New Antimicrobial Agents, Using Old Agents in New Ways and the Pipeline

Helen Whamond Boucher MD FACP FIDSA
Disclosures

• Editor
  — ID Clinics of North America
  — Antimicrobial Agents and Chemotherapy
• Treasurer, Infectious Diseases Society of America
• Member, ID Board, American Board of Internal Medicine
• Voting Member, Presidential Advisory Council on Combating Antibiotic Resistant Bacteria (PACCARB)
What’s new?
Pew Development Pipeline June 2019

• 42 New antibiotics in development
  — > 89% small companies
  — 11 phase 1 - Not a good sign!
  — 13 phase 2
  — 13 phase 3
    — 60% likely to make it to FDA approval
• 16 + potential to treat G- ESKAPE pathogens
  — 11/16 + potential activity against carbapenem-resistant organisms
• 9 + potential to treat *N. gonorrhoeae* or *C. difficile*
• 1 in 4 = novel drug class or mechanism of action
• Initial indications: cUTI, cIAI, ABSSSI

Focus on systemically available antibiotics in phase 2 or beyond

Status of IDSA 10 x ‘20 Initiative

13 Lefamulin
Nabirva; Approved August 19, 2019

12 Imipenem/cilastatin+relebactam
Merck; Approved July 17, 2019

11 omadacycline
Paratek Pharmaceuticals; Approved: October 2, 2018

10 eravacycline
Tetraphase; Approved: August 28, 2018

9 plazomicin
Achaogen; Approved: June 26, 2018

8 meropenem/vaborbactam
The Medicines Company; Approved: August 30, 2017

7 delafloxacin
Melinta Therapeutics; Approved: June 17, 2017

6 ceftazidime/avibactam
Actavis plc; Approved: February 25, 2015

5 ceftolozane/tazobactam
Cubist Pharmaceuticals, Inc.; Approved: December 19, 2014

4 ertapenem
The Medicines Company; Approved: August 6, 2014

3 tedizolid phosphate
Cubist Pharmaceuticals, Inc.; Approved: June 20, 2014

2 dalbavancin
Durata Therapeutics; Approved: May 23, 2014

1 ceftaroline fosamil
Forest Laboratories, Inc.; Approved: October 29, 2010
Delafloxacin (Baxdela®)

- Broad spectrum anionic fluoroquinolone
- Potential advantages:
  - MRSA activity
  - Gaps in Gram-negative coverage
  - Oral bioavailability
  - Accumulates in acid pH (intracellular)
  - Broad spectrum
  - Efficacy in obese patients
- Dosing
  - 300mg IV every 12 hours
    - Dose adjust for CrCl 15-29ml/min
  - 450mg orally every 12 hours

www.fda.gov
## Delafloxacin

### Antibiotic MIC$_{50}$ / MIC$_{90}$

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>N</th>
<th>Dela</th>
<th>Levo</th>
<th>Cipro</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>E. coli</em></td>
<td>4436</td>
<td>0.06/4</td>
<td>&lt;=0.12/&gt;4</td>
<td>&lt;=0.03/&gt;4</td>
</tr>
<tr>
<td><em>K. pneumoniae</em></td>
<td>2417</td>
<td>0.12/&gt;4</td>
<td>&lt;=0.12/&gt;4</td>
<td>&lt;=0.03/&gt;4</td>
</tr>
<tr>
<td><em>P. aeruginosa</em></td>
<td>2181</td>
<td>0.5/&gt;4</td>
<td>0.5/&gt;4</td>
<td>0.12/&gt;4</td>
</tr>
<tr>
<td><em>K. oxytoca</em></td>
<td>601</td>
<td>0.12/0.5</td>
<td>&lt;=0.12/0.25</td>
<td>&lt;=0.03/0.12</td>
</tr>
<tr>
<td><em>E. cloacae</em></td>
<td>783</td>
<td>0.06/2</td>
<td>&lt;=0.12/0.5</td>
<td>&lt;=0.03/0.5</td>
</tr>
<tr>
<td><em>P. mirabilis</em></td>
<td>907</td>
<td>0.06/2</td>
<td>&lt;=0.12/&gt;4</td>
<td>&lt;=0.03/&gt;4</td>
</tr>
</tbody>
</table>

Flamm et al. IDWeek 2017
Delafloxacin Phase III ABSSSI

Adults with major abscess, cellulitis, wound infection

Delafloxacin

Vancomycin + Aztreonam

Early clinical response (ECR) in mITT population

PROCEED 1: 78%
PROCEED 2: 84%

PROCEED 1: 81%
PROCEED 2: 81%

Response rates similar in patients with BMI < 30 kg/m² and BMI ≥ 30 kg/m²

PROCEED 1 Delta (95% CI): -2.6 (-8.8, 3.6)
PROCEED 2 Delta (95% CI): +3.1 (-2.0, 8.3)

Delafloxacin Status

- FDA approved ABSSSI 2017
- FDA approved CABP 24 October 2019
  - Delafloxacin vs moxifloxacin

Ongoing:
- Phase 1 complicated UTI

Ceftolozane/Tazobactam (Zerbaxa®)

- **Dose:** Ceftolozane 1g/tazobactam 0.5g (total 1.5g) every 8h
  - 1 hour infusion
- **P. aeruginosa** MIC$_{50/90}$ = 0.5/2 mg/L
- Inhibits some carbapenem-R **P. aeruginosa**
- Enterobacteriaceae - inhibits most class A and some class C β-lactamases (CTX-M, ESBLs)
  - No inhibition of KPC-producing Enterobacteriaceae (tazobactam is poor inhibitor)
- Poor activity in **Acinetobacter** spp. (MIC$_{50}$ = 32)
  - Not active against bacteria that produce certain serine carbapenamases (KPC), metallo-beta lactamases, stable derepressed ampC (**Enterobacter** spp.)
  - Safety similar to other β-lactams (cephalosporins)
- FDA approved
  - cUTI (1.5g vs. levofloxacin 750 QD)
  - cIAI (1.5g vs. meropenem 1g q8) - VNP (3g every 8h vs. meropenem)
Clinical cure rates in phase 3 trial of cIAI by baseline renal function (MITT population)

<table>
<thead>
<tr>
<th>Baseline Renal Function</th>
<th>Ceftolozane/Tazobactam + Metronidazole n/N (%)</th>
<th>Meropenem n/N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal/mild impairment</td>
<td>312/366 (85.2)</td>
<td>355/404 (87.9)</td>
</tr>
<tr>
<td>(CrCL ≥50 mL/min)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate impairment</td>
<td>11/23 (47.8)</td>
<td>9/13 (69.2)</td>
</tr>
<tr>
<td>(CrCL 30- &lt;50 mL/min)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Decreased efficacy in patients with baseline creatinine clearance (CrCL) of 30 to ≤50 mL/min
- Monitor CrCL at least daily in patients with changing renal function and adjust the dose of ceftolozane/tazobactam accordingly

Ceftolozane/tazobactam Phase 3 NP (ASPECT-NP) Trial Design

- Phase 3, randomized, controlled, double-blind, multicenter trial in adult ventilated patients with nosocomial pneumonia (VNP)
- Primary objective: demonstrate noninferiority of ceftolozane/tazobactam to meropenem, based on difference in:
  - Day 28 all-cause mortality rates in the ITT population (per FDA)
  - Clinical response rates at the TOC visit (7 days post EOT) in the CE population (for EMA)

ASPECT-NP, Assessment of the Safety Profile and Efficacy of ZERBAXA in Nosocomial Pneumonia; EMA, European Medicines Agency; FDA, Food and Drug Administration; HABP, hospital-acquired bacterial pneumonia; TOC, test-of-cure; VABP, ventilator-associated bacterial pneumonia; VNP, ventilator-associated pneumonia; IV, intravenous; q8h, every 8 hours; ITT, intent-to-treat; EOT, end of treatment.
# Ceftolozane/tazobactam Phase 3 NP (ASPECT-NP)

<table>
<thead>
<tr>
<th></th>
<th>Cefto-tazo N = 362</th>
<th>Mero N = 364</th>
<th>Tx Diff (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>VABP</td>
<td>263 (73)</td>
<td>256 (72)</td>
<td></td>
</tr>
<tr>
<td>TOC Cure (CE population)</td>
<td>139/218 (64)</td>
<td>143/221 (65)</td>
<td>-1.3 (-10.21, 7.67)</td>
</tr>
<tr>
<td>Mortality day 28</td>
<td>87 (24)</td>
<td>92 (25)</td>
<td>1.1 (-2.84, 5.18)</td>
</tr>
<tr>
<td>Mortality d 28 VABP</td>
<td>63/263 (24)</td>
<td>52/256 (20)</td>
<td>-3.6 (-10.74, 3.52)</td>
</tr>
<tr>
<td>Mortality d 28 vHABP</td>
<td>24/99 (24)</td>
<td>40/108 (37)</td>
<td>12.8 (0.18, 24.75)</td>
</tr>
</tbody>
</table>

- DRAEs: 11% ceftol-taz vx 8% mero
- DRAE leading to discontinuation: 2% ceftol-taz vs 1% mero

Kollef et al. ECCMID 2019; P1917
Ceftazidime-Avibactam (Avycaz®)

- Dose: ceftazidime 2g / avibactam 500 mg every 8 hours
  - 2 hour infusion
- GNB potency:
  - ESBL-producing Enterobacteriaceae including class A, class C, and some class D (e.g. OXA-48); CREs – KPCs and others
  - *Pseudomonas* spp. with class A/C beta-lactamases
- QIDP
- FDA approved
  - cUTI
  - cIAI (vs. meropenem; CID 2016)
  - Pathogen focused study - CAZ-AVI comparable to other drugs (carbapenems in CAZ-R (not CRE; Lancet ID 2016)
  - nosocomial pneumonia (including VABP)
- Descriptive case series in patients with CRE from early exp published/presented
### Exploratory Analyses: Clinical Outcome by Renal Function (mMITT)

<table>
<thead>
<tr>
<th>Renal Function (CrCl at Baseline)</th>
<th>CAZ-AVI + MTZ</th>
<th>Meropenem</th>
<th>Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal (&gt;80 mL/min)</td>
<td>n / N</td>
<td>Cure Rate (%)</td>
<td>n / N</td>
</tr>
<tr>
<td>232 / 271</td>
<td>248 / 283</td>
<td>85.6 87.6 -2.0 (-7.81, 3.68)</td>
<td></td>
</tr>
<tr>
<td>Mild (&gt;50 to 80)</td>
<td>90 / 108</td>
<td>83.3 81.1 2.2 (-8.46, 13.35)</td>
<td></td>
</tr>
<tr>
<td>Moderate (MRIB) (&gt;30 to 50)</td>
<td>14 / 31</td>
<td>45.2 74.3 -29.1 (-50.05, -5.36)</td>
<td></td>
</tr>
</tbody>
</table>

- Magnitude of MRIB dose adjustment differed between groups
  - 66% reduction in CAZ-AVI (7.5 to 2.5 g/day)
  - 33% reduction in meropenem (3 to 2 g/day)

# Ceftazidime-Avibactam Revised Renal Dosing

<table>
<thead>
<tr>
<th>Estimated Creatinine Clearance (mL/minute)</th>
<th>Ceftazidime-avibactam Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>31-50</td>
<td>1.25g every 8 hrs</td>
</tr>
<tr>
<td>16-30</td>
<td>0.94g every 12 hrs</td>
</tr>
<tr>
<td>6-15</td>
<td>0.94g every 24 hrs</td>
</tr>
<tr>
<td>&lt;= 5</td>
<td>0.94g every 48 hrs</td>
</tr>
</tbody>
</table>

www.FDA.gov
# Ceftazidime-avibactam for CRE - Outcomes

## Toxicity and Emergence of Resistance

<table>
<thead>
<tr>
<th></th>
<th>Caz-avi</th>
<th>N = 37</th>
</tr>
</thead>
<tbody>
<tr>
<td>Success</td>
<td>22 (59%)</td>
<td></td>
</tr>
<tr>
<td>30-day survival</td>
<td>28 (76%)</td>
<td></td>
</tr>
<tr>
<td>90-day survival</td>
<td>23 (62%)</td>
<td></td>
</tr>
<tr>
<td>Microbiologic failure</td>
<td>10 (27%)</td>
<td></td>
</tr>
<tr>
<td>Caz-avi resistance</td>
<td>3/10 (30%)</td>
<td></td>
</tr>
</tbody>
</table>

- Series of patients over 10 months at UPMC
  - 1/3 transplant
  - Infection type: 12 pneumonia, 10 bacteremia
  - 30% caz-avi + another abx

- **Recurrent CRE**: 5/22 successful pts (23%), med 74 days (34-84)

- Outcomes not better with combination therapy


- Spellberg & Bonomo Clin Infect Dis 2016; 63(12): 1619
REPRISE - Ceftazidime-avibactam vs BAT CRE & *P. aeruginosa* Infections – cUTI/cIAI

<table>
<thead>
<tr>
<th></th>
<th>Caz-avi N = 154</th>
<th>BAT N = 148</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td></td>
</tr>
<tr>
<td>cUTI (10 + bacteremia)</td>
<td>144 (94%)</td>
<td>137 (93%)</td>
</tr>
<tr>
<td>cIAI</td>
<td>10 (6%)</td>
<td>11 (7%)</td>
</tr>
<tr>
<td>Baseline pathogen</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>E. Coli</em></td>
<td>63 (41)</td>
<td>63 (43)</td>
</tr>
<tr>
<td><em>K. Pneumoniae</em></td>
<td>60 (39)</td>
<td>68 (46)</td>
</tr>
<tr>
<td>Outcome</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cure at TOC</td>
<td>140 (91%)</td>
<td>135 (91%)</td>
</tr>
</tbody>
</table>

- Open-label, Eastern Europe, 2013-14
- Ceftazidime resistant at baseline
- 163/168 (97%) BAT rec’d carbapenem tx, 161 (96%) as monotx
- AEs:
  - 51/164 caz-avi (31%) vs 66/168 (39%) BAT

Carmeli et al. Lancet ID 2016 (16): 661
### Ceftazidime-Avibactam

**REPROVE Study Nosocomial Pneumonia**

<table>
<thead>
<tr>
<th></th>
<th>Caz-avi</th>
<th>Mero</th>
<th>Tx Diff (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N = 356</td>
<td>N = 370</td>
<td></td>
</tr>
<tr>
<td><strong>VABP</strong></td>
<td>118 (33)</td>
<td>128 (35)</td>
<td></td>
</tr>
<tr>
<td><strong>No prior abx</strong></td>
<td>122 (34)</td>
<td>117 (32)</td>
<td></td>
</tr>
<tr>
<td><strong>Cure MITT</strong></td>
<td>245 (69)</td>
<td>270 (73)</td>
<td>-4.2 (-10.76, 2.46)</td>
</tr>
<tr>
<td><strong>Mortality day 28</strong></td>
<td>30 (8.4)</td>
<td>27 (7.3)</td>
<td>1.1 (-2.84, 5.18)</td>
</tr>
<tr>
<td>Mortality d 28 caz NS*</td>
<td>8.2%</td>
<td>8.5%</td>
<td></td>
</tr>
</tbody>
</table>

- NO US patients (China 33%, Eastern Europe 26%), Prior abx <= 48 hrs
- 355 (44%) micro MITT pop – K. pneumo, *P. aeruginosa* most freq GNB
- 100 (28%) + ceftaz NS GNB
- Overall mortality LOWER than expected
- SAEs: 19% caz-avi (N=4 drug-related) vs 13% meropenem

Ceftazidime-avibactam for MDR Gram-negative Bacteremia

- Data
  - case series
  - compassionate use
  - Subsets of registrational and strategy trials
- Superiority to colistin?
  - Efficacy and toxicity
- Gaps
  - Prospective trials, RCTs
  - Cost effectiveness
Meropenem-Vaborbactam (Vabomere®, formerly RPX7009)

- Vaborbactam pK matched with meropenem
- Inhibits class A & C serine B-lactamases (including KPC)
  - Distinct binding site from avibactam and tazobactam
- BARDA funding
- QIDP
- Dose: meropenem 2g / vaborbactam 2g as 3 h infusion every 8 h
  - Dose adjust for renal dysfunction
- FDA approved cUTI
- NDA submitted
  - Pathogen focused
  - HABP/VABP
## TANGO I - Meropenem-vaborbactam vs Piperacillin-tazobactam for cUTI/AP

<table>
<thead>
<tr>
<th></th>
<th>Mero-vabor</th>
<th>Pip-Tazo</th>
<th>Tx Diff (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>n/N (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>End of IV therapy (FDA)</td>
<td>189/192 (98.4)</td>
<td>171/182 (94.0)</td>
<td>4.5 (0.7, 9.1)</td>
</tr>
<tr>
<td>Micro erad TOC (EMA)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Micro MITT</td>
<td>128/192 (66.7)</td>
<td>105/182 (57.7)</td>
<td>9.0 (-0.9, 18.7)</td>
</tr>
<tr>
<td>Micro Eval</td>
<td>118/178 (66.3)</td>
<td>102/169 (60.4)</td>
<td>5.9 (-4.2, 16.0)</td>
</tr>
</tbody>
</table>

- Mero-vabor 2g/2g over 3 hrs vs Pip-tazo 4.5/0.5 over 30 mins every 8h; both with option to switch to oral levofloxacin p 5 days; total 10 d therapy
- 59% acute pyelonephritis/40-41% + complicated UTI
- FDA endpoint: clin cure/improved + micro erad at end of IV tx in mMITT population

TANGO-II: meropenem-vaborbactam vs. Best Available Therapy in suspected or documented CRE infection

Screening day -1 to 1

Subjects
- cUTI or AP
- HABP/VABP
- cIAI
- Bacteremia

CRE known or susp.
- Culture
- Phenotypic
- Molecular

Randomization (2:1)

Treatment up to 14 days

Meropenem-vaborbactam
2 g/2 g q8h via IV infusion over 3 hours

Best Available Therapy
Polymyxin/colistin, aminoglycoside, carbapenem, tigecycline, either alone or in combination
Ceftazidime-avibactam as monotherapy

End-of-treatment
Day 7-14

Follow-up
Test-of-cure
Day 7 (±2) post-EOT

Last follow-up
Day 14 (±2) post-EOT

Randomized study stopped upon recommendation of DSMB after interim analysis of 72 patients showed efficacy and safety advantage for meropenem-vaborbactam

Assessment of efficacy at two time points
TANGO II - Meropenem-vaborbactam vs BAT
CRE Infections

<table>
<thead>
<tr>
<th></th>
<th>Mero-vabor N = 32</th>
<th>BAT N = 15</th>
<th>Tx Diff (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n/N (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cure at EOT</td>
<td>21 (65.6)</td>
<td>5 (33.3)</td>
<td>32.3 (3.3, 61.3)</td>
</tr>
<tr>
<td>Cure at TOC</td>
<td>19 (59.4)</td>
<td>4 (26.7)</td>
<td>32.7 (4.6, 60.8)</td>
</tr>
<tr>
<td>Micro Cure at EOT</td>
<td>21 (65.6)</td>
<td>6 (40.0)</td>
<td>25.6 (-4.1, 55.4)</td>
</tr>
<tr>
<td>Micro Cure at TOC</td>
<td>17 (53.1)</td>
<td>5 (33.3)</td>
<td>19.8 (-9.7, 49.3)</td>
</tr>
<tr>
<td>Day 28 Mortality</td>
<td>5 (15.6)</td>
<td>5 (33.3)</td>
<td>-17.7 (-44.7, 9.3)</td>
</tr>
</tbody>
</table>
Meropenem-Vaborbactam

- Meropenem-vaborbactam better than “best available therapy” against CRE (not OXA-48 or MBLs)
- Active against most KPC-producing CRE resistant to ceftazidime-avibactam
- Potent and “optimized” PK/KD
- High barrier for resistance? Uptake affected by porin changes
- No advantage over meropenem against *P. aeruginosa* or *Acinetobacter*
- Complexities of MDROs require all therapeutic options
- “Real world” evidence will be crucial to define the niche of each B-lactam/ B-lactamase inhibitor combination
Imipenem/relebactam
(formerly MK-7655)

- Imipenem/cilastatin + relebactam
- Inhibits class A & C serine β-lactamases, ESBLs, some CREs (no MBLs), *P. aeruginosa*
- Dose: imipenem 500mg /relebactam 250mg every 6 h over 30 minutes
- FDA approved cUTI and cIAI (significant # R GNB)
- Resistant pathogen study vs colistin (N = 54) complete
  - Imi-resistant but IMI/rel and colisitin-susceptible
- Phase 3 complete
  - HABP/VABP vs pip-tazo 4.5g every 6 hrs
    - Linezolid allowed for MRSA
    - Primary endpoint
      - All cause mortality day 28

# Imipenem-relebactam vs Colistin + Imipenem

<table>
<thead>
<tr>
<th></th>
<th>IMI-REL N = 21</th>
<th>CST + IMI N = 10</th>
<th>Tx Diff (90% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Success</td>
<td>15/21 (71.4)</td>
<td>7/10</td>
<td>1.4 (-27.5, 21.4)</td>
</tr>
<tr>
<td>HABP/VABP</td>
<td>7/8</td>
<td>2/3</td>
<td></td>
</tr>
<tr>
<td>cIAI</td>
<td>0/2</td>
<td>0/2</td>
<td></td>
</tr>
<tr>
<td>cUTI</td>
<td>8/11 (72.7)</td>
<td>5/5</td>
<td>-27.3 (-52.8, 12.8)</td>
</tr>
<tr>
<td>Success at day 28</td>
<td>15/21 (71.4)</td>
<td>4/10</td>
<td>31.4 (1.3, 51.5)</td>
</tr>
<tr>
<td>Day 28 mortality</td>
<td>2/21 (9.5)</td>
<td>3/10</td>
<td>-20.5 (-46.4, 6.7)</td>
</tr>
</tbody>
</table>

- 31/47 randomized in mMITT
- Pathogens: 77% *P. aeruginosa*, 16% *K. pneumoniae*, 6% other Enterobacteriaceae
- BLA: 85% Amp C, 39% ESBL, 16% KPC, 3% OXA-48
- Tx-emerg nephrotox: 3/29 (10%) Imi-rel vs 9/16 (56%) CST+IMI

Motsch, et al. CID 2019
Aztreonam/Avibactam

- Potent vs
  - Enterobacteriaceae
    - Including ESBLs and KPCs
    - Active vs metallo-β-lactamase producers
  - A. baumannii
  - NOT P. aeruginosa

- Dose: Aztreonam 6500mg /2167mg avibactam loading dose, extended infusion day one, then 6000mg aztreonam/2000mg avibactam daily via extended infusion; adjust for renal dysfunction

- Phase 3 studies ongoing
  - Pathogen specific vs meropenem/colistin
  - cIAI – Aztreonam/avibactam + metronidazole
  - HABP/VABP  
    Sader et al. AAC 2017; Karlowsky et al. AAC 2017; www.clinicaltrials.gov
Plazomicin

- Aminoglycoside designed to not be affected by major AG modifying enzymes
- Active vs. Enterobacteriaceae including CRE (but not in methylase co-producing strains, e.g. NDM) and ESBLs, MBLs, fluoroquinolone-R and aminoglycoside-R GNB
- Organisms with antibiotic modifying enzymes or efflux pumps (Acinetobacter/Providencia/Proteus spp.) and ribosomal methylase are resistant
- 15 mg/kg IV daily over 30 minutes
- Dose based on AUIC
- FDA approved –25 June 18
  - cUTI (vs. levofloxacain)
- Not approved: pathogen focused study CRE (combo Rx)
### EPIC
Plazomicin vs Meropenem cUTI/AP

<table>
<thead>
<tr>
<th></th>
<th>Plazomycin N = 191</th>
<th>Meropenem N = 197</th>
<th>Tx Diff (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 5</td>
<td>168 (88.0)</td>
<td>180 (91.4)</td>
<td>-3.4 (-10.0, 3.1)</td>
</tr>
<tr>
<td>End of IV</td>
<td>179 (93.7)</td>
<td>187 (94.9)</td>
<td>-1.2 (-6.5, 4.0)</td>
</tr>
<tr>
<td>TOC</td>
<td>156 (81.7)</td>
<td>138 (70.1)</td>
<td>11.6 (2.7, 20.3)</td>
</tr>
</tbody>
</table>

- Similar results: IV only, IV + oral levofloxacin
- Bacteremia composite cure: 18/25 (72%) plazo vs 13/23 (56.5%) mero
- Adverse events similar
- Creat increase: 7% plazo vs 4% mero

## Plazomicin vs Colistin for CRE Infections

<table>
<thead>
<tr>
<th></th>
<th>Plazomicin N = 17</th>
<th>Colistin N = 20</th>
<th>Tx Diff (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BSI, HABP/VABP</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mortality d 28</td>
<td>2 (11.8)</td>
<td>8 (40.0)</td>
<td>28.2 (0.7, 52.5)</td>
</tr>
<tr>
<td>Mortality d 28/cx</td>
<td>4 (23.5)</td>
<td>10 (50.0)</td>
<td>26.5 (-0.7, 51.2)</td>
</tr>
</tbody>
</table>

• Plazo vs Colisitin BOTH + meropenem or tigecycline

• Significant benefit in 60-day survival in BSI pts, HR 0.37 (0.15, 0.91)

• Fewer AEs, less renal dysfunction in plazomicin-treated patients

* 2100+ patients screened

Plazomicin

Regulatory Status

- FDA approved: cUTI (vs. levofloxacin)
- Not approved: pathogen focused study CRE (combo Rx)

- FDA Advisory Committee 2 May 18
  - 15 vs 0 vote in favor of effectiveness/safety in cUTI
  - 4 vs 11 vote against effectiveness/safety in BSI

  - Issues:
    - Small numbers
    - Risk vs benefit/LPAD
Should We Use Polymyxin or Aminoglycoside-based Therapy?

- CRE
  - Small studies
  - Less toxicity
  - ? Improved outcomes, mortality

<table>
<thead>
<tr>
<th>Pseudomonas aeruginosa</th>
<th>Ceftolozane-tazobactam</th>
<th>Polymyxin/ Aminoglycoside</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N = 100</td>
<td>N = 100</td>
</tr>
<tr>
<td>Clinical cure</td>
<td>81%</td>
<td>61%</td>
</tr>
<tr>
<td>Acute kidney injury</td>
<td>6%</td>
<td>34%</td>
</tr>
<tr>
<td>In hospital mortality</td>
<td>20%</td>
<td>25%</td>
</tr>
</tbody>
</table>

Retrospective, observational study
NNT with ceft/tazo for cure = 5

Pogue et al. CID 2019
NEW Tetracyclines
Aminomethylcycline and Fluorotetracycline

PTK 0796-
Omadacycline

TP 434-
Eravacycline
Omadacycline (IV/Oral)

- Minocycline derivative, active against tetracycline resistant pathogens – IV/oral
- Gram+: VRE, MRSA, VRSA, MDR S. pneumoniae, GAS, GBS
- GNB coverage:
  - Carbapenem-resistant *E. coli*
    - Limited activity vs carbapenem-resistant *K. pneumoniae*
  - ESBL, drug-resistant *Salmonella* spp.
- Anaerobes: *C. difficile* (not being developed for this indication)
- Potential advantages:
  - MRSA activity, Oral bioavailability
- FDA Approved CABP and ABSSSI
- Safety issues – class effects:
  - GI, skin rash, Heart rate

www.clinicaltrials.gov; www.paratekpharm.com
Omadacycline Phase III CABP (OPTIC)

**Adults with CAP**

**Omadacycline**

**Moxifloxacin**

**Early clinical response* in mITT population**

81% **vs.** 83%

ECR: survival with improvement of at least one level compared to baseline (e.g., severe to moderate) of at least 2 CABP symptoms (cough, sputum, CP, SOB) at 72-120 hours

**OPTIC Delta (95% CI): -0=1.6 (-7.1, 3.8)**

**Non-inferiority study (NI margin 10%)**

100 mg IV Q12 day one then 100 mg daily with option to switch to oral after 3 days, Treatment 7-14 days

**Patient characteristics**

- 60% >65 years
- 60% PORT risk class III, 25% PORT risk class IV
- 21% with COPD/structural lung ds

**Bacterial pathogen identified in ~50% of patients; more H flu on omadacycline arm**

**N/V in 2.5%; 8 patient with CDI in moxi group**

Stets et al. NEJM 2019; 380 (6): 517
Omadacycline

- FDA approved CABP and ABSSSI
  - ABSSSI IV/ORAL OASIS study
    - Omadacycline not inferior to linezolid
  - ABSSSI ORAL only OASIS-2 study
    - Omadacycline 300mg daily vs linezolid 600mg twice daily
- CABP OPTIC
- Phase 2 uUTI oral omada vs nitrofurantoin and cUTI (AP) oral-IV omada vs oral-IVlevoflox
  - Comparable efficacy but lower micro success with omada
  - Analysis pending

Eravacycline (IV/Oral)

- Overall ~ 2-fold more potent than tigecycline
- Active vs gram- (ESBL, CRE, *A. baumannii*, colistin-resistant GNB), gram+ (MRSA, VRE), anaerobes
- Not active vs. *Pseudomonas* spp or *Acinetobacter* spp.
- Orally bioavailable (but new formulation in development)
- Dose: Eravacycline 1mg/kg IV q 12h
- Issues:
  - High MIC *Pseudomonas*, *Burkholderia* spp.
  - Nausea, vomiting (< tigecycline)
- FDA approved for cIAI (vs. ertapenem, meropenem)
- Phase 3 trials - cUTI
  - IV/po erava vs. IV/PO levofloxacin failed
  - IV erava vs IV ertapenem failed

IGNITE1 and 4: Primary Efficacy Endpoint Clinical Response in micro-ITT at TOC

- Eravacycline demonstrated non-inferiority to ertapenem (IGNITE 1) and meropenem (IGNITE 2) in the FDA primary analyses

### Lefamulin CABP – LEAP 1
FDA Analysis/Early Endpt (ITT)

<table>
<thead>
<tr>
<th></th>
<th>Lefamulin</th>
<th>Moxifloxacin+/- LZD</th>
<th>Tx Diff (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N = 276</td>
<td>N = 275</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Day 4 Response</strong></td>
<td>87.3%</td>
<td>90.2%</td>
<td>-2.9 (-8.5, 2.8)</td>
</tr>
<tr>
<td><strong>S. Pneumo</strong></td>
<td>82/93 (88.2%)</td>
<td>91/97 (93.8%)</td>
<td>ND</td>
</tr>
<tr>
<td><strong>S. aureus</strong></td>
<td>10/10</td>
<td>4/4</td>
<td>ND</td>
</tr>
</tbody>
</table>

- *IV therapy with oral step down allowed*
- *PORT > III; 25% PORT IV or V*

File et al. CID 2019
## Oral Lefamulin vs Moxifloxacin for CABP

**LEAP 2**

<table>
<thead>
<tr>
<th></th>
<th>Lefamulin N = 370</th>
<th>Moxifloxacin N = 368</th>
<th>Tx Diff (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 4 (FDA)</td>
<td>336 (90.8)</td>
<td>334 (90.8)</td>
<td>0.1 (-4.4, ∞)</td>
</tr>
<tr>
<td>TOC (EMA)</td>
<td>322 (87.5)</td>
<td>328 (89.1)</td>
<td>-1.6 (-6.3, ∞)</td>
</tr>
<tr>
<td><strong>S pneumo day 4</strong></td>
<td>110/123 (89.4)</td>
<td>115/126 (91.3)</td>
<td></td>
</tr>
</tbody>
</table>

**Oral therapy: 5 days lefamulin vs 7 days moxifloxacin (PORT II, III, IV)**
- GI AEs: 17.9% lefamulin vs 7.6% moxi
  - Diarrhea 12.2% lefamulin vs 1.1% moxi; not tx-limiting
  - Nausea 5.2% lefamulin vs 1.9% moxi

Alexander et al. JAMA 2019
Cefiderocol

- Cephalosporin + siderophore
  - **Catechol moiety**
    - additional stability against β-lactamases
    - binds to free iron to enhance uptake by GNB
- Broad gram-negative spectrum
- Dose: 2g IV every 8 hours
- Completed studies
  - cUTI vs imipenem
  - HABP/VABP/HCAP vs meropenem
  - CRE vs best available therapy
**Cefiderocol vs Imipenem cUTI Phase 2**

<table>
<thead>
<tr>
<th>Analysis population</th>
<th>Cefiderocol</th>
<th>Imipenem-clastatin</th>
<th>Treatment difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>mITT population</td>
<td>183/252 (73)</td>
<td>65/119 (55)</td>
<td>18.58 (8.23-28.92)</td>
</tr>
<tr>
<td>Microbiologically evaluable population</td>
<td>182/228 (80)</td>
<td>65/106 (61)</td>
<td>19.35 (8.87-29.82)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age, years</th>
<th>Cefiderocol</th>
<th>Imipenem-clastatin</th>
<th>Treatment difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;65</td>
<td>87/113 (77)</td>
<td>32/54 (60)</td>
<td>17.73 (2.50-32.96)</td>
</tr>
<tr>
<td>≥65</td>
<td>96/139 (69)</td>
<td>33/65 (51)</td>
<td>18.30 (3.92-32.67)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Sex</th>
<th>Cefiderocol</th>
<th>Imipenem-clastatin</th>
<th>Treatment difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td>84/119 (71)</td>
<td>25/48 (52)</td>
<td>18.50 (2.17-34.84)</td>
</tr>
<tr>
<td>Women</td>
<td>99/133 (74)</td>
<td>40/71 (56)</td>
<td>18.10 (4.38-31.81)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Clinical diagnosis</th>
<th>Cefiderocol</th>
<th>Imipenem-clastatin</th>
<th>Treatment difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>cUTI with or without pyelonephritis</td>
<td>129/187 (69)</td>
<td>41/84 (49)</td>
<td>20.17 (7.60-32.75)</td>
</tr>
<tr>
<td>Acute uncomplicated pyelonephritis</td>
<td>54/65 (83)</td>
<td>24/35 (69)</td>
<td>14.51 (3.37-32.38)</td>
</tr>
</tbody>
</table>

- GI AEs: 4% cefiderocol vs 6% imipenem

Portsmouth et al. Lancet ID 2018; 18: 1319
**Cefiderocol**

**Regulatory Status**

- NDA under review:
  - cUTI (vs. imipenem)
- FDA Advisory Committee 16 October 19
  - 14 vs 2 vote in favor of effectiveness/safety in cUT
  - Death imbalance in CREDIBLE-CR study
- ? warning

www.FDA.gov
Fosfomycin (ZTI-01)

- Cell wall synthesis inhibitor
- Broad spectrum
  - Active vs. MRSA, MSSA, enteric GNB (some ESBL and serine carbapenemase producers), some P. aeruginosa
  - Not active vs. Morganella, Acinetobacter, Stenotrophomonas, Burkholderia, or Bacteroides spp.
- Available in EU x 45 years IV
- Fosfomycin 3g oral (Monurol) available in US
- Dose: 6 g every 8 hours IV over 1 hour
- Phase 3
  - cUTI vs. Piperacillin-tazobactam IV only
- NDA submitted 2 November 2018
Fosfomycin
ZEUS Study cUTI/AP

- Fosfo 6g every 8 hrs vs Piperacillin-tazobactam 4.5g every 8 hrs x 7 days
- Success: 64.7% Fosfo vs 54.5% pip-tazo; diff 10.2% (95% CI: -0.4, 20.8)
- M-MITT:
  - 32% (115/362) Extended Spectrum B-lactamase (ESBL)
  - 17% (62/362) Aminoglycoside resistance (AGR)
  - 6% (22/362) Carbapenem Resistant (CR)
  - 19% (70/362) Multi-Drug Resistant (MDR)
- AEs similar; fosfo diarrhea, LFT increase, low K+

<table>
<thead>
<tr>
<th></th>
<th>ESBL</th>
<th>AGR</th>
<th>CR</th>
<th>MDR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cure (n)</td>
<td>Erad. (n)</td>
<td>Cure (n)</td>
<td>Erad. (n)</td>
</tr>
<tr>
<td>Fosfo</td>
<td>93% (52/56)</td>
<td>55% (32/58)</td>
<td>97% (29/30)</td>
<td>67% (20/30)</td>
</tr>
<tr>
<td>Pip-Tazo</td>
<td>93% (51/55)</td>
<td>47% (27/57)</td>
<td>94% (29/31)</td>
<td>38% (12/32)</td>
</tr>
</tbody>
</table>

Kaye et al. CID 2019
Using Old Antibiotics in New Ways…
Shorter is better

- Gram-negative (Enterobacteriaceae) bloodstream infection
  - 7 days not inferior to 14 days after clinical stability and source control
- ABSSI – more failure with $\geq 8$ days
- Male UTI: no increased recurrence with $\leq 7$ days

Yahav et al. CID 2019; Ihm et al. OFID 2019; Germanos et al. OFID 2019
### Stewardship: Shorter = Better

B Spellberg

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Short (d)</th>
<th>Long (d)</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>CABP</td>
<td>3 or 5</td>
<td>7-14</td>
<td>Equal</td>
</tr>
<tr>
<td>VABP</td>
<td>8</td>
<td>15</td>
<td>Equal</td>
</tr>
<tr>
<td>Pyelonephritis</td>
<td>7 or 5</td>
<td>14 or 10</td>
<td>Equal</td>
</tr>
<tr>
<td>Intra-abdominal infection</td>
<td>4</td>
<td>10</td>
<td>Equal</td>
</tr>
<tr>
<td>Gram-neg bloodstream inf</td>
<td>7</td>
<td>14</td>
<td>Equal</td>
</tr>
<tr>
<td>AECB</td>
<td>≤5</td>
<td>≥7</td>
<td>Equal</td>
</tr>
<tr>
<td>Cellulitis</td>
<td>5-6</td>
<td>10</td>
<td>Equal</td>
</tr>
<tr>
<td>Osteomyelitis</td>
<td>42</td>
<td>84</td>
<td>Equal</td>
</tr>
<tr>
<td>Septic Arthritis</td>
<td>14</td>
<td>28</td>
<td>Equal</td>
</tr>
<tr>
<td>Neutropenic Fever</td>
<td>AF x 72 h</td>
<td>+ANC &gt; 500</td>
<td>Equal</td>
</tr>
<tr>
<td><em>P. vivax</em> Malaria</td>
<td>7</td>
<td>14</td>
<td>Equal</td>
</tr>
</tbody>
</table>
### Pragmatic Randomized control trial, UK
- 13% vs 14% FAILURE
- Standard IV therapy vs early oral switch
- Included both PJI and hardware-assoc infections
- Tx tailored individually by ID experts
  - Rifampin and follow-on tx allowed


### Table: Treatment Failure Rates

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Oral Group</th>
<th>Intravenous Group</th>
<th>Risk Difference (90% CI; 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intention-to-treat population</td>
<td>70.0/527</td>
<td>77.3/527</td>
<td>-1.4 (-4.9 to 2.2; -5.6 to 2.9)</td>
</tr>
<tr>
<td>Modified intention-to-treat population</td>
<td>67/509</td>
<td>74/506</td>
<td>-1.5 (-5.0 to 2.1; -5.7 to 2.8)</td>
</tr>
<tr>
<td>Per-protocol population</td>
<td>61/466</td>
<td>69/443</td>
<td>-2.5 (-6.3 to 1.3; -7.0 to 2.1)</td>
</tr>
<tr>
<td>Worst-case sensitivity analysis</td>
<td>85/527</td>
<td>74/527</td>
<td>2.1 (-1.5 to 5.7; -2.2 to 6.4)</td>
</tr>
</tbody>
</table>
Oral Step-down Therapy for Osteomyelitis

OVIVA

Strengths
- Pragmatic
- Diverse bone infections
- Long follow-up, low attrition rate

Limitations
- No set treatment strategy
- Diverse bone infections/tx (heterogenity), mild disease
- Open label, selection bias
- Few MRSA, MDRs
- Patients with “poor adherence” excluded

Oral therapy is better

• Early oral switch in left-sided endocarditis
  — POET 3.5 year follow-up
  — Mortality, unplanned surgery, embolic event, relapsed BSI: 38% IV vs 26% oral, HR 0.64
  — No difference: relapse and infection-related death
  — Limitations: no MRSA, few IVDU, comorbidity imbalance

• Linezolid to complete *S. aureus* bloodstream infection therapy?

NEJM 2019; 380: 415; Boucher NEJM 2019 380;5; Jorgensen et al. JAC 2019
10 x ‘20 but Nobody’s Buying

13 Lefamulin
Nabriva; Approved August 19, 2019
12 Imipenem/cilastatin+relebactam
Merck; Approved July 17, 2019
11 omadacycline
Paratek Pharmaceuticals; Approved: October 2, 2018
10 eravacycline
Tetraphase; Approved: August 28, 2018
9 plazomicin
Achaogen; Approved: June 26, 2018
8 meropenem/vaborbactam
The Medicines Company; Approved: August 30, 2017
7 delafloxacin
Melinta Therapeutics; Approved: June 17, 2017
6 ceftazidime/avibactam
Actavis plc; Approved: February 25, 2015
5 ceftolozane/tazobactam
Cubist Pharmaceuticals, Inc.; Approved: December 19, 2014
4 ertapenem/cilastatin
The Medicines Company; Approved: August 6, 2014
3 tedizolid phosphate
Cubist Pharmaceuticals, Inc.; Approved: June 20, 2014
2 dalbavancin
Durata Therapeutics; Approved: May 23, 2014
1 ceftaroline fosamil
Forest Laboratories, Inc.; Approved: October 29, 2010
Over the last 18 months, stock prices for all late stage antibiotic companies have fallen precipitously.

April 18, 2019:
- Achaogen: $0.17
- Melinta: $4.33
- Nabriva: $2.72
- Paratek: $5.57
- Tetraphase: $1.06
Broad Agreement: Fix the Antibiotic Pipeline

STAT NEWS FIRST OPINION
Medicare payment rules hinder the fight against superbugs
By KEVIN OUTTERSON and HELEN W. BOUCHER
APRIL 17, 2019

The antibiotic market is broken and won't fix itself
New Agents for Gram-negative Pathogens
Progress, Challenges, Incentives

• Progress
  — New agents in existing classes, activity vs MBLs
  — Stewardship – inpatient, outpatient, long-term care
  — Study design/development
    • HABP/VABP
    • Single pathogen studies (MDR)

• Challenges
  — New classes, mechanisms
  — Alternative types of therapeutics (antibodies, vaccines, phage)
  — Lack of Big Pharma engagement, poor return on investment
  — Poor uptake, delayed publication, guidelines

• Incentives
  — Push – grants, R&D tax credits, CARB-X, BARDA, GAIN, 21st Century Cures (LPAD)
  — Pull – market entry rewards, de-linkage
Thank You!

- Sue Cammarata
- G. Ralph Corey
- Sara Cosgrove
- Mike Dunne
- Roger Echols
- EJ Ellis-Grosse
- Amanda Jezek

- Kenneth Lawrence
- Evan Loh
- Brad Spellberg
- George H. Talbot
- Our patients and their families