**PHA5128 – Dose Optimization II**
**Homework 3**
**Spring 2013**

1. While on vancomycin, a male patient 70 years of age, 6'3" in height, weighing 209 pounds had a loss of volume of distribution of 20% and a corresponding increase in serum creatinine level by 20%. Adjust his vancomycin dose, assuming that his previous serum creatinine was 1.8 mg/dL. Compute the steady state Cmax and Cmin for an intravenous bolus for his new condition. With the dosing regimen that you have recommended, is the therepeutic goal achieved with this dosing regimen (i.e. trough concentrations between 15 and 25 mg/L)? **(4 points)**
   If the therapeutic goal is not achieved, estimate the next dose based on a desired steady-state concentration between 15 and 45 mg/L. Evaluate whether the 24-h AUC/MIC ratio is greater than 400 for the new dose assuming that the MIC for vancomycin against *S. pneumoniae* is 1 mg/L. Use a one-compartment body model to compute the AUC. **(2 points)**

| $Cl_{cr}$ (ml/min) → / Weight (kg) ↓ | 30 | 40 | 50 | 60 | 70 | 80 | 90 | 100 | ≥ 110 |
|---|---|---|---|---|---|---|---|---|---|
| 50 | 500 q24h | 500 q24h | 500 q12h | 500 q12h | 500 q12h | 500 q12h | 500 q12h | 500 q8h | 500 q8h |
| 55 | 500 q24h | 500 q24h | 500 q12h | 500 q12h | 500 q12h | 500 q12h | 500 q12h | 500 q8h | 500 q8h |
| 60 | 500 q24h | 500 q24h | 500 q12h | 500 q12h | 1000 q12h | 1000 q12h | 1000 q12h | 500 q8h | 500 q8h |
| 65 | 1000 q24h | 1000 q24h | 1000 q24h | 1000 q12h | 1000 q12h | 1000 q12h | 1000 q12h | 1000 q12h | 1000 q8h |
| 70 | 1000 q24h | 1000 q24h | 1000 q24h | 1000 q12h | 1000 q12h | 1000 q12h | 1000 q12h | 1000 q8h | 1000 q8h |
| 75 | 1000 q24h | 1000 q24h | 1000 q24h | 1000 q12h | 1000 q12h | 1000 q12h | 1000 q12h | 1000 q8h | 1000 q8h |
| 80 | 1000 q24h | 1000 q24h | 1000 q24h | 1000 q12h | 1000 q12h | 1000 q12h | 1000 q12h | 1000 q8h | 1000 q8h |
| 85 | 1000 q24h | 1000 q24h | 1000 q24h | 1000 q12h | 1000 q12h | 1000 q12h | 1000 q8h | 1000 q8h | 1000 q8h |
| 90 | 1000 q24 | 1000 q24h | 1000 q12h | 1000 q12h | 1000 q12h | 1000 q8h | 1000 q8h | 1000 q8h | 1000 q8h |
| 95 | 1000 q24h | 1000 q24h | 1000 q12h | 1000 q12h | 1000 q12h | 1000 q8h | 1000 q8h | 1000 q8h | 1000 q8h |
| 100 | 1000 q24h | 1000 q24h | 1000 q12h | 1000 q12h | 1000 q12h | 1000 q8h | 1000 q8h | 1000 q8h | 1000 q8h |
| 105 | 1000 q24h | 1000 q24h | 1000 q12h | 1000 q12h | 1000 q12h | 1000 q8h | 1000 q8h | 1000 q8h | 1000 q8h |
| ≥ 110 | 1000 q24h | 1000 q24h | 1000 q12h | 1000 q12h | 1000 q12h | 1000 q8h | 1000 q8h | 1000 q8h | 1000 q8h |

**Figure 1.** Detroit Receiving Hospital and University Health Center vancomycin dosing nomogram. (Updated 5/99)

Solution:

209 lbs = 95 kg
6'3" = 75 inches

$$IBW = 45 + 2.3(height\ in\ inches - 60) = 79.5\ kg$$
$$ABW = IBW + 0.4(TBW - IBW) = 79.5 + 0.4(95 - 79.5) = 85.7\ kg$$

We will use the ideal body weight given that the total body weight is within 120% of the ideal body weight. Vancomycin is primarily cleared via the kidney. We can compute its clearance using the creatinine clearance estimation.

$$CL_{cr}(male) = \frac{79.5 * (140 - 70)}{72 * (1.8 * 1.2)} = 35.8\ mL/min$$

Based on the nomogram, you will use 1000 q24h dosing regimen.
To compute the steady state concentration, first transform the clearance to L/h unit.

$$CL = 35.8\frac{mL}{min} * \frac{1L}{1000mL} * \frac{60min}{h} = 2.14\frac{L}{h}$$

$$V_d = 0.8(0.17(age\ in\ yrs) + 0.22(TBW\ in\ kg) + 15) = 0.8(0.17(70) + 0.22(95) + 15) = 38\ L$$

$$k = \frac{CL}{V_d} = \frac{2.14}{38} = 0.056\ h^{-1}$$

For IV bolus,

$$C_{max,ss} = \frac{S * F * dose}{V_d} \cdot \frac{1}{1 - \exp(-k\tau)} = \frac{1000}{38} \cdot \frac{1}{1 - \exp(-0.056 * 24)} = 35.6 \frac{mg}{L}$$

$$C_{min,ss} = C_{max,ss} \exp(-0.056 * 24) = 9.28\ mg/L$$

No, the therapeutic goal is not achieved.

If we use the trough concentration at 15 mg/L and peak concentration at 45 mg/L, then we will estimate the following parameters:

$$\tau = \frac{\ln\left(\frac{45}{15}\right)}{0.056} = 19.6\ hr \sim 24\ hr$$

$$Dose = V_d * Cmax * (1 - \exp(-k\tau) = 1264 \sim 1300\ mg$$

1300 mg q24h is the estimated dosing regimen.

We evaluate whether 24 hour AUC/MIC ratio is >400

$$AUC = \frac{Dose}{CL} = \frac{1300}{2.14} = 607.5\ mg.h/L$$

$$\frac{AUC}{MIC} = \frac{607.5}{1} = 607.5 > 400$$

The 24-h AUC/MIC is greater than 400.

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2. You are told that vancomycin pharmacokinetic is best described by a 2-compartment model. The drug is administered as an intravenous bolus and its pharmacokinetic profile is best characterized by this equation: $C(t) = 60\exp(-0.145t) + 35\exp(-0.097t)$, where the concentration is in mg/L and time is in hour. Compute the area under the curve and determine whether the AUC/MIC ratio is greater than 400 if the MIC against the infection for vancomycin is 1 mg/L. Use the following equation to compute the AUC: $AUC = \frac{A}{\alpha} + \frac{B}{\beta}$. **(2 points)**

$$AUC = \frac{60}{0.145} + \frac{35}{0.097} = 774.62$$

$$\frac{AUC}{MIC} = \frac{774.62}{1} = 774.62 > 400$$

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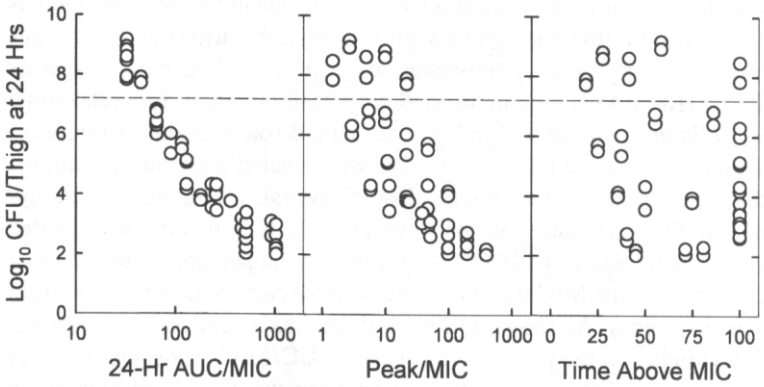
3. Use the following graph to answer the question regarding temafloxacin against *S. pneumoniae* in neutropenic mice based on the graph below:




Explain which parameter(s) you will use to evaluate efficacy of temafloxacin against the infection of *S. pneumoniae* 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 how the drug relates to bactericidal versus bacteriostatic killing of antibiotics. **(2 points)**

Solution:
The pharmacological index that best characterize the kill property of the drug is the 24-h AUC/MIC ratio. The graphs above show that this parameter provides the tightest relationship with effect, as characterized by the $log_{10}$ CFU/thigh at 24 h. Therefore, the 24-h AUC/MIC ratio is the parameter of choice to evaluate efficacy of temafloxacin against *S. pneumoniae*. The parameter that achieves the minimum effect is approximately 50 AUC/MIC ratio. The value that achieves the maximum effect is close to 1000 AUC/MIC ratio. Bactericidal refers to drugs that kill the organism whereas bacteriostatic drugs only inhibit growth. Increasing the 24-h AUC/MIC ratio or peak/MIC ratio resulted in a decrease in CFU, suggesting that this drug has bactericidal effects.