Case 6. SW is a 45 YO 180cm white male with a *Pseudomonas* pneumonia. His weight is 196 lb. and his serum creatinine is 0.9 mg/dl. Blood pressure, heart rate, skin turgor and vascular filling of neck veins indicate that SW is normally hydrated. The physician wants to use MDD. What dose (mg) of gentamicin would you recommend for initiation of therapy and what dosing interval would you recommend?

Determine IBW: 75.0 Kg

$$IBW = 50Kg + 2.3 * (Htin. - 60) \qquad = 50 + 2.3 * (180/2.54 - 60) = 75.0\,Kg \qquad \text{Eq. 1}$$

$$AdjWT = IBW + 0.4(ActWT - IBW) \quad \text{(If ActBW > 1.3×IBW)}$$

DWT: 89.1 Kg $= 196/2.2 = 89.1\ Kg$ (Because it is not 30% over ideal) Eq. 2

$$BMI = {ActBW}\big/{Ht(m)^2} = {89.1Kg}\big/{1.8m^2} = 27.5 \quad \text{(BMI > 25, so)}$$

CrClWt: = IBW + 0.4*(ActBW – IBW) = 75 Kg + 0.4*(89.1 Kg – 75 Kg) = 80.6 Kg Eq. 3

Estimate CrCl. When you enter SrCr, first convert it the standardized (corrected) value. (SrCr = (0.9+0.07)/0.987 = 0.98 mg/dL. Then you must decide to use 1.0, not 0.9 mg/dl.
CrCl = 98.9 ml/min using 1.0 (or 109.9 ml/min using 0.9 – not correct).

$$CrCl = \frac{(140 - Age) \cdot CrClWt}{SrCr \cdot 72} \qquad = 118.2 \text{ ml/min} \qquad \text{Eq. 4}$$

Population PK data for gentamicin estimates the elimination rate constant and half-life:

$$k_e = 0.015 + (0.00285 \cdot CrCl) \qquad = 0.352\ Hr.^{-1} \qquad \text{Eq. 5}$$

$$t_{1/2} = \frac{\ln 2}{k_e} \qquad = 2.0\ Hr \qquad \text{Eq. 6}$$

Estimate the volume of distribution (you must know the hydration status):

$$V_{ss} = V_d\, factor \cdot DWT \qquad V_{ss} = 0.225\ L/Kg \cdot 89.1\ Kg = 20.0\ L \qquad \text{Eq. 7}$$

Estimate Tau (the 5th equation in the Sawchuk-Zaske list):

$$\tau = \frac{\ln(C_{\text{max/desired}}/C_{\text{min/desired}})}{k_e} + t_{\text{inf}} \qquad = \frac{\ln(7/1)}{0.352\ Hr^{-1}} + 0.5\ Hr = 6.03\ Hr \qquad \text{Eq. 8}$$

Select a practical Tau (e.g. Q6H, Q8H, Q12H or Q24H) based on this estimate or you could choose tau based on half-life (just under 3) – that would be a Tau of 6 hours.. Q6H dosing is less convenient more costly, so let's first try Q8H and see what levels might result.

Using the practical interval, and we'll go with 8, estimate the new dose (the 6th equation in the Sawchuk-Zaske list):

$$R_0 = C_{\text{max,desired}} \cdot V_{ss} \cdot k_e \left[\frac{1 - e^{-k_e \tau}}{1 - e^{-k_e t_{\text{inf}}}} \right] \qquad \text{Eq. 9}$$

$$= 7\ mg/L \cdot 20.0\ L \cdot 0.352 Hr^{-1}\left[\frac{1-e^{-0.352 Hr^{-1} 8 Hr}}{1-e^{-0.352 Hr^{-1} 0.5 Hr}}\right] = 287.1\ mg/Hr$$

$$Dose = R_0 \cdot t_{inf} \qquad = 287.1\ mg/Hr \cdot 0.5\ Hr = 143.5\ mg \qquad \text{Eq. 3}$$

Make a practical recommendation (Gentamicin is usually dosed in 10 mg increments):

140 mg Q8H

Verify that this will give you desirable steady state peak and trough concentrations:

$$C_{ss,pk} = \frac{R_0}{V_{ss} \cdot k_e} \bullet \frac{\left(1-e^{-k_e t_{inf}}\right)}{\left(1-e^{-k_e \tau}\right)} \qquad \text{Eq. 4}$$

$$C_{ss,pk} = \frac{140\ mg / 0.5\ Hr.}{20.0\ L \cdot 0.352\ Hr^{-1}} \bullet \frac{\left(1-e^{-0.352 \cdot 0.5}\right)}{\left(1-e^{-0.352 \cdot 8}\right)} = 6.8\ mg/L$$

$$C_{ss,tr} = C_{ss,pk} \cdot e^{-k_e(\tau - t_{inf})} \qquad = 6.8\ mg/L \cdot e^{-0.352(8-0.5)} = 0.5\ mg/L \qquad \text{Eq. 5}$$

Note, if you would have used 140 mg Q6H, the P/T would be 7.3/1.1 mg/L

Case 7. If we went with the 140 mg Q8H and the levels came back at 3.3 mg/L at 9:15 am and 0.4 mg/L at 07:50 am and the dose was scheduled to be given at 8:00 am, what recommendation would you make?

Calculate the elimination rate constant:

$$k_e = \frac{\ln\left(C_{pk}/C_{tr}\right)}{t_{tr} - t_{pk}} \qquad = \frac{\ln\left(3.3/0.4\right)}{8-1.25} = \frac{\ln\left(3.3/0.4\right)}{6.75\ Hr.} = 0.313\ Hr^{-1} \qquad \text{Eq. 1}$$

(In terms of the dosing interval the infusion was started at t = 0, it stopped at 0.5 hr, and the pk was measured at 1.25 hr and the trough (extrapolated) was at 8 hours, therefore t_2 -t_1 is 8 - 1.25 = 6.75. Or (Tau – t_{inf} – t_{pi}) = 8 – 0.5 – 0.75 = 6.75 hours. (This is where many errors in calculations are made.)

$$t_{1/2} = \frac{\ln 2}{k_e} = 2.2\ Hr$$

Calculate the maximum concentration:

$$C_0 = \frac{C_{pk}}{e^{-k_e\left(t_{pk} - t_{inf}\right)}} \qquad = \frac{3.3 mg/L}{e^{-0.313 Hr^{-1}(1.25\ Hr - 0.5\ Hr)}} = 4.2\ mg/L \qquad \text{Eq. 2}$$

Calculate the volume of distribution:

$$V_{ss} = \frac{R_0}{k_e} \cdot \frac{1-e^{-k_e t_{inf}}}{(C_0 - C_{tr} \cdot e^{-k_e t_{inf}})} \qquad \text{Eq. 3}$$

$$= \frac{140 mg / 0.5\ Hr}{0.313\ Hr^{-1}} \cdot \frac{1-e^{-0.313 Hr^{-1} \cdot 0.5 Hr}}{(4.2\ mg/L - 0.4\ mg/L \cdot e^{-0.313\ Hr^{-1} \cdot 0.5 Hr})} = 33.8\ L$$

Using C_o, k_e and V_{ss} estimate a dosing interval, a dose and predict the steady state peak and trough using a practical regimen.

$$\tau = \frac{\ln(7/1)}{0.313\,Hr^{-1}} + 0.5\,Hr = 6.7\,Hr \approx \quad 6\,Hr \quad or \quad 8\,Hr$$

$$R_0 = 7\,mg/L \cdot 33.8\,L \cdot 0.313\,Hr^{-1}\left[\frac{1-e^{-0.313Hr^{-1}8Hr}}{1-e^{-0.313Hr^{-1}0.5Hr}}\right] = 469.4\,mg/Hr$$

$$Dose = 469.4\,mg/Hr \cdot 0.5\,Hr = 234.7\,mg \approx 230mg$$

Make a practical recommendation and then verify:

<u>230 mg Q8H</u>

$$C_{ss,pk} = \frac{230mg / 0.5\,Hr.}{33.8\,L \cdot 0.313\,Hr^{-1}} \bullet \frac{\left(1-e^{-0.313\cdot 0.5}\right)}{\left(1-e^{-0.313\cdot 8}\right)} = 6.9\,mg/L$$

$$C_{ss,tr} = 6.9\,mg/L \cdot e^{-0.313(8-0.5)} = 0.7\,mg/L$$

If you had gone with a Tau of 6 you would have come up with a dose of 220 mg Q6H that would have given a P/T = 7.1/1.3 mg/L. It takes more nursing time to administer 4 times a day, and hence is more costly to give the drug every 6 hours instead of every 8, so I tried the Q8H first.

Case 8. You have a 64 YO WF who will have abdominal surgery and the physician wants to initiate EID Gentamicin. The patient weighs 79 Kg and is 5'2" and has a SrCr of 1.3. What should be her EID?

Determine IBW: 50.1 Kg

$$IBW = 45.5Kg + 2.3 * (Htin. - 60) \qquad = 45.5 + 2.3*(2) = 50.1\,Kg \qquad \text{Eq. 1}$$

DWT: 61.7 Kg (Because she is more than 30% over ideal)

$$AdjWT = IBW + 0.4(WT - IBW) \;\; (\text{If ActWT} > 1.3\times\text{IBW}) = 50.1 + 0.4\cdot(79-50.1) = 61.7\;Kg \qquad \text{Eq. 2}$$

Estimate CrCl (Sex = 0 for a female).

BMI = 79 Kg / (62 in * 0.0254 m/in)^2 = 31.9 (Greater than 25 so CrClWt = AdjWT)

$$CrCl = \frac{(140 - Age)\cdot CrClWt}{SrCr \cdot 72}\cdot(0.85 + 0.15 * Sex) = \frac{(140-64)\cdot 61.7}{1.3\cdot 72}\cdot(0.85) = 42.6\,\text{ml/min} \qquad \text{Eq. 3}$$

Dose is 7mg/Kg * DWT = 7 * 61.7 = 431.9 mg ~ 430 mg

Interval based on CrCl of 42.6 ml/min is 36 Hr

Starting dose: **430** mg Gentamicin **Q36H**

Following the initial EID of gentamicin, the patient has a gentamicin level drawn 10.5 hours after the infusion was started. The level came back at 7.5 mg/L. What should be the new EID regimen of gentamicin for the patient based on the Hartford nomogram?

430 mg Gentamicin Q**48**H (Same dose new interval from the graph.)