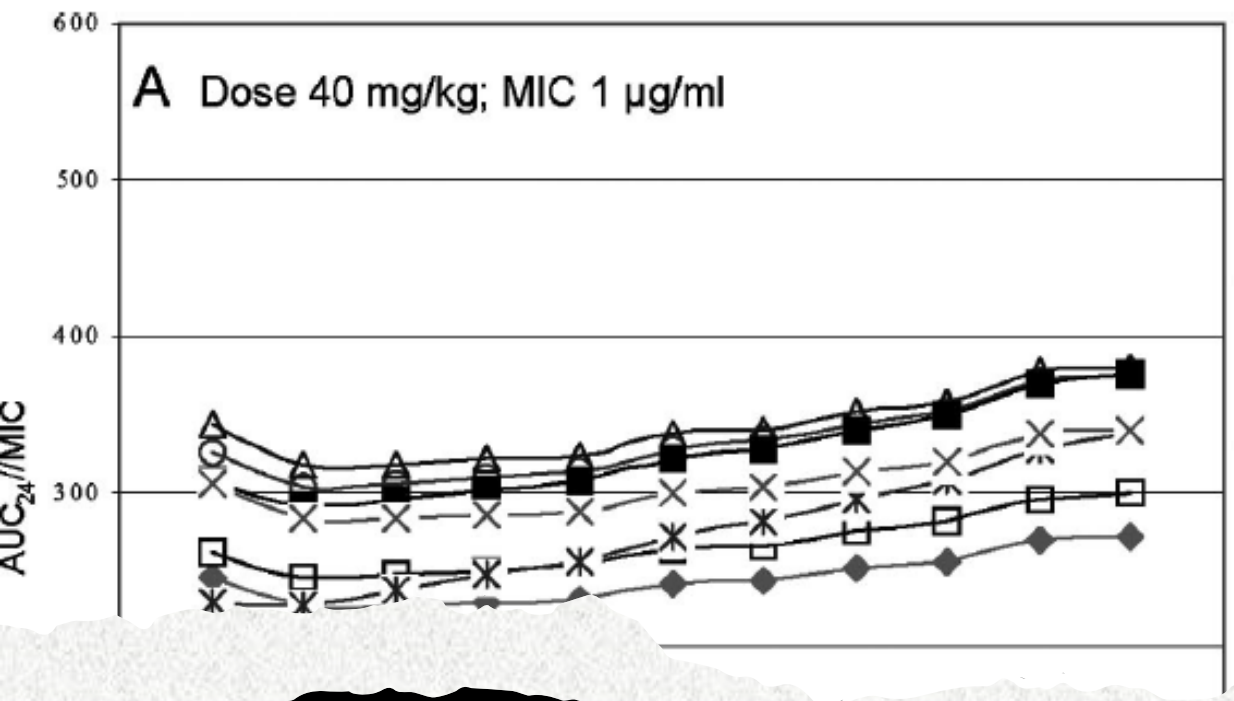
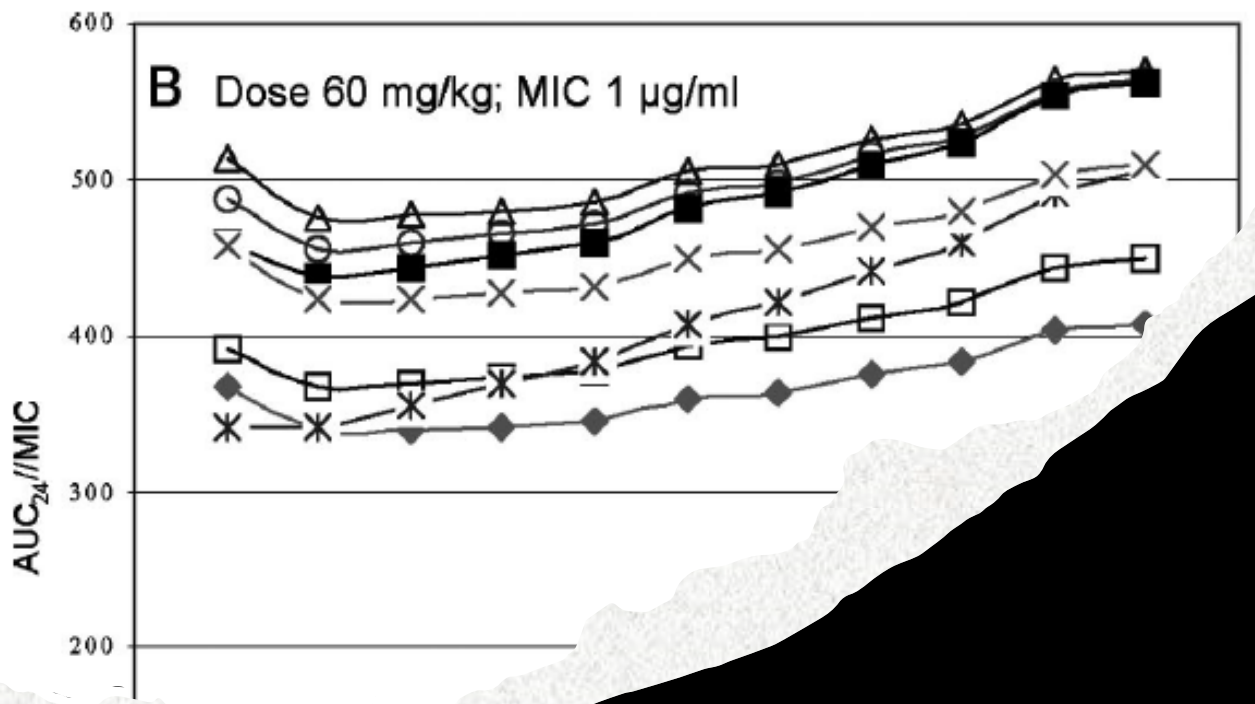
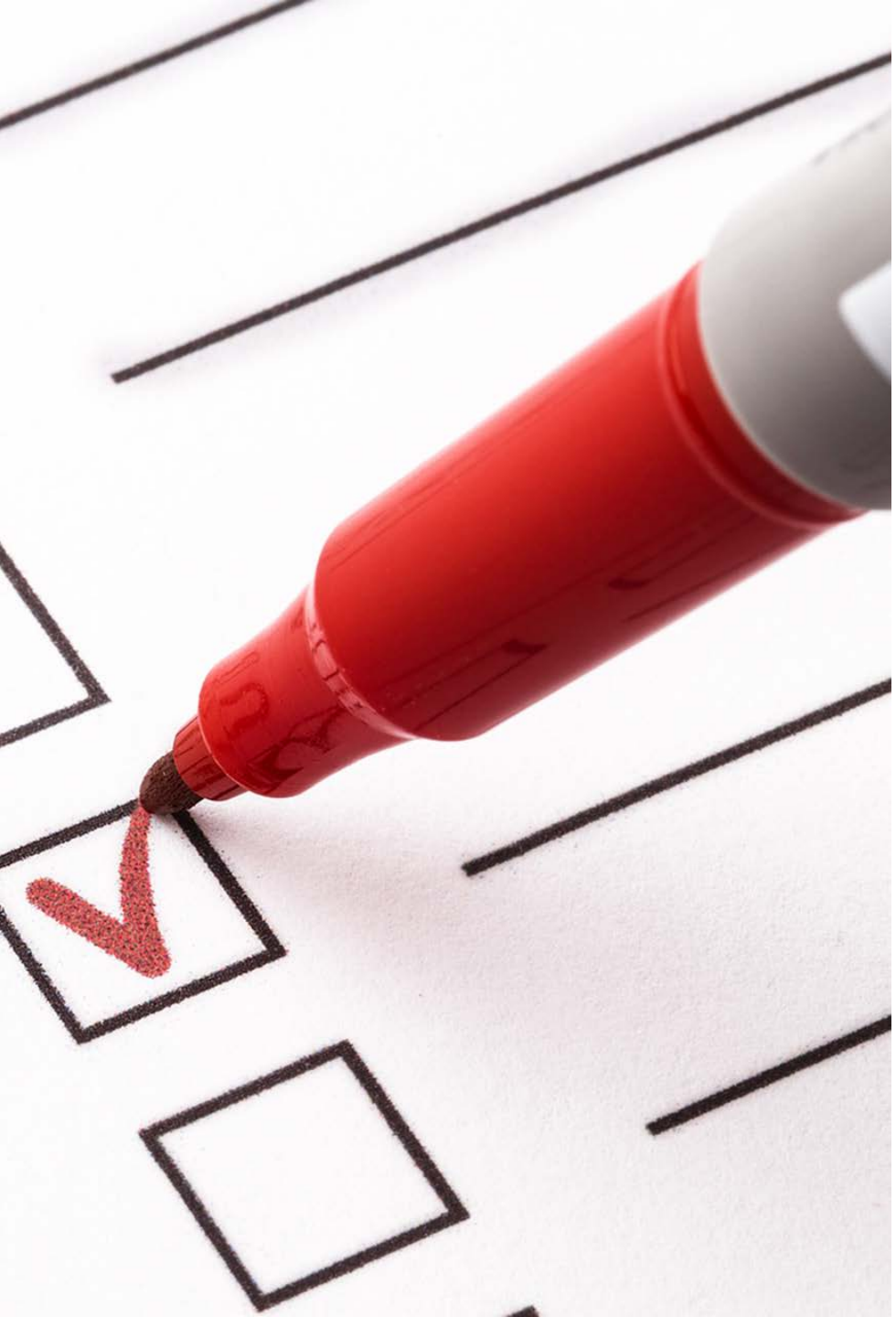




Vancomycin AUC dosing in pediatrics: Practical applications

Jared Olson, PharmD, BCPPS

2/24/2021



Objectives

- Evaluate the renal function of a pediatric patient
- Choose an appropriate starting dose of vancomycin for a child greater than 1 month of age
- Change the target dose based on AUC calculation
- Convert patient to continuous infusion therapy for home

NOTE: Although cases are pediatric many principles apply to adults

Quick summary of pediatric vancomycin CPA

- Children >=30 days generally require 60 mg/kg/day to achieve AUC_{24} target between 400 and 750
  - Max dose 3-4.5 g/day
- Delaying TDM in children with normal renal function for up to 72 hours is safe and prevents unnecessary work
  - ~90% of patients receive 72 hours or less of drug
  - Collect prior to 72 hours when committed to therapy or concern for toxicity
- AUC-based monitoring decreases dose modifications
  - Perform after steady state attainment
  - Midpoint and trough

Intermountain® Healthcare

Pediatric Vancomycin Collaborative Practice Agreement Manual

Assessment of renal function is crucial

- Modified Schwartz formula
  - eGFR = 0.413 * Ht (cm) / serum creatinine (mg/dL)
    - Used data from children 1-16 years with mild to severe chronic kidney disease
    - eGFR = ml/min/1.73 m^2
  - Normalized for an adult sized patient, so can use adult references
- Does it apply to other patients?
  - Limitations, but in short
    - Tends to overestimate true GFR in < 3 yr old
    - Tends to underestimate true GFR in > 3 years of age
- This is the equation we use to screen children!
- Normal dose if eGFR >= 50 ml/min/1.73 m^2

Schwartz. J Am Soc Nephrol. 2009:629.

Case 1: Muscle Matters

- A 5 yr old male with cerebral palsy and is wheelchair bound. He presents to your ED. Est GFR = 100 ml/min/1.73 m^2. The physician orders vancomycin pharmacy to dose and adjust the vancomycin. Which of the following is the best recommendation?

A. Vancomycin 20 mg/kg IV q 8 hrs, wait up to 72 hours to monitor
B. Vancomycin 20 mg/kg IV q6 hrs, wait up to 72 hours to monitor
C. Vancomycin 20 mg/kg IV q 8 hrs monitor vancomycin trough after 3rd dose

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Initial dosing

B. Vancomycin Dosing Flow Diagram

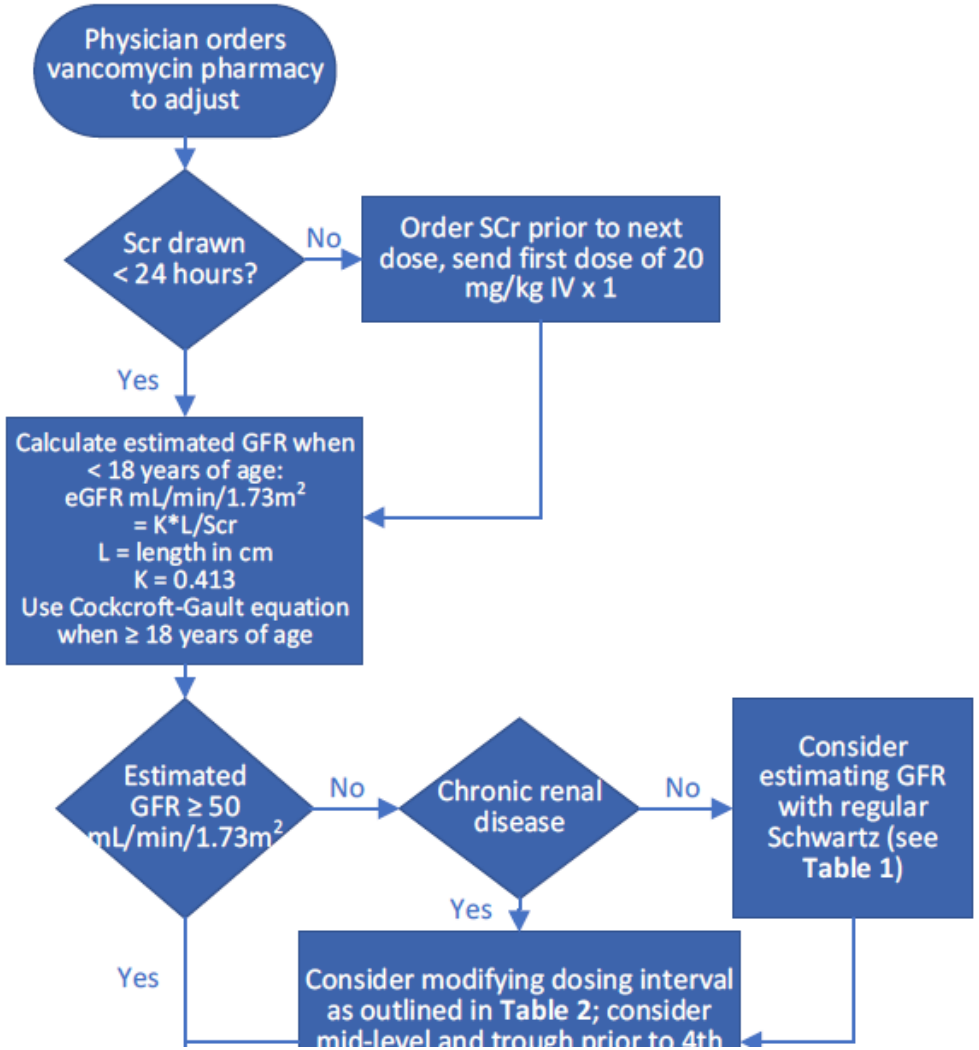

Table 1: Schwartz Muscle Factor (K)

Patient age	K
Low birth weight ≤ 1 year	0.33
Full-term ≤ 1 year	0.45
2 to 18 years	0.55

Table 2: Suggested Dosing Interval

Age	GFR	Interval	Recommended mg/kg/day
30 days to 1 year	≥ 50	Every 8 hours	60
1 to 3 years	≥ 50	Every 8 hours	60 to 80
4 to 18 years	≥ 50	Every 8 hours	60 (max 3000 mg)
	30 to 49	Every 12 hours	40 to 45
	15 to 29	Every 24 hours	20 to 25
	< 15 or dialysis	Obtain vancomycin level at 24 hours	15 to 20 mg/kg/dose
	Peritoneal dialysis	Obtain vancomycin level 3 days after dose	15 to 20 mg/kg/dose

From the CPA

- Vancomycin Initial Dosing
- 3.4.2.The initial vancomycin dose will be chosen based on the flow diagram in Appendix B. If serum creatinine (SCr) has not been checked within 24 hours of vancomycin initiation, the pharmacist will order a serum creatinine prior to the second dose of vancomycin. Renal function should be assessed based on laboratory values (e.g., BUN/SCr), urine output, modes of dialysis, previous vancomycin regimens, and past medical history (e.g., quadriplegia, low muscle mass) for dosage selection. Maximum infusion rate 1 g/hr or 20 mg/kg/hr whichever is less.
- 3.5.6. In general, for patients with normal renal function, delaying vancomycin serum concentration up to 72 hours is acceptable. In patients with poor renal function, low muscle mass or unknown renal function (including ECMO, CRRT), earlier monitoring is encouraged

Caveats in assessment of renal function

- Creatinine is derived from metabolism of skeletal muscle and dietary meat intake
  - Lagging indicator
  - If serum creatinine is increasing, equations overestimate GFR
  - If serum creatinine is decreasing, equations underestimate GFR
- Variations of creatinine production compared to average population
  - Creatine supplements
  - Reduction in muscle mass
  - Rhabdomyolysis
- Bottom line, in situations like these, trough monitoring prior to committing to vancomycin therapy can be spot check for inaccurate eGFR

Case 2: Give a little more

- A 2-year old female is started on vancomycin 20 mg/kg IV q8 hrs for MRSA bacteremia and osteomyelitis. The team is planning on continuing vancomycin, so a midpoint and a trough is obtained. The calculated AUC is 340 and the trough is 5 mcg/ml. What would you like to do?
  A. Increase dose to 20 mg/kg IV q 6 hours, obtain midpoint and trough after 3rd dose
  B. Increase dose to 20 mg/kg IV q 8 hrs, obtain trough after 3rd dose
  C. Switch to daptomycin 10 mg/kg IV q 24 hrs

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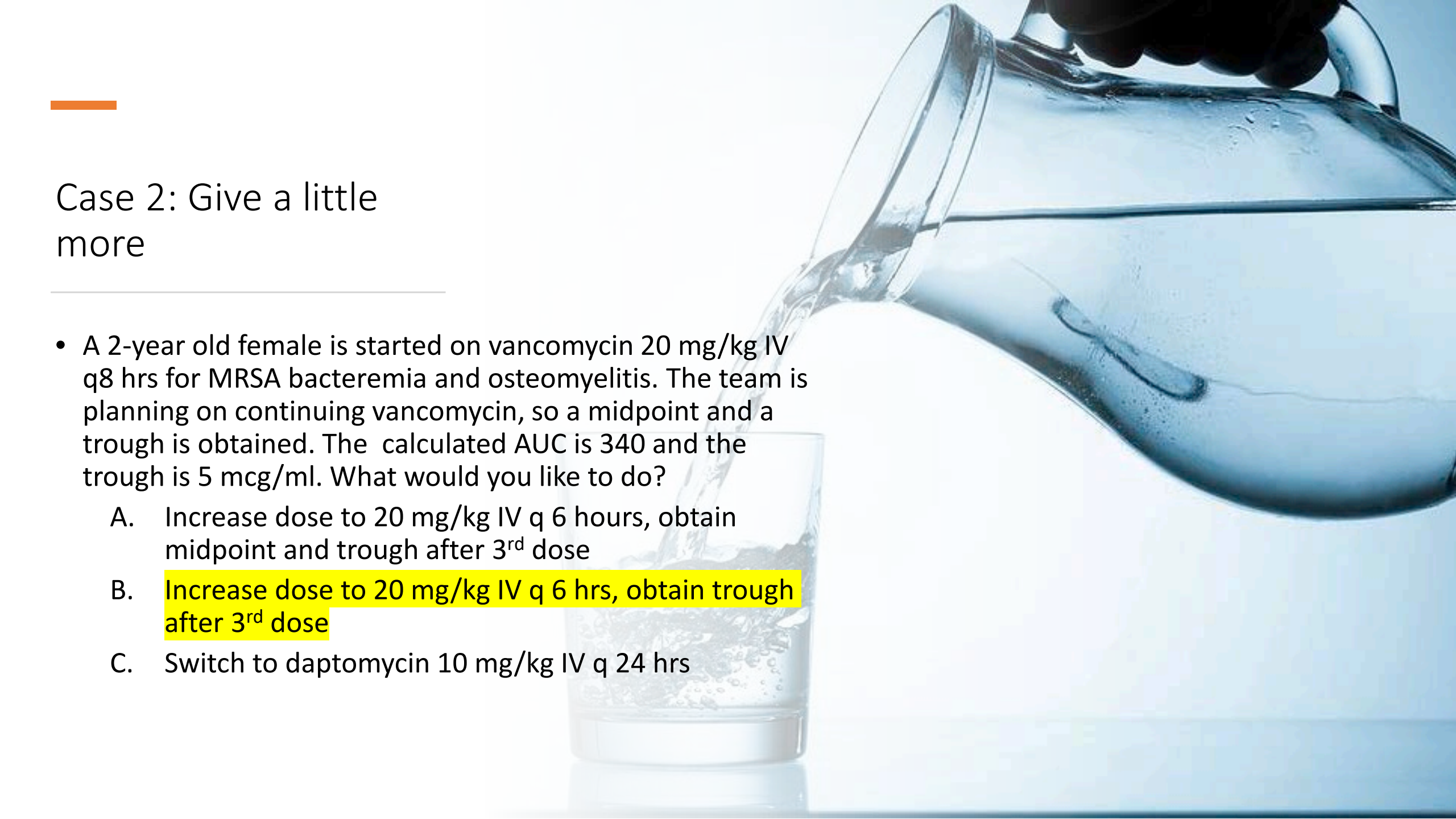


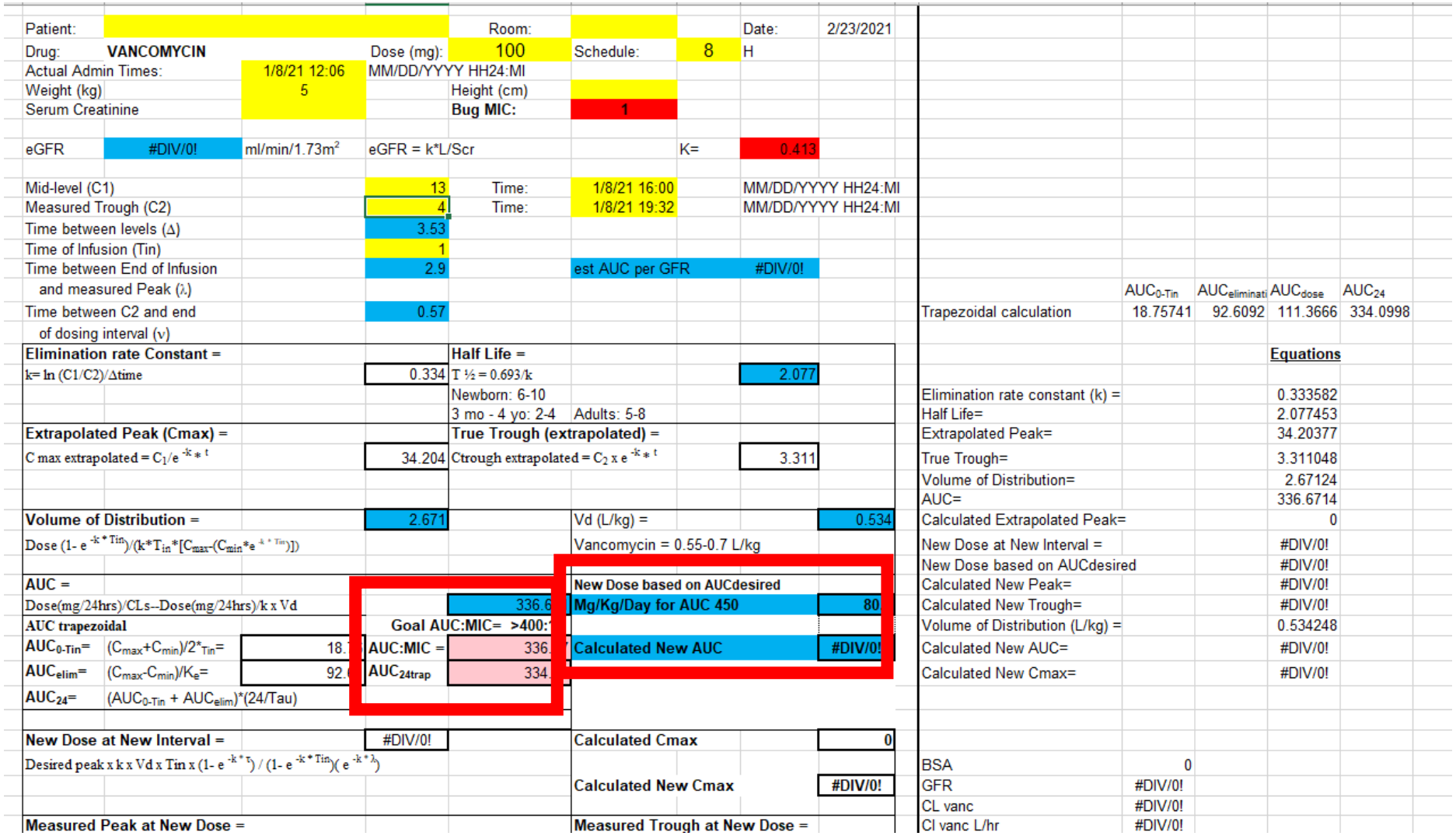
AUCs and proportional equations

- Children between 1 and 3 years of age often require 80 mg/kg/day to achieve target AUCs
  - 90% of patients don't need vanco, ~half of these patients are therapeutic on 60 mg/kg/day, so in general we still start at 60 mg/kg/day
- To determine the necessary dose to achieve AUC target of 450, we use proportional equation

$$\frac{60}{340} = \frac{x}{450}$$

X = 80

The peds dosing calculator makes it easy



Patient:			Room:			Date:	2/23/2021
Drug:	VANCOMYCIN		Dose (mg):	100	Schedule:	8	H
Actual Admin Times:		1/8/21 12:06	MM/DD/YYYY HH24:MI				
Weight (kg)		5	Height (cm)				
Serum Creatinine			Bug MIC:	1			
eGFR	#DIV/0!	ml/min/1.73m²	eGFR = k*L/Scr		K=	0.413	
Mid-level (C1)			13	Time:	1/8/21 16:00		MM/DD/YYYY HH24:MI
Measured Trough (C2)			4	Time:	1/8/21 19:32		MM/DD/YYYY HH24:MI
Time between levels (Δ)			3.53				
Time of Infusion (Tin)			1				
Time between End of Infusion and measured Peak (λ)			2.9		est AUC per GFR	#DIV/0!	
Time between C2 and end of dosing interval (ν)			0.57				
Elimination rate Constant =				**Half Life =**			
k= ln (C1/C2)/Δtime			0.334	T ½ = 0.693/k		2.077	
				Newborn: 6-10			
				3 mo - 4 yo: 2-4	Adults: 5-8		
Extrapolated Peak (Cmax) =				**True Trough (extrapolated) =**			
C max extrapolated = C_1/e^{-k*t}			34.204	Ctrough extrapolated = $C_2 \times e^{-k*t}$		3.311	
Volume of Distribution =			2.671		Vd (L/kg) =		0.534
Dose $(1- e^{-k*Tin})/(k*T_{in}*[C_{max}-(C_{min}*e^{-k*Tin})])$					Vancomycin = 0.55-0.7 L/kg		
AUC =					**New Dose based on AUCdesired**		
Dose(mg/24hrs)/CLs--Dose(mg/24hrs)/k x Vd				336.6	**Mg/Kg/Day for AUC 450**		80
AUC trapezoidal			**Goal AUC:MIC= >400:1**				
AUC_{0-Tin}=	$(C_{max}+C_{min})/2*_{Tin}$=	18.7	**AUC:MIC =**	336.	**Calculated New AUC**		#DIV/0!
AUC_{elim}=	$(C_{max}-C_{min})/K_e$=	92.6	**AUC_{24trap}**	334.			
AUC_{24}=	$(AUC_{0-Tin} + AUC_{elim})*(24/Tau)$						
New Dose at New Interval =			#DIV/0!		**Calculated Cmax**		0
Desired peak x k x Vd x Tin x $(1- e^{-k*\tau}) / (1- e^{-k*Tin})(e^{-k*\lambda})$							
					Calculated New Cmax		#DIV/0!
Measured Peak at New Dose =					**Measured Trough at New Dose =**		

	AUC_{0-Tin}	$AUC_{eliminati}$	AUC_{dose}	AUC_{24}
Trapezoidal calculation	18.75741	92.6092	111.3666	334.0998

Equations

Elimination rate constant (k) =	0.333582
Half Life=	2.077453
Extrapolated Peak=	34.20377
True Trough=	3.311048
Volume of Distribution=	2.67124
AUC=	336.6714
Calculated Extrapolated Peak=	0
New Dose at New Interval =	#DIV/0!
New Dose based on AUCdesired	#DIV/0!
Calculated New Peak=	#DIV/0!
Calculated New Trough=	#DIV/0!
Volume of Distribution (L/kg) =	0.534248
Calculated New AUC=	#DIV/0!
Calculated New Cmax=	#DIV/0!

BSA	0
GFR	#DIV/0!
CL vanc	#DIV/0!
Cl vanc L/hr	#DIV/0!

Why get a new trough?

- The new measured trough (as long as the renal function doesn’t change) is the new target
  - This way we can avoid measuring 2 levels again
  - This is especially important when we are changing the dosing frequency!!

Case 3: Home again, home again, jiggety jig

- A 14 year-old male with MRSA endocarditis will be discharged tomorrow to complete his 6 weeks of IV vancomycin. Currently the patient is receiving vancomycin 1 g IV q 8 hrs with an AUC of 475. The MD wants to send him home on continuous vancomycin. What do you recommend?

  A. Are you crazy, we don't do that!

  B. Change to vancomycin 3 g IV infused continuously over 22 hours. Check random level immediately after infusion

  C. Change vancomycin to 3 g IV infused continuously over 12 hours. Don't worry about checking a random level

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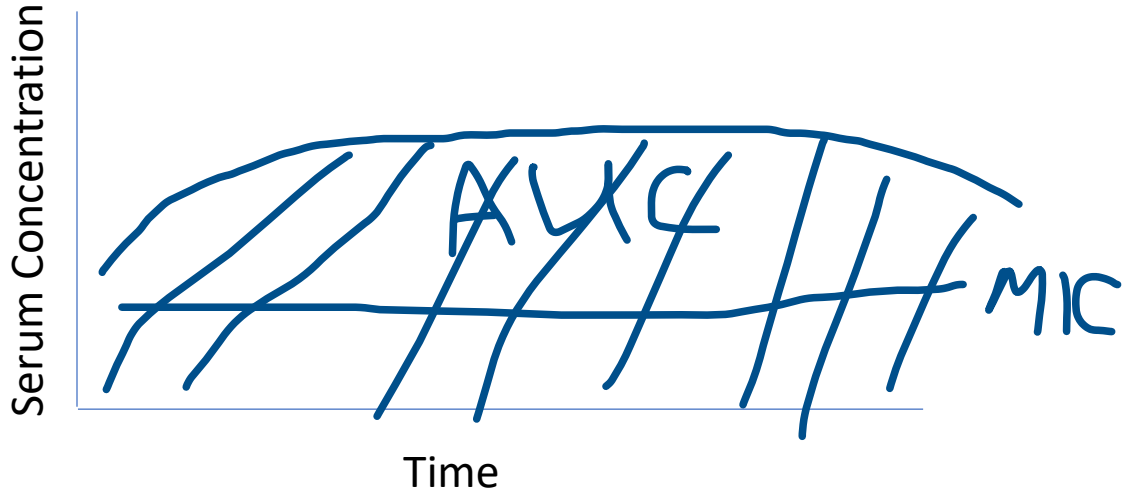
A. Are you crazy, we don't do that!

B. Change to vancomycin 3 g IV infused continuously over 22 hours daily. Check random level immediately after infusion

C. Change vancomycin to 2 g IV infused continuously over 12 hours daily. Don't worry about checking a random level

Don’t be a square, be a rectangle



- AUC calculation becomes a rectangle!!! Multiply the infusion duration by the number of hours infusing the drug and voila!
- Makes it easy for nursing staff in outpatient world
- Same total daily dose is used

Continuous Infusion from CPA

- 3.5.3.Vancomycin serum concentration monitoring is recommended midway through the dosing interval and within 60 minutes (ideally 30 minutes) prior to the next dose. For patients with planned continuation of vancomycin at home, conversion to continuous infusion vancomycin is encouraged in-house prior to discharge. Continuous infusion is generally run over 22 hours and a single concentration any time after 10 hours of infusion is appropriate. For patients with ports, consider peripheral stick. Otherwise, vancomycin level can be collected from the central line. Ensure nurse flushes line prior to collecting sample per nurse protocol.

Summary

- ✓Evaluate the renal function of a pediatric patient
- ✓Choose an appropriate starting dose of vancomycin for a child greater than 1 month of age
- ✓Change the target dose based on AUC calculation
- ✓Convert patient to continuous infusion therapy for home

Questions?