Reducing duration of vancomycin for pneumonia with MRSA nasal polymerase chain reaction (PCR)

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“I have had no financial relationship over the past 12 months with any commercial sponsor with a vested interest in this presentation”

Case 1

- **HPI:** Patient is a 67 year-old male who was admitted with an acute exacerbation of heart failure and AKI. On the sixth day of hospitalization, he developed a fever, chills, and productive cough. Chest x-ray indicated a LLL infiltrate. He was subsequently diagnosed with hospital acquired pneumonia. The patient has not had antibiotics in the last year and review of previous microbiology records was unrevealing for MDR organisms.
- **PMH**: hypertension, hyperlipidemia, heart failure (EF 30%), COPD, diabetes mellitus
- **SH**: smoker (1 ppd x 30 years)
- **Allergies**: NKDA
- **VS**: Ht 5'7", Wt 60kg, T 101.1^{o}F, P 99 bpm, BP 115/75 mmHg, RR 22 breaths/min, O_2 sat 89%
- **Labs:** WBC 17.1, Creatinine 0.9 mg/dL
- **Microbiology**: Sputum culture ordered
- **Antibiotic orders**: cefepime 2 g IV q8H, vancomycin 1500 mg IV x 1, then pharmacy to dose

Case 1: Questions to think about…

1. Does this patient really need vancomycin?
2. Is there any diagnostic testing that can help us figure this out?

Case 1

Any MRSA risk factors?

- IV antibiotic use in last 90 days
- High local prevalence of MRSA
- Long length of hospitalization
  - 5 days or more
- Known history of MRSA colonization or infection
- Intravenous drug use
- Necrotizing pneumonia
- Ill-appearing patient with recent stay in nursing home or long-term care facility

Would testing MRSA Nasal PCR help?

Let's look at the evidence.

Kalil et al. Clin Infect Dis 2016
Wooten et al. Respir Med 2013
Dangerfield et al. Antimicrob Agents Chemother 2014

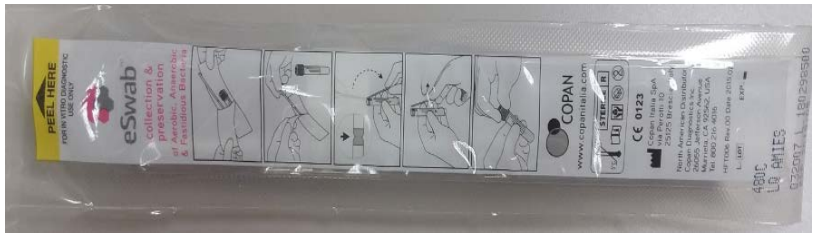
MRSA Nasal PCR and Pneumonia: Key references

- Parente DM, et al. *Clin Infect Dis* 2018;67(1):1-7.
- Baby N, et al. *Antimicrob Agents Chemother* 2017; 61(4): e02432-16.
- Willis C, et al. *Am J Health-Syst Pharm* 2017; 74:1765-73.

	Study population	Intervention	Key Findings
Parente 2018	Meta-analysis 22 studies n = 5243 CAP, HCAP, VAP Prevalence of MRSA PNA = 10%	Screening by both nasal culture and PCR	**All types:** Sensitivity 70.9%, Specificity 90.3%, PPV 44.8%, NPV 96.5% **CAP/HCAP:** Sensitivity 85%, Specificity 92.1%, PPV 56.8%, NPV 98.1% VAP: Sensitivity 40.3%, Specificity 93.7%, PPV 35.7%, NPV 94.8%
Baby 2017	Retrospective 57 patients (27 pre-PCR, 30 PCR protocol) CAP, HCAP, HAP	PCR per pharmacy-driven protocol; vancomycin or linezolid for pneumonia	Pre-PCR vs PCR: Reduced duration of empiric MRSA-targeted agents: 74 h vs 27.4 h, $p < 0.0001$ Reduced % patients with a vancomycin level: 48.1% vs 16.7%, $p = 0.02$ Days to clinical improvement, LOS, mortality: No difference Less AKI, 26% vs 3.3%, $p = 0.02$
Willis 2017	Retrospective 300 patients (150 pre-PCR, 150 PCR protocol) CAP, HCAP, HAP, AECOPD	PCR per pharmacy-driven protocol; vancomycin for pneumonia or AECOPD	Pre-PCR vs PCR: Reduced duration of vancomycin: 4.2 vs 2.1 days of therapy, $p < 0.0001$ Reduced median vancomycin levels: 2 vs 1, $p < 0.0001$ Days to clinical improvement, AKI, LOS, mortality: no difference 55.2% of patients with neg PCR had vancomycin stopped within 24h

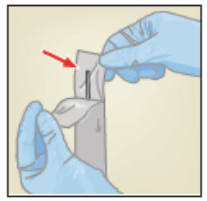
MRSA PCR: Nurse obtains STAT sample

Follow directions below—making sure to swab both nostril openings and not swab past the point of resistance, only swabbing right inside of the nostrils

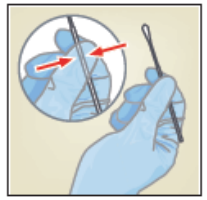


1 Open the package that contains the swab and transport medium tube. Set the tube aside before collecting the specimen.

2 Open the swab wrapper and remove the swab, taking care not to touch the tip of the swab to any surface.

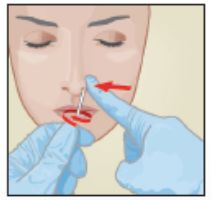


3 Hold the swab in your hand, pinching in the middle of the swab shaft on the scoreline.



4 Rotate swab against the inside of the nostril for 3 seconds while applying pressure with a finger to the outside of the nostril.

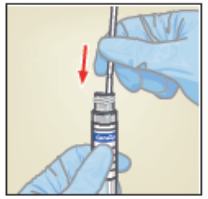
Do not insert the swabs more than 1-1.5 cm.



5 Repeat Step 4 on the other nostril with the same swab.

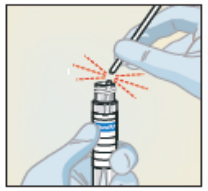
To avoid specimen contamination, do not touch the swab tip to anything after collecting the specimen.

6 Remove the cap from the tube. Insert the swab into the transport medium.



7 Break the swab shaft against the side of the tube at the scoreline.

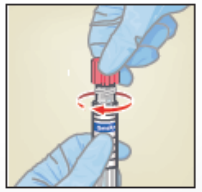
Avoid splashing contents on the skin. Wash with soap and water if exposed.



8 Replace the cap on the tube and close tightly.

Specimen should be transported at 2-8 °C.

Prior to testing, specimen may be stored for 24 hours at 15–30 °C or up to 7 days at 2-8 °C



Case 1

- Vancomycin dosing consult initiated
- MRSA Nasal PCR ordered by pharmacy per protocol
- Vancomycin loading dose given while awaiting results of PCR test
- Within three hours of the order, MRSA nasal PCR reported as NEGATIVE

- What antimicrobial stewardship recommendation should be made?
  - Discontinuation of vancomycin is reasonable

Case 1:

48 hours from culture procurement, the patient's sputum culture returns with growth of *Pseudomonas aeruginosa*, with the following susceptibilities:

- cefepime (S)
- ciprofloxacin (R)
- levofloxacin (R)
- meropenem (S)
- piperacillin-tazobactam (S)

- Remains on cefepime monotherapy (day 3)
- Patient has shown significant improvement and plan is 7 days of total therapy

- **Biggest impact: Vancomycin X 1 dose**
  - **Limited exposure**
  - **No trough necessary**
  - **Minimal monitoring and follow up required due to vancomycin**

Case 2

- **HPI:** Patient is a 75 year-old female nursing home resident admitted with suspicion of pneumonia due to fever, chills, and productive cough. Chest x-ray indicated a LLL infiltrate. The patient received ciprofloxacin 3 months ago for a urinary tract infection (*E. coli*)but review of previous microbiology records was unrevealing for MDR organisms.
- **PMH**: hypertension, hyperlipidemia, diabetes mellitus, and osteoarthritis.
- **Allergies**: NKDA
- **VS**: Ht 5' 4", Wt 70 kg, T 101.7^{o}F, P 105 bpm, BP 127/91 mmHg, RR 24 breaths/min, O_2 sat 90%
- **Labs:** WBC 15.1, Creatinine 0.9 mg/dL
- **Microbiology**: Sputum culture ordered
- **Antibiotic orders**: Piperacillin-tazobactam 4.5 g IV q6H, vancomycin 1500 mg IV x 1, then pharmacy to dose

Case 2: Same questions…

Any MRSA risk factors?

- IV antibiotic use in last 90 days
- High local prevalence of MRSA
- Long length of hospitalization
  - 5 days or more
- Known history of MRSA colonization or infection
- Intravenous drug use
- Necrotizing pneumonia
- Ill-appearing patient with recent stay in nursing home or long-term care facility

Would testing MRSA Nasal PCR help?

Seems justified

Kalil et al. Clin Infect Dis 2016
Wooten et al. Respir Med 2013
Dangerfield et al. Antimicrob Agents Chemother 2014

Case 2

- Vancomycin dosing consult initiated
- MRSA Nasal PCR ordered by pharmacy per protocol
- Vancomycin loading dose given while awaiting results of PCR test
- Within three hours of the order, MRSA nasal PCR reported as POSITIVE

- Any antimicrobial stewardship recommendation to be made here?
  - Due to low Positive Predictive Value, need for vancomycin still unclear
  - Suggest continue vancomycin pending culture results

Case 2:

48 hours from culture procurement, the patient's sputum culture returns with growth of *E. coli*, with the following susceptibilities:

- ampicillin-sulbactam (R)
- cefepime (S)
- ceftriaxone (S)
- ciprofloxacin (R)
- levofloxacin (R)
- meropenem (S)
- piperacillin-tazobactam (S)

- Patient has shown significant improvement and plan is 7 days of total therapy

- Any other antimicrobial stewardship recommendation(s) to be made?
  - Does vancomycin need to continue due to positive MRSA nasal PCR?

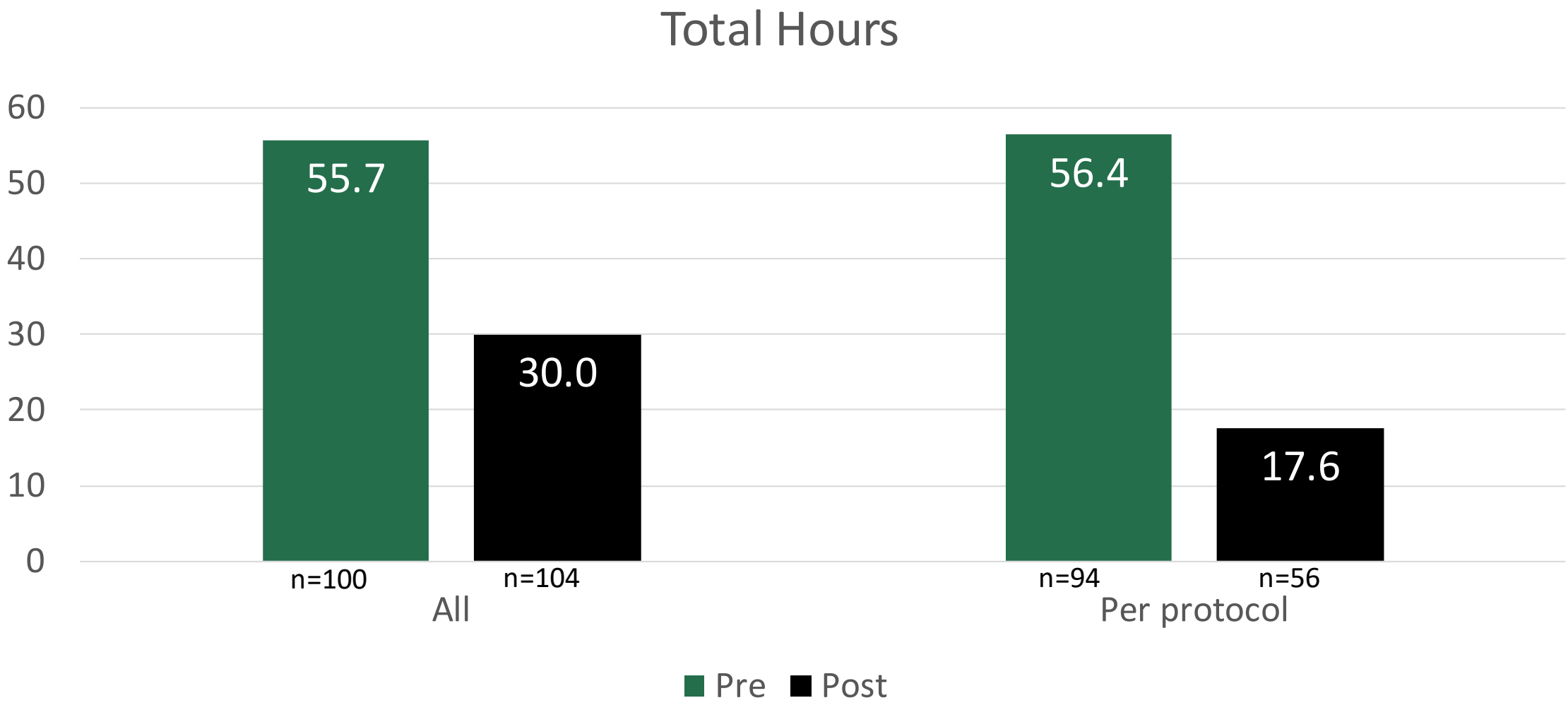
  - Likely not. Positive MRSA nasal PCR may merely represent colonization.

Outcomes of a pharmacist driven methicillin-resistant staphylococcus aureus (MRSA) surveillance protocol using polymerase chain reaction (PCR) technology

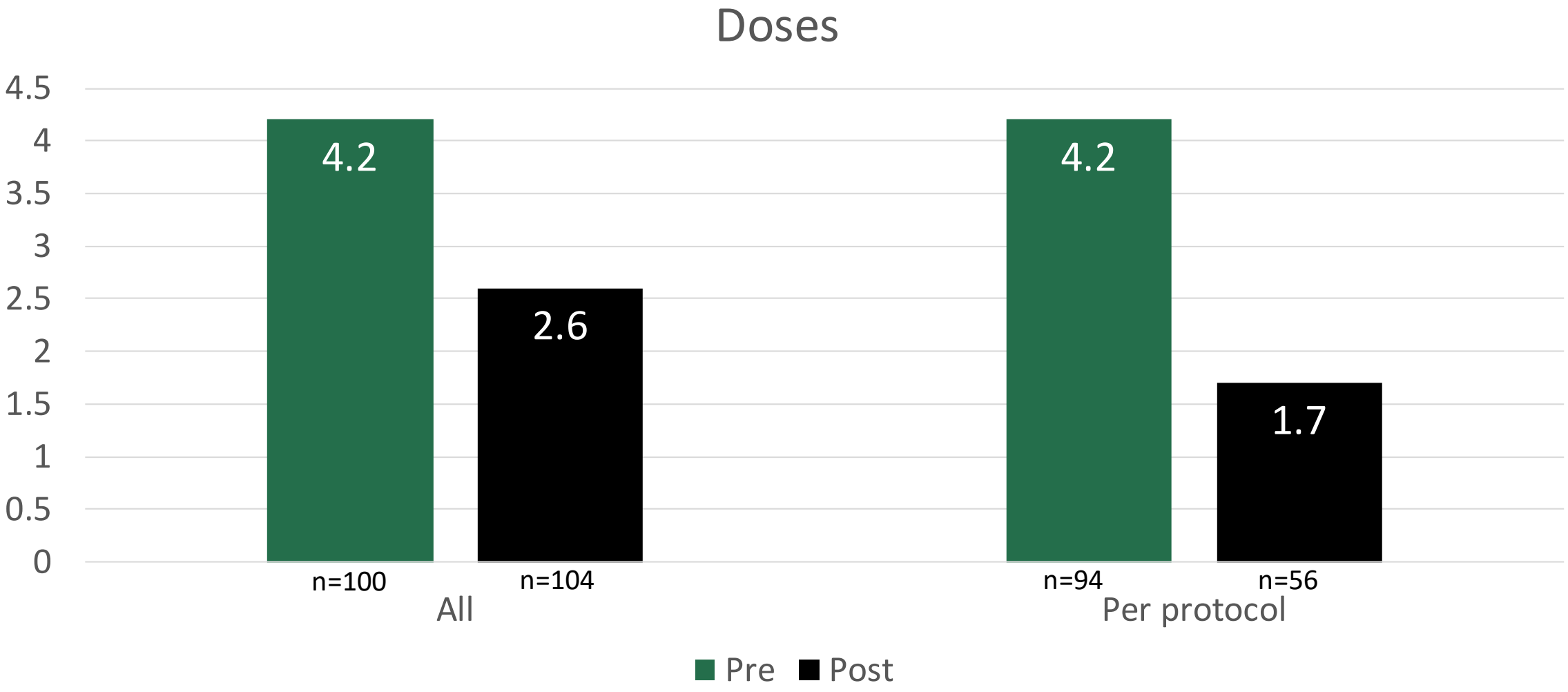
Kevin Wintz
PGY1 Pharmacy Resident
Avera McKennan Hospital and University Health Center
Sioux Falls, SD

Avera

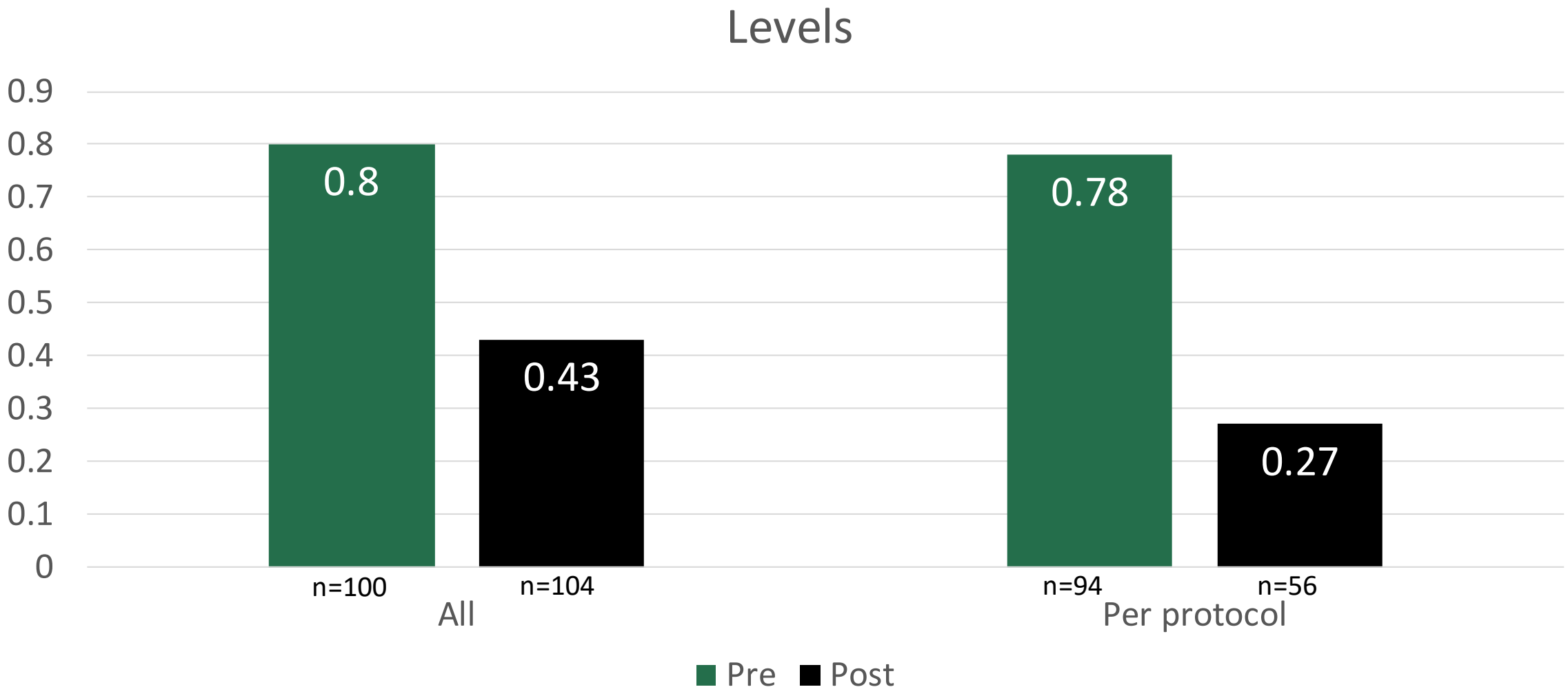
Primary Outcome



Secondary Outcome



Secondary Outcome



Secondary Outcomes

Secondary Outcome	Pre-Protocol (n=100)	Post-Protocol (n=104)	P Value
In hospital mortality	n=14	n=17	0.7
Length of stay	8.6 days	7.9 days	0.53
Δ Serum creatinine	-0.255 (n=75)	-0.035 (n=85)	0.019
MRSA + culture (respiratory or blood)	n=4	n=2	0.41

Take home points…

- Due to the high negative predictive value, MRSA nasal PCR can be a useful tool
  - Reduced vancomycin duration, doses and levels
  - No apparent negative impact
- Positive MRSA nasal PCR results have poor positive predictive value and may merely represent colonization

- Ongoing questions
  - How long to we consider someone “negative” after a negative MRSA nasal PCR test?
    - 7 days?
  - How often will we see a negative MRSA nasal PCR test but positive culture results for MRSA?
    - Probably depends on prevalence
  - Can MRSA nasal PCR testing be used to rule out MRSA for infections other than pneumonia?
    - Some data for bloodstream, skin/soft tissue, bone/joint, UTI, Intra-abdominal
    - Data not as strong

AUC-Based Dosing of Vancomycin

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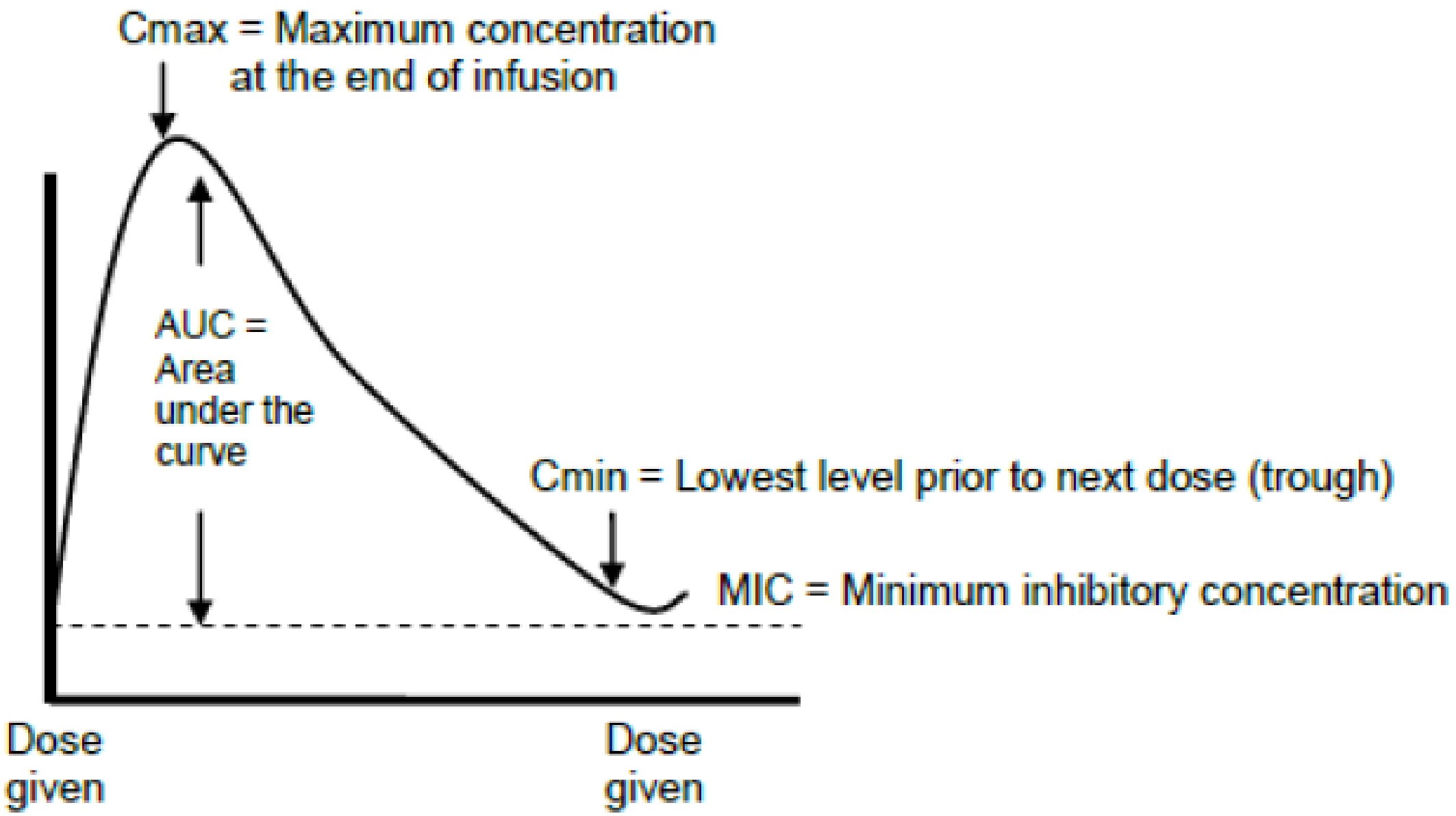
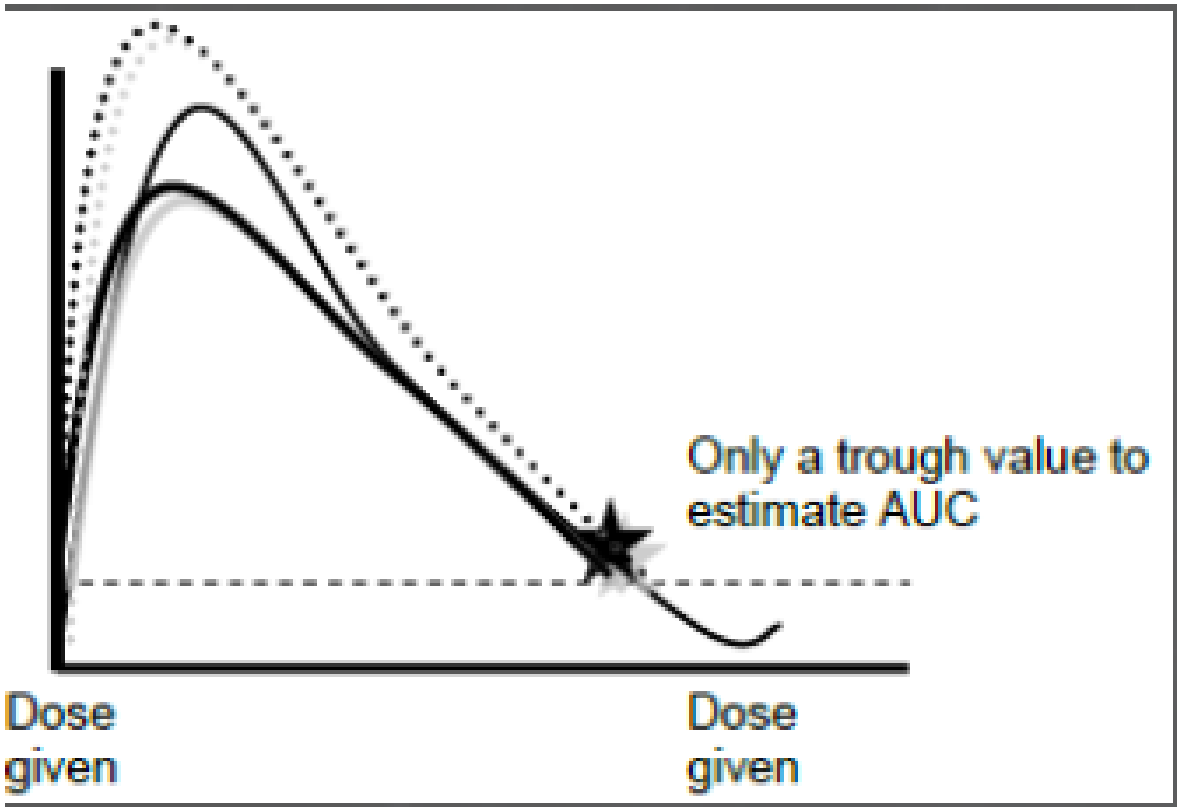

Cmax = Maximum concentration
at the end of infusion
AUC =
Area
under the
curve
Cmin = Lowest level prior to next dose (trough)
MIC = Minimum inhibitory concentration
Dose
given
Dose
given

2009 Vancomycin Dosing Guidelines

- Concentrations
  - AUC/MIC ratio $\geq$ 400 mg*h/L is the target for effectiveness
    - Mainly based on *S. aureus* pneumonia data
  - Troughs are a practical surrogate
  - Troughs before 4th dose
  - Troughs should be > 10 mg/L to avoid resistance development
    - Goal trough 15 – 20 mg/L for bacteremia, endocarditis, osteomyelitis, meningitis and pneumonia

Rybak MJ, et al. AJHP 2009
Moise-Broder, et al. Clin Pharmacokinet 2004

The problems with trough-only monitoring…



- Troughs only measure one concentration at a specific time
- Dosing curves can look different but result in the same trough
  - Size of dose
  - Elimination rate
- Often a trough of 15 mcg/mL is NOT necessary to achieve an adequate AUC/MIC of 400 mg*h/L

Patel N, et al. Clin Infect Dis 2011
Neely MN, et al. Antimicrob Agent Chemother 2013

The problems with trough-only monitoring…

- Limited data to suggest a target trough of 15 – 20 mg/L improves efficacy
- Troughs $\geq$ 15 mg/L associated with increased risk of acute kidney injury (AKI) compared to troughs < 15 mg/L in one meta-analysis
  - OR 2.76 (95% CI, 1.94 – 3.93)
- Several studies suggest higher rates of AKI when daily AUC/MIC exceeds 700 – 1300 mg*h/L

Van Hal SJ, et al. Antimicrob Agent Chemother 2013
Suzuki Y, et al. Chemotherapy 2012
Lodise TP, et al. Clin Infect Dis 2009

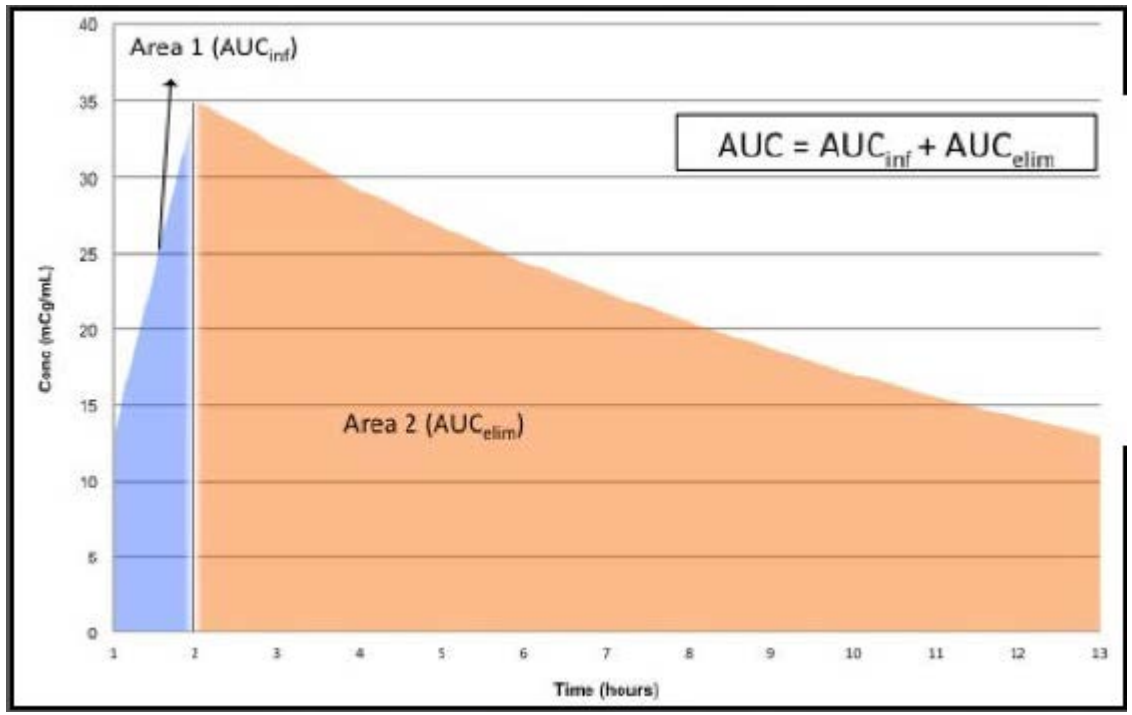
Proposed Update to 2009 Vancomycin Dosing Guidelines

Summary and Recommendations:

1. Based on the current body of evidence of vancomycin PK/PD and clinical outcomes in patients with serious MRSA infections, a Bayesian-derived AUC/MIC_{BMD} ratio of 400 to 600 (assuming a vancomycin MIC_{BMD90} of 1 mg/L) should be advocated as the target to achieve clinical efficacy while improving patient safety **(IA+)**.

5. Trough only monitoring, with target between 15-20 mg/L, is no longer recommended for patients with serious infections due to MRSA **(IIB-).**

So how are we going to do this???



Predicted steady-state AUC_{24}

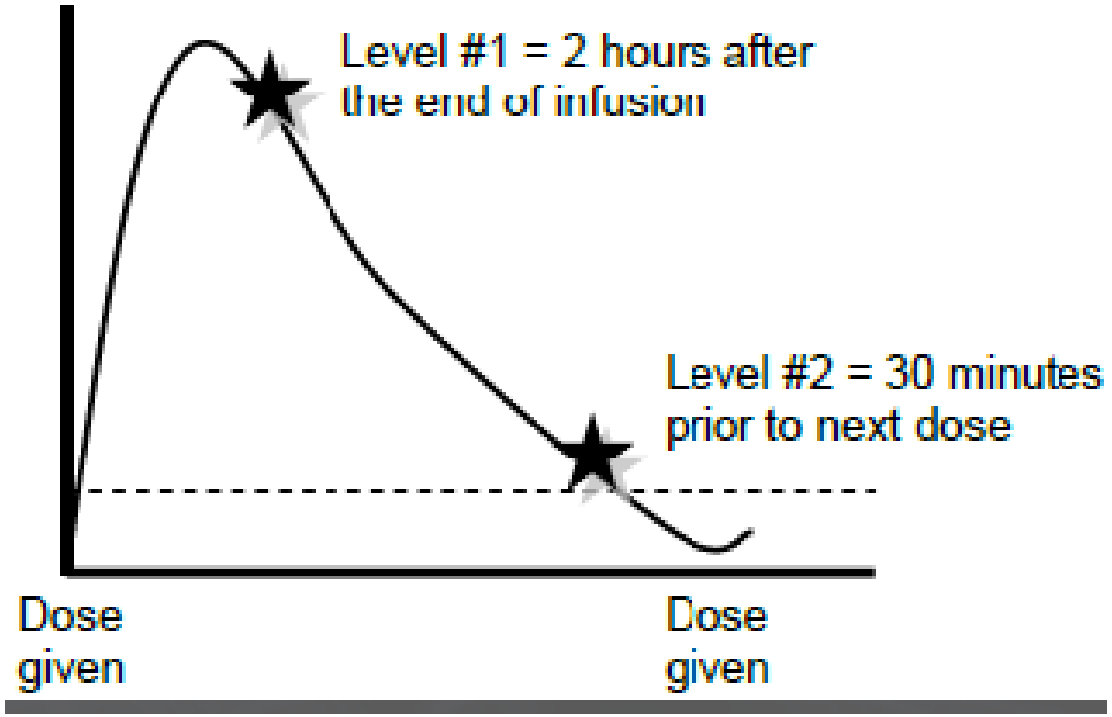
$$AUC_{24} = (AUC_{inf} + AUC_{elim}) \times (24/\tau au)$$

$$AUC_{inf} = \frac{(C_{max} + C_{min})}{2} \times t$$

$$AUC_{elim} = \frac{(C_{max} - C_{min})}{Ke}$$

- Excel-based calculators (homegrown)
- Calculator built into EMR
- Bayesian software
- Various on-line calculators

Calculation with Excel



- Will require 2-level sampling, at least to confirm initial dose
- Levels will be used to calculate relevant parameters necessary to determine AUC
- Once dose established, should be able to do once weekly trough monitoring if renal function stable

Vancomycin Dosing Nomogram A for AUC24 400 - 600 mg*h/L (target: 500 mg*h/L)

***Notes:**

1) This nomogram is NOT intended for use in patients with unstable renal function or acute kidney injury - track creatinine changes closely!

2) Intended for use in patients with total body weight between 40 kg and 140 kg and CrCl ≥ 30 mL/min

3) Assumes maximum CrCL of 140 mL/min

4) All doses are in mg

BMI < 40

	CrCl (mL/min)												
Wt (kg)	**30**	**40**	**50**	**60**	**70**	**80**	**90**	**100**	**110**	**120**	**130**	**140**	Loading Dose
120	1000q24	1500q24	1000q12	1000q12	1000q8	1000q8	1000q8	1000q8	1000q6	1000q6	1000q6	1000q6	2000
110	1000q24	1500q24	1000q12	1000q12	1000q12	1000q8	1000q8	1000q8	1000q8	1000q6	1000q6	1000q6	2000
100	1000q24	1250q24	750q12	1000q12	1000q12	1000q12	1000q8	1000q8	1000q8	1000q6	1000q6	1000q6	2000
90	1000q24	1250q24	750q12	750q12	1000q12	1000q12	1000q12	1000q8	1000q8	1000q8	1000q6	1000q6	1750
80	750q24	1000q24	1000q24	750q12	1000q12	1000q12	1000q12	1000q12	1000q8	1000q8	1000q8	1000q8	1750
70	750q24	1000q24	1000q24	750q12	750q12	750q12	1000q12	1000q12	1000q12	750q8	1000q8	1000q8	1500
60	500q24	750q24	1000q24	1000q24	750q12	750q12	750q12	1000q12	1000q12	1000q12	750q8	750q8	1250
50	500q24	750q24	750q24	1000q24	1000q24	500q12	750q12	750q12	750q12	1000q12	750q8	750q8	1000
40	500q24	500q24	750q24	750q24	750q24	500q12	500q12	500q12	750q12	750q12	500q8h	500q8h	1000

BMI ≥ 40

	CrCl (mL/min)												
Wt (kg)	**30**	**40**	**50**	**60**	**70**	**80**	**90**	**100**	**110**	**120**	**130**	**140**	Loading Dose
140	1000q24	1500q24	1750q24	1000q12	1000q12	1250q12	1000q8	1000q8	1000q8	1000q6	1000q6	1000q6	2000
130	1000q24	1250q24	1500q24	1000q12	1000q12	1250q12	1000q8	1000q8	1000q8	1000q6	1000q6	1000q6	2000
120	1000q24	1250q24	1500q24	1750q24	1000q12	1000q12	1250q12	1000q8	1000q8	1000q8	1000q6	1000q6	2000
110	1000q24	1000q24	1250q24	1500q24	1000q12	1000q12	1000q12	1250q12	1000q8	1000q8	1000q8	1000q6	2000
100	750q24	1000q24	1250q24	1500q24	750q12	1000q12	1000q12	1250q12	1250q12	1250q12	1000q8	1000q8	2000
90	750q24	1000q24	1000q24	1250q24	750q12	1000q12	1000q12	1000q12	1250q12	1250q12	1000q8	1000q8	1750

*****NEXT STEP: DETERMINE PATIENT-SPECIFIC AUC24 USING EMPIRIC VANCO DOSING CALCULATOR*****

	A	B	C	D	E	F	G	H	I
1	**Vanco Predictive Kinetics**								
2	**Estimated CrCl**	100	mL/min						
3	Predicted Ke	0.087	h-1						
4	Predicted half-life	7.9	hours						
5									
6	**Predict doses / variables**								
7	Weight	100	kg						
8	Infusion Duration	1.5	hours						
9	Dose	1000	mg						
10	Interval	8	hours						
11	Vd conversion factor* (dropdown)	0.7	liters/kg						
12	Vd estimate	70	liters						
13	Ke	0.087	hours-1						
14	Half Life	7.9	hours						
15	Predicted CpMax	26.6	mcg/ml						
16	Predicted CpMin	15.1	mcg/ml						
17									
18	CpMax (mcg/mL)	CpMin (mcg/mL)	Infusion Duration (h)	AUC inf	Ke h-1	Interval (h)	AUCelim	**AUC 24**	
19	26.6	15.1	1.5	31.3	0.087	8	132.0	489.8	
20									
21	*Suggest Vd conversion factor of 0.7 L/kg if BMI < 30, 0.6 L/kg if BMI 30 - 40, and 0.5 L/kg if BMI > 40								
22									
23	Formula Cells - No changes								
24	Default Cells - Can be changed								
25	Data Cells - Manually entered								

*****Empiric Dosing Calculator*****

Goal AUC 24: 400 - 600 mg*h/L

Targets:
500 mg*h/L for most infections including bacteremia
600 mg*h/L for CNS infections

Vancomycin Peak/Trough at Steady State

Patient Specific Kinetics

Scheduled infusion duration	1.5	hour(s)
Dose	1500	mg
Interval	12	hours
Time from end of infusion to 1st level (Peak)	1.5	hours
Drawn 1st Level (Peak)	35	mcg/ml
Drawn 2nd Level (Trough)	16	mcg/ml
Time between 1st & 2nd Level	8	hours
Ke	0.098	hours-1
Half Life	7.1	hours
CpMax	40.5	mcg/ml
CpMin	14.5	mcg/ml
Vd	49.8	Liters

2-Level Dosing Calculator at Steady-State

THIS CALCULATOR IS PREFERRED FOR BLOODSTREAM AND CNS INFECTIONS

Goal AUC 24: 400 - 600 mg*h/L

Targets:
500 mg*h/L for most infections including bacteremia
600 mg*h/L for CNS infections

CpMax (mcg/mL)	CpMin (mc	Infusion Duration (h)	AUC inf	Ke h-1	Interval (h)	AUCelim	AUC 24
40.5	14.5	1.5	41.3	0.098	12	266.0	614.5

Adjustment Equations

Infusion Duration	1.5	hours
Dose	1250	mg
Interval	12	hours
Vd	49.8	Liters
Ke	0.098	hours-1
Predicted CpMax	33.8	
Predicted CpMin	12.1	

CpMax (mcg/mL)	CpMin (mc	Infusion Duration (h)	AUC inf	Ke h-1	Interval (h)	AUCelim	AUC 24
33.8	12.1	1.5	34.4	0.098	12	221.6	512.1

Formula Cells - no changes
Default Cells - Can be changed
Data Cells - Manually entered

Potential pitfalls…

- Potential for increased resource utilization
  - Drug concentrations
  - Pharmacist time in evaluation
- Education/awareness
  - Breaking the “trough of 15 - 20 mg/L” mindset
  - Re-familiarize all staff with vancomycin peaks again
- Transitions of care
  - Will this be realistic outside of the acute care setting?

Questions?