adjust the dosing frequency based on the computation that you have obtained? If so, estimate the next dose based on a desired steady-state concentration between 15 and 45 mg/L. Evaluate whether 24hr-AUC/MIC ratio is >400 for the new dosage. (6 points)

130 lbs = 59 kg

Use the following equation to compute the volume of distribution:

$V_d (in L) = 0.17(age in years) + 0.22(TBW in kg) + 15$

$V_d = 35.6 L$

$IBW = 45 + 2.3 \times (height in inches - 60) = 45 + 2.3 \times (62 - 60) = 49.6 kg$

We will use the TBW since TBW is less than 120% of IBW.
\[ CL_{\text{Cr, for female}}(mL/min) = \frac{(140 - \text{Age})(TBW in kg)}{(85)(SCr_{ss} in mg/dL)} \]

\[ CL_{\text{Cr}} = \frac{(140 - 45 \text{ yr})(59 \text{ kg})}{85(0.75)} = 87.9 \text{ mL/min} \]

*Vancomycin CL \sim CL_{\text{Cr}}*

*Based on the nomogram, you will use 1000 q12h dosage regimen.*

\[ 87.9 \text{ mL/min} * \frac{1L}{1000 \text{ mL}} * \frac{60 \text{ min}}{1 \text{ hr}} = 5.3 \text{ L/hr} \]

\[ K_e = \frac{CL}{V_d} = \frac{5.3 \text{ L/hr}}{35.6 \text{ L}} = 0.15 \text{ hr}^{-1} \]

\[ t_{1/2} = \frac{\ln 2}{0.15} = 4.6 \text{ hr} \]

*For IV bolus,*

\[ C_{\text{max,ss}} = \frac{S \cdot F \cdot \text{dose}}{V_d} \cdot \frac{1}{1 - \exp(-k\tau)} = \frac{1(1)(1000 \text{ mg})}{35.6 \text{ L}} \cdot \frac{1}{1 - \exp(-0.15 \text{ hr}^{-1} \cdot 12 \text{ hr})} = 33.7 \text{ mg/L} \]

\[ C_{\text{min,ss}} = C_{\text{max,ss}} \exp(-k\tau) = 33.7 \text{ mg/L} \cdot \exp(-0.15 \text{ hr}^{-1} \cdot 12 \text{ hr}) = 5.6 \text{ mg/L} \]

*For IV infusion (OPTIONAL),*

\[ C_{\text{max,ss}} = \frac{S \cdot F \cdot \text{dose}}{CL \cdot T} \cdot \frac{1 - \exp(-kT)}{1 - \exp(-k\tau)} = \frac{1(1)(1000 \text{ mg})}{5.3 \text{ L/hr} \cdot 1 \text{ hr}} \cdot \frac{1 - \exp(-0.15 \text{ hr}^{-1} \cdot 1 \text{ hr})}{1 - \exp(-0.15 \text{ hr}^{-1} \cdot 12 \text{ hr})} = 31.5 \text{ mg/L} \]

\[ C_{\text{min,ss}} = C_{\text{max,ss}} \exp(-k\tau) = 31.5 \text{ mg/L} \cdot \exp(-0.15 \text{ hr}^{-1} \cdot 11 \text{ hr}) = 6.05 \text{ mg/L} \]

*The trough is a concern since it is below 15 mg/L. You will need to either decrease the dosing interval or increase the dose.*

*If we use the trough concentration at 15 mg/L and peak concentration at 45 mg/L, then you will get*

\[ \tau = \frac{\ln \left(\frac{45}{15}\right)}{0.15 \text{ hr}^{-1}} = 8.0 \text{ hr} \]

\[ \text{Dose} = V_d \cdot C_{\text{max}} \cdot (1 - e^{-k\tau}) = 35.6 \cdot 44 \cdot (1 - e^{-0.15 \text{ hr}^{-1} \cdot 8 \text{ hr}}) = 1119 \text{ mg} \approx 1100 \text{ mg} \]

*1100 mg q8h is a more convenient dosing regimen.*
We evaluate whether 24hr-AUC/MIC ratio is >400.

\[
C(t = 0) = \frac{Dose}{V_d} = \frac{1100}{35.6} = 30.9 \text{ mg} / \text{L}
\]

\[
AUC = 30.9 / 0.15 = 206 \text{ mg} * \text{h} / \text{L}
\]

Since the drug is given q8h, we multiply the AUC by 3 assuming that linear superposition holds in this case.

\[
24hr~AUC / MIC = 206 * 3 / 1.5 > 400
\]

5. An aminoglycoside was administered as an IV infusion over 30 minutes q24h. The “clinical” peak \(C_{p_{\text{max}}}^*\) (measured 30 minutes after the end of the infusion) was reported to be 8.8 \(\mu\text{g/mL}\) and “clinical” trough \(C_{p_{\text{min}}}^*\) (measured 30 minutes before the end of the dosing interval) was 0.2 \(\mu\text{g/mL}\). Calculate the expected peak and troughs. If the MIC for the specific infection is 1 \(\mu\text{g/mL}\), compute the time above MIC after a single infusion dose. Compute the individual’s volume of distribution, if the original dose was 180 mg. What is the optimized dosing interval so that the trough concentration is maintained at 1 \(\mu\text{g/mL}\)? (4 points)

First, compute the elimination rate constant.

\[
slope = \frac{\ln(8.8) - \ln(0.2)}{1 - 23.5 \text{ hr}} = -0.168 \text{ hr}^{-1}
\]

slope = \(-k\)

To compute time above MIC, substitute the MIC value to the one compartment model to obtain the time corresponding to the MIC value on the descending phase. Assume that the ascending phase is so fast that the time corresponding to the MIC value of the ascending phase is 0. Then add the infusion time (0.5 hr) and the time lapse between the end of infusion (0.5 hr) and the time that \(C_{p_{\text{max}}}^*\) was determined.

\[
MIC = 8.8 \exp(-0.168t)
\]

1 = 8.8 \exp(-0.168t)

\[
t = 12.9 \text{ hr}
\]

\[
t_{MIC} = 12.9 + 0.5 + 0.5 = 13.9 \text{ hr}
\]

To compute the expected peak and trough, we use the slope of the curve, \(C_{p_{\text{max}}}^*\) as initial concentration and back extrapolate to half an hour earlier (i.e. \(t = -0.5 \text{ hr}\)) to obtain \(C_{\text{max}}\) (see graph from the aminoglycoside handout below). Back-extrapolation is possible because we assume that the \(C_{\text{max}}\) value lies along the slope of the log-linear portion of the graph.

\[
C_{\text{max}} = C_{\text{max}}^* \exp(-k \cdot (-0.5)) = 8.8 \exp(-0.168 \cdot (-0.5)) = 9.57 \mu\text{g/mL}
\]
\[ C_{\text{min}} = C_{\text{max}} \exp(-k \cdot (23.5)) = 9.57 \exp(-0.168 \cdot (23.5)) = 0.184 \, \mu g/mL \]

Use the following equation to compute the volume of distribution,

\[ V_d = \frac{D}{k \cdot t} \cdot \frac{(1 - e^{-kt})}{C_{\text{max}} - C_{\text{min}} e^{-kt}} = \frac{180}{0.168 \cdot 0.5} \cdot \frac{1 - \exp(-0.168 \cdot 0.5)}{9.7 - 0.184 \exp(-0.168 \cdot 0.5)} = 18.1 L \]