“Nightmare Bacteria”
How to Deal with the Reality of Carbapenem-resistant Organisms

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Pharmacist Objectives
- Describe mechanisms of carbapenem-resistance
- Design treatment regimens for carbapenem-resistant organisms
- Identify emerging antibiotics with activity against carbapenem-resistant organisms

Disclosures
- I have no conflicts of interest relative to the content of this presentation

Technician Objectives
- Describe the impact of carbapenem-resistance on public health
- Identify antibiotics used to treat carbapenem-resistant organisms
- Recognize antibiotic doses used to treat carbapenem-resistant organisms

Carbapenem Resistance in 2005

Carbapenem Resistance in 2017
Centers for Disease Control and Prevention 2017
**Carbapenem-resistant Organisms**

- Growing threat to public health
  - *Enterobacteriaceae*
  - *Pseudomonas aeruginosa*
  - *Acinetobacter baumannii*
- Limited therapeutic options
- High mortality rate

Tacconelli E, et al. WHO 2017

**Carbapenem Resistance Mechanisms**

**Carbapenem-resistant Organisms**

- Carbapenemase-producers
  - KPC
  - OXA
  - NDM
  - IMP
  - VIM
- Non-carbapenemase-producers
  - Contain combinations of:
    - ESBL
    - AmpC
    - Porin mutations
    - Efflux pumps
    - Altered binding sites

Clinical and Laboratory Standards Institute 2017

**Antibiotic Armamentarium**

**Carbapenem-resistant *Enterobacteriaceae***

<table>
<thead>
<tr>
<th>Core agents</th>
<th>Adjunctive Agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbenepen + polymyxin</td>
<td>Aminoglycoside</td>
</tr>
<tr>
<td>Ceftazidime-avibactam</td>
<td>Tigecycline</td>
</tr>
<tr>
<td>Meropenem-vaborbactam</td>
<td>Fosfomycin</td>
</tr>
</tbody>
</table>

The Medicines Company 2017

**Treatment Considerations**

- Combination vs. monotherapy
- Site of infection
- Dose optimization
- Duration of therapy
- Adverse effects
- Role of novel agents

**Combination vs. Monotherapy**

- **Carbapenem-resistant *Enterobacteriaceae***

<table>
<thead>
<tr>
<th>Mortality</th>
<th>Combination vs. Monotherapy</th>
<th>Carbapenem combo vs. Non-carbapenem combo</th>
<th>Carbapenem MIC ≤8 vs. Carbapenem MIC &gt;8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combination vs. Monotherapy</td>
<td>50%</td>
<td>40%</td>
<td>30%</td>
</tr>
<tr>
<td>Carbapenem combo vs. Non-carbapenem combo</td>
<td>40%</td>
<td>30%</td>
<td>20%</td>
</tr>
<tr>
<td>Carbapenem MIC ≤8 vs. Carbapenem MIC &gt;8</td>
<td>30%</td>
<td>20%</td>
<td>10%</td>
</tr>
</tbody>
</table>

$p = 0.018$


**Combination vs. Monotherapy**

- **Carbapenem-resistant *Enterobacteriaceae***

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Combination Therapy</th>
<th>Monotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recommended if using traditional agents*</td>
<td>Use carbapenem-containing combination if carbapenem MIC ≤8</td>
<td></td>
</tr>
<tr>
<td>May be reasonable for urinary tract infections in non-critically ill patients</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*MBenefit of combination therapy with novel agents is unclear*

Site of Infection

<table>
<thead>
<tr>
<th>Select Sites</th>
<th>Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bloodstream</td>
<td>Typically avoid tigecycline</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>Consider adjunctive use of inhaled agents (e.g., colistin, aminoglycosides)</td>
</tr>
<tr>
<td>Intra-abdominal</td>
<td>Tigecycline may be a useful adjunct</td>
</tr>
<tr>
<td>Urinary</td>
<td>Aminoglycoside or fosfomycin may be useful</td>
</tr>
<tr>
<td>Central nervous system</td>
<td>Consider adjunctive use of intraventricular agents (e.g., colistin, polymyxin B, aminoglycosides)</td>
</tr>
</tbody>
</table>


Dose optimization

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Dose Optimization Strategies</th>
</tr>
</thead>
</table>
| Carbapenems | • High-dose, prolonged infusions  
• Meropenem 2 g every 8 hours, 3-4 hour infusion |
| Polymyxins  | • Loading dose recommended  
• Polymyxin B does not need renal dosage adjustment |
| Aminoglycosides | • Once-daily dosing  
• Gentamicin or tobramycin 7-10 mg/kg  
• Amikacin 15-20 mg/kg |
| Tigecycline | • High-dose  
• 200 mg loading dose, then 100 mg every 12 hours |


Duration of Therapy

- Optimal duration has not been determined
- Prolonged therapy should be avoided to minimize further development of resistance
- Utilize evidence-based durations according to the site of infection
- Consider the clinical response of the patient
- Guidance by an infectious diseases physician is preferred

Spellberg B. JAMA intern Med 2016;176(9):1254-55

Adverse Effects

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Select Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbapenems</td>
<td>• Seizures (more likely with high doses or dual-carbapenem therapy)</td>
</tr>
</tbody>
</table>
| Polymyxins  | • Nephrotoxicity: colistin (~55%); polymyxin B (~30%)  
• Neurotoxicity |
| Aminoglycosides | • Nephrotoxicity (less likely with once-daily dosing; shortest possible course) |
| Tigecycline | • Gastrointestinal effects may be more severe and dose-limiting when using high-dose therapy |


Novel Agents

- Ceftazidime-avibactam and meropenem-vaborbactam  
  - Active against many (but not all) carbapenemases  
  - Combine ceftazidime-avibactam with aztreonam for metallo-β-lactamases  
- More effective and less toxic than traditional options  
- Limited clinical experience  
- Resistance already detected

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Ceftazidime-avibactam vs. Others

Carbapenem-resistant Klebsiella pneumoniae Bacteremia

- Ceftazidime-avibactam
- Carbapenem + Colistin
- Carbapenem + Aminoglycoside
- Other regimens

Other Carbapenem-resistant Organisms

Organism Specific Considerations

<table>
<thead>
<tr>
<th>Pseudomonas aeruginosa</th>
<th>Acinetobacter baumannii</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Non-carbapenem β-lactams may have activity</td>
<td>• Use ampicillin-sulbactam if active (≥6 g sulbactam/day)</td>
</tr>
<tr>
<td>• Ceftolozane-tazobactam has excellent activity</td>
<td>• High-dose minocycline (200 mg BID) may be useful</td>
</tr>
<tr>
<td>• Benefit of combination therapy is less clear</td>
<td>• Carbapenem-containing combination therapy preferred</td>
</tr>
</tbody>
</table>

Summary

- Carbapenem-resistant organisms are an increasing threat to public health
- The “best” approach to treatment has not been determined
- Novel agents seem to offer enhanced efficacy and safety compared with traditional treatment options

References


Emerging Therapies

- Imipenem-relebactam
- Plazomicin
- Eravacycline
- Aztreonam-avibactam
- Ceftaroline-avibactam
- Alternative agents:
  - Antibiotics, bacteriophages, vaccines, etc.

References


References

Self-assessment – Question 1

- Carbapenem-resistant organisms have not been isolated in Alabama.
  
  A. True
  B. False

Self-assessment – Question 2

- When using a carbapenem to treat carbapenem-resistant organisms, use:
  
  A. Traditional doses
  B. Low doses, intermittent infusions
  C. High doses, prolonged infusions
  D. Never use a carbapenem when it is resistant in vitro

Self-assessment – Question 3

- Novel agents, such as ceftazidime-avibactam, seem to be more effective and less toxic than traditional agents used to treat carbapenem-resistant organisms.
  
  A. True
  B. False

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