Breaking the Ring
β-Lactamases and the Great Arms Race

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Mayo Clinic - Rochester
Disclosures

• I have no relevant financial relationships to disclose
Objectives

• Discuss the evolving epidemiology of multi-drug resistant gram negative organisms.

• Review pertinent differences between several classes of beta lactamases.

• Review new agents available for the treatment of multi-drug resistant gram negative organisms.

• Discuss the pharmacologic management of patients infected with carbapenemase-producing bacteria.
Beta Lactamases

- Penicillin
- Cephalosporin
- Carbapenem
- Monobactam
Beta Lactamases

- Ancient enzymes that have evolved in bacteria over the last 2 billion years
- Structurally similar to penicillin binding proteins
A Growing Threat

Annual Deaths in the United States in Thousands

Motor Vehicle Accident
Firearms
Falls
MDR Infection

National Health Interview Survey. CDC. 2014
### Beta Lactamase Classification

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Beta Lactamases – TEM-1, TEM-2

- “Broad spectrum”
  - Penicillins, 1st generation cephalosporins
- Very common in the United States
- Responsible for ampicillin and cefazolin resistance in most Enterobacteriaceae, as well as H. influenzae.
- Reliably inhibited by clavulanic acid, sulbactam, and tazobactam
- Cannot hydrolyze 3rd/4th generation cephalosporins

Beta Lactamases – TEM-3, CTX-M

- "Extended spectrum"
  - Penicillins, aztreonam, oxyimino beta lactams

- Increasingly common in the United States
- Variable susceptibility to beta lactamase inhibitors

Ceftriaxone  
Cefepime  
Ceftaroline

Case #1

TJ, a 68 year old male, is admitted to the general ward with community acquired pneumonia.

PMHx: T2DM, hypertension, COPD

A sputum gram stain reveals gram negative rods and the next day, the lab reports the following:

Sample: induced sputum        April 5, 2016

4+ *Haemophilus influenzae*

* Beta-lactamase positive (susceptibilities in progress)
Case #1

Which of the following agents are expected to remain active against TJ’s *H. influenzae* isolate?

1. Cefazolin
2. Ampicillin
3. Ampicillin/Sulbactam
4. Ceftriaxone
5. 3 & 4
Beta Lactamases – Amp-C

• Produced by *Serratia*, *Enterobacter*, and *Citrobacter*

• Most commonly encoded on the bacterial chromosome (rather than plasmid)
  • Not constitutively expressed

• Production is induced by exposure to certain beta lactams:
  • Strong inducers: ampicillin, cefazolin, cephalothin
  • Weak inducers: Ceftriaxone, ceftazidime, cefepime, piperacillin, aztreonam, beta-lactamase inhibitors

Case #2

ST is a 21 year old female with fistulizing Crohn’s disease admitted to the SICU with septic shock secondary to an intestinal perforation.

- Blood cultures are drawn and antibiotics initiated
  - Vancomycin, piperacillin/tazobactam, caspofungin
- Ex-lap with closure performed in the OR
- Blood cultures are reported positive with 6/6 bottles growing Gram negative rods
Case #2

Enterobacter aerogenes

<table>
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<th>Antibiotic</th>
<th>MIC (μg/mL)</th>
<th>Susceptibility</th>
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<td>&gt;16</td>
<td>R</td>
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<td>R</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>1</td>
<td>S</td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>2</td>
<td>S</td>
</tr>
<tr>
<td>Cefepime</td>
<td>≤ 2</td>
<td>S</td>
</tr>
<tr>
<td>Meropenem</td>
<td>≤ 1</td>
<td>S</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>4</td>
<td>S</td>
</tr>
<tr>
<td>Tobramycin</td>
<td>2</td>
<td>S</td>
</tr>
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<td>TMP/SMX</td>
<td>&gt; 2/38</td>
<td>R</td>
</tr>
<tr>
<td>Aztreonam</td>
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<td>&gt;4</td>
<td>R</td>
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<td>4</td>
<td>S</td>
</tr>
<tr>
<td>Minocycline</td>
<td>1</td>
<td>S</td>
</tr>
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- Vancomycin and levofloxacin are discontinued and piperacillin/tazobactam is continued as definitive therapy.
- Three days later, ST remains febrile, hypotensive, and bacteremic.
Case #2

Which of the following most likely explains ST’s clinical failure?

1. Non-optimized pharmacokinetics/dynamics
2. Lack of source control
3. Inducible beta lactamases
4. Piperacillin allergy
Case #2

Your team asks the lab to re-run antimicrobial susceptibilities on a new blood culture:

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<td>R</td>
<td></td>
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<td>&gt;16</td>
<td>R</td>
<td>Pip/Taz</td>
<td>&gt;64/16</td>
<td>R</td>
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<td>2</td>
<td>S</td>
<td></td>
<td>Meropenem</td>
<td>1</td>
<td>S</td>
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<td></td>
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<td>&gt; 16</td>
<td>R</td>
<td>Minocycline</td>
<td>1</td>
<td>S</td>
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How should ST’s treatment be modified?
The Use of Cefepime for Treating AmpC Beta-Lactamase-Producing Enterobacteriaceae

Pranita D. Tamma, Sonta C. T. Girdwood, Ravindra Gopaul, Tsigereda Tekle, Ava A. Roberts, Anthony D. Harris, Sara E. Cosgrove, Karen C. Carroll

Tamma PD, Clin Infect Dis. 2013
399 Patients w/ cultures growing Enterobacter, Serratia, or Citrobacter.

96 (24%) isolates tested positive for AmpC

78 (81%) met eligibility for inclusion

- Enterobacter: 38%
- Serratia: 15%
- Citrobacter: 1%

46 prescribed cefepime (1-2 g q8h)

32 prescribed meropenem (1-2 g q8h)

More likely to have:
- History of MDR organisms
- Comorbidities
- Compromised immunity

Tamma PD, Clin Infect Dis. 2013
Tamma, et al.

- Mortality was best predicted by ICU stay, need for mechanical ventilation, and vasopressor use, but not antibiotic selection.
- One possible case of emergence of cefepime resistance occurred
- > 93% of patients had adequate source control
Amp-C Take-Home Points

• Amp-C producing bacteria can “trick” the clinician into prescribing inappropriate therapy.
• Enterobacter spp. are most likely to produce Amp-C beta lactamases. Amp-C production by Citrobacter is rare.
• Cefepime is a reasonable alternative to carbapenems, but the MIC matters.
• Beware of the “inoculum effect.”
Cefepime MIC and Amp-C

Enterobacter cloacae BSI 30-Day Mortality

# Amp-C and the Inoculum Effect

**Amp-C-Producing *Klebsiella pneumoniae* (n = 28)**

<table>
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<tr>
<th>Inoculum Size</th>
<th>10⁵ cfu/mL</th>
<th>10⁷ cfu/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Range</td>
<td>50%</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>8 - &gt;256</td>
<td>&gt;256</td>
</tr>
<tr>
<td>Cefepime</td>
<td>≤ 0.25 – 16</td>
<td>1</td>
</tr>
<tr>
<td>Imipenem</td>
<td>≤ 0.25 – 1</td>
<td>0.25</td>
</tr>
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**Bottom Line**

- Use a carbapenem when you have suboptimal source control.
- Use a carbapenem if the cefepime MIC is > 2.

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A Growing Threat

Scopes That Spread UCLA 'Superbug' Were Awaiting FDA Clearance
By SYDNEY LUPKIN • Mar 4, 2015, 1:49 PM ET

Science Says Super Bacteria Coming to Kill Us Is Imminent, "People Will Die"
By Jon Levine
November 19, 2015 10:42 AM

HUNTING THE NIGHTMARE BACTERIA
Illinois “Nightmare Bacteria” Outbreak Raises Alarms
JANUARY 8, 2014 / by JASON M. BRESLOW

HUNTING THE NIGHTMARE BACTERIA
OCTOBER 22, 2013 // 54:11
Carbapenemases Around the Globe

NDM-1
OXA-48
KPC


CDC. 2015
CRE – Treatment Options

• Carbapenems
• Polymyxins
  • Colistin and polymyxin B
• Tetracyclines
  • Tigecycline
• Aminoglycosides
• Fosfomycin
• Avibactam
Carbapenems

- *Enterobacteriaceae* is considered “resistant” to meropenem when the MIC is $\geq 4$ mcg/mL

- Time above MIC of 40% (40% T>MIC) is achievable with high doses and extended infusions

Carbapenems – The MIC Matters

Probability of ≥40% T>MIC (%)

Meropenem MIC (mcg/mL)

Carbapenems - Synergy

- Dual carbapenem treatment has been described
  - Ertapenem + meropenem
  - Ertapenem + doripenem

- Both combinations are synergistic *in vitro*
  - Several reports of synergy in truly carbapenem resistant organisms

- Limited to case reports
  - Largest case series published to date reports 39% overall success rate, and 79% microbiological success rate

Polymyxins

• Utility is limited by significant nephro- and neurotoxicity.

• *Serratia, Proteus, and Providencia* are intrinsically resistant.

• Often the sole “sensitive” antimicrobial on the panel.

Polymyxin monotherapy **will** fail.


Fosfomycin

• In general, treatment should be limited to lower urinary tract infections

• A single case report describes clearance of KPC bacteremia after high dose oral therapy with fosfomycin, in addition to doxycycline and meropenem

• 9 grams orally every 8 hours

Avibactam

Clavulanic Acid

Sulbactam

Tazobactam

Avibactam

Avibactam

- Non-beta lactam beta lactamase inhibitor with activity against Ambler Class A, C, and D enzymes.
  - Including KPC
  - No activity against metallo-beta lactamases
- FDA approval in combination with ceftazidime for complicated intraabdominal infections and complicated urinary tract infections
  - CRE poorly represented in phase 3 studies

## Avibactam

<table>
<thead>
<tr>
<th>Antibiotic Concentration (mcg/mL)</th>
<th>0.5</th>
<th>1</th>
<th>2</th>
<th>4</th>
<th>8</th>
<th>16</th>
</tr>
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<tr>
<td>Ceftazidime</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>4%</td>
<td>7%</td>
</tr>
<tr>
<td>Ceftazidime + Avibactam</td>
<td>38%</td>
<td>79%</td>
<td>92%</td>
<td>97%</td>
<td>100%</td>
<td>-</td>
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% of KPC Isolates Inhibited (n = 108)

Case

- You receive a call from a frantic provider who exclaims over the phone, “I have a patient growing Klebsiella that’s resistant to everything!” What should I do?

You look up the patient’s medical record and find the following culture:
### Case

**Klebsiella pneumoniae**

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<tr>
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<td>2 S</td>
<td>Fosfomycin</td>
<td>&gt;128 R</td>
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**BLOOD (aerobic)**

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- The provider explains that this patient has recurrent episodes of urosepsis due to a chronic indwelling urinary catheter and “each subsequent infection is more resistant.”
Case

- Which of the following statements is true?
  1. This organism produces a carbapenase and meropenem should be avoided.
  2. Tigecycline + polymyxin B is a viable treatment option.
  3. Extended infusion meropenem + colistin is a viable treatment option.
  4. Colistin monotherapy is a viable treatment option.
Case

• Suppose the meropenem MIC > 16. Which of the following would be reasonable salvage options?
  1. Initiate treatment with ceftazidime/avibactam
  2. Attempt dual carbapenem treatment
  3. Extended infusion meropenem + colistin
  4. 1 & 2

★ 4. 1 & 2
Summary

• Not all beta lactamases require “big gun antibiotics.”

• Beware of AmpC production in Enterobacter.
  • Have a low threshold to redo susceptibilities in a patient failing therapy.

• Carbapenemases are becoming increasingly common.
  • Creativity is needed to treat patients with carbapenemase-producing bacteria.
Questions & Discussion