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°F, P 99 bpm, BP 115/75 mmHg, RR 22 breaths/min, O₂ 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.

Wooten et al. Respir Med 2013
MRSA Nasal PCR and Pneumonia: Key references

<table>
<thead>
<tr>
<th>Study population</th>
<th>Intervention</th>
<th>Key Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Parente 2018</strong></td>
<td>Meta-analysis 22 studies&lt;br&gt;n = 5243&lt;br&gt;CAP, HCAP, VAP&lt;br&gt;Prevalence of MRSA PNA = 10%</td>
<td>Screening by both nasal culture and PCR</td>
</tr>
<tr>
<td><strong>Baby 2017</strong></td>
<td>Retrospective 57 patients&lt;br&gt;(27 pre-PCR, 30 PCR protocol)&lt;br&gt;CAP, HCAP, HAP</td>
<td>PCR per pharmacy-driven protocol; vancomycin or linezolid for pneumonia</td>
</tr>
<tr>
<td><strong>Willis 2017</strong></td>
<td>Retrospective 300 patients&lt;br&gt;(150 pre-PCR, 150 PCR protocol)&lt;br&gt;CAP, HCAP, HAP, AECOPD</td>
<td>PCR per pharmacy-driven protocol; vancomycin for pneumonia or AECOPD</td>
</tr>
</tbody>
</table>
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°F, P 105 bpm, BP 127/91 mmHg, RR 24 breaths/min, O₂ 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

Wooten et al. Respir Med 2013
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

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PGY1 Pharmacy Resident
Avera McKennan Hospital and University Health Center
Sioux Falls, SD
Secondary Outcome

Doses

- All: n=100, Pre = 4.2, Post = 2.6
- Per protocol: n=94, Pre = 4.2, n=56, Pre = 1.7

Legend: Pre, Post
Secondary Outcome

Levels

- All: n=100, Pre = 0.43, Post = 0.8
- Per protocol: n=94, Pre = 0.78, Post = 0.27

Pre: Green
Post: Black
### Secondary Outcomes

<table>
<thead>
<tr>
<th>Secondary Outcome</th>
<th>Pre-Protocol (n=100)</th>
<th>Post-Protocol (n=104)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>In hospital mortality</td>
<td>n=14</td>
<td>n=17</td>
<td>0.7</td>
</tr>
<tr>
<td>Length of stay</td>
<td>8.6 days</td>
<td>7.9 days</td>
<td>0.53</td>
</tr>
<tr>
<td>Δ Serum creatinine</td>
<td>-0.255 (n=75)</td>
<td>-0.035 (n=85)</td>
<td>0.019</td>
</tr>
<tr>
<td>MRSA + culture (respiratory or blood)</td>
<td>n=4</td>
<td>n=2</td>
<td>0.41</td>
</tr>
</tbody>
</table>
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 do 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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C\text{max} = \text{Maximum concentration at the end of infusion}

AUC = \text{Area under the curve}

C\text{min} = \text{Lowest level prior to next dose (trough)}

\text{MIC} = \text{Minimum inhibitory concentration}
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

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

The problems with trough-only monitoring...

- Limited data to suggest a target trough of 15 – 20 mg/L improves efficacy
- Troughs > 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

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???

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

Predicted steady-state AUC_{24}:

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

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

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

<table>
<thead>
<tr>
<th>BMI &lt; 40</th>
<th>CrCl (ml/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>30</td>
</tr>
<tr>
<td>Vt (kg)</td>
<td></td>
</tr>
<tr>
<td>120</td>
<td>1000q24</td>
</tr>
<tr>
<td>110</td>
<td>1000q24</td>
</tr>
<tr>
<td>100</td>
<td>1000q24</td>
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<td>90</td>
<td>1000q24</td>
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<td>70</td>
<td>750q24</td>
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<td>60</td>
<td>500q24</td>
</tr>
<tr>
<td>50</td>
<td>500q24</td>
</tr>
<tr>
<td>40</td>
<td>500q24</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>BMI ≥ 40</th>
<th>CrCl (ml/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>30</td>
</tr>
<tr>
<td>Vt (kg)</td>
<td></td>
</tr>
<tr>
<td>110</td>
<td>1000q24</td>
</tr>
<tr>
<td>130</td>
<td>1000q24</td>
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<tr>
<td>120</td>
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<tr>
<td>110</td>
<td>1000q24</td>
</tr>
<tr>
<td>100</td>
<td>750q24</td>
</tr>
<tr>
<td>90</td>
<td>750q24</td>
</tr>
</tbody>
</table>

***NEXT STEP: DETERMINE PATIENT-SPECIFIC AUC24 USING EMPIRIC VANCO DOSING CALCULATOR***
# Vanco Predictive Kinetics

**Estimated CrCl**

100 mL/min

**Predicted Ke**

0.087 h⁻¹

**Predicted half-life**

7.9 hours

## Predict doses / variables

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight</td>
<td>100 kg</td>
</tr>
<tr>
<td>Infusion Duration</td>
<td>1.5 hours</td>
</tr>
<tr>
<td>Dose</td>
<td>1000 mg</td>
</tr>
<tr>
<td>Interval</td>
<td>8 hours</td>
</tr>
<tr>
<td>Vd conversion factor* (dropdown)</td>
<td>0.7 liters/kg</td>
</tr>
<tr>
<td>Vd estimate</td>
<td>70 liters</td>
</tr>
<tr>
<td>Ke</td>
<td>0.087 hours⁻¹</td>
</tr>
<tr>
<td>Half Life</td>
<td>7.9 hours</td>
</tr>
<tr>
<td>Predicted CpMax</td>
<td>26.6 mcg/ml</td>
</tr>
<tr>
<td>Predicted CpMin</td>
<td>15.1 mcg/ml</td>
</tr>
</tbody>
</table>

## AUC Calculation

<table>
<thead>
<tr>
<th>CpMax (mcg/mL)</th>
<th>CpMin (mcg/mL)</th>
<th>Infusion Duration (h)</th>
<th>AUC inf</th>
<th>Ke h⁻¹</th>
<th>Interval (h)</th>
<th>AUCelim</th>
<th>AUC 24</th>
</tr>
</thead>
<tbody>
<tr>
<td>26.6</td>
<td>15.1</td>
<td>1.5</td>
<td>31.3</td>
<td>0.087</td>
<td>8</td>
<td>132.0</td>
<td>489.8</td>
</tr>
</tbody>
</table>

*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

***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

**Formula Cells - No changes**

**Default Cells - Can be changed**

**Data Cells - Manually entered**
### Vancomycin Peak/Trough at Steady State

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scheduled infusion duration</td>
<td>1.5 hour(s)</td>
</tr>
<tr>
<td>Dose</td>
<td>1500 mg</td>
</tr>
<tr>
<td>Interval</td>
<td>12 hours</td>
</tr>
<tr>
<td>Time from end of infusion to 1st level (Peak)</td>
<td>1.5 hours</td>
</tr>
<tr>
<td>Drawn 1st Level (Peak)</td>
<td>35 mcg/ml</td>
</tr>
<tr>
<td>Drawn 2nd Level (Trough)</td>
<td>16 mcg/ml</td>
</tr>
<tr>
<td>Time between 1st &amp; 2nd Level</td>
<td>8 hours</td>
</tr>
<tr>
<td>Ke</td>
<td>0.096 hours⁻¹</td>
</tr>
<tr>
<td>Half Life</td>
<td>7.1 hours</td>
</tr>
<tr>
<td>Cmax</td>
<td>40.5 mcg/ml</td>
</tr>
<tr>
<td>Cmin</td>
<td>14.5 mcg/ml</td>
</tr>
<tr>
<td>Vd</td>
<td>43.8 Liters</td>
</tr>
</tbody>
</table>

### Adjustment Equations

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infusion Duration</td>
<td>1.5 hour(s)</td>
</tr>
<tr>
<td>Dose</td>
<td>1250 mg</td>
</tr>
<tr>
<td>Interval</td>
<td>12 hours</td>
</tr>
<tr>
<td>Vd</td>
<td>43.8 Liters</td>
</tr>
<tr>
<td>Ke</td>
<td>0.096 hours⁻¹</td>
</tr>
</tbody>
</table>

**Predicted Cmax**: 33.8

**Predicted Cmin**: 12.1

### 2-Level Dosing Calculator at Steady-State

***This calculator is preferred for bloodstream and CNS infections***

**Goal AUC24**: 400 - 600 mg*h/L

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