The Role of Antibiotic Stewardship in Optimizing the Use of New Antibiotics

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Disclosures

• Theravance: consulting—external infection adjudication committee (past)
• Basilea: consulting—external infection adjudication committee (ongoing)
Objectives

• Discuss challenges with positioning the use of new antibiotics in hospitalized patients
• Discuss the role of antibiotic stewardship programs in implementing use of new antibiotics to improve patient care and minimize emergence of resistance
Use of Polymyxins vs. All New $\beta$-Lactam/$\beta$LIs

Unpublished data courtesy of Katherine Goodman and Anthony Harris

Ceftazidime/avibactam available 2015

Meropenem/vaborbactam available
Survey of Pharmacists on Guidelines for Anti-CRE Agents
• 110 pharmacists in 41 states in 12/2018

<table>
<thead>
<tr>
<th></th>
<th>FDA approvals</th>
<th>Type of CRE Infection</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>Pneumonia</td>
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<tr>
<td><strong>Ceftazidime-avibactam</strong></td>
<td>cUTI (2/15)</td>
<td>54%</td>
</tr>
<tr>
<td></td>
<td>cIAI (2/15)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>HAP/VAP (2/18)</td>
<td></td>
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<tr>
<td><strong>Meropenem-vaborbactam</strong></td>
<td>cUTI (8/17)</td>
<td>32%</td>
</tr>
<tr>
<td><strong>Plazomicin</strong></td>
<td>cUTI (6/18)</td>
<td>2%</td>
</tr>
<tr>
<td><strong>Polymyxin</strong></td>
<td></td>
<td>4%</td>
</tr>
<tr>
<td><strong>Aminoglycoside</strong></td>
<td></td>
<td>2%</td>
</tr>
<tr>
<td><strong>Ceftolozane-tazobactam</strong></td>
<td>cUTI (12/14)</td>
<td>n/a</td>
</tr>
<tr>
<td></td>
<td>cIAI (12/14)</td>
<td></td>
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<tr>
<td></td>
<td>HAP/VAP (6/19)</td>
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Why is Uptake Slow?

• Primary studies for FDA approval are non-inferiority studies in patients without resistant organisms
  – Pneumonia indications/dosing late or don’t exist

• Low numbers of patients with CRE and MDR-PSA in studies for FDA approval
  – Don’t actually want to have an abundance of MDR-GNRs to study

<table>
<thead>
<tr>
<th>New agent (% success)</th>
<th>Best available therapy (BAT) (% success)</th>
</tr>
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<tbody>
<tr>
<td>Meropenem/vaborbactam for CRE all sites</td>
<td>N = 32 (59%)</td>
</tr>
<tr>
<td>Imipenem/relebactam for MDR-PSA and CRE all sites</td>
<td>N = 21 (71%)</td>
</tr>
</tbody>
</table>

• Post-approval studies take time to be done and published

• Agents are expensive compared to older agents

• Difficulties with susceptibility testing
  – Mainly an issue with ceftolozane/tazobactam early on now much improved

[https://clsi.org/media/2277/clsi_astnewsupdate_june2018_final61118.pdf](https://clsi.org/media/2277/clsi_astnewsupdate_june2018_final61118.pdf)
ASP Considerations

• ASPs recognize that these are the agents of choice for resistant GNRs
  – ASPs are often the primary driver of formulary addition of new agents
  – ASPs often coordinate micro testing, selection of optimal agent(s), duration
  – ASPs critical in recommending optimal dosing strategies
• ASPs desire to ensure that the agents are used in a way to preserve their utility
  – Concerns about emergence of resistance across the population
  – Concerns about emergence of resistance within a patient
  – Concerns about avoiding treatment of colonization (which leads to resistance)
• ASPs unlikely to support routine empiric use of these agents
Resistance To New Agents

- Some baseline resistance
- Differences in resistance based on patient population

<table>
<thead>
<tr>
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<th>Cystic fibrosis patients</th>
<th>Non-cystic fibrosis patients</th>
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<tbody>
<tr>
<td><strong>P. aeruginosa ceftolozane-tazobactam susceptibilities 2017-19 at Johns Hopkins Hospital</strong></td>
<td>10/26 (38.5%)</td>
<td>54/72 (75%)</td>
</tr>
</tbody>
</table>

- Emergence of resistance on therapy
  - 37 CRE infections treated with ceftazidime/avibactam
    - Most pneumonia, bacteremia, intra-abdominal
    - Microbiologic failure in 27%
      - Resistance in 3/10 failures developing at a median of 15 days
  - 35 MDR *P. aeruginosa* infections treated with ceftolozane/tazobactam
    - Most pneumonia and intra-abdominal
    - Microbiologic failure in 26%
      - Resistance in 6/10 failures developing at a median of 6 days

Why Does Emergence of Resistance Matter?

- Most patients with MDR GNR infections have significant medical complications
  - Issues with source control (particularly intra-abdominal infections)
  - Need for future solid organ transplant, HSCT, chemotherapy
- Often need to consider timing of use of last-resort antibiotics to maximize utility in the window before emergence of resistance
Other Challenges

• Paying for agents after discharge from the hospital
  – Insurance often does not cover outpatient antibiotics, particularly when used off-label
  – Nursing homes often don’t have the agents and balk about obtaining them due to cost

• Changes to the Inpatient Prospective Payment System and the Long-Term Care Hospital Prospective Payment System for FY2020 do not address these problems
Agents Not Directed at MDR-GNRs

• FDA approved based on non-inferiority studies for infections that we do not have a big problem with
  – Delafloxacin (CAP, ABSSSI)
  – Omadacycline (CAP, ABSSSI)
  – Lefamulin (CAP)

• Cost 10-25 times more than standard therapy

• Hard to justify preferential use of these agents in the hospital for current indications

• BUT—these agents may be important for other infections
  – Need a mechanism to keep them available to investigate them further (e.g., omadacycline for *M. abscessus*, Acinetobacter; lefamulin for *M. genitalium*)
What Can Be Done to Ensure Optimal Use of New Agents?

• Better education of ID specialists and others who care for patients with CRE and MDR PSA, Acinetobacter
  – Guidelines/guidance for these infections that can be modified/updated regularly
• Post-approval data on utility for MDR GNRs from all sites is essential
  – New study designs such as adaptive clinical trials
• Development of approaches to predict what patients may benefit from empiric treatment with these agents to avoid overuse
  – Role of predictive models using machine learning
  – Role of surveillance cultures
  – Role of rapid diagnostics
• Colistin/polymyxin B breakpoint changes will help
  – Intentional decision by CLSI
  – All isolates are either Intermediate (</=2) or Resistant (>/=4)
• Continue to ensure that methods for susceptibility testing are available when the agent becomes available