Bugs, Drugs, and Resistance

Whitney R. Buckel, PharmD, BCPS

*Infectious Diseases/Antimicrobial Stewardship, Advanced Clinical Pharmacist, Intermountain Medical Center, Intermountain Healthcare; Murray, Utah*

Objectives:
- Describe the value of an methicillin-resistant Staphylococcus aureus (MRSA) PCR nasal swab for pneumonia and its role in therapy
- Identify the recommend treatment options for chromosomal AmpC harborers ("SPACE" bugs)
- Evaluate data behind probiotics in the treatment and prevention of Clostridium difficile
Bugs, Drugs, and Resistance

Whitney Buckel, PharmD
Infectious Diseases Pharmacist
Intermountain Medical Center
Disclosure

• Pfizer Independent Grant for Learning and Change administered by The Joint Commission
  • PI: Eddie Stenehjem, MD, MSc

• Off-label indications will be discussed
Objectives

• Describe the value of a methicillin-resistant Staphylococcus aureus (MRSA) PCR nasal swab for pneumonia and its role in therapy

• Recommend treatment options for chromosomal AmpC harborers ("SPACE" bugs)

• Evaluate data behind probiotics in the treatment and prevention of Clostridium difficile
MRSA Nasal PCR
Interactive Question

What percent of patients admitted to the ICU are colonized with *S. aureus* and MRSA in their nose?

a. Less than 5%

b. 5 – 10%

c. 10 – 15%

d. 15 – 20%

Interactive Question

What percent of patients admitted to the ICU are colonized with *S. aureus* and MRSA in their nose?

a. Less than 5%

b. 5 – 10 %  

5.8 – 8.3%

c. 10 – 15%

d. 15 – 20%

Background

- Hospitals have significant MRSA burden
  
  Delay treatment → worse outcomes
  Broad treatment → ADEs, resistance

  Under-treat

  Over-treat

- Guidelines recommend empiric MRSA coverage if:
  - Necrotizing or cavitary pneumonia
  - Long-term dialysis
  - Injection drug abuse
  - Prior influenza
  - Prior antibiotic therapy
  - Local prevalence is high

<table>
<thead>
<tr>
<th>Type</th>
<th>MRSA Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAP</td>
<td>&lt;1 – 9%</td>
</tr>
<tr>
<td>HCAP</td>
<td>2 – 27%</td>
</tr>
<tr>
<td>HAP</td>
<td>Up to 23%</td>
</tr>
</tbody>
</table>

• Failure to detect *S. aureus* in good-quality specimens is strong evidence against the presence of *S. aureus*
  • *Sometimes difficult to obtain good-quality specimens*

• Nasal MRSA colonization = risk factor for infection
  • 8-fold increased risk of associated infections during ICU stay
  • MRSA infections develop in 25% of patients who are colonized on admission (compared to 3% in non-colonized patients)

• Nasal MRSA colonization can be used as a predictor of the risk of MRSA pneumonia

MRSA Nasal Swab PCR

- Positive MRSA:

- Positive MSSA:

- Negative for both MRSA and MSSA:
Literature Evaluation

- Retrospective evaluation of 164 patients with confirmed pneumonia who had an MRSA nasal PCR and respiratory and/or blood cultures obtained
  - 183 (24.4%) patients had a positive MRSA nasal PCR
  - 100 (13.4%) patients had an MRSA ICU-acquired lower respiratory tract infections

<table>
<thead>
<tr>
<th>Test characteristic</th>
<th>Result</th>
<th>95% confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity (%)</td>
<td>27.5</td>
<td>24.3-30.7</td>
</tr>
<tr>
<td>Specificity (%)</td>
<td>76.2</td>
<td>73.2-79.2</td>
</tr>
<tr>
<td>Positive predictive value (%)</td>
<td>18.0</td>
<td>15.2-20.8</td>
</tr>
<tr>
<td>Negative predictive value (%)</td>
<td>84.6</td>
<td>82.0-87.2</td>
</tr>
</tbody>
</table>

Retrospective evaluation of 435 patients with confirmed pneumonia who had an MRSA nasal PCR and respiratory and/or blood cultures obtained

- 62 (14.3%) patients had a positive MRSA nasal PCR
- 25 (5.7%) patients had positive cultures for MRSA

<table>
<thead>
<tr>
<th>Test characteristic</th>
<th>Result</th>
<th>95% confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity (%)</td>
<td>88.0</td>
<td>67.6-96.9</td>
</tr>
<tr>
<td>Specificity (%)</td>
<td>90.1</td>
<td>86.6-92.8</td>
</tr>
<tr>
<td>Positive predictive value (%)</td>
<td>35.4</td>
<td>24.0-48.7</td>
</tr>
<tr>
<td>Negative predictive value (%)</td>
<td>99.2</td>
<td>97.4-99.8</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>n (inf.)</th>
<th>Method of swab</th>
<th>% pos nasal MRSA</th>
<th>% pos cx MRSA</th>
<th>Sens</th>
<th>Spec</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sarikonda et al. 2010</td>
<td>164 (PNA) Nasal PCR</td>
<td>183 (24%)</td>
<td>100 (13%)</td>
<td>27.5 (24.3-30.7)</td>
<td>76.2 (73.2-79.2)</td>
<td>18.0 (15.2-20.8)</td>
<td>84.6 (82.0-87.2)</td>
</tr>
<tr>
<td>Chan et al. 2012</td>
<td>388 (VAP) Nares, trach, wound cx</td>
<td>54 (14%)</td>
<td>37 (10%)</td>
<td>70.3 (52.8-83.6)</td>
<td>92.0 (88.5-94.5)</td>
<td>48.1 (34.5-62.0)</td>
<td>96.7 (94.0-98.3)</td>
</tr>
<tr>
<td>Tilahun et al. 2015</td>
<td>165 (PNA) Nasal PCR</td>
<td>28 (17%)</td>
<td>10 (6%)</td>
<td>80.0 (44.2-96.5)</td>
<td>87.1 (80.5-91.8)</td>
<td>28.6 (14.0-48.9)</td>
<td>98.5 (94.3-99.7)</td>
</tr>
<tr>
<td>Dangerfield et al. 2014</td>
<td>435 (PNA) Nasal PCR</td>
<td>62 (14%)</td>
<td>25 (6%)</td>
<td>88.0 (67.6-96.9)</td>
<td>90.1 (86.6-92.8)</td>
<td>35.4 (24.0-48.7)</td>
<td>99.2 (97.4-99.8)</td>
</tr>
</tbody>
</table>

Inf: infection; VAP: ventilator-associated PNA; cx: culture; PCR: polymerase chain reaction; PNA: pneumonia
Patient Case

A 76 year old female residing in a care center with recent admission one month prior was admitted for fever and shaking chills and confusion.

VS: 101.2 F, BP 146/100 → 66/52, and O2 saturation 72% requiring 15 L flow mask (improved to 99%)

CXR: some improvement in areas of prior multifocal pneumonia

Started on vancomycin and meropenem in the ED

Unable to provide adequate sputum sample

An MRSA Nasal PCR was ordered.
Patient Case: Question

A 76 yof re-admitted with multifocal pneumonia. Started on vancomycin and meropenem.

A. The MRSA nasal PCR is positive for MRSA, continue vancomycin.

B. The MRSA nasal PCR is positive for MSSA, discontinue vancomycin.

C. The MRSA nasal PCR is positive for MSSA, narrow to nafcillin.
A 76 yof re-admitted with multifocal pneumonia. Started on vancomycin and meropenem.

A. The MRSA nasal PCR is positive for MRSA, continue vancomycin.
B. The MRSA nasal PCR is positive for MSSA, discontinue vancomycin.
C. The MRSA nasal PCR is positive for MSSA, narrow to nafcillin.
Conclusion

- An MRSA nasal PCR screen:
  - Negative: suggests the patient most likely does not have an LRTI caused by MRSA
  - Positive: suggests the patient is at higher risk of developing an MRSA LRTI, but should not necessarily be started on MRSA-targeted therapy
SPACE Bugs and AmpC
Interactive Question

What is inducible AmpC?

a. Ampicillin resistance on the Chromosome that is always expressed

b. Ampicillin resistance on the Chromosome that can mutate to an always expressed state

c. Ceftriaxone resistance on the Chromosome that is always expressed

d. Ceftriaxone resistance on the Chromosome that can mutate to an always expressed state
Interactive Question

What is inducible AmpC?

a. Ampicillin resistance on the Chromosome that is always expressed

b. Ampicillin resistance on the Chromosome that can mutate to a derepressed state

c. Ceftriaxone resistance on the Chromosome that is always expressed

d. Ceftriaxone resistance on the Chromosome that can mutate to a derepressed state
The Problem

- 129 consecutive patients with *Enterobacter* bacteremia were enrolled over 18-months at 6 hospitals
  - 37 (29%) were multidrug resistant initially
  - Risk factors for resistance was previous antibiotics

- Emergence of resistance during antibiotic therapy occurred in 6% (7 of 118) of the bacteremias
  - In 6 of these 7 pairs, resistance emerged to the third-generation cephalosporin administered
  - Emergence of resistance to third-generation cephalosporins (19%) occurred more often than emergence to aminoglycosides (1%)

(MY) SPACE Bugs

- Guidelines do not recommend routine AmpC testing
- Organisms with inducible AmpC mediated by chromosomal rather than plasmid resistance, a mutation can lead to a de-repressed mutant (high levels of AmpC)
  - *Morganella morganii* (0% emergence of resistance)
  - *Yersinia* spp.
  - *Serratia marcescens* (3% emergence of resistance)
  - *Pseudomonas* spp.
  - *Acinetobacter* spp.
  - *Citrobacter freundii* (8% emergence of resistance)
  - *Enterobacter* spp. (5% emergence of resistance; 13% with bacteremia)

## AmpC vs ESBL

<table>
<thead>
<tr>
<th>Susceptibility</th>
<th>AmpC</th>
<th>ESBL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pip/tazo, amp/sulb, amox/clav</td>
<td>R</td>
<td>S/R</td>
</tr>
<tr>
<td>Cefoxitin, cefotetan</td>
<td>R</td>
<td>S/R</td>
</tr>
<tr>
<td>Ceftazidime, ceftriaxone</td>
<td>R</td>
<td>R</td>
</tr>
<tr>
<td>Cefepime</td>
<td>S</td>
<td>S/R</td>
</tr>
<tr>
<td>Carbapenems</td>
<td>S</td>
<td>S</td>
</tr>
</tbody>
</table>
Antibiotic Choice

- Classically, carbapenems have been used as the drug of choice

- Cefepime
  - Poor inducer
  - Relatively more stable to AmpC beta-lactamases
  - Zwitteronic structure allows it to more rapidly penetrate bacterial cell membranes

Literature Evaluation

- Single-center study, 2-year period
- 399 patients with Enterobacter, Citrobacter or Serratia
  - 38% AmpC producing Enterobacter
  - 15% AmpC producing Serratia
  - 1% AmpC producing Citrobacter
- No organisms with ceftriaxone MIC ≤ 1 mcg/mL were producing AmpC
- Propensity score matching of 32 pairs receiving either cefepime or meropenem demonstrated no difference in mortality or length of hospital stay after first positive culture

Two major academic hospitals, 6-year period

- 368 patients with *Enterobacter* spp. bacteremia
  - 29 patients had repeat positive blood cultures
    - 0 of 36 (0%) who received cefepime monotherapy
      - MIC: 28 of 30 had MICs ≤ 2 mcg/mL
    - 4 of 16 (25%) who received carbapenem monotherapy
    - 0 of 3 (0%) who received ceftriaxone monotherapy
  - However, patients who received carbapenems were sicker, and no agent was associated with persistent bacteremia or mortality in a propensity score-matched analysis of 30 pairs

Conclusion

- In patients with good source control or low-risk infections (e.g., urinary tract infections)
  - Trust susceptibilities reported for SPACE bugs
- In patients with limited source control, high severity, high-risk infections (e.g., bacteremia, CNS infections)
  - Don’t trust susceptibilities to 3rd gen cephalosporins
  - Cefepime and carbapenems are likely equally effective in setting of good source control
A 58 year old female with end stage renal disease presents with high fevers and myalgias, unresponsive to cefdinir prescribed by her primary care physician.

Blood cultures are growing:

- *Enterobacter cloacae* by MALDI-TOF

What treatment would you recommend?

A. Piperacillin/tazobactam
B. Cefepime
C. Meropenem
A 58 year old female with end stage renal disease presents with high fevers and myalgias, unresponsive to cefdinir prescribed by her primary care physician.

Blood cultures are growing:
- *Enterobacter cloacae* by MALDI-TOF

What treatment would you recommend?

A. Piperacillin/tazobactam

B. Cefepime

C. Meropenem/Imipenem
Probiotics and *C. difficile*
Interactive Question

Disturbances in the normal microbiota may occur due to changes in diet, radiation or administration of antimicrobial agents. How long does a 10 day course of ciprofloxacin disrupt natural flora?

a. No effect on natural flora
b. Up to 6 weeks
c. Up to 3 months
d. Up to 12 months

Interactive Question

Disturbances in the normal microbiota may occur due to changes in diet, radiation or administration of antimicrobial agents. How long does a 10 day course of ciprofloxacin disrupt natural flora?

a. No effect on natural flora
b. Up to 6 weeks
c. Up to 3 months
d. Up to 12 months

A story of C diff

Antimicrobial exposure asymptotically impairs the microbiome, leading to overgrowth or blooming of toxigenic C. difficile, toxin production leads to clinical CDI symptoms

Treatment attempts to balance pathogen eradication, with further adverse or beneficial effects on the residual normal intestinal flora

Post-treatment a dynamic struggle occurs between the normal microbiota reconstituting itself in both numbers and diversity vs regrowth of the pathogen

Background - Probiotics

• Per FAO/WHO: “live microorganisms which, when administered in adequate amounts, confer a health benefit on the host”
  • The efficacy of probiotics was discovered to be strain-specific and dose-specific

• Ideal properties: resistance to gastric and bile acidity, ability to adhere to mucosal surfaces, ability to inhibit pathogenic organisms or alter host’s immune system, good safety profile, product stability over time

• Effectiveness A rating for AAD, but only B/C rating for prevention of *C. difficile* infection

Literature Evaluation

- Cochrane Review of 23 randomized controlled trials
- Moderate Quality: Further research is likely to have an important impact on our confidence on the estimate of effect and may change the estimate

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Illustrative Comparative Risks</th>
<th>Relative Effect</th>
<th>Quality of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clostridium difficile</strong></td>
<td>Control: 55 per 1,000 Probiotic: 20 per 1,000</td>
<td>RR 0.36 (0.26-0.51) NNT = 29</td>
<td>Moderate</td>
</tr>
<tr>
<td>associated diarrhea</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Clostridium difficile</strong></td>
<td>Control: 127 per 1,000 Probiotic: 113 per 1,000</td>
<td>RR 0.89 (0.68-0.95)</td>
<td>Moderate</td>
</tr>
<tr>
<td>infection</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Antibiotic</strong></td>
<td>Control: 209 per 1,000 Probiotic: 125 per 1,000</td>
<td>RR 0.60 (0.49-0.72)</td>
<td>Low</td>
</tr>
<tr>
<td>associated diarrhea</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Literature Evaluation

- Systematic review with meta-analysis
- 21 randomized controlled trials
  - *S boulardii* reduced the risk of *Clostridium difficile*-associated diarrhea only in children
    - Children: 2 trials, n=579, RR: 0.25 (CI 0.08-0.73)
    - Adults: 9 trials, n=1,441, RR 0.8 (CI 0.47-1.34)

Non-toxigenic C. difficile

- Randomized, double-blind, placebo-controlled, phase II trial of NTCD-M3 spores
- 173 adults with primary or first CDI recurrence who clinically recovered after treatment
- NTCD-M3 $10^{4-7}$ spores/day for 7-14 days or placebo and followed for 26 weeks
- NTCD-M3 colonization occurred in 69% of patients and lasted up to 22 weeks

Non-toxigenic *C. difficile*

- NTCD-M3 colonization occurred in 69% of patients and lasted up to 22 weeks
  - Colonization lower if toxigenic *C. difficile (TCD)* positive on day 1 of treatment

- *C. difficile* recurrence:
  - 11% M3 vs 30% placebo (OR 0.28; 95% CI 0.11-0.69)
  - 2% M3-colonized vs 31% not-colonized (OR 0.01)
  - 6% TCD(-) on day 1 vs 27% if TCD(+)

Conclusion

• Conflicting data regarding the benefit of probiotics for the prevention of *Clostridium difficile* infection

• The concept makes sense – but the details are important – specific strains and specific strain doses need to be further studied

• Expect to see more data on the horizon!
Patient Case

55 yo male is admitted with T8-9 discitis/osteomyelitis

- Blood: E. coli
- Disc biopsy: E coli

The ID consult team recommends levofloxacin 750 mg PO q24h x8 weeks. The patient’s wife asks you about the utility of probiotics. What do you recommend?

A. No probiotic.
B. Probiotic with S. boulardii
C. Probiotic with multiple species
55 yo male is admitted with T8-9 discitis/osteomyelitis

- Blood: E. coli
- Disc biopsy: E. coli

The ID consult team recommends levofloxacin 750 mg PO q24h x8 weeks. The patient’s wife asks you about the utility of probiotics. What do you recommend?

A. No probiotic.
B. Probiotic with S. boulardii
C. Probiotic with multiple species
Take Home Points

• Consider ordering MRSA nasal PCRs on your patients with pneumonia to assist with de-escalation.

• For severe *Enterobacter, Serratia, and Citrobacter* infections, use a carbapenem or cefepime if good source control.

• Consider probiotics to reduce the risk of antibiotic-associated diarrhea; however, for the prevention of *C. difficile* be on the look out for new strategies.
Thank you for your time!
Retrospective evaluation of 388 patients with VAP who had MRSA detected from nares, trachea or wounds at least 24 hours preceding bronchoscopy

- 54 (13.9%) patients had a positive MRSA nasal PCR
- 37 (9.5%) patients had positive cultures for MRSA

<table>
<thead>
<tr>
<th>Test characteristic</th>
<th>Result</th>
<th>95% confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity (%)</td>
<td>70.3</td>
<td>52.8-83.6</td>
</tr>
<tr>
<td>Specificity (%)</td>
<td>92.0</td>
<td>88.5-94.5</td>
</tr>
<tr>
<td>Positive predictive value (%)</td>
<td>48.1</td>
<td>34.5-62.0</td>
</tr>
<tr>
<td>Negative predictive value (%)</td>
<td>96.7</td>
<td>94.0-98.3</td>
</tr>
</tbody>
</table>
Literature Evaluation

- Retrospective evaluation of 165 patients with confirmed pneumonia who had an MRSA nasal PCR and lower respiratory tract cultures within 24 h of ICU admission
- 28 (17%) patients had a positive MRSA nasal PCR
- 10 (6%) patients had positive cultures for MRSA

<table>
<thead>
<tr>
<th>Test characteristic</th>
<th>Result</th>
<th>95% confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity (%)</td>
<td>80.0</td>
<td>44.2-96.5</td>
</tr>
<tr>
<td>Specificity (%)</td>
<td>87.1</td>
<td>80.5-91.8</td>
</tr>
<tr>
<td>Positive predictive value (%)</td>
<td>28.6</td>
<td>14.0-48.9</td>
</tr>
<tr>
<td>Negative predictive value (%)</td>
<td>98.5</td>
<td>94.3-99.7</td>
</tr>
</tbody>
</table>

Clinical Experience

- Antimicrobial stewardship study; 2009-2011; 139 patients, 8.6% MRSA positive throat or nasal culture on chromogenic agar, test rec by ASP for cx neg HCAP, CPIS <6 and neg surveillance cultures thought safe to discontinue anti-MRSA therapy

Background - Concern

- Multidrug resistant organisms
  - Plasmids (e.g., carbapenemases, ESBLs, some AmpC)
  - Chromosomal (e.g., mecA (methicillin-resistance))
  - Inducible chromosomal: other AmpC

- Which organisms carry inducible AmpC?
  - Genetically:
  - Phenotypically: 38% Enterobacter spp, 15% Serratia marcescens, 1% Citrobacter spp.

Interactive Question

Which of the following is true:

A. A positive MRSA nasal PCR is helpful, but a negative test doesn’t mean much

B. A negative MRSA nasal PCR is helpful to de-escalate anti-MRSA therapy for most patients

C. A positive MRSA nasal PCR means you should always treat for MRSA, and a negative test means you should never treat for MRSA
Interactive Question

Which of the following is true:

A. A positive MRSA nasal PCR is helpful, but a negative test doesn’t mean much

B. A negative MRSA nasal PCR is helpful to de-escalate anti-MRSA therapy for most patients

C. A positive MRSA nasal PCR means you should always treat for MRSA, and a negative test means you should never treat for MRSA
AmpC vs ESBL

<table>
<thead>
<tr>
<th>Susceptibility</th>
<th>Expressed AmpC</th>
<th>ESBL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbapenems</td>
<td>97%</td>
<td></td>
</tr>
<tr>
<td>Cefepime</td>
<td>96%</td>
<td></td>
</tr>
<tr>
<td>Piperacillin-tazobactam</td>
<td>22%</td>
<td></td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>0% (&lt;=1)</td>
<td></td>
</tr>
<tr>
<td>Ceftazidime</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aztreonam</td>
<td>19%</td>
<td></td>
</tr>
</tbody>
</table>

In a study of 472 patients with ESBL E. coli, K. pneumoniae, and E. cloacae bacteremia, propensity score matching between cefepime and carbapenem therapy

- 30-day mortality rates of those empirically, appropriately treated with cefepime was higher than a carbapenem: 58.8% vs 17.9%
- Mortality was associated with cefepime MIC
- Authors suggest an MIC breakpoint of 1, rather than 8 for the treatment of potentially ESBL organisms