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I. Vancomycin Therapeutic Drug Monitoring Update

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- a. The old vancomycin trough of 15-20 mg/dL surrogate goal is outdated and linked to 30% increase in development of acute kidney injury (AKI)
- b. Under most circumstances, we can consider MRSA infections to have a minimum inhibitory concentration (MIC) = 1 mg/L (unless the MIC is known and above 1 by broth microdilution or other method verified for accuracy) review of literature has identified no evidence of MIC creep phenomenon.
- c. Transitioning to 24 hour area under the curve (AUC₂₄)/MIC with a goal of 400-600 via direct PK/PD monitoring is a more accurate predictor of clinical efficacy

II. Indications for AUC₂₄/MIC monitoring:

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Invasive MRSA infections, including:

- a. Bacteremia
- b. Pneumonia
- c. Meningitis
- d. Endocarditis
- e. Osteomyelitis
- f. Sepsis
- g. Intra-abdominal infections

EXCLUSIONS for AUC24/MIC dosing: III.

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- a. Skin and soft tissue infections (ABSSSI): 10 15 mg/dL trough target efficacious
- b. Enterococcal infections: 10 15 mg/dL trough target efficacious
- c. Staphylococcus epidermidis infections: 10 15 mg/dL
- d. Urinary tract infections
- e. Acute kidney injury/Rapidly changing renal function
- f. ERSD on Hemodialysis or Peritoneal Dialysis (Chronic kidney disease, but stable residual renal function, should get AUC based dosing)
- g. Surgical prophylaxis

IV. Dosing:

- a. Loading doses (20-35 mg/kg Actual Body Weight (ABW) up to 3000 mg based on patient population) for:
 - i. All ED patients will get loading dose due to uncertainty of critical illness
 - ii. Critically ill or ICU patients
 - iii. Documented serious MRSA infections
 - iv. Hemodialysis, Peritoneal Dialysis or CRRT Patients
 - v. Obese pediatric patients
- b. Maintenance doses will be based on empiric dosing calculator population estimates (maximum 4500 mg/day). In the calculator, any doses > 4500 mg/day will appear in red.
- c. Hemodialysis: 20 25 mg/kg ABW loading dose followed by 7.5 10 mg/kg maintenance dose after hemodialysis
- d. Continuous Renal Replacement (effluent rates 20 25 mg/kg/h): 20 25 mg/kg ABW loading dose followed by 7.5 – 10 mg/kg maintenance dose every 12 hours CVVHD, every 24 hours for CVVH; consideration should be given to the lowering Vd as fluid overload resolves (Nebraska Renal Dosing Guidelines)

e. Peritoneal Dialysis: 20 – 25 mg/kg IV or IP loading dose, followed by 7.5 – 10 mg/kg IV or IP Q48-72hrs based on serum levels

V. Post Dose Levels:

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- Two post dose levels are utilized to calculate AUC₂₄/MIC ratio → should be ordered as Peak and Trough levels
- Priority for measuring levels:
 - Measuring levels after the first dose is recommended for:
 - a. Severe infection (Bacteremia, meningitis)
 - b. High risk for AKI (ICU residence, CKD, concurrent nephrotoxin exposure)
 - c. Obese BMI \geq 30 kg/m²
 - d. Large empiric maintenance doses
 - i. Adults ≥ 4000 mg/day
 - ii. Pediatrics ≥ 2500 mg/day
 - e. Continuous renal replacement (CRRT)
 - All other levels should be measured at or close to steady state, typically ii. after the 4th dose
- Level order timing; order two (2) random vancomycin levels at least one (1) estimated half-live $(t_{1/2})$ apart.
 - First level schedule at least one (1) hour after the end of the first dose infusion to allow for proper distribution.
 - Second level should be at end of the dosing interval, before the next dose.
 - The dosing frequency of vancomycin may make it difficult to schedule two post levels at least 1 t ½, apart (i.e. extended infusion time, short t ½, short dosing interval), the levels may need to be drawn at shorter than one t ½ interval.
 - Ensure line where vancomycin was infusing is properly flushed prior to level collection to prevent falsely elevated levels.
- Hemodialysis: maintaining pre-dialysis concentrations between 15 and 20 mg/L is likely to achieve the AUC₂₄/MIC of 400 to 600 mg·h/L in the previous 24 hours; predialysis level preferred, may be drawn 4 hours after the end of hemodialysis prior to next dose if pre-dialysis window is missed.
- Continuous Renal Replacement Therapy (CRRT) Monitor random level in first 24 hours with goal of 15 - 20 mg/L to ensure AUC₂₄/MIC targets are met
- Peritoneal Dialysis monitor one random level every 2 3 days as needed, re-dose when serum levels fall below 15 mcg/mL (ISPD Guidelines)

VI. **Monitoring Frequency:**



- a. Hemodynamically stable, await culture results. If vancomycin is to be continued, initial steady state monitoring and then weekly monitoring is sufficient.
- b. Hemodynamically unstable or at higher risk of nephrotoxicity (critically ill, concurrent nephrotoxins), more frequent monitoring recommended
- c. Hemodialysis: predialysis serum concentration monitoring should be performed weekly
- d. Peritoneal dialysis: serum concentration monitoring should be performed weekly once clearance rate identified\

VANCOMYCIN THERAPEUTIC DRUG MONITORING, AUC24/MIC RATIO & TROUGH BASED

e. CRRT: daily evaluation of modality and ultrafiltration rate to guide level monitoring [back to table of contents $^{1/2}$] VII. Vancomycin Time Out at 24 – 48 Hours Checklist The following questions should be considered prior to continuing antibiotic therapy. Is a bacterial infection present? \square Yes \square No If No, vancomycin should be discontinued. Has the site of infection been determined? \square No \square Yes If Yes, select one: ii. ☐ Deep-seated endovascular infection (e.g., S. aureus bacteremia, endocarditis, meningitis, osteomyelitis, necrotizing fasciitis, mediastinitis, epidural or visceral abscess) ☐ Diabetic foot infection ☐ Intra-abdominal infection ☐ IV catheter related bloodstream infection ☐ Pneumonia ☐ Sepsis ☐ Skin/soft tissue infection (non-surgical site related) ☐ Surgical site or device/prosthesis-related infection ☐ Urinary tract infection □ Other Has an infectious disease physician recommended continuation of vancomycin? iii. ☐ Yes - continue vancomycin □ No Has the culprit bacterial pathogen(s) been identified? iv. ☐ Yes, definitively known – therapy is for an infection known to be caused by a culture proven gram positive organism - continue vancomycin until at least susceptibilities are known. ☐ Yes, definitively known – therapy is for an infection known to be caused by a culture proven gram positive organism susceptible only to vancomycin or patient has a serious beta-lactam allergy continue vancomycin, determine length of therapy. ☐ Yes, definitively known – therapy is for an infection known to be caused by a culture proven gram positive organism susceptible to beta-lactam antibiotics. Recommend vancomycin discontinuation vancomycin may be less rapidly bactericidal than beta-lactam agents for methicillin-susceptible staphylococci (MSSA). ☐ Possibly, a gram positive pathogen is suspected (microbiological results are pending) – follow-up in 48 hours. Has the patient had a positive MRSA nasal surveillance culture or PCR within 24 ٧. hours of starting vancomycin?

Yes

No - Negative MRSA surveillance cultures have a 99% negative predictive value of MRSA HCAP.

vi. Is the patient clinically stable? \square No \square Yes - if Yes can the patient be switched to an oral antibiotic?

VIII. Oral De-escalation Options According to Underlying Infection*:

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Infection	MRSA COVERAGE WARRANTED	MRSA COVERAGE NOT WARRANTED
Skin and soft tissue infection (suspect MRSA if induration, fluctuance, or purulence is present; diffuse cellulitis suggests a streptococcal etiology)	 TMP-SMZ 2 DS Tab q12h Clindamycin 450 mg q8h Doxy/minocycline 100 mg q12h Linezolid 600 mg q12h 	 Dicloxacillin 500 mg q6h Cephalexin 500 mg q6h
Diabetic foot infection (suspect MRSA if prior history of infection or colonization with MRSA)	Mild to moderate infection: Cephalexin 1000 mg TID OR Amoxicillin-clavulanate 875/125 mg q12h OR PLUS Doxy/minocycline 100 mg q12h OR SMT-TMZ 2 DS Tab q12h With or without metronidazole 500 mg TID Severe PCN Allergy: Clindamycin 300 mg 450 q8h *Verify osteomyelitis has been ruled out via MRI	 Cephalexin 1000 mg TID Amoxicillin-clavulanate 875/125 mg q12h Severe PCN Allergy: Clindamycin 450 mg PO q8h
Community Acquired Pneumonia (consider continuation of anti-MRSA therapy past 3d only in cases where lower respiratory cultures have grown MRSA or MRSA is otherwise strongly suspected)	 Linezolid 600 mg q12h Clindamycin 600 mg q8h* 	Doxycycline 100 mg BID Azithromycin 500 mg Daily Levofloxacin 750 mg QD (in severe penicillin allergy)
MRSA Bacteremia <u>Uncomplicated</u> (source: UTI, SSTI) - check with ID	Linezolid 600 mg q12h	For MSSA bacteremia, recommend to rule out endocarditis and consider nafcillin for high inoculum (i.e. repeated positive bacteremia) and transition to cefazolin. Consideration can be given to SMT-TMZ 2 DS Tab q12h Cephalexin 1 g TID

^{*}Please corroborate with antimicrobial susceptibility testing before starting.

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Other considerations for recommending the discontinuation of vancomycin:

- Patient is identified as low risk for MRSA infection:
 - Skin and soft tissue infection not present
 - No recent surgery or hemodialysis
 - o No recent homelessness, hospitalization, incarceration, or nursing home residence
 - o Patient has no surveillance or clinical culture proven MRSA within the past 12 months AND
 - o Patient has not received parenteral antibiotics in preceding 90 days
 - Clinical cultures obtained during the admission are negative for MRSA 48-72 hours after collection OR a cause of infection other than MRSA has been identified.



About The AUC24/MIC Calculator

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This vancomycin calculator uses a variety of published pharmacokinetic equations and principles to estimate an initial vancomycin dosing regimen for a patient based on population estimates. Subsequently, a regimen may be calculated based two vancomycin levels for severe MRSA infections. The AUC₂₄/MIC is calculated using the trapezoidal method.

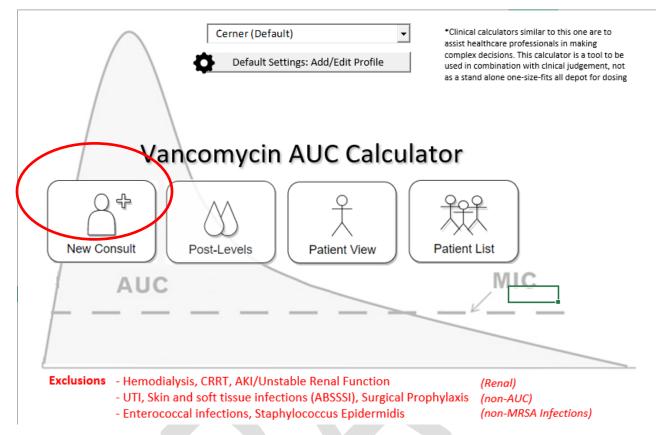
Rule of Thumb

If vancomycin is likely not to be continued after 48-72 hours, go easy on the vancomycin LEVEL monitoring!

Pharmacist Vancomycin AUC₂₄/MIC Workshop:

- 1. Patient example
- 2. 2 Patient problems
 - a. Empiric Dosing
 - b. 2 Levels with first dose
 - c. 2 Levels at steady state

Patient Example 1: New Consults - Empiric AUC/MIC

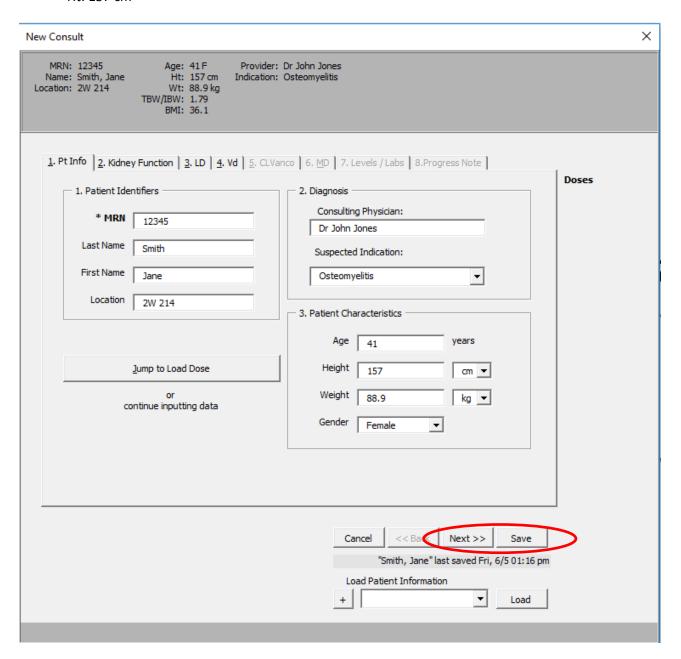


1. Patient Info:

[back to table of contents $^{\checkmark}$]

41 yo Female with MRSA Osteomyelitis

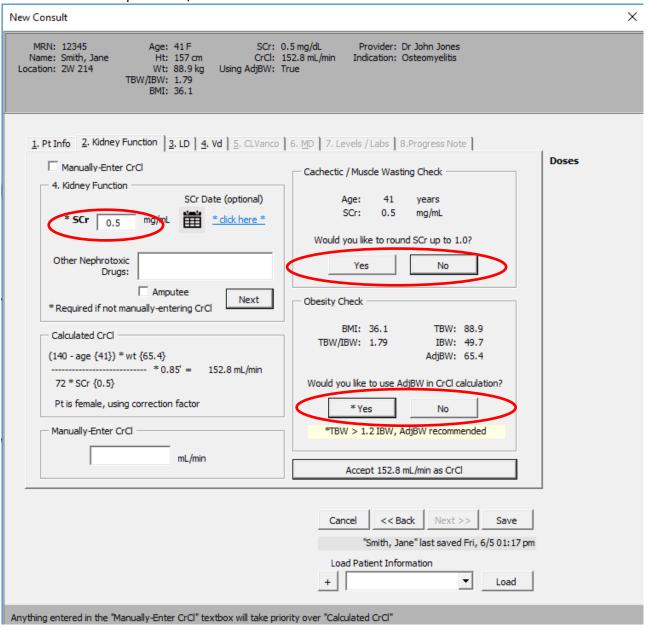
Wt: 88.9 kgHt: 157 cm



- 1. Choose the New Consult button
- 2. Enter the patient information into the calculator and choose Next. Choosing Next will save the information automatically.
- 3. Select save to add/update information in database
- 4. Entering the medical record number will allow patient to be identified during future admissions in the database
- 5. Previously added patients can be identified and loaded in the "Load Patient Information" section

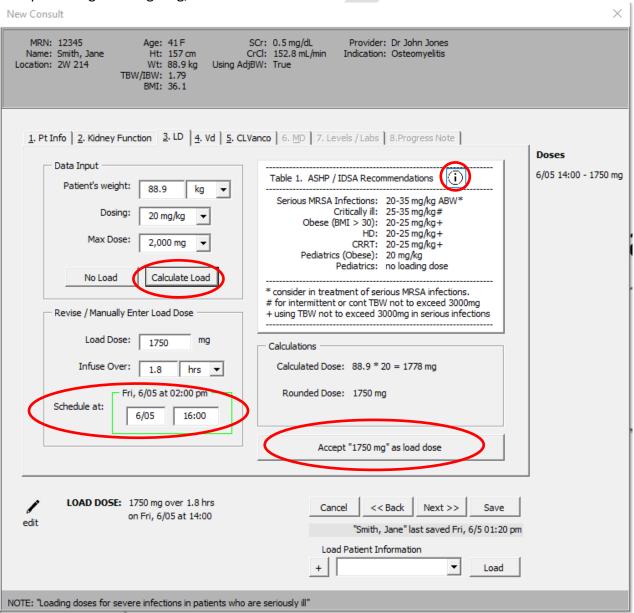
2. Kidney Function

- Patient example: This patient has stable renal function with a SCr 0.5 and no concurrent nephrotoxic medications, no amputations
- Enter patient's current serum creatinine into the calculator
- There is also an option to enter concurrent nephrotoxic agents and amputee status into the calculator. It will then provide a Caution pop-up for more careful monitoring.
- If patient is muscle wasted or cachectic, the SCr can be rounded by selecting "Yes"
- If patient is obese (>120% IBW) the AdjBW can be used to calculate CrCl by selecting "Yes"
- Select "Accept ### ml/min as CrCl"



3. LD - Loading Dose

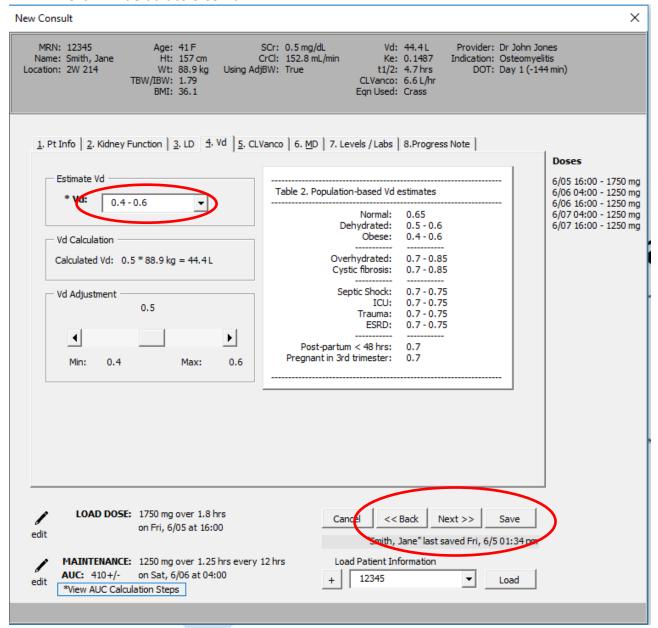
- New IDSA Vancomycin Guidelines from March 2020 recommend giving a loading dose for critically ill patients, ICU patients, those that require dialysis or renal replacement therapy. Consider whether patient requires a loading dose and if so, what category they fall into, and select "Calculate Load" or "No Load".
- Loading dose max will be hospital specific, but according new guidelines may go up to 3000
- Calculator will estimate what time the loading dose will be given, adjust time based on expectations (consider time to dispense and potential delay from administering other antibiotics before vancomycin)
- Accept loading dose if giving, or hit next.



4. Vd: Volume of distribution

[back to table of contents $\sqrt[5]{1}$

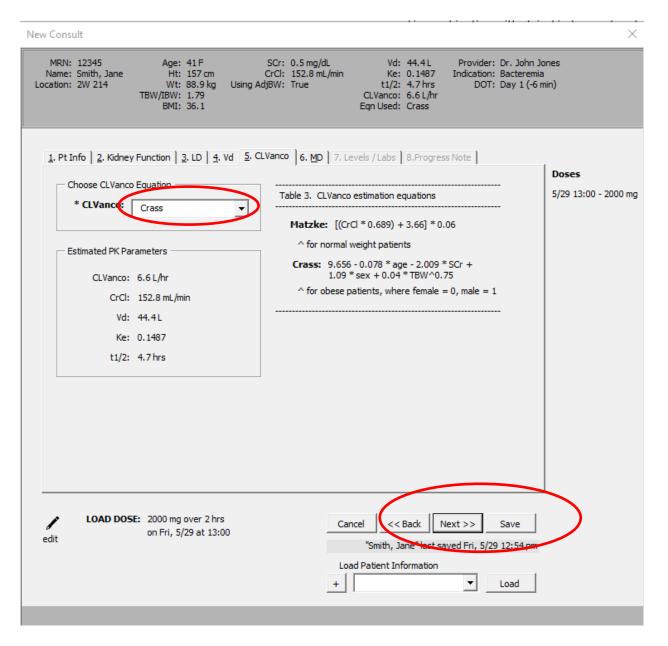
Select desired Volume of distribution based on Table and patient characteristics and hit Next. Will default to 0.65 Vd.



5. Cl Vanco [back to table of contents 5]

 Select the vancomycin clearance equation to estimate vancomycin clearance based on the patients renal function +/- weight.

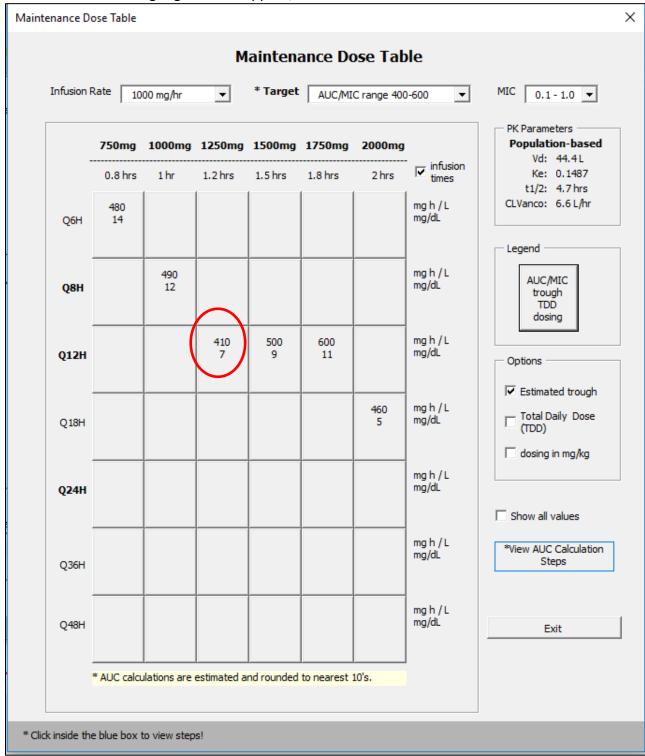
• Crass is more appropriate for obese patients. Matze may be used for all others.



6. Maintenance Dose Table

[back to table of contents $\sqrt[5]{1}$

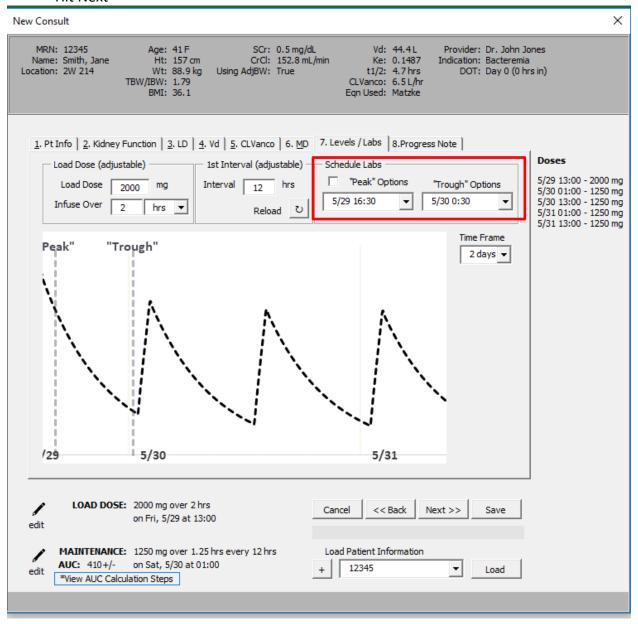
- Potential doses will populate in the table based on a Target AUC₂₄/MIC 400-600
- Boxes will populate with estimated AUC on top and troughs on bottom
- Choose an appropriate dosage regimen based on target AUC₂₄/MIC 400-600 by selecting the box. Keep in mind the troughs may be low, but we are dosing on target AUC.
- The selected dosing regimen will appear, hit next



7. Levels/Labs

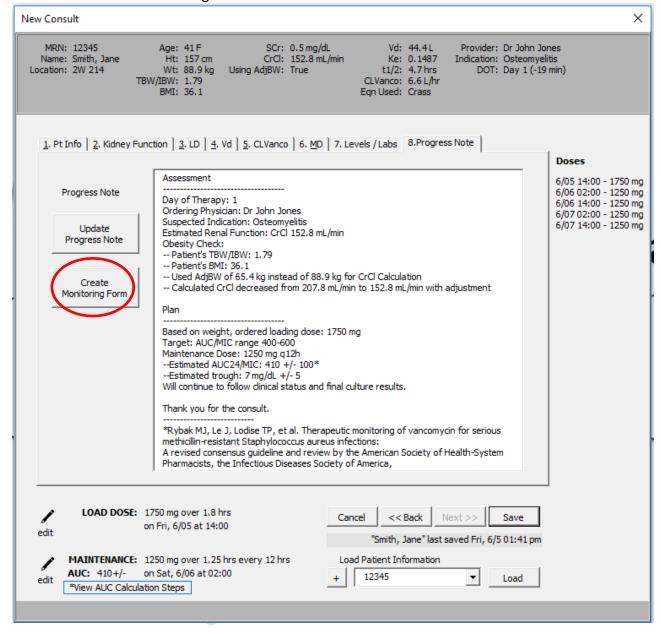
[back to table of contents $\sqrt[5]{1}$

- Under Schedule Labs, the desired time for post dose levels will populate based on when the loading dose was given. They should be collected after the 1st dose or at steady state, depending on the infection severity and patient risk for AKI.
- Hit Next



8. Progress Note

- This page will populate with the information that was used to determine the LD (if giving) and MD. It can be copied and pasted into a Cerner Progress Note.
- Hit "Create Monitoring Form"



Calculator Generated Monitoring Form: [back to table of contents 5]

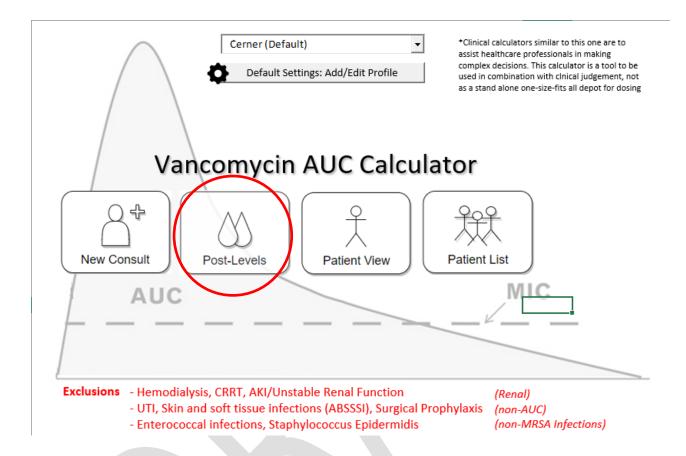
7	

Vano	omycir	n Moni	toring	Form			
dentifiers	Characteristics		Diagnosis				
MRN: 12345 Name: Smith, Jane Location: 2W 214		41 F 157 cm 88.9 kg		Provider: Dr John Jones Indication: Osteomyelitis Target: AUC/MIC range 400-600			
Anthropomorphics	Kidney Function			Loading Dose			
TBW: 88.9 TBW/IBW: 1.79 IBW: 49.7 BMI: 36.1 AdjBW: 65.4	SCr: 0.5 Bun: 0 CrCl: 152.8 mL/min Drugs:			Dose: 1750 mg over 1.8 hrs Scheduled: Fri, 6/05 14:00 mg/kg 19.7 mg/kg			
Day of Therapy /Date	Day 1 6/05	Day 2 6/06	Day 3 6/07	Day 4 6/08	Day 5 6/09	Day 6 6/10	Day 7 6/11
Maintenance dose (mg)							
Maintenance dose (mg/kg)							
Frequency (hrs)							
Administration times per MAR							
Labs		-					
Trough Level/Time Drawn							
Trough Level Ordered for: date/time)							
SCr (daily for adults)							
BUN (daily for adults)							
CrCl estimate (ml/min)							
VBC							
Procalcitonin							
Other nephrotozic drugs: MSAIDs, ACE abibitar, diaretics, pieftaza, varapressars,			I				
ctc. Culture & Sensitivity results / MRSA PCR results for respiratory and	II—— Bioca calcaic			e organism(s):			
sepsis indications:	organism(s):()		()			Resp culture; Date: Other:	
Evaluate for de-escalation		[] MRSA PCR follow up	[] Action on culture informatio n if applicable		,	G-al Day	
			. In the state of				
Comments:							

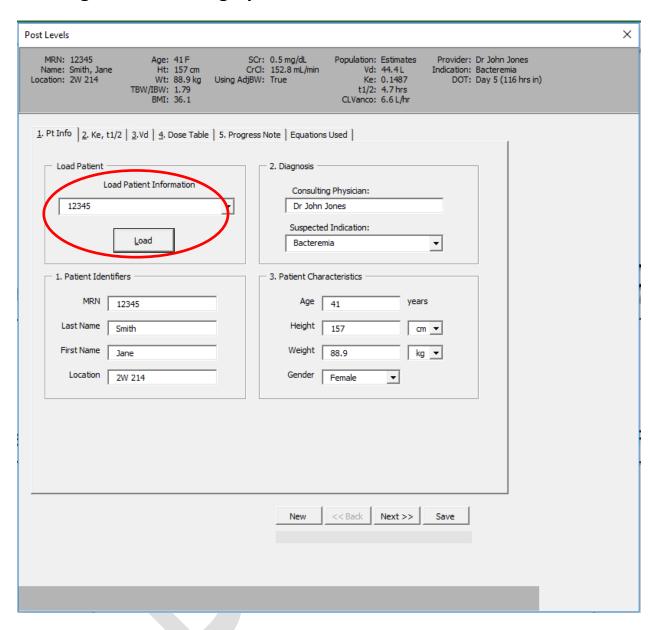
Two post dose levels:

[back to table of contents $\sqrt[5]{1}$

• Use "Post-Level" portion of calculator once two post dose levels are available – ideally close to steady state (after 4th dose) and at least 1 half-life apart.



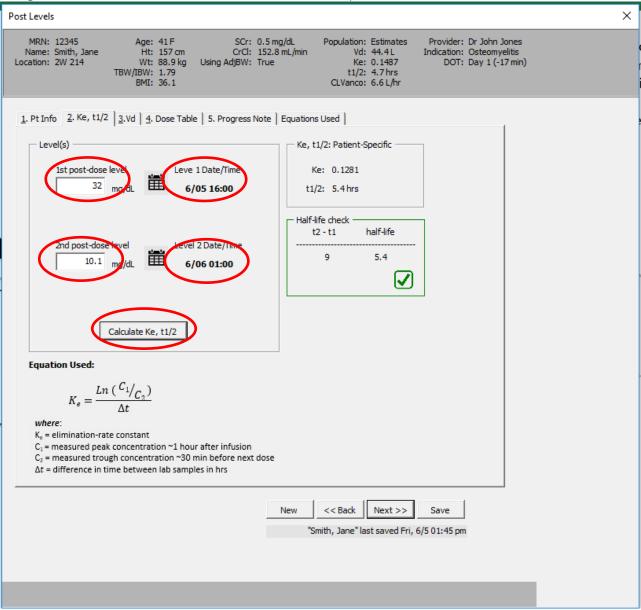
1. Search patient and load patient information input from initial empiric dosing or fill in demographic information: [back to table of contents 5]



2. Post dose level entry – patient specific Ke, $t_{1/2}$ results [back to

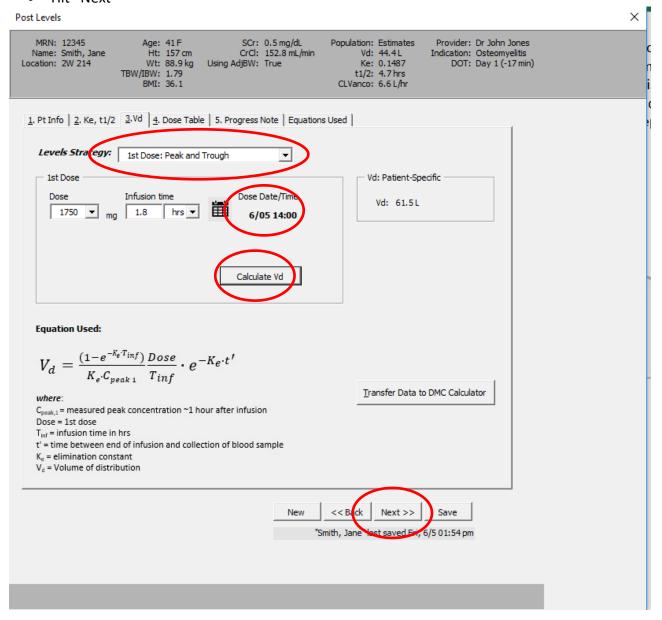
table of contents $\sqrt{}$

- Enter post dose levels, ensure times and dates are correct based on when last dose was given
- Hit the "Calculate the Ke, t_{1/2}" and Next
- The green check mark indicates there is at least one t_{1/2} between the levels



3. Volume of Distribution

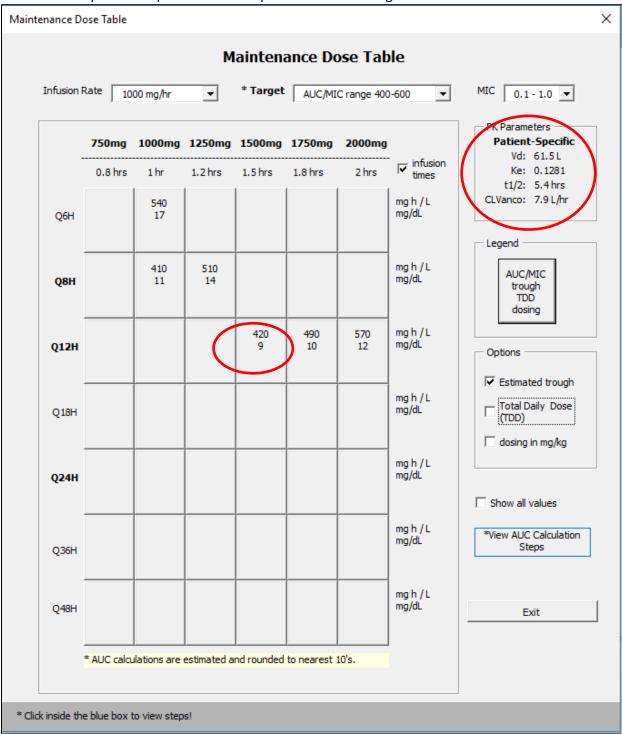
- Select Level Strategy: after 1st dose vs steady state
- Enter the dose the patient received, verify the infusion time, and date/time administered. If level is at steady state, enter and verify the dosing interval.
- Hit "Calculate Vd"
- Hit "Next"



4. New Maintenance Dose Table:

[back to table of contents $\[\]$]

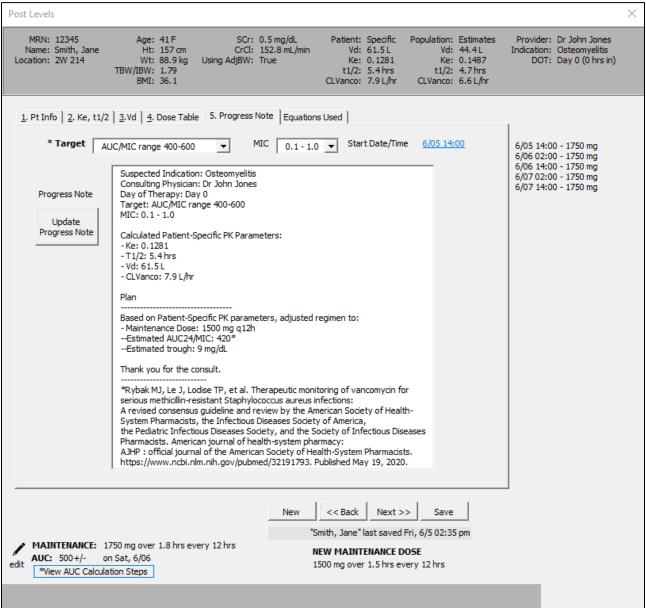
- If necessary, select a new maintenance dose based on the AUC target. Usually the lowest clinically effective AUC dose should be used, along with consideration for more convenient dosing (i.e. avoid q18H, q36H intervals if possible)
- Patient specific PK parameters are presented on the right



5. Progress Note Update

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• The progress note is now updated with the patient specific PK parameters and dosage adjustment information.



VANCOMYCIN THERAPEUTIC DRUG MONITORING, AUC24/MIC RATIO & TROUGH BASED

Patient 2:	[back to table of contents $^{\bigvee}$]
MRN: 123456, Location: 314 (ICU)	
Name: Jimmy Dean	
Age: 72	
Gender: Male	
Height/weight: 180.34 cm 102.3 kg measured	
SrCr 1.3 – stable	
Other medications: Metformin, metoprolol, aspirin, Lisinopril & Pip/tazo	
WBC 18,000, temperature 39.5 C	
Indication: Pneumonia	
Questions:	
Creatinine Clearance: ml/min	
2. Loading dose:	
a. Patient should receive a loading dose? [] Yes [] No	
b. Why or why not:	
c. If yes, loading dose selected:	
3. Vd selected & why:	
4. CL Vanco Equation Selected:	
5. Maintenance Dose:	
6. Schedule post-dose levels after:	
[] 1 st dose why?	
[] 4 th dose; why?	
[] Wait and re-evaluate in 24 hours; why?	
Dationt 2 continued:	
Patient 2 continued:	
Loading dose (2000 mg) administered on 6/5 @ 12:00 (over 2 hours)	
1st Post dose level = 31.2 on 6/5 @ 15:00	1
2 nd Post dose level: 30 minutes prior to subsequent dose = 7.8 on 6/6 @ 00:30	1
Questions:	
1. Patient specific Vd:	
2. New maintenance dose: mg Q h	
3. Estimated AUC:	
Why did you choose this regimen?	
willy did you choose this regimen:	
What is the total gram/day?	
Does this place the patient at additional risk for nephrotoxicity.	

VANCOMYCIN THERAPEUTIC DRUG MONITORING, AUC24/MIC RATIO & TROUGH BASED

Patient Case 3: MRN 56789, Location: 612 (Med/Surg) Age: 59 years Gender: Male Height/weight: 180.34 cm 63.3 kg measured SrCr 0.8 (4/27/20 0352) stable WBC 9.31, Afebrile Indication: Sepsis	[back to table of contents $\ \ \ \ \ \ \ \ \]$
Questions: 1. Creatinine Clearance: ml/min 2. Loading dose: a. Patient should receive a loading dose? [] Yes [] No b. Why or why not: c. If yes, loading dose selected: 3. Vd selected & why: 4. CL Vanco Equation Selected: 5. Maintenance Dose: 6. Schedule post-dose levels after: [] 1 st dose why? [] 4 th dose; why? [] Wait and re-evaluate in 24 hours; why?	
Patient 3 continued: Maintenance Regimen Selected (no LD given): Vancomycin 1 gm q12h, 1 dose "Peak": 2/12 @ 2001 - 24.3 "Trough": 2/12 @ 0510 - 15.9	at 1734 on 2/10 over 1 hr
Questions: 7. Patient specific Vd:L 8. New maintenance dose: mg Q h 9. Estimated AUC: Why did you choose this regimen?	
What is the total gram/day? Does this place the patient at additional risk for nephrotoxicity. How would you treat this patient differently if the vancomycin was indicated for the patient differently if the vancomycin was indicated for the patient differently if the vancomycin was indicated for the patient differently if the vancomycin was indicated for the patient differently if the vancomycin was indicated for the patient differently if the vancomycin was indicated for the patient differently if the vancomycin was indicated for the patient differently if the vancomycin was indicated for the patient differently if the vancomycin was indicated for the patient differently if the vancomycin was indicated for the patient differently if the vancomycin was indicated for the patient differently if the vancomycin was indicated for the patient differently if the vancomycin was indicated for the patient differently if the vancomycin was indicated for the patient differently if the vancomycin was indicated for the patient differently if the vancomycin was indicated for the patient differently if the vancomycin was indicated for the patient differently if the vancomycin was indicated for the patient differently in the patient differently indicated for the patient diffe	for cellulitis?

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