Clinical Pharmacy Continuing Education

Implementing AUC:MIC Vancomycin Monitoring

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OBJECTIVES

- Examine PK/PD, mechanism of action, and adverse effects
- Analyze the difference between trough v.s. AUC based dosing
- Apply AUC:MIC based vancomycin dosing

PHARMACOKINETICS

ABSORPTION

- Oral - poor
- Rectal - colonic mucosa is significant
- Intraperitoneal - 60% in 6 hrs

DISTRIBUTION

- Vd in adults - 0.4 to 1 L/kg

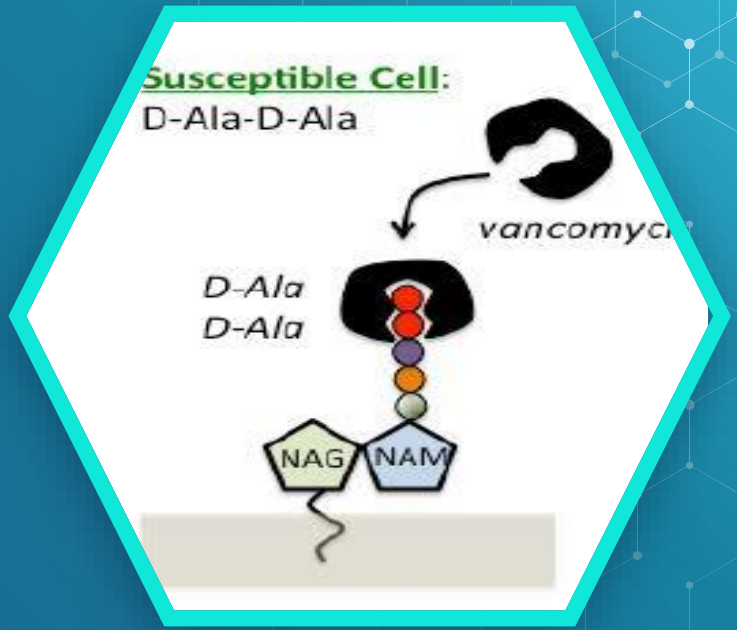
ELIMINATION

- $T_{1/2}$ - 4 to 6 hours
- Oral- feces
- IV - glomerular filtration

Vancomycin.https://online-lexi-com.ezproxy.ttuhsc.edu/lco/action/doc/retrieve/docid/patch_f/7856?cesid=aNINmpQodjv&searchUrl=%2Flco%2Faction%2Fsearch%3Fq%3Dvancomycin%26t%3Dname%26va%3Dvancomycin. Accessed October 6, 2020.

VANCOMYCIN MECHANISM OF ACTION

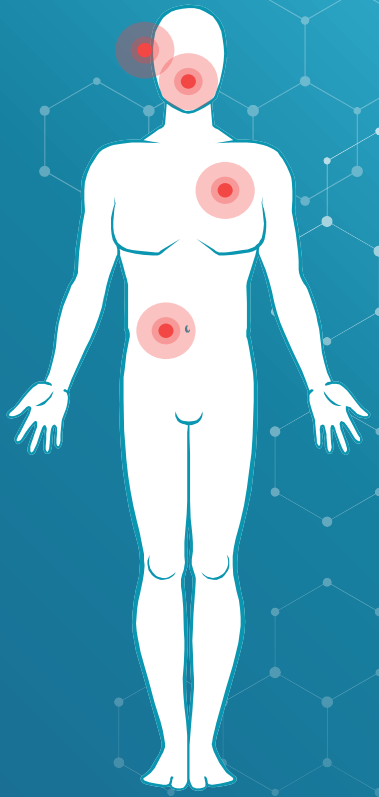
- Glycopeptide antibiotic
- Changes D-Ala, D-Ala to D-Ala, D-lac
- Inhibits cell wall synthesis
- Bactericidal
- Gram (+) coverage



Hu Q et al. Front Microbiol. 13 October 2016

ADVERSE EFFECTS

- Vancomycin Flushing Syndrome
- Nausea (17%)
- Abdominal Pain (15%)
- Hypokalemia (13%)
- Nephrotoxicity (5%)
- Ototoxicity (2%)
- Steven Johnson Syndrome



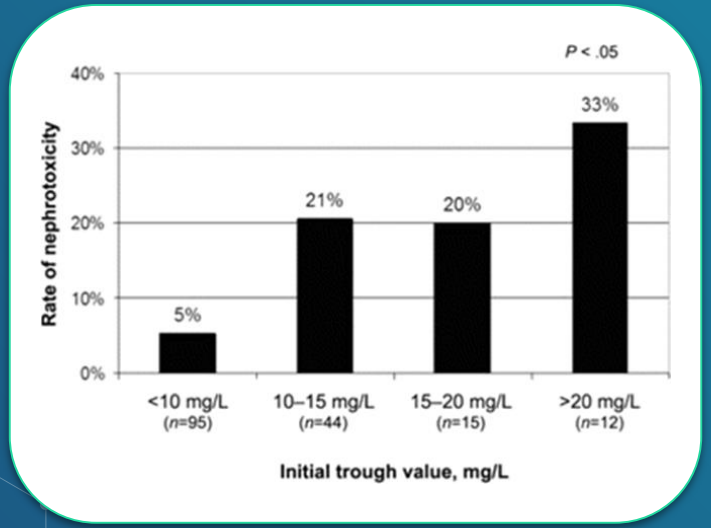
Vancomycin.https://online-lexi-com.ezproxy.ttuhsc.edu/lco/action/doc/retrieve/docid/patch_f/7856?cesid=aNlNmpQodjv&searchUrl=%2Flco%2Faction%2Fsearch%3Fq%3Dvancomycin%26t%3Dname%26va%3Dvancomycin. Accessed October 6, 2020.

2009 VANCOMYCIN GUIDELINES

- AUC:MIC is most useful PK/PD parameter
- Minimum serum trough concentrations should be maintained above 10 mg/L
- Trough serum concentrations are the most practical as a surrogate marker for AUC:MIC
  - Steady state drawn before the 4th dose
  - Optimal drug exposure goal is 15-20 mg/L

Rybak MJ, Lomaestro BM, Rotschafer JC, et al. Vancomycin Therapeutic Guidelines: A Summary of Consensus Recommendations from the Infectious Diseases Society of America, the American Society of Health-System Pharmacists, and the Society of Infectious Diseases Pharmacists. Clinical Infectious Diseases. 2009;49(3):325-327. doi:10.1086/600877

NEPHROTOXICITY

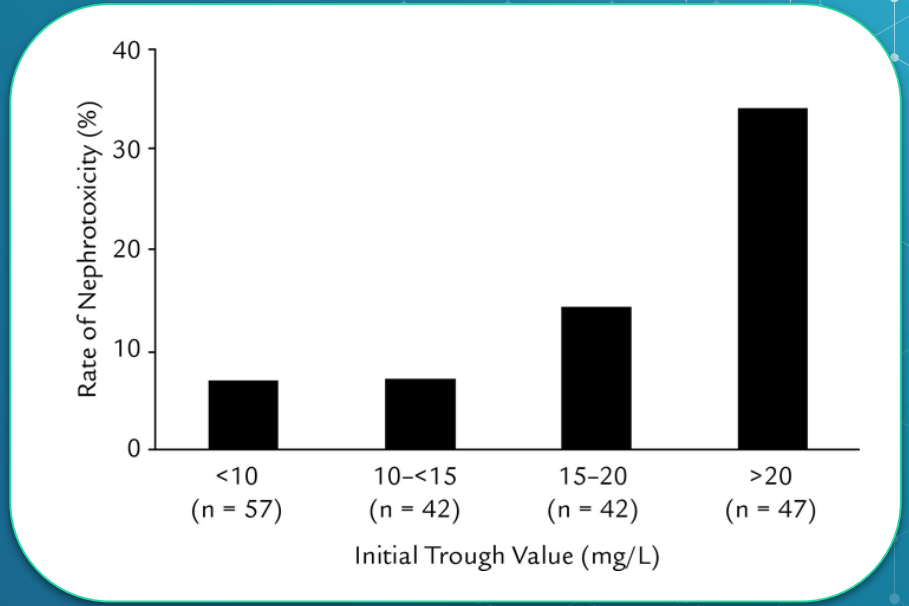


Graph showing the relationship between the initial vancomycin trough value and the rate of nephrotoxicity

Clin Infect Dis, Volume 49, Issue 4, 15 August 2009, Pages 507–514, https://doi.org/10.1086/600884

NEPHROTOXICITY

Relationship between initial vancomycin value and the frequency of nephrotoxicity for 188 vancomycin treated patients (P = 0.001)



Clinical Therapeutics 2012 34149-157DOI: (10.1016/j.clinthera.2011.12.013)

WE NOW KNOW…

- Trough concentration >15 mg/L is linked to higher risk of toxicity
- Approximately 60% of patients with AUC:MIC > 400 results in trough concentrations of < 15 mg/L
- It is estimated there is a 20-25% mortality for inpatients with AKI
- AKI = increased LOS by 2.8 days and costs of $7082

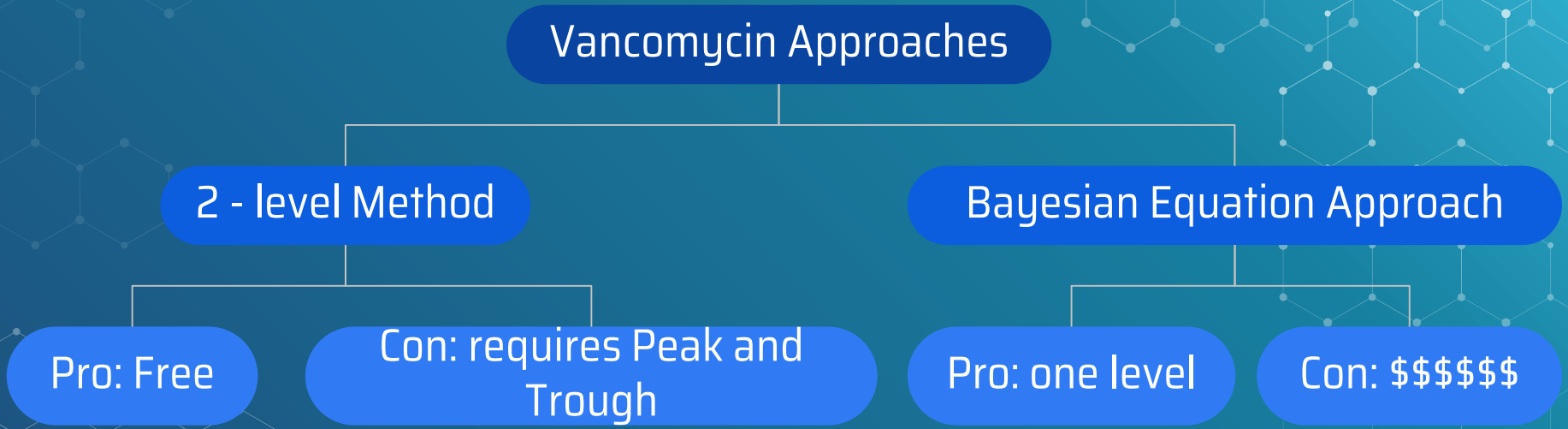
Neely MN, Youn G, Jones B, et al. Are vancomycin trough concentrations adequate for optimal dosing?. Antimicrob Agents Chemother. 2014;58(1):309-316. doi:10.1128/AAC.01653-13
Susantitaphong P, Cruz DN, Cerda J, et al. World incidence of AKI: a meta-analysis [published correction appears in Clin J Am Soc Nephrol. 2014 Jun 6;9(6):1148]. Clin J Am Soc Nephrol. 2013;8(9):1482-1493. doi:10.2215/CJN.00710113
Zeng X, McMahon GM, Brunelli SM, Bates DW, Waikar SS. Incidence, outcomes, and comparisons across definitions of AKI in hospitalized individuals. Clin J Am Soc Nephrol. 2014;9(1):12-20. doi:10.2215/CJN.02730313

2020 VANCOMYCIN GUIDELINES

- Trough-based dosing is **NO longer** recommended
- To reduce nephrotoxicity and enhance efficacy, the **AUC within 24 hrs (AUC_{24}) goal is 400-600 mg *hr/L**
- AUC can be calculated with a bayesian software **or** 2-level method.

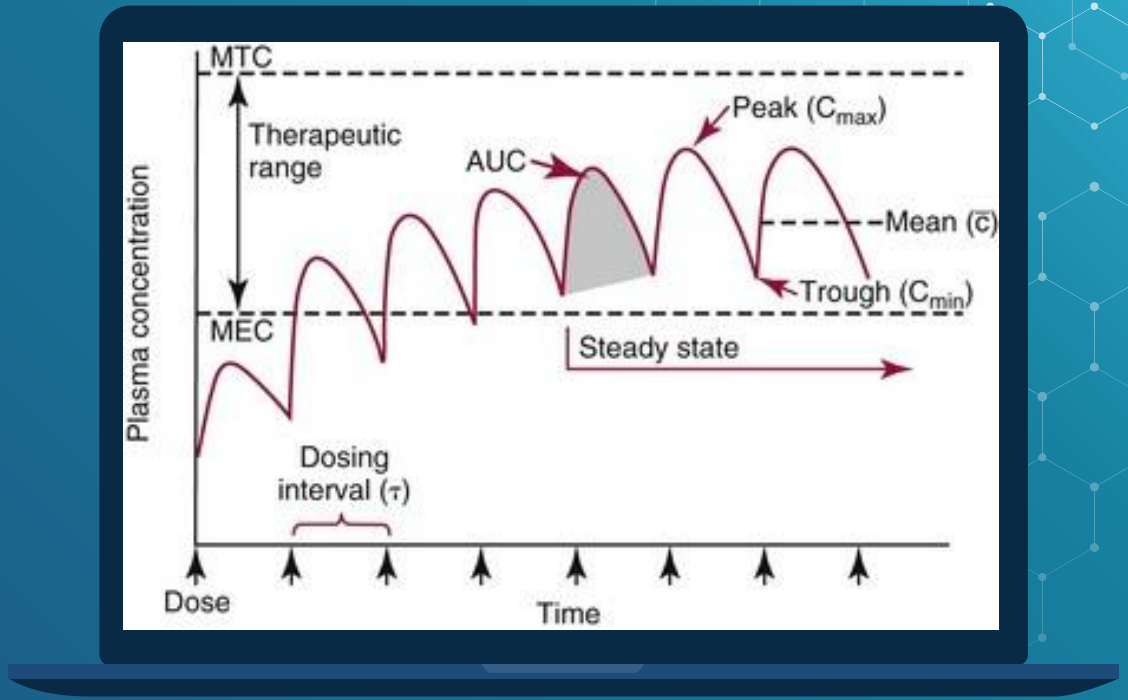
Rybak MJ, Le J, Lodise TP, et al. Therapeutic monitoring of vancomycin for serious methicillin-resistant Staphylococcus aureus infections: A revised consensus guideline and review by the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, the Pediatric Infectious Diseases Society, and the Society of Infectious Diseases Pharmacists. American Journal of Health-System Pharmacy. 2020;77(11):835-864. doi:10.1093/ajhp/zxaa036

DOSING STRATEGIES



CALCULATING AUC

$$AUC = \frac{(F * Dose)}{Cl}$$



2020. [online] Available at: <https://basicmedicalkey.com/therapeutic-drugs-and-their-management/> [Accessed 7 October 2020].

EMPIRIC DOSE WILL NOT CHANGE

STANDARD NOMOGRAM (PREDICTED TROUGH 10-15 mg/L)

(For routine use in skin/skin structure infections)

CrCl → (ml/min)	30 - 39	40 - 49	50 -59	60 -69	70 -79	80 -89	90 -99	100 – 109	≥ 110
40 – 49 kg	500 q24h	750 q24h	1000 q24h	500 q12h	500 q12h	500 q12h	750 q12h	750 q12h	1000 q12h
50 – 59 kg	500 q24h	750 q24h	1000 q24h	500 q12h	500 q12h	750 q12h	750 q12h	1000 q12h	1000 q12h
60 – 69 kg	750 q24h	1000 q24h	1250 q24h	500 q12h	750 q12h	750 q12h	1000 q12h	1000 q12h	1250 q12h
70 – 79 kg	750 q24h	1000 q24h	1500 q24h	750 q12h	750 q12h	1000 q12h	1000 q12h	1250 q12h	1250 q12h
80 – 89 kg	1000 q24h	1250 q24h	1500 q24h	750 q12h	1000 q12h	1000 q12h	1250 q12h	1250 q12h	1000 q8h
90 – 99 kg	1000 q24h	1250 q24h	750 q12h	1000 q12h	1000 q12h	1000 q12h	1500 q12h	1000 q8h	1000 q8h
100 – 109 kg	1000 q24h	1500 q24h	750 q12h	1000 q12h	1000 q12h	1250 q12h	1000 q8h	1000 q8h	1000 q8h
110 – 119 kg	1000 q24h	1500 q24h	750 q12h	1000 q12h	1000 q12h	1500 q12h	1000 q8h	1000 q8h	1000 q8h
120 – 129 kg	1250 q24h	750 q12h	1000 q12h	1000 q12h	1250 q12h	1000 q8h	1000 q8h	1000 q8h	1250 q8h
≥ 130 kg	1250 q24h	750 q12h	1000 q12h	1000 q12h	1250 q12h	1000 q8h	1000 q8h	1000 q8h	1250 q8h

"HIGH TARGET" NOMOGRAM: PREDICTED TROUGH 15-20 mg/L*

* Indications: Bacteremia; Osteomyelitis; Hospital-acquired pneumonia; Meningitis; or Endocarditis. For all other indications, use standard nomogram (target trough of 10-15 mg/L)

CrCl → (ml/min)	LOADING DOSE	30 - 39	40 - 49	50 -59	60 - 69	70 -79	80 -89	90 -99	100 – 109	≥ 110
40 – 49 kg	1000 mg	500 q24h	1000 q24h	1250 q24h (no load)*	500 q12h	750 q12h	750 q12h	1000 q12h	1000 q12h (no load)*	1000 q12h (no load)*
50 – 59 kg	1500 mg	750 q24h	1000 q24h	1500 q24h (no load)*	750 q12h	750 q12h	1000 q12h	1000 q12h	750 q8h	750 q8h
60 – 69 kg	1500 mg	1000 q24h	1250 q24h	1500 q24h (no load)*	750 q12h	1000 q12h	1000 q12h	1250 q12h	750 q8h	1000 q8h
70 – 79 kg	2000 mg	1000 q24h	1500 q24h	750 q12h	1000 q12h	1000 q12h	1250 q12h	1500 q12h	1000 q8h	1000 q8h
80 – 89 kg	2000 mg	1250 q24h	1500 q24h	750 q12h	1000 q12h	1250 q12h	1250 q12h	1000 q8h	1000 q8h	1250 q8h
90 – 99 kg	2000 mg	1500 q24h	750 q12h	1000 q12h	1000 q12h	1250 q12h	1000 q8h	1000 q8h	1250 q8h	1250 q8h
100 – 109 kg	2000 mg	1500 q24h	750 q12h	1000 q12h	1250 q12h	1500 q12h	1000 q8h	1000 q8h	1250 q8h	1500 q8h
110 – 119 kg	2000 mg	1500 q24h	1000 q12h	1000 q12h	1250 q12h	1000 q8h	1000 q8h	1250 q8h	1500 q8h	1500 q8h
120 – 129 kg	2000 mg	1500 q24h	1000 q12h	1250 q12h	1500 q12h	1000 q8h	1250 q8h	1250 q8h	1500 q8h	1500 q8h
≥ 130 kg	2000 mg	1500 q24h	1000 q12h	1250 q12h	1500 q12h	1000 q8h	1250 q8h	1250 q8h	1500 q8h	1500 q8h

*No loading dose indicated as maintenance dose is greater than indicated loading dose.

ONCE YOU REACH STEADY STATE…

Pharmacist needs to input values in all YELLOW BOXES.	Times
Time of Dose	1/1/19 1:00
End of Infusion Time	1/1/19 3:00
Time of Peak	1/1/19 4:30
Time of Trough **OR** Time of Trough + the time of dosing interval	1/1/19 12:30

Dosing Information		
Trough Level	14	
Peak Level	26	**Ideally 1.5 hours** after end of infusion
Dosing Interval	12	Must be 6, 8, 12, or 24 hours
Dose	1250	

Peak and Trough Estimated AUC		
Estimated AUC	**492**	Underestimation of AUC; This does not include the distribution phase of vancomycin
Estimated AUC	**533**	Overestimation of AUC; This does include the distribution phase of vancomycin
Average	**512**	

Screenshot above this point

Other Kinetic Information		
Time Between End of Infusion and Peak (hours)	1.5	Ideally ≥ 1.5 hours
Time Between Measured Peak and Trough (hours)	8	
Time of Infusion (hours)	2	
End of Infusion Peak	29.2	
Start of Infusion Peak	34	
Time from Start of Infusion to Peak	3.5	
True Trough	13.5	
Ke	0.077	
Volume of Distribution	66	
Half-life (hours)	9	If dosing interval is shorter than half-life, patient will accumulate vancomycin
Clearance	5.1	

Notes

Troughs: Collect 30 minutes before the next dose. Ensure trough is drawn correctly according to previous dose. Calculations may still be done if collected early or late

Peaks: Ideally **taken 1.5 hours** after end of infusion. Peaks taken before the 1 hour mark are not usable. Please order a STAT repeat peak.

LET'S PRACTICE

You are dosing vancomycin in a patient with MRSA bacteremia. Which of the following pharmacodynamic targets would provide the best balance of achieving clinical efficacy while minimizing nephrotoxicity?

- a. AUC target of 400-600 mg*h/L
- b. Trough of 15-20 mcg/mL
- c. Vancomycin dose achieving BOTH a trough of 15-20 mcg/mL and AUC of 400-550 mg*h/L
- d. AUC target of 600-800 mg*h/L

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LET'S PRACTICE

What is most significant adverse effect from vancomycin which justifies the reason for switching from trough based dosing to AUC clinical monitoring?

- A. Nausea
- B. Vancomycin Flushing Syndrome
- C. Nephrotoxicity
- D. Abdominal Pain

LET'S PRACTICE

What is most significant adverse effect from vancomycin which justifies the reason for switching from trough based dosing to AUC clinical monitoring?

- A. Nausea
- B. Vancomycin Flushing Syndrome
- **C. Nephrotoxicity**
- D. Abdominal Pain

LET'S PRACTICE

LC is a 39 year old male who weighs 67 kg who was started on vancomycin 1000mg IV q8h (2 hr infusion) for pneumonia and is clinically stable at this time with normal renal function. No concomitant nephrotoxins. A peak and trough level is obtained after the 4th dose and results are as follows:

Peak: 32.1 (Collection date: 3/9 @00:50), **Trough 16.2** (Collection date: 3/9@04:55)

Prior dose administered 3/8@21:33

Choose the most appropriate dose adjustment based on indication:

a. Continue Vancomycin 1000mg IV q8h

b. Vancomycin 1000mg IV q12h

c. Vancomycin 750mg IV q8h

CALCULATE YOUR AUC

Pharmacist needs to input values in all YELLOW BOXES.	Times
Time of Dose	3/8/20 21:33
End of Infusion Time	3/8/20 23:33
Time of Peak	3/9/20 0:50
Time of Trough **OR** Time of Trough + the time of dosing interval	3/9/20 4:55

Dosing Information		
Trough Level	16.2	
Peak Level	32.1	**Ideally 1.5 hours** after end of infusion
Dosing Interval	8	Must be 6, 8, 12, or 24 hours
Dose	1000	

Peak and Trough Estimated AUC		
Estimated AUC	**615**	Underestimation of AUC; This does not include the distribution phase of vancomycin
Estimated AUC	**736**	Overestimation of AUC; This does include the distribution phase of vancomycin
Average	**675**	

LET'S ADJUST OUR DOSE

- Since AUC and Dose is 1:1

$$AUC = \frac{(F * Dose)}{Cl}$$

$$\frac{\text{Total Daily Dose}}{\text{Current AUC}} = \frac{\text{Calculated New Total Daily Dose}}{\text{Desired AUC}}$$

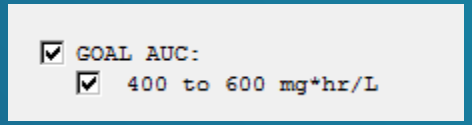
$$\frac{3000\ mg}{675} = \frac{(x?)}{500}$$

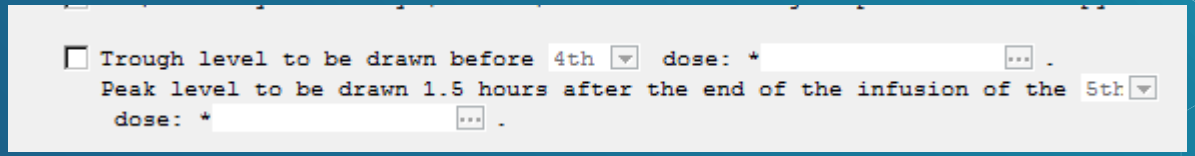
X = 2,222 mg Total Daily Dose

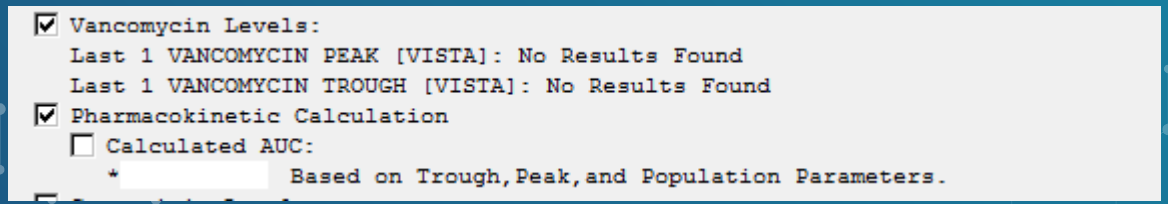
1) 750 mg q8h - (AUC = 506)
2) 1250 mg q12h - (AUC = 562.5)
3) 2000 mg q24h - (AUC = 450)
4) 1000 mg q12h - (AUC= 450)

***** Of Note, AUC dosing should NOT replace Clinical Judgment*****

DOCUMENTATION







DOCUMENTATION

☑ Modify regimen
☑ Adjusted Therapy to * based on predicted AUC
* calculation.

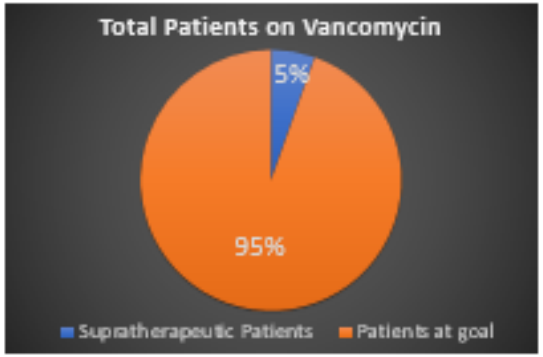
☑ Repeat trough level before 4th dose: * .
Pharmacy will follow up.
1. Choose this option for vancomycin (initial dosing, or in f/u note if dose changed)
2. Standard is before 4th dose, can adjust for conventience (e.g. can wait longer if pt at low risk for toxicity).
☑ Repeat peak level 1.5 hours after end of the 5th infusion dose: * .
Pharmacy will follow up.
☑ Repeat trough level in 3 to 5 days (next trough *16-Oct-2020 19:54)(sooner if change in renal function).
Repeat peak level in 3 to 5 days (next peak *16-Oct-2020 19:54 .

STANDARD VANCOMYCIN ADMINISTRATION TIMES

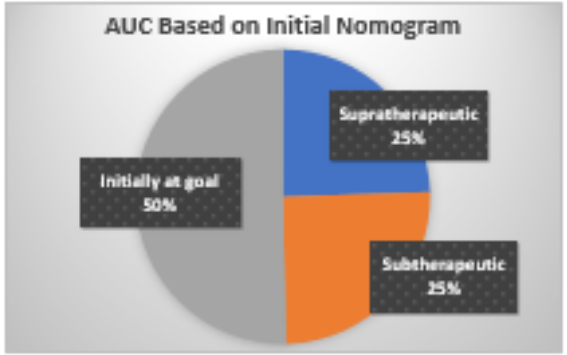
Q8H Dosing will be as follows (0500-1300-2100)
Q12H Dosing will be as follows (0500-1700)
Q24H Dosing will be as follow (0500)

GO-LIVE November 16th , 2020

DATA COLLECTION



PRE-IMPLEMENTATION



POST IMPLEMENTATION

IMPLEMENTATION ISSUES

- Lab draws
  - Peak and troughs
  - Hard sticks
- Inconsistent renal adjustment calculation
- Interdisciplinary team turnover
- Potential for User Errors

SEEKING SUSTAINABLE SOLUTIONS

- Bayesian Equation Approaches
  - InsightRx
  - Precise Rx
  - DoseMe Rx
  - APK/Rx Kinetics
  - Best Dose

SEEKING SUSTAINABLE SOLUTIONS

InsightRX | NOVA

Product sheet

Deliver higher quality care **with model-informed precision dosing.**

What's better than software that helps you optimize your dosing practice today? Knowing it will continue to improve over time.

InsightRX Nova

Individualize dosing with precision dosing software that improves over time, helping you achieve clinical targets to improve treatment efficacy and reduce adverse events.*

Why choose InsightRX Nova?

Designed by pharmacists, for pharmacists
View the most important information when and where you need it for seamless integration into your daily workflow.

Quality and rigor you can trust
Trust that dosing predictions are generated with models that have been scientifically verified and externally validated to exacting standards.

Your practice = best practice
Future-proof your dosing practice with automatic access to the most up-to-date, clinically validated models curated from the literature.

A continuously learning dosing system
Improve dosing accuracy over time with new and updated models developed using real-world data from the InsightRX network.

Find the right dose faster

Improve patient outcomes with a comprehensive clinical decision support system that goes well beyond a simple dosing calculator.

InsightRX Nova

Leap ahead into data-driven patient care with a suite of powerful tools designed to seamlessly incorporate model-informed precision dosing into clinical practice. Key features include:

DoseAssist™
Eliminate repetitive, trial-and-error data entry with the first and only precision dosing system to suggest regimens predicted to meet PK targets*.

Efficacy and toxicity assessments
Adopt outcomes-based treatment with individualized, evidence-based probability estimates of efficacy and toxicity.

88 %	20 %	12%
66 %	1 %	6 %
66 %	3 %	6 %
66 %	2 %	7 %

Real-time PK advisories
Avoid medication errors with real-time notifications of poor PK model fit, possible data misentry, and other potential risks to patient safety.

EHR integration
Streamline clinical workflow with integration via Epic App Orchard, Cerner App Gallery, or custom API, as well as through Premier Inc.'s TheraDoc clinical surveillance system.

"Overall, InsightRX was the easiest to use, the most visually appealing, best technical and customer support, and most likely to be continually improved to maximize customer experience and improve pharmacokinetic estimation."

Turner et al. Pharmacotherapy. 2018;38(12):1174-1183.

Ready to transform your pharmacy practice?

Visit us at **www.insightrx.com** or email us at **sales@insightrx.com**.

*Available for vancomycin and other select modules

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San Francisco, CA 94104

Insight RX

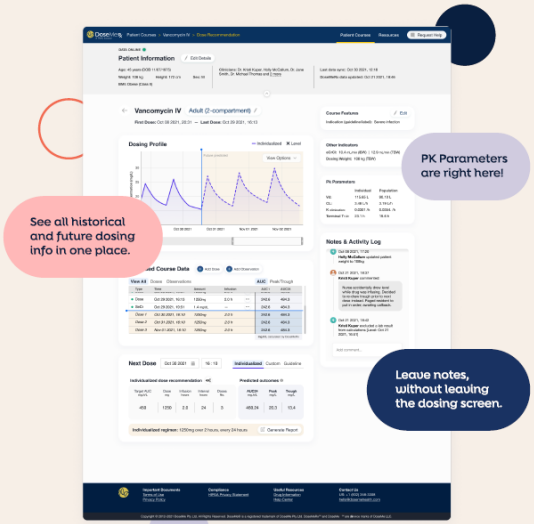
The essential step on your journey to new horizons.

www.insightrx.com
sales@insightrx.com

SEEKING SUSTAINABLE SOLUTIONS

Meet DoseMeRx 2.0

So, what's new?



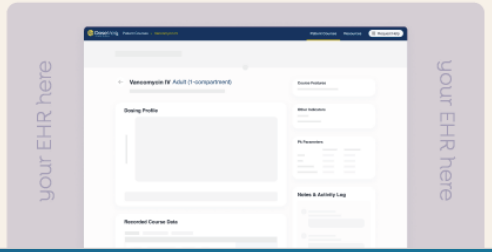
DoseMeRx
A 7RHC Solution

Everything is right there, in one place.

It's easy to discover different features and information, all from a single screen:

- Patient information is right there
- Dosing plot is right there
- Course data is right there
- PK parameters data is right there
- Course notes and activity log is right there
- Next dose calculation is right there

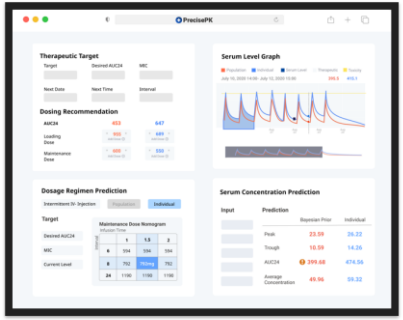
Cerner Epic Sentri7® VigiLanz Ilum Insight



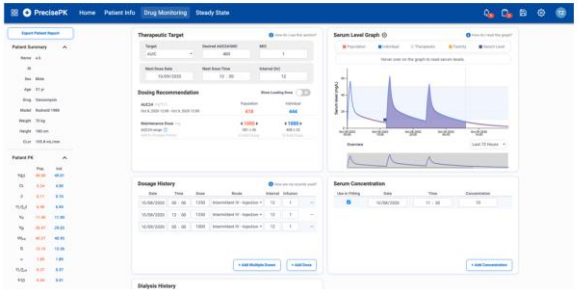
SEEKING SUSTAINABLE SOLUTIONS

PrecisePK
A PreciseRX product

Validated, by independent, peer-reviewed research, as the **most accurate Vancomycin AUC Bayesian Dosing** Software



Quick dosing based on AUC targets using Bayesian and Population models



A growing drug model library featuring Bayesian forecasting for individualized dosing

- **Amikacin**
- **Busulfan**
- Carboplatin
- Ciprofloxacin
- Digoxin
- Flucytosine
- **Gentamicin**
- Levofloxacin/ofloxacin
- Lithium
- Phenobarbital
- **Piperacillin (Beta-Lactam)**
- Phenytoin
- Procainamide
- Quinidine
- Theophylline/aminophylline
- **Tobramycin**
- Valproic acid
- **Vancomycin**
- **Voriconazole**

Coming soon:

- Tacrolimus
- Methotrexate
- Cyclosporine
- Sirolimus
- Carbamazepine
- Everolimus
- Infliximab

Superior Precision Dosing

When compared to reference AUC using a single trough serum blood level, PrecisePK was evaluated among a handful of different software as **the most accurate and least biased Bayesian precision dosing software** according to an independent research study conducted in 2018 (Turner et al.)

The graph on the right shows the ratio of the AUC as predicted by the program and AUC obtained empirically. The ratio close to 1.00 signifies a perfect prediction. PrecisePK was the only program consistently showing a ratio close to perfect 1.00 mark.

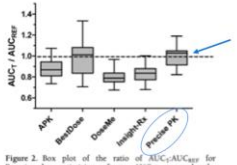


Figure 2. Box plot of the ratio of AUC_T:AUC_{REF} for Bayesian dose-optimizing software. AUC = area under the curve; AUC_T = estimated AUC when using only the trough value; AUC_{REF} = AUC calculated by the linear-log trapezoidal rule using the full data set.

PrecisePK's Vancomycin Advantage

PrecisePK is fully compliant with the latest IDSA 2020 guidelines. It includes all the models related to all types of patients and patient cases, including:

- Obese
- Critically-ill (ICU)
- Neonates
- Pediatrics
- Renal Impairment
- Hemodialysis etc.

PrecisePK **automatically adjusts and selects the most appropriate model** based on the patient characteristics, while giving full transparency and control to the users to change the parameters and models

NEXT STEPS...

- Finalize solution
- Implement new solution
- Onboard current staff
- Quality improvement

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THANK YOU

ANY QUESTIONS?

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