Frequency of Occurrence and Antimicrobial Susceptibility of Bacteria from ICU Patients with Pneumonia

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- VenatoRX
- Vertex
- Wockhardt
- Zavante
- Other corporations

Some JMI employees are advisors/consultants for Allergan, Astellas, Cubist, Pfizer, Cempra, and Theravance.
Ceftazidime-avibactam (Allergan/AstraZeneca)

- Ceftazidime is a well described third-generation cephalosporin with broad-spectrum activity
- Avibactam (formerly NXL-104) is a member of a novel class of non-β-lactam β-lactamase inhibitors, the diazabicyclooctanes (DBOs)
- Avibactam can effectively inactivate:
  - Class A: ESBL and KPC
  - Class C: AmpC
  - Some Class D: OXA
β-lactamase Inhibitors

Clinically available

Monobactam derivatives

Penicillin derivative

Penems

Penam Sulphones

Penam Sulphones

Non-β-lactams

MBL inhibitors

Drawz & Bonomo, CMR 2010; 23:160-201
Avibactam

- Avibactam is a non-β-lactam diazabicycloclooctane (DBO)
- Prolonged deacylation rate (slow deacylation through hydrolysis or reversibility)

\[
E + I \rightleftharpoons EI \rightleftharpoons EI^*
\]

- Using a model for slow binding enzymes demonstrated that formation of EI and EI* is fast and more efficient than β-lactam-based BLI

## Spectrum of Activity of Avibactam

<table>
<thead>
<tr>
<th>β-Lactamase</th>
<th>Clavulanate</th>
<th>Tazobactam</th>
<th>Avibactam</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Class A</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TEM, SHV and ESBLs</td>
<td>√</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>CTX-M and ESBLs</td>
<td>√</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>PER, VEB, GES</td>
<td>√</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>KPC</td>
<td>X</td>
<td>X</td>
<td>√</td>
</tr>
<tr>
<td><strong>Class B</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IMP, VIM, NDM</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td><strong>Class C</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chromosomal <em>Enterobacteriaceae</em> AmpC</td>
<td>X</td>
<td>X</td>
<td>√</td>
</tr>
<tr>
<td>Chromosomal <em>Pseudomonas</em> AmpC</td>
<td>X</td>
<td>X</td>
<td>√</td>
</tr>
<tr>
<td>Plasmidic ACC, DHA, FOX, LAT, MIX, MIR, ACT</td>
<td>X</td>
<td>X</td>
<td>√</td>
</tr>
<tr>
<td><strong>Class D</strong></td>
<td>Variable OXA-1, -10</td>
<td>Variable OXA-23, -48</td>
<td>Variable OXA-1, 31</td>
</tr>
<tr>
<td>Penicillinase-type OXA-1, -31, -10, -13</td>
<td>Variable OXA-1, -10</td>
<td>Variable OXA-23, -48</td>
<td>Variable OXA-1, 31</td>
</tr>
<tr>
<td>Carbapenemase-type OXA-23, -40, -48, -58</td>
<td>Variable OXA-23, -48</td>
<td>Variable OXA-48</td>
<td>Variable OXA-48</td>
</tr>
</tbody>
</table>
Ceftazidime-avibactam has been approved by the US FDA and the European Medicine Agency to treat:

- Complicated intra-abdominal infections (in combination with metronidazole)
- Complicated urinary tract infections, including pyelonephritis
- Hospital-acquired pneumonia, including ventilator-associated pneumonia (Europe only)

Dosage: 2,000/500mg q8h (2h infusion)
Objectives

• To evaluate the frequency of occurrence of bacteria isolated from ICU patients with pneumonia, including VAP (2013-2015)

• To evaluate the antimicrobial activities of ceftazidime-avibactam (CAZ-AVI) and comparator agents against bacteria isolated from ICU patients with pneumonia (2013-2015)
Materials and Methods

Bacterial Isolates

• Collected in 2013-2015 as part of the International Network for Optimal Resistance Monitoring (INFORM) Program

• 65 medical centers among 37 states from all nine US Census divisions

• Consecutive collected bacterial isolates from lower respiratory tract sites determined to be significant by local criteria as the reported probable cause of pneumonia
Materials and Methods

Bacterial Isolates

• Only isolates from invasive sampling (transtracheal aspiration, bronchoalveolar lavage, protected brush samples, qualified sputum samples, etc.) were accepted.

• The frequency of occurrence of organisms was based on all organisms collected from patients hospitalized with pneumonia in the same participant medical centers.

• Species identification was confirmed by standard biochemical tests and using the MALDI-TOF, where necessary.
Susceptibility testing

- Broth microdilution test methods by CLSI standards
- Ceftazidime-avibactam with avibactam at fixed concentration of 4 µg/mL
- US FDA breakpoint criteria applied for ceftazidime-avibactam when testing Enterobacteriaceae and *P. aeruginosa*
  - Susceptible at ≤8 µg/mL
  - Resistant at ≥16 µg/mL
Results

- A total of 9,179 isolates from patients with pneumonia
  - 3,632 from ICU patients, including 918 with VAP
- Among organisms from ICU patients
  - 63.7% Gram-negatives
  - 35.7% Gram positives (mainly *S. aureus* 32.9%)
Frequency of Occurrence of Organisms Isolated from Patients with Pneumonia (ICU vs. non-ICU)

**ICU (%)**
- S. aureus: 32.9%
- P. aeruginosa: 7.8%
- Klebsiella spp.: 20.5%
- E. coli: 5.2%
- Enterobacter spp.: 3.1%
- S. maltophilia: 2.4%
- Acinetobacter spp.: 1.4%
- H. influenzae: 1.2%
- S. pneumoniae: 8.7%
- P. mirabilis: 13.0%
- Others: 5.2%

**non-ICU (%)**
- S. aureus: 34.4%
- P. aeruginosa: 6.5%
- Klebsiella spp.: 25.5%
- E. coli: 4.2%
- Enterobacter spp.: 10.0%
- S. maltophilia: 2.8%
- Acinetobacter spp.: 1.9%
- H. influenzae: 2.8%
- S. pneumoniae: 4.3%
- P. mirabilis: 2.2%
- Others: 4.3%
Antimicrobial Susceptibility of *S. aureus* from ICU Patients with Pneumonia (n=1,196)

<table>
<thead>
<tr>
<th>Antimicrobial Agent</th>
<th>% Susceptible</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxacillin</td>
<td>56</td>
</tr>
<tr>
<td>Ceftaroline</td>
<td>97.4</td>
</tr>
<tr>
<td>Linezolid</td>
<td>100</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>100</td>
</tr>
</tbody>
</table>
Antimicrobial Susceptibility of *P. aeruginosa* from Patients with Pneumonia (n=744)

<table>
<thead>
<tr>
<th>Antimicrobial Agent</th>
<th>% Susceptible</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAZ-AVI</td>
<td>97.4</td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>84.1</td>
</tr>
<tr>
<td>Cefepime</td>
<td>85.1</td>
</tr>
<tr>
<td>Pip/Taz</td>
<td>79</td>
</tr>
<tr>
<td>Meropenem</td>
<td>75.8</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>74.6</td>
</tr>
<tr>
<td>Amikacin</td>
<td>98.7</td>
</tr>
<tr>
<td>Colistin</td>
<td>99.9</td>
</tr>
</tbody>
</table>
Antimicrobial Susceptibility of Enterobacteriaceae from Patients with Pneumonia (n=1,365)
Overall Gram-negative Coverage (n=2,335)

<table>
<thead>
<tr>
<th>Antimicrobial Agent</th>
<th>% Susceptible</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAZ-AVI</td>
<td>96.2</td>
</tr>
<tr>
<td>Meropenem</td>
<td>88.1</td>
</tr>
<tr>
<td>Pip/Taz</td>
<td>83.2</td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>84.4</td>
</tr>
<tr>
<td>Levofoxacin</td>
<td>81.5</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>89.7</td>
</tr>
<tr>
<td>Amikacin</td>
<td>97</td>
</tr>
<tr>
<td>Colistin</td>
<td>86.9</td>
</tr>
</tbody>
</table>
Conclusions

• Two-thirds (65.3%) of organisms isolated from ICU patients with pneumonia were Gram-negatives.
• High resistance rates were observed among Gram-positive and Gram-negative organisms isolated from ICU patients with pneumonia.
• Ceftazidime-avibactam (96.2% overall coverage) and amikacin (97.0%) were the most active agents tested against Gram-negative organisms.
• Meropenem and piperacillin/tazobactam were active against 88.1 and 83.1% of Gram-negative organisms overall.
• Ceftazidime-avibactam represents a valuable treatment option for empiric antimicrobial therapy of pneumonia in ICU patients.