Latest Evidence and Guidelines on New Antibiotics: What Antibiotic for which Patient?

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Disclosures

- **Research grants**
  - Astellas, Pfizer, MSD, Gilead

- **Advisor/consultant**
  - Angelini, Astellas, AstraZeneca, Bayer, Basilea, Gilead, Menarini, MSD, Pfizer, Novartis, Shionogi, Vifor, The Medicines company, Tetraphase, Achaogen, Paratek, Cidara

- **Speaker/chairman**
  - Angelini, Astellas, AstraZeneca, Bayer, Pfizer, MSD, Gilead, Vifor, Novartis, Bayer, Tetraphase, Cidara
Defining the best anti-pseudomonas treatment

- Early
- Adequate
- Bactericidal
- Continuous/extended infusion
- In combination
- Old vs new option
Combination therapy: when?

The antimicrobial regimen should be promptly narrowed or discontinued based on culture and susceptibility profile results and on clinical stability.

Empiric
- HAP / VAP / septic shock
- Pts at risk for MDR
- High risk of *P. aeruginosa*

Targeted
- *P. aeruginosa*: Only in empiric initial treatment
- *A. baumannii*?
- *K. pneumoniae* (KPC)

Empirical treatment of severe Pseudomonas aeruginosa infection.
Superior microbiological activity based on the available microbiological data.

- Underlying comorbidities (neutropenia, severe immunosuppression, structural lung disease, solid tumour)
- Previous colonization by MDR/XDR P. aeruginosa strain?
- Previous therapy (within 3 months) with an antipseudomonal β-lactam?
- Hospital setting with a prevalence >15-20% of MDR P. aeruginosa

**YES**
(at any)

**BACKBONE DRUG**
Ceftolozane- tazobactam > ceftazidime- avibactam> meropenem> piperacillin-tazovactam/ ceftazidime/ cefepime

**SECOND ANTI-PSEUDOMONAL AGENT**
Aminoglycoside/ colistin/ fosfomycin> fluoroquinolones

**ALWAYS CONSIDER AN ADEQUATE SOURCE CONTROL OF INFECTION**

**NO (to all)**

**BACKBONE DRUG**
Piperacillin/tazobactam/ carabapenem (mainly meropenem)/ ceftazidime/ cefepime
ANTI-PSEUDOMONAL BETA-LACTAM

+ Fluoroquinolone or aminoglycoside iv/ae or Colistin iv + aerosol

+ Aminoglycoside or colistin or fosfomycin

+ Aminoglycoside or colistin
MDR Gram-Negative Infections and C/T: Impact of Delayed Initiation
Multicenter, Retrospective Study (US Jan 2015 – Feb 2018)

- Delaying ceftolozane/tazobactam (C/T) initiation by ~5 days substantially increases the risk of mortality in patients with MDR GNB infections.
- Multivariable logistic regression confirmed the independent association between early C/T initiation and 30-day mortality:
  - Delayed C/T was associated with a > 3-fold increase in 30-day mortality ($aOR$ 3.22, 95% CI 1.11, 9.40).

### Patient Characteristics (N=144)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (IQR)</td>
<td>61 (49-71)</td>
</tr>
<tr>
<td>Respiratory infection</td>
<td>64%</td>
</tr>
<tr>
<td>MDR <em>P. aeruginosa</em></td>
<td>92%</td>
</tr>
</tbody>
</table>

### 30 day Mortality Rates in MDR PsA

- 11.8% with early initiation of C/T (within ~5 days)
- 26.2% with delayed initiation of C/T (after ~5 days)

Clinical characteristics and outcomes were compared between patients receiving early or delayed C/T, defined by the CART time point.

Classification and regression tree (CART) analysis was used to determine the time point of C/T initiation from index culture or diagnosis most predictive of 30-day mortality:
- A breakpoint in time was identified of 119 hours where 30-day mortality was significantly increased (11.8% vs. 26.2%; $P=0.032$).
- Absence of prior infection or colonization with MDR GNB was the only variable independently associated with delayed C/T ($aOR$ 3.28, 95% CI 1.53, 7.01).
<table>
<thead>
<tr>
<th></th>
<th>ESBL</th>
<th>CRE</th>
<th>MDR P. aeruginosa</th>
<th>MDR Acinetobacter</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cefiderocol</td>
<td>YES</td>
<td>KPC and NDM-1</td>
<td>YES</td>
<td>YES</td>
</tr>
<tr>
<td>Ceftolozane- Tazobactam</td>
<td>YES</td>
<td>NO</td>
<td>YES</td>
<td>NO</td>
</tr>
<tr>
<td>Ceftazidime-avibactam</td>
<td>YES</td>
<td>KPCs and OXA-48 (not active against MBLs)</td>
<td>YES</td>
<td>NO</td>
</tr>
<tr>
<td>Ceftaroline fosamil-avibactam</td>
<td>YES</td>
<td>KPCs and OXA-48 (not active against MBLs)</td>
<td>NO</td>
<td>NO</td>
</tr>
<tr>
<td>Aztreonam-avibactam</td>
<td>YES</td>
<td>MBLs such as NDM</td>
<td>YES</td>
<td>NO</td>
</tr>
<tr>
<td>Meropenem/vaborbactam</td>
<td>YES</td>
<td>KPCs</td>
<td>NO^</td>
<td>NO</td>
</tr>
<tr>
<td>Imipenem/cilastatin-relebactam</td>
<td>YES</td>
<td>KPCs and OXA-48 (not active against MBLs)</td>
<td>YES</td>
<td>NO</td>
</tr>
<tr>
<td>Plazomicin</td>
<td>YES</td>
<td>most KPCs (not active against many NDMs)</td>
<td>NO</td>
<td>NO</td>
</tr>
<tr>
<td>Eravacycline</td>
<td>YES</td>
<td>KPCs</td>
<td>NO</td>
<td>YES</td>
</tr>
</tbody>
</table>


Products in yellow are not licensed by EMA (status: phase II or III, pre-registration)
Ceftolozane/Tazobactam Overview

Class
- Antipseudomonal cephalosporin + β-lactamase inhibitor
- Fixed 2:1 ratio

Mechanism of action
- Rapidly bactericidal
- Inhibits cell wall synthesis
- Active against organisms with porin deficiencies or mutations
- Inhibits β-lactamases, broadens coverage to most ESBL-producing Enterobacteriaceae

In vitro activity
- Pseudomonas aeruginosa, including drug-resistant strains
- Escherichia coli, including ESBL-positive strains
- Klebsiella pneumoniae, including ESBL-positive strains
- Minimal activity against Gram-positive bacteria
- Limited activity against anaerobes
- No activity against KPC, MBL

Development stage
- Approved in >60 countries for treatment of cIAI and cUTI
- Phase 3 trial for nosocomial pneumonia completed

In vivo efficacy
- Activity in mouse models of sepsis, pneumonia, urinary tract infection, burn wound infection, and thigh infection
- Positive outcomes and adhered to an expected safety profile in Phase 2 and 3 trials in adult patients with cUTI and cIAI

Pharmacokinetics
- Linear PK
- Lung penetration
- Rapid tissue distribution
- Minimal accumulation
- Extensive renal excretion
- Low protein binding
- Minimal CYP450 drug-drug interactions

Result:
C/T in vitro activity against Enterobacteriaceae

Pseudomonas aeruginosa Italian countrywide surveillance (20 hospitals, 2013-14)

- XDR (n=82)
- R to all β-lactams (n=185)
- All isolates (n=939)

- AK
- COL
- CIP
- IMI
- MEM
- PIP/TAZ
- CAZ
- FEP
- CT/TAZ

- S (Green)
- I (Yellow)
- R (Red)
What Makes Ceftolozane/Tazobactam Different? Activity vs. *Pseudomonas aeruginosa*

Ceftolozane
- Stable against common *P. aeruginosa* resistance mechanisms, including loss of outer membrane porin (OprD), chromosomal AmpC, and up-regulation of efflux pumps (MexXY, MexAB)
- Isolates resistant to other cephalosporins may be susceptible, although cross-resistance may occur

<table>
<thead>
<tr>
<th>Resistance Mechanisms</th>
<th>Outer Membrane Porin Loss</th>
<th>β-lactamase Enzyme</th>
<th>Efflux Pump</th>
<th>Efflux Pump</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OprD</td>
<td>AmpC</td>
<td>MexXY</td>
<td>MexAB</td>
</tr>
<tr>
<td>Ceftolozane</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>●</td>
<td>○</td>
<td>●</td>
<td>○</td>
</tr>
<tr>
<td>Cefepime</td>
<td>●</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>Piperacillin/tazobactam</td>
<td>●</td>
<td>○</td>
<td>●</td>
<td>○</td>
</tr>
<tr>
<td>Imipenem</td>
<td>○</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>Meropenem</td>
<td>●</td>
<td>●</td>
<td>○</td>
<td>●</td>
</tr>
</tbody>
</table>

○ Activity greatly decreased >> ● Retains activity

2. Ceftolozane/Tazobactam prescribing information.

Table adapted from Castanheira M, et al. 2014
Ceftolozane/Tazobactam ELF Penetration in Hospitalized Patients with Pneumonia

Ceftolozane Penetration: ~50%

Tazobactam Penetration: ~62%

MIC = 4

Product is not licensed by EMA (status: phase III)
Caro L et al. ECCMID 2018 #P2225
Several studies document excellent *in vitro* activity of both ceftolozane/tazobactam and ceftazidime/avibactam against multi-drug resistant isolates of *P. aeruginosa*.

However, only 4 studies have evaluated the activity of ceftolozane/tazobactam and ceftazidime/avibactam in parallel against *P. aeruginosa*.

<table>
<thead>
<tr>
<th></th>
<th>Ceftolozane/tazobactam</th>
<th>Ceftazidime/avibactam</th>
</tr>
</thead>
<tbody>
<tr>
<td>% susceptible</td>
<td>MIC50/90</td>
<td>% susceptible</td>
</tr>
<tr>
<td><strong>Buehrle (n=38)</strong></td>
<td>92/1/4</td>
<td>92/1/8</td>
</tr>
<tr>
<td><strong>Gonzalez (n=45)</strong></td>
<td>87/1/8</td>
<td>82/2/16</td>
</tr>
<tr>
<td><strong>Grupper (n=290)</strong></td>
<td>91/1/4</td>
<td>81/1/8</td>
</tr>
<tr>
<td><strong>Humphries (n=309)</strong>*</td>
<td>73/NR</td>
<td>62/NR</td>
</tr>
</tbody>
</table>

*Isolates included if resistant to ≥1 antipseudomonal b-lactam (ceftazidime, cefepime, meropenem, imipenem or piperacillin-tazobactam)

## Ceftolozane/Tazobactam Real World Experience against *P. aeruginosa* (PsA)

<table>
<thead>
<tr>
<th>Citation</th>
<th>Study type</th>
<th>n</th>
<th>Infection type</th>
<th>Immuno-compromised (n)</th>
<th>Clinical / microbiological cure</th>
<th>30-day all cause mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caston JJ et al.</td>
<td>Multicenter retrospective</td>
<td>12</td>
<td>Mixed MDR PsA</td>
<td>4</td>
<td>83%</td>
<td>25% (3/12)</td>
</tr>
<tr>
<td>Munita JM et al.</td>
<td>Multicenter retrospective</td>
<td>35</td>
<td>Mixed Carb-R PsA</td>
<td>10</td>
<td>74% Combo= 87% cure</td>
<td>23% in hospital</td>
</tr>
<tr>
<td>Dinh A et al.</td>
<td>Retrospective compassionate access</td>
<td>15</td>
<td>Mixed XDR PsA</td>
<td>10</td>
<td>67%</td>
<td>27% in hospital</td>
</tr>
<tr>
<td>Haidar G et al.</td>
<td>Case series</td>
<td>21</td>
<td>Mixed MDR PsA</td>
<td>9</td>
<td>71%</td>
<td>10%</td>
</tr>
<tr>
<td>Diaz-Canestro</td>
<td>Prospective, observational</td>
<td>58</td>
<td>Mixed 97% MDR PsA</td>
<td>7</td>
<td>64%</td>
<td>28% (16/58)</td>
</tr>
<tr>
<td>Escola-Verge</td>
<td>Retrospective single center</td>
<td>38</td>
<td>Mixed XDR PsA</td>
<td>20</td>
<td>87%</td>
<td>13%</td>
</tr>
<tr>
<td>Xipell X et al.</td>
<td>Case series</td>
<td>23</td>
<td>Mixed MDR-PsA</td>
<td>10</td>
<td>87.5%</td>
<td>22% at 6 weeks</td>
</tr>
</tbody>
</table>

*Diaz-Canestro et al. EJCMID 2018*
*Escola-Verge et al. Infection 2018*
*Xipell X et al. J Glob Antimicrob Res 2018 in press*
C/T vs. Poly/AG Based Regimen for MDR / XDR P. aeruginosa: Multicenter Comparative Effectiveness Study

- 191 patients (94 C/T, 97 Poly/AG) from 5 US Medical Centers
- Severe sepsis or septic shock: 42%
- ICU at the onset of the infection: 69%

Pogue JM et al. IDWeek 2018; Poster 2406
Ceftolozane/tazobactam for the treatment of serious P. aeruginosa infections: a multicenter nationwide clinical experience- Ceftabuse

Retrospective study in 22 Italian hospitals - June 2016 March 2018

- 101 patients
  - nosocomial pneumonia (31.7%)
  - acute bacterial skin and skin structure infections (30.8%)
  - cUTI (13.8%)
  - cIAI (12.8%)
  - bone infections (8.9%)
  - primary bacteraemia (7.9%)

Almost half of P.aeruginosa strains were XDR (51%), with 78% of the isolates resistant to at least one carbapenem.

Bassetti M, Vena A, in revision
Clinical success rates according to the type of infections

<table>
<thead>
<tr>
<th>Type of Infection</th>
<th>Clinical Failure</th>
<th>Successful Clinical Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall (n=101)</td>
<td>83.2%</td>
<td>16.8%</td>
</tr>
<tr>
<td>Nosocomial Pneumonia (n=32)</td>
<td>75.0%</td>
<td>25.0%</td>
</tr>
<tr>
<td>ABSSSI (n=21)</td>
<td>90.5%</td>
<td>9.5%</td>
</tr>
<tr>
<td>cUTI (n=14)</td>
<td>92.9%</td>
<td>7.1%</td>
</tr>
<tr>
<td>cIAI (n=13)</td>
<td>76.9%</td>
<td>23.1%</td>
</tr>
<tr>
<td>Bone Infection (n=9)</td>
<td>88.9%</td>
<td>11.1%</td>
</tr>
<tr>
<td>Primary Bacteremia (n=6)</td>
<td>100%</td>
<td>0%</td>
</tr>
<tr>
<td>Others (n=6)</td>
<td>66.7%</td>
<td>33.3%</td>
</tr>
</tbody>
</table>

Bassetti M, Vena A, in revision
Clinical success rates according to susceptibility profile of P. aeruginosa (non-MDR, MDR, XDR/PDR)

- Overall (n=101): 83.2%
- Non-MDR (n=30): 90.0%
- MDR (n=18): 77.7%
- XDR/PDR (n=53): 81.1%
Kenilworth, N.J.--(Business Wire)-- It was announced that the pivotal Phase 3 clinical study evaluating ceftolozane/tazobactam at an investigational dose for the treatment of adult patients with either ventilated HABP or VABP met the pre-specified primary endpoints, demonstrating non-inferiority to meropenem, the active comparator, in Day 28 all-cause mortality and in clinical cure rate at the test-of-cure visit. In the U.S., ceftolozane/tazobactam is currently indicated in adult patients for the treatment of complicated urinary tract infections, including pyelonephritis, caused by certain Gram-negative microorganisms, and is indicated, in combination with metronidazole, in adult patients for the treatment of complicated intra-abdominal infections caused by certain Gram-negative and Gram-positive microorganisms.

Based on these results, the company plans to submit supplemental new drug applications to the U.S. FDA and EMA seeking regulatory approval of ceftolozane/tazobactam for this potential new indication. The company plans to submit results from the study for presentation at a future scientific conference. “HABP and VABP are serious and life-threatening hospital related pulmonary infections, especially in patients with severe underlying medical conditions,” said Dr. Roy Baynes, senior vice president, head of global clinical development and chief medical officer. “The results from the ASPECT-NP study demonstrate the potential role of ceftolozane/tazobactam for the treatment of patients with HABP and VABP.”

About the ASPECT-NP study
This prospective, randomized, double-blind, multicenter, non-inferiority, Phase 3 study assessed the safety and efficacy of ceftolozane/tazobactam compared with meropenem in 726 adult patients diagnosed with either ventilated HABP or VABP requiring intravenous antibiotic therapy. In the study, ceftolozane/tazobactam was administered in an investigational 3g dose compared with meropenem 1g, each given intravenously every eight hours for 8 to 14 days, or for 14 days for Pseudomonas aeruginosa infection. Meropenem is an approved broad-spectrum injectable antibiotic widely used to treat serious infections.

Additional details about the study can be found online at https://www.clinicaltrials.gov/ct2/show/NCT02070757.
Ceftolozane/tazobactam

**Pro**
- Predictable PK
- Rapid tissue distribution - Lung
- Renal excretion
- Safely
- High activity against ESBLs & PSA
- Carbapenem-sparing

**Limitations**
- No oral formulation to allow for step-down therapy
- Two dosages (1.5 vs 3 g)
- No KPC activity

Empiric choice for Gram-negative MDR (P. aeruginosa/ESBL) in UTI, c-IAI and HCAP/HAP/VAP*

* C/T not approved for pneumonia
Ceftolozane/tazobactam patients profile for empiric use in hospitalized patients

- Clinical entities:
  1. Sepsis related to UTI and cIAI hospital-acquired
  2. cUTI – Urosepsis
  3. Tertiary peritonitis

- Associated Comorbidities:
  - Diabetes
  - COPD/structural lung disease
  - Moderate/severe renal/liver disease
  - Immunosuppression/neutropenia
  - Elderly
  - Solid tumor

- Consider local epidemiological data:
  - P. aeruginosa
  - R to cefta 0-25%
  - R to pip/tazo 0-25%
  - R to carba 0-25%
  - And/or
  - ESBL
  - 0-20% in E. coli and/or Klebsiella

- Consider local epidemiological data:
  - P. aeruginosa
  - R to cefta >25%
  - R to pip/tazo >25%
  - R to carba >25%
  - And/or
  - ESBL
  - >20% in E. coli and/or Klebsiella
Ceftazadime/Avibactam
(Cephalosporin/Inhibitor)

- Approved for:
  - Complicated intra-abdominal infection (cIAI)
  - Complicated urinary tract infection (cUTI), including pyelonephritis
  - Hospital-acquired pneumonia (HAP), including ventilator associated pneumonia (VAP)
  - indicated for the treatment of infections due to aerobic Gram-negative organisms in adult patients with limited treatment options

- GNB coverage:
  - ESBL-producing Enterobacteriaceae including class A, C, and some D (e.g. OXA-48)
  - CREs – KPCs and others
  - Pseudomonas sp. with class A/C beta-lactamases

- Gaps
  - ESBL-Acinetobacter, Burkholderia, Stenotrophomonas, NDM, Pseudomonas with ceftaz-efflux pumps, anaerobes, MRSA

Ceftazidime-avibactam Phase III clinical trial programme

Seven prospective, international, multicentre, randomised Phase III studies

**Double-blind randomisation (1:1):**
- CAZ 2000 mg + AVI 500 mg + metronidazole 500 mg IV q8h or
- MER 1000 mg IV + placebo q8h

**Primary objective:**
- RECLAIM 1 and 2:
  - Assess non-inferiority of CAZ-AVI re: clinical cure at TOC visit in patients with ≥1 identified pathogen (mMITT populations)
- RECLAIM 3:
  - Proportion of patients with clinical cure at TOC visit (CE populations)

---

**Double-blind randomisation (1:1):**
- CAZ 2000 mg + AVI 500 mg q8h IV or
- DOR 500 mg + placebo q8h IV

**Primary objective:**
- RECAPTURE 1 and 2:
  - Adults with cUTI (including acute pyelonephritis)
  - Assess non-inferiority of CAZ-AVI on co-primary endpoints in mMITT analysis set:
    1) Resolution of UTI-specific symptoms
    2) Resolution/improvement of flank pain
    3) Per-patient microbiol eradication and symptomatic resolution

---

**Open-label randomisation (1:1):**
- CAZ 2000 mg + AVI 500 mg + metronidazole 500 mg q8h IV or
- DOR 500 mg + placebo q8h IV
- Best available therapy

**Primary objective:**
- REPRISE:
  - Adults with CAZ-resistant pathogens
  - Estimate per-patient clinical response to CAZ-AVI and best available therapy at TOC visit in cUTI and cIAI caused by CAZ-resistant Gram-negative pathogens

---

**Double-blind randomisation (1:1):**
- CAZ 2000 mg + AVI 500 mg q8h IV or
- MER 1000 mg + placebo q8h IV
- Plus open-label empiric linezolid + aminoglycoside

**Primary objective:**
- REPROVE:
  - Adults with nosocomial pneumonia (including VAP)
  - Assess non-inferiority of CAZ-AVI on clinical cure rate at TOC visit in cMITT and CE populations

---

AVI, avibactam; CAZ, ceftazidime; CE, clinically evaluable; cIAI, complicated intra-abdominal infection; cMMIT, clinically modified intent-to-treat; cUTI, complicated urinary tract infection; DOR, doripenem; IV, intravenous; MER, meropenem; mMITT, microbiological modified intent-to-treat; q8h, every 8 h; TOC, test of cure; UTI, urinary tract infection; VAP, ventilator-associated pneumonia.
REPROVE study

1:1 randomisation

EOT (within 24 h of last IV infusion)

12.5% NI margin

Hospitalised patients aged ≥18 years with NP,† including VAP

Diagnosis based on:
• clinical assessment (new worsening infiltrate on chest X-ray within 48 h of randomisation), and
• ≥2 respiratory signs of pneumonia‡

REPROVE was a prospective, multicentre, international, randomised, double-blind, double-dummy, Phase III study, evaluating efficacy and safety of ceftazidime–avibactam compared with meropenem

It is the first Phase III study of ceftazidime–avibactam in the treatment of adults with NP compared to a carbapenem comparator

Primary endpoint: clinical cure at the TOC visit in the co-primary cMITT and CE populations

Hospitalised patients aged ≥18 years with NP,† including VAP

Diagnosis based on:
• clinical assessment (new worsening infiltrate on chest X-ray within 48 h of randomisation), and
• ≥2 respiratory signs of pneumonia‡

CE, clinically evaluable; cMITT, clinically modified intent-to-treat; EOT, end-of-treatment; FPFU, final protocol follow-up; IV, intravenous; NI, non-inferiority; NP, nosocomial pneumonia; q8h, every 8 hours; TOC, test-of-cure; VAP, ventilator-associated pneumonia.
Primary endpoint efficacy: clinical cure rates at TOC (CE and cMITT populations)

- Ceftazidime–avibactam was non-inferior to meropenem for the treatment of HAP/VAP in this setting.

**Clinical cure rate at test of cure**

<table>
<thead>
<tr>
<th></th>
<th>CE population</th>
<th>cMITT population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ceftazidime–avibactam</td>
<td>77.4% (n=199/257)</td>
<td>68.8% (n=245/356)</td>
</tr>
<tr>
<td>Meropenem</td>
<td>78.1% (n=211/270)</td>
<td>73.0% (n=270/370)</td>
</tr>
</tbody>
</table>

Difference (95% CI): -0.7% (-7.86, 6.39) for CE population and -4.2% (-10.76, 2.46) for cMITT population.

CE, clinically evaluable; CI, confidence interval; cMITT, clinically modified intention-to-treat; HAP, hospital-acquired pneumonia; TOC, test of cure; VAP, ventilator-associated pneumonia.
Per-pathogen favourable microbiological response rate at TOC according to Gram-negative pathogen isolated (eME population)

<table>
<thead>
<tr>
<th>Patients, m/n (%)</th>
<th>Ceftazidime-avibactam (N=125)</th>
<th>Meropenem (N=131)</th>
<th>Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Enterobacteriaceae</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Klebsiella pneumoniae</td>
<td>29/37 (78.4)</td>
<td>39/49 (79.6)</td>
<td>–1.2 (–19.60, 15.96)</td>
</tr>
<tr>
<td>Enterobacter cloacae</td>
<td>18/21 (85.7)</td>
<td>7/11 (63.6)</td>
<td>22.1 (–8.07, 53.69)</td>
</tr>
<tr>
<td>Escherichia coli</td>
<td>10/11 (90.9)</td>
<td>16/18 (88.9)</td>
<td>2.0 (–29.11, 26.44)</td>
</tr>
<tr>
<td>Serratia marcescens</td>
<td>9/12 (75.0)</td>
<td>5/8 (62.5)</td>
<td>12.5 (–27.47, 51.82)</td>
</tr>
<tr>
<td>Proteus mirabilis</td>
<td>9/11 (81.8)</td>
<td>6/8 (75.0)</td>
<td>6.8 (–30.73, 46.51)</td>
</tr>
<tr>
<td>Enterobacter aerogenes</td>
<td>5/6 (83.3)</td>
<td>3/5 (60.0)</td>
<td>23.3 (–31.30, 68.33)</td>
</tr>
<tr>
<td><strong>Gram-negative pathogens other than Enterobacteriaceae</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pseudomonas aeruginosa</td>
<td>18/42 (42.9)</td>
<td>14/35 (40.0)</td>
<td>2.9 (–19.13, 24.32)</td>
</tr>
<tr>
<td>Haemophilus influenzae</td>
<td>11/11 (100)</td>
<td>12/13 (92.3)</td>
<td>7.7 (–20.08, 34.00)</td>
</tr>
</tbody>
</table>

eME, extended microbiologically evaluable; m, number of patients with favourable microbiological response; n, number of patients in subgroup; N, number of patients in treatment group; TOC, test-of-cure
Ceftazidime–avibactam in patients with MDR *P. aeruginosa* infection: compassionate-use programme in Spain

- Retrospective study from January 2016 to May 2017
- Patients (N=8) received ceftazidime–avibactam as initial or continuation therapy for infections due to MDR and XDR *P. aeruginosa* on a compassionate-use basis
- Patients had hospital-acquired lower respiratory tract infection (n=5; 62.5%), osteomyelitis, meningitis and catheter-related bacteraemia (n=1 each)
  - All patients had comorbidities, with diabetes mellitus being most prevalent (62.5%)
  - Median SOFA score was 4 (range 0–8)
- Clinical cure was achieved in 50% of patients, comparing favourably with results of the REPROVE study in patients with HAP, including VAP
- Ceftazidime–avibactam may be a valuable option for serious infections due to resistant *P. aeruginosa*

HAP, hospital-acquired pneumonia; MDR, multidrug resistant; SOFA, Sepsis-related organ failure assessment; VAP, ventilator-associated pneumonia; XDR, extensively drug resistant.

PP-ZVA-EUR-0137. Date of preparation: September 2018
Ceftazidime–avibactam

Pros

- Predictable PK\(^1\)
- Rapid tissue distribution - lung
- Safety profile\(^1\)
- Inhibits ESBLs, AmpC, KPC, OXA-48\(^1\)
- *Pseudomonas aeruginosa* and Enterobacteriaceae enhanced activity\(^1\)
- Approved for empiric and targeted therapy\(^1\)

Limitations

- Does not inhibit class B enzymes & many class D enzymes\(^1\)
- Not susceptible: *Acinetobacter* spp., anaerobes\(^1\)
- Avoid if β-lactam allergy (10% of patients) \(^1\)
- Salvage vs. empiric Tx\(^2\)
- Combination vs no combination\(^3\)

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Proposed algorithm for management of antibiotic therapy in patients with MDR/XDR/PDR pathogens.

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