Interactive Cases: Management of Multidrug-Resistant GNB

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Disclosures

Honoraria:
Merck (Advisory Boards, Speaker)
Verity (Advisory Boards)
Cipher (Advisory Board)

Travel Reimbursement:
Merck (Symposium)
Copan (User Group, Scientific Workshop)

Research Support:
Accelerate Diagnostics (Summer Student Funding)
Objectives

By the end of this session, you should be able to:

1. Discuss case-based scenarios for the management of multi-drug resistant Gram-negative infections
Question 1

In which area do you primarily work?
1. Infectious Disease
2. Microbiology
3. Antimicrobial Stewardship
4. Infection Control
5. Pharmacy
6. Other
Case 1 - You’re in Trouble

- 88F admitted to Gen Medicine from home admitted with fever and dysuria and frequency
- Recent admission for feeling unwell:
  - BC 2/2 negative
  - Admission rectal swab positive for NDM+ *E. coli*
- Urine and BC 2/2 sent
Question 2

Which agent would you consider empirically?
1. TMP-SMX
2. Ciprofloxacin
3. Oral fosfomycin
4. Ceftriaxone
5. Ertapenem
6. Meropenem
7. Piperacillin-tazobactam
8. Other antimicrobial agent
9. No treatment
Case 1 – Preliminary Results

Source: Blood Culture
Site: PERIPHERAL

Test Results

Culture and Sensitivity:
No growth
Case 1 – Preliminary Results

Source: Urine
Site: _____

Test Results

Culture and Sensitivity:
Klebsiella pneumoniae
>100 x E6 cfu/L
Question 3

Would this change your empiric choice?
1. Yes – narrow
2. Yes – broaden
3. No
Case 1 – Updated Results

Source: Urine
Site: _____

Test Results

Culture and Sensitivity:
Klebsiella pneumoniae

>100 x E6 cfu/L
NDM and OXA48 carbapenemase gene DETECTED by Cepheid Xpert CARBA-R Assay (for research use only). This assay is able to detect NDM, KPC, OXA48, OXA181, OXA232, IMP-1, and VIM carbapenemase genes.
Case 1 – Susceptibility Results

<table>
<thead>
<tr>
<th>K. pneumonia</th>
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<tbody>
<tr>
<td>Amikacin</td>
<td>R</td>
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<tr>
<td>Amoxicillin/Clavulanate</td>
<td>R</td>
</tr>
<tr>
<td>Ampicillin</td>
<td>R</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>R</td>
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<tr>
<td>Cephalexin</td>
<td>R</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>R</td>
</tr>
<tr>
<td>Doxycycline</td>
<td>R</td>
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<tr>
<td>Ertapenem</td>
<td>R</td>
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<tr>
<td>Gentamicin</td>
<td>R</td>
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<tr>
<td>Meropenem</td>
<td>R</td>
</tr>
<tr>
<td>Nitrofurantoin</td>
<td>R</td>
</tr>
<tr>
<td>Piperacillin/Taz</td>
<td>R</td>
</tr>
<tr>
<td>Tobramycin</td>
<td>R</td>
</tr>
<tr>
<td>Trimethoprim/sulfa</td>
<td>R</td>
</tr>
</tbody>
</table>

Meropenem MIC $\geq 16$ mg/L
Pip-tazo MIC $\geq 128/4$ mg/L
Question 4

What would you change your treatment to?

1. Tigecycline
2. Colistin
3. Oral fosfomycin
4. Ceftolozane-tazobactam
5. Prolonged infusion
6. Combination treatment
7. Other antimicrobial agent
Culture and Sensitivity:
Klebsiella pneumoniae

>100 x E6 cfu/L
NDM and OXA48 carbapenemase gene DETECTED by Cepheid Xpert CARBA-R Assay (for research use only). This assay is able to detect NDM, KPC, OXA48, OXA181, OXA232, IMP-1, and VIM carbapenemase genes.

**COLISTIN MIC is 0.125 mg/L.**
There are no CLSI standards for this drug. EUCAST suggests MICs <=2 mg/L correlate with susceptibility. Please consult the microbiologist-on-call with any questions.

**TIGECYCLINE MIC = 4 mg/L**
There are no CLSI standards for this drug. EUCAST suggests MICs >0.5 mg/L correlate with resistance. Please consult the microbiologist-on-call with any questions.

**FOSFOMYCIN zone size = 19 mm**
There are no CLSI standards for fosfomycin and this organism. CLSI suggests zones of inhibition =>16mm correlate with SUSCEPTIBILITY for E. coli. Please consult the microbiologist-on-call with any questions.

Ceftolozane-tazobactam R MIC \( \geq 256 \) mg/L
Question 5

What would you change your treatment to?

1. Tigecycline
2. Colistin
3. Oral fosfomycin
4. Ceftolozane-tazobactam
5. Prolonged infusion
6. Combination treatment
7. Other antimicrobial agent
Question 6

What if the patient’s BC was also positive for this organism? Would you change your treatment to?

1. Tigecycline
2. Colistin
3. IV fosfomycin
4. Ceftolozane-tazobactam
5. Prolonged infusion
6. Combination treatment
7. Other antimicrobial agent
Question 7

For confirmed CPO, does your microbiology laboratory reflex all β-lactam agents as resistant?

1. Yes
2. No
Case 2 – Abscess Angst

- 64M recent renal transplant with multiple past admissions for UTIs, admitted to the transplant unit after presenting with fever, flank pain, and surgical site drainage
- Found to have a peri-nephric collection on imaging
- A drain is placed and purulent material is sent for culture
- BC 2/2 are also sent
Case 2 – Preliminary Results

Source: Blood Culture
Site: PERIPHERAL

Test Results

Culture and Sensitivity:
No growth
Case 2 – Preliminary Results

Source: Wound Drainage
Site: ABDOMINAL

Test Results

Gram Stain:
  3+ pus cells
  2+ gram negative bacilli

Culture and Sensitivity:
  UPDATED REPORT
  Escherichia coli
    Heavy growth
Question 8

Which antimicrobial agent would you start?

1. TMP-SMX
2. Ciprofloxacin
3. Ceftriaxone
4. Ertapenem
5. Piperacillin-tazobactam
6. Meropenem
7. Other
## Case 2 – Susceptibility Results

<table>
<thead>
<tr>
<th></th>
<th>E. coli</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amoxicillin/Clavulanate</td>
<td>R</td>
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<tr>
<td>Ampicillin</td>
<td>R</td>
</tr>
<tr>
<td>Cefazolin</td>
<td>R</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>R</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>R</td>
</tr>
<tr>
<td>Ertapenem</td>
<td>R</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>S</td>
</tr>
<tr>
<td>Meropenem</td>
<td>S</td>
</tr>
<tr>
<td>Piperacillin/Taz</td>
<td>R</td>
</tr>
<tr>
<td>Tobramycin</td>
<td>S</td>
</tr>
<tr>
<td>Trimethoprim/sulfa</td>
<td>R</td>
</tr>
</tbody>
</table>

Gentamicin S
Tobramycin S
Meropenem S
Question 9

What would you change your treatment to?

1. Gentamicin
2. Tobramycin
3. Meropenem
4. Other
Question 10

You note that the patient had a past meropenem-I E. coli isolated from urine. What would you use?

1. Gentamicin
2. Tobramycin
3. Meropenem
4. Tigecycline
5. Colistin
6. Ceftolozane-tazobactam
7. Combination treatment
8. Other
Culture and Sensitivity:

*Updated Report*

*Escherichia coli*

- **Heavy growth**
- **Tigecycline MIC = 0.25 mg/L**
  
  There are no CLSI standards for this drug. EUCAST suggests MICs $\leq 0.5$ mg/L correlate with susceptibility. Please consult the microbiologist-on-call with any questions.

- **Colistin MIC is $\leq 0.25$ mg/L**
  
  There are no CLSI standards for this drug. EUCAST suggests MICs $\leq 2$ mg/L correlate with susceptibility. Please consult the microbiologist-on-call with any questions.

**Ceftolozane/tazobactam S MIC 0.75 mg/L**
Question 11

Which agent would you consider using?

1. Gentamicin
2. Tobramycin
3. Meropenem
4. Tigecycline
5. Colistin
6. Ceftolozane-tazobactam
7. Combination treatment
8. Other antimicrobial agent
### Test Results

<table>
<thead>
<tr>
<th></th>
<th>E. coli</th>
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<tbody>
<tr>
<td>Amoxicillin/Clavulanate</td>
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</tr>
<tr>
<td>Ampicillin</td>
<td>R</td>
</tr>
<tr>
<td>Cefazolin</td>
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</tr>
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<td>Ceftriaxone</td>
<td>R</td>
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<td>Ciprofloxacin</td>
<td>R</td>
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<tr>
<td>Ertapenem</td>
<td>R</td>
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<tr>
<td><strong>Gentamicin</strong></td>
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<td>Piperacillin/Taz</td>
<td>R</td>
</tr>
<tr>
<td><strong>Tobramycin</strong></td>
<td>S</td>
</tr>
<tr>
<td>Trimethoprim/sulfa</td>
<td>R</td>
</tr>
</tbody>
</table>

Gentamicin S  
Tobramycin S  
Meropenem R
Case 3 – Pseudo trouble

- 59M with bronchiectasis admitted to Gen Medicine from home admitted with increased sputum production and shortness of breath
- Multiple past sputum cultures positive for *Pseudomonas aeruginosa*, some intermediate to ciprofloxacin, ceftazidime, gentamicin, and piperacillin-tazobactam
- Sputum culture ordered
Question 12
Which agent would you use empirically?
1. Ciprofloxacin
2. Ceftazidime
3. Piperacillin-tazobactam
4. Meropenem
5. Gentamicin
6. Tobramycin
7. Amikacin
8. Combination treatment
9. Other antimicrobial agent
Case 3 – Culture Results

Source: Sputum
Site:
Gram Stain:
  3+ pus cells
  Few epithelial cells
  2+ commensal flora

Culture and Sensitivity:
  Pseudomonas aeruginosa
    Heavy growth

<table>
<thead>
<tr>
<th>P. aerug</th>
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<tbody>
<tr>
<td>Ceftazidime</td>
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<td>Ciprofloxacin</td>
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<td>Meropenem</td>
</tr>
<tr>
<td>Piperacillin/Taz</td>
</tr>
<tr>
<td>Tobramycin</td>
</tr>
</tbody>
</table>

Tobramycin S
Question 13

What would you choose now?
1. Tobramycin
2. Colistin
3. Ceftolozane-tazobactam
4. Meropenem prolonged infusion
5. Combination treatment
6. Other antimicrobial agent
## Case 3 – Additional Susc. Results

<table>
<thead>
<tr>
<th>P. aeruginosa</th>
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</thead>
<tbody>
<tr>
<td>Ceftazidime</td>
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</tr>
<tr>
<td>Ceftolozane-Tazobactam</td>
<td>S</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>I</td>
</tr>
<tr>
<td>Colistin</td>
<td>S</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>I</td>
</tr>
<tr>
<td>Meropenem</td>
<td>I</td>
</tr>
<tr>
<td>Piperacillin/Taz</td>
<td>R</td>
</tr>
<tr>
<td>Tobramycin</td>
<td>S</td>
</tr>
</tbody>
</table>

- Ceftolozane-tazobactam **S**
- Colistin **S**
- Tobramycin **S**
Question 14

What would you change your treatment to?
1. Tobramycin
2. Colistin
3. Ceftolozane-tazobactam
4. Meropenem prolonged infusion
5. Combination treatment
6. Other antimicrobial agent
Performance of Ceftolozane-Tazobactam Etest, MIC Test Strips, and Disk Diffusion Compared to Reference Broth Microdilution for β-Lactam-Resistant *Pseudomonas aeruginosa* Isolates

Romney M. Humphries,* Janet A. Hindler,† Paul Magnano,‡ Annie Wong-Beringer,§ Robert Tibbetts,∥ Shelley A. Miller*°

- 308 β-lactam resistant *P. aeruginosa*
- BMD used as reference

<table>
<thead>
<tr>
<th>Error</th>
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<th>Etest</th>
<th>Liofilchem</th>
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<td>0</td>
<td>0</td>
</tr>
<tr>
<td>ME</td>
<td>0</td>
<td>0</td>
<td>0.9%</td>
</tr>
<tr>
<td>mE</td>
<td>7.1%</td>
<td>3.2%</td>
<td>12.3%</td>
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<tr>
<td>EA</td>
<td>N/A</td>
<td>97.7%</td>
<td>87%</td>
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JCM 2018;56(3):e01644-17
### Cefto-tazo Etest vs. BMD:

#### Number of isolates with BMD MIC (µg/mL)

<table>
<thead>
<tr>
<th>MIC (µg/mL)</th>
<th>S</th>
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<th>R</th>
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<tr>
<td>S</td>
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<td>10</td>
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</table>

### Cefto-tazo Liofilchem vs. BMD:

#### Number of isolates with BMD MIC (µg/mL)

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<th>MIC (µg/mL)</th>
<th>S</th>
<th>I</th>
<th>R</th>
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<tbody>
<tr>
<td>S</td>
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<td>5</td>
<td>18</td>
<td>4</td>
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</table>

### Number of isolates with MTS MIC (µg/mL)

<table>
<thead>
<tr>
<th>MIC (µg/mL)</th>
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<th>I</th>
<th>R</th>
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</thead>
<tbody>
<tr>
<td>S</td>
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</tr>
<tr>
<td>0.12</td>
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<td>R</td>
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<tr>
<td>1</td>
<td></td>
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<td>62</td>
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</tbody>
</table>
Case 4 – A Negative Future

- 63F with bronchiectasis admitted for double lung transplant
- Multiple past sputum cultures positive for MDR *Pseudomonas aeruginosa*
- Pre-lung transplant surveillance BAL sent for culture with the goal to direct post-transplant prophylactic antimicrobial treatment
Case 4 – Preliminary Results

Source: Bronchial Alveolar Lavage

Site:

Test Results

Gram Stain:
- Pus cells seen.
- Epithelial cells seen.
- Gram negative bacilli seen.

Culture and Sensitivity:
Pseudomonas aeruginosa

=>10 x E6 cfu/L SIGNIFICANT RESULT. Organisms cultured in quantities =>10 x E6 cfu/L are consistent with pneumonia.
## Case 4 – Susceptibility Results

### Test Results

<table>
<thead>
<tr>
<th></th>
<th>P. aerug</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Amikacin</td>
<td>R</td>
<td></td>
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<tr>
<td>Aztreonam</td>
<td>R</td>
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<tr>
<td>Cefepime</td>
<td>R</td>
<td></td>
</tr>
<tr>
<td>Ceftazidime</td>
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<td>Ciprofloxacin</td>
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<td>Colistin</td>
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<td>Gentamicin</td>
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<td>Meropenem</td>
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<td></td>
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<tr>
<td>Tobramycin</td>
<td>R</td>
<td></td>
</tr>
</tbody>
</table>

Pip-tazo $\geq 128/4$ mg/L
Meropenem MIC $\geq 32$ mg/L
Pseudomonas aeruginosa

=>10 x E6 cfu/L SIGNIFICANT RESULT. Organisms cultured in quantities =>10 x E6 cfu/L are consistent with pneumonia.

CHLORAMPHENICOL disk diffusion zone size = 16mm
There are no CLSI standards for chloramphenicol and Ps. aeruginosa.

CLSI suggests zones of 16mm correlate with intermediate susceptibility for Enterobacteriaceae.

FOSFOMYCIN disk diffusion zone size = 6mm
There are no CLSI standards for fosfomycin and Ps. aeruginosa. EUCAST suggests combinations of fosfomycin and other agents may be useful for isolates with fosfomycin MIC <128 mg/L (equivalent to zone sizes ≥13mm based on extrapolation from CLSI fosfomycin interpretive criteria for E. coli.)

Ceftolozane-tazobactam R MIC = 64 mg/L
Question 15

What would you use prophylactically?

1. Inhaled colistin
2. Inhaled tobramycin
3. Inhaled colistin and tobramycin
4. Combination treatment
5. Other antimicrobial agent
6. Nothing
Question 16

What would you consider if this patient developed post-operative pneumonia due to this organism?

1. Combination treatment
2. Special access request for ceftazidime-avibactam
3. Special access request for imipenem-relebactam
4. Special access request for meropenem-vaborbactam
5. Special access request for plazomicin
6. Phage therapy
7. New lung transplant
8. Other
B.C. man challenging Health Canada for phage treatment

A Vancouver Island man is hoping to become the first person in Canada to receive an experimental treatment for deadly superbugs. Phage therapy works by using viruses to target antibiotic-resistant bacteria. Jeff Semple reports on the new push to give Canadians access to the potentially life-saving treatment.
Summary

• Case 1 – NDM+ OXA48+ *K. pneumoniae* UTI
  – CPO plasmids readily move between and in/out of organisms
  – Challenges with lack of breakpoints/delays for second line agents

• Case 2 - ESBL *E. coli* perinephric abscess
  – Potential for meropenem non-susceptibility due to porin changes

• Case 3 MDR *P. aeruginosa* bronchiectasis
  – Challenges with lack of breakpoints/delays for second line agents

• Case 4 PDR *P. aeruginosa* lung transplant recipient lung
  – Untreatable organisms & need for special access, phage, transplant?