Updates in Infectious Diseases

Erin K. McCreary, PharmD, BCPS, BCIDP
Antimicrobial Stewardship/Infectious Diseases Clinical Pharmacist
University of Pittsburgh Medical Center
Pittsburgh, PA
@erinmccreary
Disclosures

• I have no disclosures or financial relationships relevant to the content of this activity.
Learning Objectives

• At the completion of this activity, **pharmacists** will be able to:
  • Utilize dose-optimization techniques for vancomycin
  • Advocate for pharmacy-driven beta-lactam allergy services in all healthcare settings
  • Justify shorter durations of therapy for common infections

• At the completion of this activity, **pharmacy technicians** will be able to:
  • Explain the role of non-ID trained healthcare team members in antimicrobial stewardship
  • Identify rapid diagnostic technologies and their role in antimicrobial stewardship
  • List newly approved antimicrobial agents
Outline

• Vancomycin AUC-based dosing
• Dose-optimization of other antimicrobials
• Beta-lactam allergies
• Stewardship resources and personnel
• Optimal treatment of ESBL infections
• Rapid diagnostic technologies
• Durations of therapy for common infections
• New guidelines with a focus on asymptomatic bacteriuria
• Formulary considerations for novel antimicrobials
• Social factors in antibiotic stewardship
Disclaimer

• If I am missing your favorite article or ID-related topic, I am sorry
• ID is the best subject ever
• Every single patient will have an ID consideration (at some point)
• There are a LOT of compelling data published almost daily (yay!)
• I can’t possibly cover it all 😞
• But I will do my best 😊
A brief history of vancomycin

- Discovered: 1952
- FDA-approved: 1958
- Resistance reported: 1986 (!!!)
- Used way too much: 2019
- Dosed optimally: ???

AUC/MIC isn’t new

Fig. 4. Time (days of therapy) to bacterial eradication vs vancomycin AUC₂₄/MIC <400 and AUC₂₄/MIC ≥400 illustrated by a Kaplan-Meier survival plot of day of therapy vs the percentage of patients remaining culture-positive on that day. The two AUC₂₄/MIC groups differed significantly (p = 0.0402). AUC₂₄/MIC = steady-state 24-hour area under the concentration-time curve divided by the minimum inhibitory concentration.

Table IV. Odds ratios for clinical success

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Odds ratio</th>
<th>95% CI</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vancomycin AUC₂₄/MIC value ≥350</td>
<td>7.19</td>
<td>1.91, 27.3</td>
<td>0.0036</td>
</tr>
</tbody>
</table>


Therapeutic monitoring of vancomycin in adult patients: A consensus review of the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, and the Society of Infectious Diseases Pharmacists


The guidelines said this, too.

“AUC/MIC ratio of ≥400 has been advocated as a target to achieve clinical effectiveness with vancomycin. Animal studies and limited human data appear to demonstrate that vancomycin is not concentration dependent and that the AUC/MIC is a predictive pharmacokinetic parameter for vancomycin.”
But logistically...

• “However, because it can be difficult in the clinical setting to obtain multiple serum vancomycin concentrations to determine the AUC and subsequently calculate the AUC/MIC, trough serum concentration monitoring, which can be used as a surrogate marker for AUC, is recommended as the most accurate and practical method to monitor vancomycin.”
And so we landed on 15-20

• “Based on the potential to improve penetration, increase the probability of optimal target serum vancomycin concentrations, and improve clinical outcomes for complicated infections such as bacteremia, endocarditis, osteomyelitis, meningitis, and hospital-acquired pneumonia caused by *S. aureus*, **total trough serum vancomycin concentrations of 15–20 mg/L are recommended**. Trough serum vancomycin concentrations in that range *should* achieve an AUC/MIC of ≥400 in most patients if the MIC is ≤1 mg/L.”

• Level of evidence = III, grade of recommendation = B

Fig. 2. Scatter and linear fit plot of vancomycin area under the curve over 24 h (AUC24) versus trough vancomycin concentration from 5000 subject Monte Carlo simulation.

\[ R^2 = 0.409 \]
FIG 1 Forest plot (using Mantel-Haenszel [M-H] analysis) of events denoting nephrotoxicity associated with vancomycin, comparing rates for trough levels of ≥15 mg/dl and <15 mg/dl. Squares indicate point estimates, and the size of the square indicates the weight of each study.
But hey, that AUC/MIC thing looks pretty good

### TABLE 3 Bayesian estimated vancomycin exposure profile subgroup analysis

<table>
<thead>
<tr>
<th>Variable</th>
<th>Trough concg-guided dosing group (n = 150)</th>
<th>AUC-guided dosing group (n = 150)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>C\textsubscript{min24} (mg/liter)</td>
<td>12.7 (8.9–16.6)</td>
<td>10.0 (5.7–13.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>C\textsubscript{min48} (mg/liter)</td>
<td>14.2 (10.3–19.5)</td>
<td>12.5 (8.3–16.7)</td>
<td>0.003</td>
</tr>
<tr>
<td>AUC\textsubscript{0–24} (mg \cdot h/liter)</td>
<td>705 (540–883)</td>
<td>474 (360–611)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>AUC\textsubscript{24–48} (mg \cdot h/liter)</td>
<td>663 (538–857)</td>
<td>532 (406–667)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Data represent the median (IQR).

**FIG 1** Time to nephrotoxicity by Cox proportional hazards regression. AUC-TD, AUC- and trough concentration-guided dosing.
Caution: there is a tox threshold with AUC

![Graph showing incidence of nephrotoxicity by CART-derived exposure thresholds.]

**FIG 1** Incidence of nephrotoxicity by CART-derived exposure thresholds.

<table>
<thead>
<tr>
<th>Exposure Threshold</th>
<th>AUC0-48</th>
<th>AUC0-24</th>
<th>AUC24-48</th>
</tr>
</thead>
<tbody>
<tr>
<td>4/169 &lt; 1218</td>
<td>2.4%</td>
<td>3.3%</td>
<td>3.7%</td>
</tr>
<tr>
<td>16/154 ≥ 1218</td>
<td>10.4%</td>
<td>11.4%</td>
<td>11.5%</td>
</tr>
<tr>
<td>7/209 &lt; 677</td>
<td>13/114</td>
<td>8/219</td>
<td>12/104</td>
</tr>
<tr>
<td>677 ≥ 683</td>
<td>15/291</td>
<td>5/32</td>
<td></td>
</tr>
</tbody>
</table>

Alright...here’s where we’re at with this:

• AUC/MIC ~400 or greater is associated with ↑ efficacy
  • A trough ≥ 15 mg/L will hit this AUC:MIC target if MIC ≤ 1 mg/L

• Higher exposures = more nephrotoxicity
  • In fact, a trough ≥ 15 mg/L ↑ toxicity
  • AUC ~650 or greater ↑ toxicity
  • Yikes...

• Trough is an extremely poor surrogate of AUC

• You can hit an AUC ≥ 400 with troughs < 15 mg/L

• Consider maintaining trough above 10 mg/L to prevent emergence of resistance

• We have data to demonstrate AUC dosing increases safety
  • Importantly, we do NOT have data to demonstrate that it increases efficacy compared to troughs ≥ 15 mg/L
2019 Revised Vancomycin Consensus Guidelines

NOTE: These recommendations were posted for public comment and are not final.

• A Bayesian-derived AUC/MIC\text{BMD} \text{ ratio of 400-600} should be advocated as the target to achieve clinical efficacy while improving patient safety (IA+)
  • Assuming a vancomycin MIC\text{BMD90} of 1 mg/L

• The most accurate and optimal way to manage vancomycin dosing is through AUC-guided dosing and monitoring. This can be accomplished two ways:
  • Use Bayesian software programs (preferred)
    • Preferred to obtain two samples, especially if lacking “richly sampled” prior data for the model
  • Collect two concentrations during same interval
    • Estimate AUC via first-order PK equations

Public comment period ended 3/15/19

NOTE: These recommendations were posted for public comment and are not final.
2019 Revised Vancomycin Consensus Guidelines
NOTE: These recommendations were posted for public comment and are not final.

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

• Monitoring should be performed in patients:
  • Receiving aggressive dosing for MRSA infections to achieve sustained targeted AUC
  • At risk of nephrotoxicity
  • With unstable renal function
  • Receiving prolonged courses of therapy

• We can assume the MIC is 1 mg/L
  • MIC testing methods lack precision and have substantial variability

• Continuous infusions are “reasonable” alternatives
  • Steady state concentration 20-25 mg/L
  • Makes your AUC calculation easy!
Making the change to area under the curve–based vancomycin dosing

- Define included populations
- Pick a calculator and where that will live
  - Equations
  - Spreadsheet v. incorporate into EHR v. Bayesian modeling software
- Write a guideline
- Provide EXTENSIVE education
  - Pharmacists, nurses, physicians, laboratory staff
  - Presentations, practice cases, discussion groups, audit and feedback
- Track and report your outcomes!
What do pharmacists think?

Post AUC-implementation survey

- Initial dosing
  - ↑ use of population PK initial dose calculations (37% v 88%)
  - ↓ 15 mg/kg dosing
  - ↑ time to calculate dose (8 v 15 mins)

- ↑ proportion of respondents felt
  - Vanco dosing should be responsibility of clinical pharmacy specialists (14% v 22%)
  - AUC/MIC was the ideal PK/PD index of efficacy (42.% v 93.9%)

- Major concerns = ↑ time commitment, lack of competency

- A pharmacist-to-dose policy associated with
  - Working to the top of degree
  - Increased confidence in antimicrobial stewardship team training

- Pharmacy administrative support essential

Don’t forget!

NOTE: These recommendations were posted for public comment and are not final.

- “Extrapolation of these recommendations to methicillin-susceptible strains, coagulase-negative staphylococci, and other pathogens should be viewed with extreme caution”
  - Although...

- MRSA can be really tough to treat
  - “Combination therapy and multiple medical interventions beyond antibiotic therapy may be necessary to improve patient outcomes”

**Pharmacokinetic/Pharmacodynamic Determinants of Vancomycin Efficacy in Enterococcal Bacteremia**

Muhammed Taufiq Bin Jumah, Shawn Vasoo, Sanjay R. Menon, Partha Pratim De, Michael Neely, and Christine B. Teng

Combo therapy, huh?

- β-lactam + vancomycin or daptomycin is promising
  - “Seesaw” effect
  - PBP1 blockade most strongly associated
    - Cefazolin, nafcillin, meropenem, etc.
  - ↑ PBP2, ↓PBP4 expression
  - Inactivation of mecA gene
  - ↑ host immune response
- Daptomycin + ceftaroline is in vogue
  - Ceftaroline
    - In vitro activity against MRSA
    - Displays stronger PBP2 binding as vanco & dapto MICs ↑
    - Enhances dapto-induced cell membrane depolarization
  - Recent (published online 3/11/19!) RCT terminated early
    - Mortality: 0% (0/17) combo vs. 26% (6/23) standard monotherapy 😯
- ... but is it necessary?
  - CAMERA-2 trial: vanco or dapto + flucloxacillin/cloxacillin/cefazolin in first 7 days
  - Also terminated early....

And we’re not just rethinking how we dose vanco

<table>
<thead>
<tr>
<th>Klebsiella pneumoniae</th>
<th>Antimicrobial</th>
<th>Interpretation</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amikacin</td>
<td>≤ 16</td>
<td></td>
<td>S</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>≤ 1</td>
<td></td>
<td>S</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>&gt;32</td>
<td></td>
<td>R</td>
</tr>
<tr>
<td><strong>Cefepime</strong></td>
<td>4</td>
<td></td>
<td>SDD</td>
</tr>
<tr>
<td>Meropenem</td>
<td>≤ 1</td>
<td></td>
<td>S</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>≤ 1</td>
<td></td>
<td>S</td>
</tr>
<tr>
<td>Pip Tazobactam</td>
<td>8</td>
<td></td>
<td>S</td>
</tr>
<tr>
<td>Sulfa-Trimeth</td>
<td>&gt;16/8</td>
<td></td>
<td>R</td>
</tr>
<tr>
<td>Tobramycin</td>
<td>≤ 1</td>
<td></td>
<td>S</td>
</tr>
</tbody>
</table>
Maybe breakpoints aren’t black and white

<table>
<thead>
<tr>
<th><strong>Intermediate</strong></th>
<th><strong>Susceptible-Dose Dependent</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>“Usually attainable” blood and tissue levels</td>
<td>The susceptibility of an isolate depends on the dosing regimen used</td>
</tr>
<tr>
<td>Implies clinical efficacy in body sites where drugs are physiologically concentrated or when a higher-than-normal dose can be used</td>
<td>Must use higher doses, more frequent doses, or both to achieve higher drug exposure than we can achieve with the dose that was used to establish the susceptible breakpoint</td>
</tr>
<tr>
<td>Response rates may be lower than for susceptible isolates</td>
<td></td>
</tr>
</tbody>
</table>

**Why the switch?**

- Intermediate is overlooked or not understood by clinicians – they assume intermediate = resistant or ineffective
- SDD meant to “highlight” dose-optimization as an option for clinicians
- Due to increasing antimicrobial resistance, there is a serious need to refine susceptibility reporting to maximize clinicians use of available drugs
- SDD is assigned when higher doses are supported by the literature, widely used clinically, and/or approved

<table>
<thead>
<tr>
<th>Antimicrobial</th>
<th>MIC (µg/mL)</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cefepime</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enterobacteriaceae</td>
<td>S: ≤ 2</td>
<td>1g q12h over 30 min</td>
</tr>
<tr>
<td></td>
<td>SDD: 4</td>
<td>1g q8h or 2g q12h over 30 min</td>
</tr>
<tr>
<td></td>
<td>SDD: 8</td>
<td>2g q8h over 30 min</td>
</tr>
<tr>
<td>Pseudomonas</td>
<td>S: ≤ 8</td>
<td>1g q8h or 2g q12h over 30 min</td>
</tr>
<tr>
<td></td>
<td>I: 16</td>
<td></td>
</tr>
<tr>
<td><strong>Ceftaroline</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>S. aureus</td>
<td>S: ≤ 1</td>
<td>600mg q12h over 1 hour</td>
</tr>
<tr>
<td></td>
<td>SDD: 2-4</td>
<td>600mg q8h over 2 hours</td>
</tr>
<tr>
<td><strong>Daptomycin</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enterococcus spp.</td>
<td>S: ≤ 1</td>
<td>6 mg/kg/day TBW</td>
</tr>
<tr>
<td></td>
<td>SDD: 2-4</td>
<td>8-12 mg/kg/day TBW</td>
</tr>
<tr>
<td><strong>Fluconazole</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C. albicans,</td>
<td>S: ≤ 2</td>
<td></td>
</tr>
<tr>
<td>parapsilosis,</td>
<td></td>
<td></td>
</tr>
<tr>
<td>tropicalis</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>SDD: 4</td>
<td>In GENERAL, Dose/MIC ~50-100</td>
</tr>
<tr>
<td>C. glabrata</td>
<td>SDD: ≤ 32</td>
<td>In GENERAL, Dose/MIC ~50-100</td>
</tr>
</tbody>
</table>

**Challenges we will face when trying to take care of our patients:**

- Automated panel updates lag behind these recommendations
- Clinician fear of higher dosing
- Difficult to grasp, even for ID specialists
- System barriers to dose optimization strategies
Other “new” doses or breakpoints to be aware of in your practice

<table>
<thead>
<tr>
<th>Antimicrobial</th>
<th>MIC (µg/mL)</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Meropenem</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enterobacteriaceae</td>
<td>S: ≤ 1</td>
<td>1g q8h over 30 mins</td>
</tr>
<tr>
<td>I: 2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pseudomonas</td>
<td>S: ≤ 2</td>
<td>1g q8h over 30 mins</td>
</tr>
<tr>
<td>I: 4</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Meropenem-vaborbactam</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enterobacteriaceae</td>
<td>S: ≤ 4/8</td>
<td>4g q8h over 3 hours (2g meropenem, 2g vaborbactam)</td>
</tr>
<tr>
<td>I: 8/8</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Ceftolozane/tazboactam</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enterobacteriaceae</td>
<td>S: ≤ 2/4</td>
<td>1.5g q8h over 1 hour</td>
</tr>
<tr>
<td>I: 4/4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pseudomonas</td>
<td>S: ≤ 4/4</td>
<td>1.5g q8h over 1 hour</td>
</tr>
<tr>
<td>I: 8/4</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Ciprofloxacin</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enterobacteriaceae</td>
<td>S: ≤ 0.25</td>
<td>400mg IV q12h or 500mg PO q12h</td>
</tr>
<tr>
<td>Pseudomonas</td>
<td>S: ≤ 0.5</td>
<td>400mg IV q8h</td>
</tr>
<tr>
<td><strong>Levofloxacin</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enterobacteriaceae</td>
<td>S: ≤ 0.5</td>
<td>750mg IV or PO q24h</td>
</tr>
<tr>
<td>Pseudomonas</td>
<td>S: ≤ 1</td>
<td>750mg IV or PO q24h</td>
</tr>
</tbody>
</table>
Another year, another FQ black box warning

The truth about penicillin allergies

• They are bad
  – More FQ, clindamycin, vancomycin, aztreonam use
  – More *C. difficile*, MRSA, VRE infection and colonization
  – More surgical site infections

• They are... questionable
  – >95% of patients with reported allergies have negative skin tests
  – Rates of true anaphylaxis
    • 1/207,191 (0.00048%) → oral penicillin exposure
    • 1/95,298 (0.00105%) → parental penicillin exposure
    • No fatalities in over 100,000,000 oral amoxicillin courses

• They are not forever
• Med chem matters....
5.1. Cefazolin does not share a common side chain with any other beta-lactams

<table>
<thead>
<tr>
<th>Agent</th>
<th>Agents with Similar Side Chains</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amoxicillin</td>
<td>Ampicillin Cefaclor Cefadroxil Cefprozil Cephalexin</td>
</tr>
<tr>
<td>Ampicillin</td>
<td>Amoxicillin Cefaclor Cefadroxil Cefprozil Cephalexin</td>
</tr>
<tr>
<td>Aztreonam</td>
<td>Ceftazidime Cefitoxan</td>
</tr>
<tr>
<td>Cefaclor</td>
<td>Amoxicillin Ampicillin Cefadroxil Cefprozil Cephalexin</td>
</tr>
<tr>
<td>Cefadroxil</td>
<td>Amoxicillin Ampicillin Cefaclor Cefprozil Cephalexin</td>
</tr>
<tr>
<td>Cefdinir</td>
<td>Cefixime</td>
</tr>
<tr>
<td>Cefditoren</td>
<td>Cepeime Cefotaxime Cefpodoxime Ceftriazone Ceftridrine</td>
</tr>
<tr>
<td>Cefepime</td>
<td>Cefditoren Cefotaxime Cefpodoxime Ceftriazone Ceftridrine</td>
</tr>
<tr>
<td>Cefixime</td>
<td>Cefdinir</td>
</tr>
<tr>
<td>Cefotaxime</td>
<td>Cefditoren Cefepime Cefpodoxime Ceftriazone Ceftridrine</td>
</tr>
<tr>
<td>Cefoxitin</td>
<td>Cefuroxime Penicillin G</td>
</tr>
<tr>
<td>Cefpodoxime</td>
<td>Cefditoren Cefepime Ceftriazone Ceftridrine</td>
</tr>
<tr>
<td>Cefprozil</td>
<td>Amoxicillin Ampicillin Cefaclor Cefadroxil</td>
</tr>
<tr>
<td>Ceftaroline</td>
<td>Cefepime Cefotaxime Cefpodoxime Ceftriazone</td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>Aztreonam Ceftolozane</td>
</tr>
<tr>
<td>Ceftolozane</td>
<td>Aztreonam Ceftazidime</td>
</tr>
<tr>
<td>Ceftriazone</td>
<td>Cefditoren Cefepime Cefotaxime Cefpodoxime Ceftridrine</td>
</tr>
<tr>
<td>Cefuroxime</td>
<td>Cefoxitin</td>
</tr>
<tr>
<td>Cephalexin</td>
<td>Amoxicillin Ampicillin Cefaclor Cefadroxil</td>
</tr>
<tr>
<td>Penicillin G</td>
<td>Cefoxitin</td>
</tr>
</tbody>
</table>

*Agents not listed are either not approved for use in the United States (cefizoxime, cefibiprole) or do not share common side chains (e.g. piperacillin, ticarcillin, nafcillin, dicloxacillin).

*Aztreonam cross-reacts with ceftazidime and ceftolozane, with which it shares an identical side-chain.

*Identical R1 side chain

*Identical R2 side chain
A good history takes care of the majority of “allergies”

- **What** age reaction occurred
- **What** reaction looked like (*prompt “hives”*)
- **Where** reaction occurred (*e.g., localized v. whole body*)
- **When** reaction occurred in relation to taking the antibiotic
- **How** long did reaction last
- **How** reaction was treated (*did they need to seek urgent medical care?*)
- Was the medication was ever **re-challenged**?
- Have they have tried **similar antibiotics**?
  - *E.g. Augmentin, Amoxicillin, Keflex/Cephalexin*
- **Educate the patient** why your questions are important
- **DOCUMENT your findings** – the more detailed, the better
Pharmacist extenders can do this!

Pharmacist-Led β-Lactam Allergy Interview (BLAI) Reduces Duration of Fluoroquinolones Within a Community Hospital

Elizabeth W. Covington, PharmD1, Beth Jobson Baldwin, PharmD and Emily Warren, PharmD2

Evaluation of a pharmacist-led penicillin allergy de-labelling ward round: a novel antimicrobial stewardship intervention

M. Devchand3-4, C. M. J. Kirkpatrick3, W. Stevenson5, K. Garrett2, D. Perera1,2, S. Khumra1-3, K. Urbanbice1,2,6, M. L. grayson1,5 and J. A. Trubiano1,4,5

Initiative to reduce aztreonam use in patients with self-reported penicillin allergy: Effects on clinical outcomes and antibiotic prescribing patterns

Anthony Phan, Pharm.D., Department of Pharmacy, St. Vincent’s Healthcare, Jacksonville, FL. Bryan Allen, Pharm.D., BCPS

Optimizing preoperative prophylaxis in patients with reported β-lactam allergy: a novel extension of antimicrobial stewardship

Alon Vaisman1, Janine McCready2, Sandy Hicks3 and Jeff Powis2
• Each 0.50 increase in combined FTE availability resulted in a 1.48-fold increase in the odds of demonstrating effectiveness (95% confidence interval, 1.06–2.07)

• Even programs with positive outcomes perceive understaffing
You’re gonna need more people to review all those carbapenems...

- Piperacillin-tazobactam vs. meropenem for bloodstream infections caused by ceftriaxone-resistant *E. coli* or *K. pneumoniae*
  - Min = 4, max = 14 days treatment
- 30-day mortality
  - Pip/tazo: 23/187 (12.3%)
  - Meropenem: 7/191 (3.7%)
- Conclusion: Pip/tazo is not noninferior
- So that settles it, right?

Antimicrobial stewardship teams implementing and optimizing **rapid diagnostics technologies** will be the new normal.

**Microbiology S.O.C.**
- Turn around times
- Available technology
- Staffing

**Local epidemiology**
- Bloodstream pathogens
- Resistance patterns
- Adequacy of empiric therapy

**Stewardship capabilities**
- ASP model/approach
- Staffing/availability
- Well-defined algorithms

**Diagnostic stewardship team**
- Onsite validation and performance testing

**Implement and track outcomes**
- Budget justification

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Slide adopted from Ryan K. Shields, PharmD, MS
Rapid diagnostic budget justification

“Improving patient care” doesn’t cut it anymore

**Antibiotic consumption**
- Discontinuation of empiric vancomycin
- Escalation to active therapy earlier
- ↓ combination agents
- De-escalation to narrow spectrum antibiotics
- ↓ total antibiotic days

**Decreased LOS**
- De-escalation for patients with uncomplicated BSI
- Escalation for patients with BSI due to MDRO
- Shorter durations of antibiotics for BSI

**Collateral benefits**
- Decreased adverse events
- Fewer cases of *C. difficile*
- Less hands-on time for microbiology
- ↓ readmissions
- ↑ collaboration with and confidence in stewie program

Slide adopted from Ryan K. Shields, PharmD, MS
2018: The Year of the MRSA PCR

- Pooled prevalence of MRSA pneumonia: 10%

<table>
<thead>
<tr>
<th>Type of Pneumonia</th>
<th>No. Studies</th>
<th>Sensitivity, % (95% CI)</th>
<th>Specificity, % (95% CI)</th>
<th>PPV, %</th>
<th>NPV, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>22</td>
<td>70.9 (58.8-80.6)</td>
<td>90.3 (86.1-93.3)</td>
<td>44.8</td>
<td>96.5</td>
</tr>
<tr>
<td>CAP/HCAP</td>
<td>4</td>
<td>85 (59.7-95.6)</td>
<td>92.1 (81.5-96.9)</td>
<td>56.8</td>
<td>98.1</td>
</tr>
<tr>
<td>VAP</td>
<td>5</td>
<td>40.3 (17.4-68.4)</td>
<td>93.7 (77.1-98.4)</td>
<td>35.7</td>
<td>94.8</td>
</tr>
</tbody>
</table>

The Clinical Utility of Methicillin-Resistant *Staphylococcus aureus* (MRSA) Nasal Screening to Rule Out MRSA Pneumonia: A Diagnostic Meta-analysis With Antimicrobial Stewardship Implications

A “nudge” works too

<table>
<thead>
<tr>
<th>Specimen:</th>
<th></th>
</tr>
</thead>
</table>
| **Sputum Culture** | Moderate Growth of Normal Oral Flora  
Negative For Methicillin Resistant Staphylococcus aureus.  
Negative for Staphylococcus aureus.  
Negative for Pseudomonas aeruginosa. |
| **Gram Stain** | Few WBC Seen  
 Few Epithelial Cells Seen  
 Rare Gram Negative Rods  
 Moderate Gram Positive Cocci  
 Rare Gram Positive Rods  
 Specimen Optimum for Culture |
How low can we go?

<table>
<thead>
<tr>
<th>Disease</th>
<th>Short Duration</th>
<th>Long Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Community acquired pneumonia</td>
<td>3-5</td>
<td>7-10</td>
</tr>
<tr>
<td>Asymptomatic bacteriuria, bronchitis</td>
<td>0</td>
<td>Anything else</td>
</tr>
<tr>
<td>Hospital-acquired, ventilator-associated pneumonia</td>
<td>7-8</td>
<td>10-15</td>
</tr>
<tr>
<td>Pyelonephritis</td>
<td>7</td>
<td>10-14</td>
</tr>
<tr>
<td>Intraabdominal infections</td>
<td>3-4</td>
<td>10</td>
</tr>
<tr>
<td>Acute exacerbation of chronic bronchitis</td>
<td>( \leq 5 )</td>
<td>7-10</td>
</tr>
<tr>
<td>Acute bacterial sinusitis</td>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td>Uncomplicated gram-negative bacteremia (Enterobacteriaceae)</td>
<td>7</td>
<td>14</td>
</tr>
<tr>
<td>Uncomplicated gram-negative bacteremia (Pseudomonas)</td>
<td>8-10</td>
<td>14-17</td>
</tr>
<tr>
<td>Cellulitis</td>
<td>5-6</td>
<td>10</td>
</tr>
<tr>
<td>Neutropenic fever</td>
<td>Afebrile x 72h</td>
<td>ANC &gt; 500</td>
</tr>
<tr>
<td>Osteomyelitis</td>
<td>42</td>
<td>84</td>
</tr>
</tbody>
</table>

You must understand the patient populations of these studies and how they relate to your patient and your patient’s infection. This is not black and white.

BALANCE Trial: Clinical Trials NCT03005145
New guidelines

• IDSA
  • Outpatient Parenteral Antimicrobial Therapy
  • Diagnosis, Treatment, Chemoprophylaxis, and Institutional Outbreak Management of Seasonal Influenza
  • Clostridium difficile Infection in Adults and Children 😷
  • Antimicrobial Prophylaxis for Adult Patients With Cancer-Related Immunosuppression
  • Fever and Neutropenia in Adults with Cancer
  • Guidelines for the Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents
  • Laboratory Diagnosis of Infectious Diseases

• International Consensus Guidelines for the Optimal Use of the Polymyxins

• The Third International Consensus Guidelines on the Management of Cytomegalovirus in Solid-organ Transplantation

• Hepatitis C

• And more!
In older patients with bacteriuria and no local symptoms or other systemic signs of infection, assess for other causes and observe carefully rather than treat!

- Functional and/or cognitive impairment
- Delirium
- Acute mental status change
- Confusion
- Experience a fall

Do not screen and treat ASB in anyone EXCEPT:

- Pregnant women
- Renal transplant recipients within 1 month of surgery
- Pre-op endoscopic urologic procedures associated with mucosal trauma (1-2 doses!)

No recommendation for high-risk neutropenia (lack of data)
<table>
<thead>
<tr>
<th>Drug</th>
<th>Approved</th>
<th>Indications</th>
<th>What you need to know</th>
</tr>
</thead>
</table>
| Ceftolozane/tazobactam      | 2014     | IAI cUTI    | More effective and less toxic than polymyxins or aminoglycosides for *Pseudomonas*  
More effective for ESBLs (useful with mixed infections)  
Phase 3 trial using 3g dose in HABP/VABP completed                                                     |
| Ceftazidime/avibactam       | 2015     | IAI cUTI HABP/VABP | Only beta-lactamase inhibitor for Class D (OXA-48-like)  
Superior to historical agents for CRE, watch resistance development, approved in peds!  
Can be useful for non-fermenters                                                                  |
| Meropenem/vaborbactam       | 2017     | cUTI        | Potent KPC inhibitor paired with dose-optimized meropenem; role for caz/avi-resistant CRE  
No role for carbapenem-resistant *Pseudomonas*  
Superior to best available therapy for CRE                                                        |
| Plazomicin                  | 2018     | cUTI        | Stable to all aminoglycoside-modifying enzymes  
Dosed on AUC in Phase III bloodstream infection trial                                               |
| Eravacycline                | 2018     | cIAI        | Similar to tigecycline (maybe slightly more potent) for CRE, *Acinetobacter*, ESBLs  
Failed UTI trial with oral formulation, only available PO                                          |
<table>
<thead>
<tr>
<th>Agent</th>
<th>KPC-producer</th>
<th>NDM-producer</th>
<th>OXA-48-like-producer</th>
<th>Carbapenem-resistant <em>Pseudomonas aeruginosa</em></th>
<th>Carbapenem-resistant <em>Acinetobacter baumannii</em></th>
<th><em>Stenotrophomonas maltophilia</em></th>
</tr>
</thead>
<tbody>
<tr>
<td>Aztreonam-avibactam</td>
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<td>Cefiderocol</td>
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<tr>
<td>Ceftazidime-avibactam</td>
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<tr>
<td>Ceftolozane-tazobactam</td>
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<tr>
<td>Eravacycline</td>
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<tr>
<td>Fosfomycin (intravenous)</td>
<td></td>
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<tr>
<td>Imipenem-relebactam</td>
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<tr>
<td>Meropenem-vaborbactam</td>
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<tr>
<td>Plazomicin</td>
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<tr>
<td>Polymyxin B or Colistin</td>
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<tr>
<td>Tigecycline</td>
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</tbody>
</table>

**Susceptibility anticipated > 80%**

**Susceptibility anticipated 30-80%**

**Susceptibility anticipated < 30%**
Bugs don’t care how the drugs get there!

Partial Oral versus Intravenous Antibiotic Treatment of Endocarditis


Clinical Infectious Diseases

Major Infectious Diseases

Oral versus Intravenous Antibiotics for Bone and Joint Infection


Early Oral Switch to Linezolid for Low-risk Patients With *Staphylococcus aureus* Bloodstream Infections: A Propensity-matched Cohort Study


1Department of Infectious Diseases, Hospital Universitari Vall d’Hebron. 2Department of Medicine, Universitat Autònoma de Barcelona, and 3Department of Microbiology, Hospital Universitari Vall d’Hebron, Barcelona, Spain
“There is a need for stewardship interventions specifically tailored to the social norms, professional identities, and motivations of physicians in different medical specialties in order to change the culture surrounding antimicrobials on a broad scale.”

The science is important, but we must appreciate beliefs and behaviors to truly change practice.
Stewardship and common infections

- 5-day nitrofurantoin vs. single-dose fosfomycin for uUTI in woman: PMID 29710295
- Prophylactic antimicrobial therapy for acute aspiration pneumonia: PMID 29438467
- ARREST trial: PMID 29249276
- Increasing duration of surgical prophylaxis does not decrease infection but increases ADRs (IDWeek 2018)
- OPAT among PWID may be safe and effective: PMID 30211247
- “Jumping the gun” with renal dosing: PMID 30219824

Global infections

- Antifungal combinations for cryptococcal meningitis in Africa: PMID 29539274
- Four months of rifampin or nine months of isoniazid for latent tuberculosis: PMID 30067931
- Continued experience with 8 weeks of treatment with glecaprevir and pibrentasvir (Mavyret) approved for all HCV genotypes
- Ceftriaxone-resistant Neisseria gonorrhoeae: PMID 29131780, 29553335

Immunocompromised patients

- ANTIBIOSTOP: Early discontinuation of empirical antibacterial therapy in febrile neutropenia: PMID 29451055
- ACTIVE: Isavuconazole versus caspofungin in the treatment of candidemia: PMID 30289478
- Oral versus aerosolized ribavirin for RSV infections in HCT recipients: PMID 30202920
- Extended infusions associated with superior outcomes in patients with febrile neutropenia: PMID 29608680
- High-dose influenza vaccine for solid-organ transplant recipients: PMID 29253089
- Preemptive therapy preferred to universal prophylaxis for D+/R- liver transplant recipients (IDWeek 2018)

HIV

- MONCAY trial: PMID 30601976
- SWORD-1 and SWORD-2 trials: PMID 29310899
- Another patient was “cured” of HIV (N=2); and there might be a third!
- TAF/FTC noninferior to TDF/FTC for PrEP
- ATLAS and FLAIR trials of monthly, long-acting injectable cabotegravir and rilpivirine
- INSTIs associated with weight gain?
- CASCADE trial: PMID 29509839
- GEMINI-1 and GEMINI-2 trials: PMID 30420123
- U=U: PMID 30025681
- Primary prophylaxis against disseminated MAC disease no longer recommended for adults and adolescents with HIV who immediately initiate ART
Everyone can (and should) be a steward

• **SIDP Antimicrobial Stewardship Certificate**
  • Acute care: [https://www.sidp.org/StewardshipCertificate](https://www.sidp.org/StewardshipCertificate)
  • Long-term care: [https://www.sidp.org/LTCStewardship/](https://www.sidp.org/LTCStewardship/)

• **CDC Antibiotic Stewardship Training Series**
  • 9 modules: [https://www.train.org/cdctrain/training_plan/3697](https://www.train.org/cdctrain/training_plan/3697)

• **MAD-ID**
  • Basic Training Program: [https://mad-id.org/antimicrobial-stewardship-programs/antimicrobial-stewardship-programs-basic-program/](https://mad-id.org/antimicrobial-stewardship-programs/antimicrobial-stewardship-programs-basic-program/)
  • Advanced Training Program: [https://mad-id.org/antimicrobial-stewardship-programs/advanced-program/](https://mad-id.org/antimicrobial-stewardship-programs/advanced-program/)

• **IDStewardship.com**
  • Collection of resources: [https://www.idstewardship.com/resources/](https://www.idstewardship.com/resources/)
Updates in Infectious Diseases

Erin K. McCreary, PharmD, BCPS, BCIDP
Antimicrobial Stewardship/Infectious Diseases Clinical Pharmacist
University of Pittsburgh Medical Center
Pittsburgh, PA
@erinnmccreary