Novel Approaches in the Management of *C. difficile* Infection

**Stuart Johnson, MD**

Professor, Department of Medicine
Stritch School of Medicine
Loyola University
Chicago, IL
Overview

• Pathogenesis of CDI* and risk for infection
• Current guideline recommendations for CDI treatment
• Alternative approaches to therapy for recurrent CDI
• Emerging approaches in treating CDI

*CDI, Clostridium difficile infection

Case History

66-year-old woman with multiple medical problems:
• Developed CDI with diarrhea 5 days after finishing a course of clindamycin for a dental infection; she responded to treatment with metronidazole (500 mg TID x 14 d), but
• Developed recurrent CDI with diarrhea & severe abdominal cramping 3 days after stopping metronidazole (WBC 16,000/mm³, serum creatinine 2.5 mg/dL); she responded to treatment with oral vancomycin (125 mg QID x 10 d), but
• Developed recurrent CDI with diarrhea 10 days after stopping vancomycin; she responded to vancomycin treatment followed by a vancomycin taper, but
• Developed recurrent CDI with diarrhea 7 days after finishing the vancomycin taper

What Would You Recommend Now?

1. Fecal microbiota transplant
2. Repeat vancomycin treatment followed by taper/pulse
3. Vancomycin 125 mg QID × 10 d followed by rifaximin 400 mg BID × 14 d
4. Fidaxomicin 200 mg BID × 10 d
5. Fidaxomicin 200 mg BID × 10 d followed by fidaxomicin 200 mg QD × 7 d, then once every other day for 2–3 weeks
Pathogenesis of *C. difficile* Infection

Antibiotic therapy

↓

Disturbed colonic microflora
(loss of colonization resistance)

"Dysbiosis"

Colonization by *C. difficile*

Exposure

Anti-toxin immunity

Toxin A & Toxin B

Toxin effects

Symptomless carriage

Diarrhea & colitis


Pathogenesis of *C. difficile* Infection

Antibiotic therapy

↓

Disturbed colonic microflora
(loss of colonization resistance)

"Dysbiosis"

Colonization by *C. difficile*

Antimicrobials
Chemotherapy
Neonatal state
Enteric infection
IBD with colitis

Toxin A & Toxin B

Symptomless carriage

Diarrhea & colitis


Decreased Diversity of Fecal Microbiome in CDI

Serious Bacterial Infections: A Focus on *Clostridium difficile* and Gram-Negative Infections
Pathogenesis of *C. difficile* Infection

- **Antibiotic therapy**
  - Disturbed colonic microflora (loss of colonization resistance)
- **Colonization by *C. difficile***
  - Toxin A & Toxin B
- **Symptomless carriage**
- **Diarrhea & colitis**

**Anti-toxin Immunity**

- Anti-toxin A Antibodies
- Anti-toxin B Antibodies
- Antibodies against non-toxin antigens?


Anti-toxin Immunity Protects Against CDI

- High serum anti-toxin in symptomless carriers
- Serum anti-toxin response & protection against recurrent CDI


*C. difficile* Infection: Basic Principles of Management

- Suspect on clinical grounds
- **Discontinue non-essential antibiotics**
- Confirm presence of toxin-producing *C. difficile* by stool testing (usually PCR or EIA)
- Empiric treatment best avoided UNLESS:
  - Very high clinical index of suspicion
  - OR very severe illness

Serious Bacterial Infections: A Focus on *Clostridium difficile* and Gram-Negative Infections
Impact of Concomitant Antibiotics on Response to CDI Treatment

<table>
<thead>
<tr>
<th></th>
<th>Fidaxo</th>
<th>Vanco</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>No CA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical cure</td>
<td>92%</td>
<td>93%</td>
<td>0.80</td>
</tr>
<tr>
<td>Recurrence</td>
<td>12%</td>
<td>23%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sustained response</td>
<td>81%</td>
<td>69%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical cure</td>
<td>90%</td>
<td>79%</td>
<td>0.04</td>
</tr>
<tr>
<td>Recurrence</td>
<td>17%</td>
<td>29%</td>
<td>0.05</td>
</tr>
<tr>
<td>Sustained response</td>
<td>72%</td>
<td>59%</td>
<td>0.02</td>
</tr>
</tbody>
</table>

CA = concomitant antibiotics

Treatment Guidelines for CDI in Adults: SHEA/IDSA 2010

- Metronidazole is the drug of choice for the initial episode of mild-moderate CDI (500 mg orally TID) for 10–14 days. (A-I)
- Vancomycin is the drug of choice for an initial episode of severe CDI. The dose is 125 mg orally QID for 10–14 days. (B-I)
- Vancomycin orally (and per rectum if ileus is present) with or without metronidazole IV ... for severe, complicated CDI. Vancomycin is dosed at 500 mg. (C-III)
- Consider colectomy in severely ill patients…(ideally before) serum lactate rises to 5 mmol/L and WBC 50,000 per mL. (B-II)


Randomized Trials Supporting Vancomycin (VAN) Over Metronidazole (MTR) for Treatment of Severe CDI

<table>
<thead>
<tr>
<th></th>
<th>Overall cure</th>
<th>Cure “Severe”</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Patients</td>
<td></td>
</tr>
<tr>
<td></td>
<td>135/150 (90)</td>
<td>59/69 (86)</td>
</tr>
<tr>
<td></td>
<td>VAN</td>
<td>69/71 (97)</td>
</tr>
<tr>
<td></td>
<td>MTR</td>
<td>66/79 (84)</td>
</tr>
<tr>
<td></td>
<td>p&lt;0.02</td>
<td></td>
</tr>
</tbody>
</table>


<table>
<thead>
<tr>
<th></th>
<th>Tolevamer</th>
<th>Vanco</th>
<th>MTR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>124/266 (47)</td>
<td>35/95 (37)</td>
<td>37/57 (65)</td>
</tr>
<tr>
<td></td>
<td>109/134 (81)</td>
<td>28/33 (85)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>103/143 (72)</td>
<td>37/57 (65)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>p=0.04</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Clinical Prediction Rule for Severe CDI
Derivation & validation from a cohort of 638 patients at 3 Centers

1 point for each:
- age ≥65 years
- peak creatinine ≥2 mg/dL
- peak WBC ≥20k cells/μL

Severe CDI:
- colectomy
- admission to ICU or
- death from CDI or with CDI as a contributor

Current IDSA/SHEA guidelines definition of severity:
WBC >15,000/mm³ or,
Cr >1.5 x baseline


Colectomy vs. Temporary Loop Ileostomy in Severe Complicated or Fulminant CDI

* Subtotal colectomy can be life-saving in severe complicated CDI, but should be performed before lactate reaches 5 mg/dL or WBC is >50,000/mm³ to avoid mortality which is high even with colectomy.

* Diverting loop ileostomy followed by intraoperative lavage of 8 L of warmed polyethylene glycol and 500 mg vancomycin q8h was performed in 42 patients (35 laparoscopically) and compared to the previous 42 historical colectomy patients.
  - Mortality was 19% vs 50%; odds ratio, 0.24; p=0.006.
  - Preservation of the colon was achieved in 39 of 42 patients (93%).


Treatment Guidelines for CDI in Adults:
SHEA/IDSA 2010 – Recurrent CDI

* Treatment of the first recurrence is usually with the same regimen as for the initial episode (A-II) but should be stratified by disease severity (C-III)
* Do not use metronidazole beyond first recurrence or for long-term chronic therapy (B-II)
* Treatment of the second or later recurrence with vancomycin using a taper and/or pulse regimen is the preferred next strategy (B-III)
* No recommendations can be made regarding prevention of recurrent CDI in patients requiring continued antimicrobial therapy (C-III)

New Data on CDI Treatment Since Publication of the IDSA/SHEA Guidelines

- Fidaxomicin phase 3 trials, including a randomized sub-study of patients with first CDI recurrence
- Randomized trial of FMT
- Findings from the largest and most rigorous randomized comparison of metronidazole and vancomycin (phase 3 trials of tolevamer)

FMT, fecal microbiota transplantation

Phase 3 Trials of Tolevamer for CDI

Comparison of a non-antibiotic, toxin-binder to treatment with vancomycin and metronidazole

- 1118 patients randomized between 2005 & 2007
  - Study 301, n=574 (91 sites in the US & Canada)
  - Study 302, n=544 (109 sites in Europe, Australia, & Canada)
  - 1071 included in the full analysis set (FAS)*
    - tolevamer, n=534
    - metronidazole, n=278
    - vancomycin, n=259
- Patients similarly matched across the 3 treatment arms, but differences noted between studies in terms of age, body weight, inpatient status, and concomitant antibiotic use

*FAS: all randomized patients who received any treatment and who had any post-dose evaluation


Results: Clinical Success

![Clinical Success Graph](source.png)

Results: CDI Recurrence

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Percent of Patients</th>
<th>Recurrence</th>
<th>95% CI of Difference</th>
<th>*P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tolvamer</td>
<td>3.4%</td>
<td>N/A</td>
<td>-27.1, -2.4</td>
<td>0.003</td>
</tr>
<tr>
<td>Metronidazole</td>
<td>23.7%</td>
<td>N/A</td>
<td>-19.1, 2.0</td>
<td>0.05</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>23.4%</td>
<td>N/A</td>
<td>-19.1, 2.0</td>
<td>0.05</td>
</tr>
</tbody>
</table>

Alternative Approaches to Therapy (Recurrent CDI)

- Switch treatment agent
- Tapering/pulsed treatment regimens (vancomycin, fidaxomicin)
- Post-vancomycin chaser regimens (rifaximin, fidaxomicin)
- Host microbiota replacement (various means to deliver FMT)
- Immune approach (only anecdotal support for IVIG, but mAb will likely be available in the near future)

Phase 3 Trial Results of Fidaxomicin vs. Vancomycin for CDI

Included patients with first and second CDI episodes

Data from modified intent-to-treat population

NS, not significant; Study 003: USA, Canada; Study 004: Belgium, Canada, France, Germany, Italy, Spain, Sweden, UK, USA
Rate of Recurrent CDI in Patients Treated for 1st Recurrence of CDI: Randomized Substudy of Phase 3 Fidaxomicin Trials


Caution for Using a Standard Treatment Course of Fidaxomicin in Patients with Multiple CDI Recurrences

- 2 patients with multiple recurrences given treatment doses of fidaxomicin with improvement but followed by symptomatic recurrence
- Prior regimens
  - 62 YOF: M x 14 d followed by Sb twice, V (many), V tapers (several)
  - 44 YOF: (M x 14 d twice); V x 10 d twice, rifaximin chaser

Sb, Saccharomyces boulardii therapy

Alternative Dosing Strategies for Treatment of Recurrent CDI

Serious Bacterial Infections: A Focus on Clostridium difficile and Gram-Negative Infections
Alternative Fidaxomicin Dosing Regimens for Patients with Multiple CDI Recurrences

Symptom-free intervals (SFI) & subsequent recurrence rates

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Age, mean±SD</th>
<th>Sex (F)</th>
<th>No. of CDI episodes, mean±SD</th>
<th>Longest SFI* prior to regimen, median (IQR)</th>
<th>SFI* post FDX regimen, median (IQR)</th>
<th>Subsequent recurrence rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fidaxomicin Chaser (200 mg bid x 10d)</td>
<td>8</td>
<td>66.9±19</td>
<td>75%</td>
<td>5.5±2</td>
<td>57 (48)</td>
<td>278 (649)</td>
<td>38%</td>
</tr>
<tr>
<td>Fidaxomicin Taper (200 mg daily x 7d, then q every other day x 26d)</td>
<td>12</td>
<td>63.6±16</td>
<td>58%</td>
<td>5.1±2</td>
<td>25 (30)</td>
<td>257 (280)**</td>
<td>18%</td>
</tr>
</tbody>
</table>

*SFI: Symptom-free interval, days
**p=0.003, compared with non-fidaxomicin taper SFI, Mann-Whitney U test

Treatments prior to the fidaxomicin regimens included: metronidazole, vancomycin, rifaximin chaser, IVIG, fecal transplant, and vancomycin taper (all patients had at least 1 vancomycin taper [mean no.= 2.3])


Randomized Trial of Fecal Microbiota Transplantation (FMT)

FMT Approaches

- Multiple methods of administration
  - Overall ~75% by colonoscopy or retention enema
  - ~25% by nasogastric tube or upper GI endoscopy
    - Reported efficacy >80% for lower versus >80% for upper routes
- Recent publications provide recommendations for:
  - Donor screening, processing of donor feces, methods of administration
- “Stool banks” – improve access
  [academic, not-for-profit & commercial]
Emerging Approaches in Treating CDI and Reducing the Risk of Recurrence

- Narrow-spectrum antibiotics
  - Several new antibacterial agents under study
- Microbial approaches
  - FMT (pre-screened donors, capsules)
  - Biotherapeutics (e.g., non-toxigenic C. difficile [NTCD])
- Toxin binders
  - Tolevamer or similar agent as adjunctive therapy?
- Immune approaches
  - Monoclonal antibodies to toxin A and B, (actoxumab/bezlotoxumab)

CDI Antibacterial Agents in Clinical Trials: clinicaltrials.gov

<table>
<thead>
<tr>
<th>Drug</th>
<th>Sponsor</th>
<th>Drug Class</th>
<th>Clinical Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>CB-183,315 (surotomycin)</td>
<td>Merck</td>
<td>cyclic lipopeptide</td>
<td>Phase III</td>
</tr>
<tr>
<td>ACT-179611 (cadazolid)</td>
<td>Actelion</td>
<td>quinolonyl-oxazolidinone</td>
<td>Phase III</td>
</tr>
<tr>
<td>LFF571</td>
<td>Novartis</td>
<td>thiopptide</td>
<td>Phase II</td>
</tr>
<tr>
<td>SMT19969</td>
<td>Summit</td>
<td>?</td>
<td>Phase II</td>
</tr>
<tr>
<td>CRS3123</td>
<td>NIAID</td>
<td>methionyl-RNA synthetase inhibitor</td>
<td>Phase I</td>
</tr>
</tbody>
</table>

Evolution of Bacteriotherapy (FMT)

- Whole fecal microbes delivered by enema, NG/NJ, colonoscopy
- Whole fecal microbes in condensed form given orally, fresh, frozen, freeze dried
- Modified whole fecal microbes...some components inactivated
- Defined microbial mixtures of 4–33 strains
- Single strains: NTCD, C. scindens?
Non-toxigenic *C. difficile* Spores: Nature’s Tailor-made Probiotic?

- **NTCD** (Non-toxigenic *C. difficile*)  
  - Spores of strain VP20621
- **Protects hamsters** against colonization by toxigenic *C. difficile* and against CDI

**Phase II trial:**
- Pts with CDI on standard treatment (vanco or metro) randomized to:
  - Placebo (n=43)
  - or NTCD (Total n=125)  
    - $10^4 \times 7$ days (n=41)
    - $10^5 \times 7$ days (n=43)
    - $10^7 \times 14$ days (n=41)


### Phase 3 Trials of Actoxumab/Bezlotoxumab, mAbs as Adjunctive Therapy for CDI

- Patients receiving standard of care for primary or recurrent CDI randomly assigned to one IV infusion of:
  - ACT+BEZ 10 mg/kg each
  - ACT 10 mg/kg alone  (*MODIFY I*)
  - BEZ 10 mg/kg alone
  - Placebo
- 1\textsuperscript{st} endpoint: recurrent CDI at 12 weeks

**MODIFY I**
- 1452 patients (19 countries); 1412 (97%) received study infusion

**MODIFY II**
- 1203 patients (17 countries); 1168 (97%) received study infusion


### Recurrent CDI Rates in Two Phase 3 Trials of Actoxumab/Bezlotoxumab

**MODIFY I**

<table>
<thead>
<tr>
<th></th>
<th>ACT+BEZLO</th>
<th>ACT</th>
<th>BEZLO</th>
<th>PLACEBO</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Recurrence</td>
<td>*10%</td>
<td>26%</td>
<td><strong>17%</strong></td>
<td>28%</td>
</tr>
</tbody>
</table>

*ACT+BEZLO vs Pbo: p<0.0001  
**BEZLO vs Pbo: p=0.0003*

**MODIFY II**

<table>
<thead>
<tr>
<th></th>
<th>ACT+BEZLO</th>
<th>ACT</th>
<th>BEZLO</th>
<th>PLACEBO</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Recurrence</td>
<td>*15%</td>
<td>16%</td>
<td><strong>16%</strong></td>
<td>26%</td>
</tr>
</tbody>
</table>

*ACT+BEZLO vs Pbo: p<0.0001  
**BEZLO vs Pbo: p=0.0003*


Serious Bacterial Infections: A Focus on *Clostridium difficile* and Gram-Negative Infections
Summary

- Accumulating data indicate that metronidazole is inferior to vancomycin for treatment of CDI.
- Vancomycin and fidaxomicin are similarly effective for primary CDI and fidaxomicin is superior for sustained response.
- Most patients with recurrent CDI can be managed with currently available anti-infectives (e.g., vancomycin and fidaxomicin) but novel regimens need to be used (e.g., taper, post-vancomycin chaser regimens) and patients need careful follow-up.
- Unresolved issues: In what setting should fidaxomicin and FMT be used? Primary CDI, 1st, 2nd, 3rd or later recurrence?
- Potential new treatments for CDI include additional narrow-spectrum antibiotics, biotherapeutics (NTCD), and immune-based therapy (mAb).
The Growing Concern of Bacterial Infections in Hospitals: Epidemiology and Gram-Negative Resistance Mechanisms

James S. Lewis II, PharmD, FIDSA
ID Clinical Pharmacy Coordinator & Adjunct Associate Professor
Oregon Health and Science University
Departments of Pharmacy & Infectious Diseases
Portland, OR
Overview

- Epidemiology
- Mechanisms of resistance
- Patient risk factors for resistant infections
- Consequences of inappropriate empiric therapy

Bacterial Pathogens Representing a Threat (CDC 2013)

- Urgent Threats
  - *Clostridium difficile*
  - Carbapenem-resistant Enterobacteriaceae
  - Drug-resistant *Neisseria gonorrhoeae*
- Serious Threats
  - MDR *P. aeruginosa* and *Acinetobacter*
  - ESBL-producing Enterobacteriaceae
  - MRSA and VRE
  - Various drug-resistant species (*Campylobacter, S. pneumoniae, Salmonella, tuberculosis, Shigella*)

Antibiotic Resistance Threats in the United States, 2013

<table>
<thead>
<tr>
<th>Gram-negative Organism</th>
<th>Cases (%)</th>
<th>Deaths (%)</th>
<th>Threat Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESBL-producing Enterobacteriaceae</td>
<td>26,000 (1.93)</td>
<td>1700 (7.44)</td>
<td>Serious</td>
</tr>
<tr>
<td>Carbapenem-resistant Enterobacteriaceae</td>
<td>9300 (0.69)</td>
<td>610 (2.67)</td>
<td>Urgent</td>
</tr>
<tr>
<td>Multidrug-resistant <em>Pseudomonas aeruginosa</em></td>
<td>6700 (0.5)</td>
<td>440 (1.92)</td>
<td>Serious</td>
</tr>
<tr>
<td>Multidrug-resistant <em>Acinetobacter</em> spp.</td>
<td>7300 (0.54)</td>
<td>500 (2.18)</td>
<td>Serious</td>
</tr>
</tbody>
</table>

Estimated annual incidence of infection due to notable antimicrobial-resistant organisms
Total: 1,349,766 cases and 22,840 deaths
ESBL, extended-spectrum beta-lactamase
Rising Incidence of MDR Pathogens

Retrospective analysis of ~500,000 K. pneumoniae isolates from throughout the US

CRKP, carbapenem-resistant K. pneumoniae; G3CRKP, third-generation cephalosporin-resistant K. pneumoniae


Available at: https://www.whitehouse.gov/sites/default/files/docs/national_action_plan_for_combating_antibiotic-resistant_bacteria.pdf - accessed 2/8/16

AMR, antimicrobial resistance.
Antibiotic-resistant Bacteria: Fast Facts

- Resistant organisms cause more than 2 million illnesses and at least 23,000 deaths each year in the US.
- Up to 70% fewer patients will get CRE in 5 years if facilities coordinate to protect patients.
- Preventing infections and improving antibiotic prescribing could save 37,000 lives from drug-resistant infections over 5 years.

INTEGRATED EFFORTS ARE KEY!!!!

CRE, carbapenem-resistant Enterobacteriaceae infection.

FDA Reboot of Antibiotic Development: Antimicrobial Agents Approved

Challenges

- *E. coli* is the most common pathogen in hospitals
- ESBLs are common, clonal and spreading rapidly
- ESBLs are MDR and also XDR
- Carbapenemase-producing Enterobacteriaceae are game changers and spreading worldwide

MDR, multidrug resistant; XDR, extensively drug resistant.
Pathogens Associated with HCAIs

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>All HCAIs (N=504)</th>
<th>Pneumonia (n=110)</th>
<th>Surgical Site Infections (n=110)</th>
<th>GI Infections (n=86)</th>
<th>UTIs (n=65)</th>
<th>Bloodstream Infections (n=50)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number (%)</td>
<td>Number (%)</td>
<td>Number (%)</td>
<td>Number (%)</td>
<td>Number (%)</td>
<td>Number (%)</td>
</tr>
<tr>
<td>Clostridium difficile</td>
<td>61 (12.1)</td>
<td>0</td>
<td>0</td>
<td>61 (70.9)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td>54 (10.7)</td>
<td>18 (16)</td>
<td>17 (16)</td>
<td>1 (1)</td>
<td>2 (3)</td>
<td>7 (14)</td>
</tr>
<tr>
<td>Klebsiella pneumoniae or oxytoca</td>
<td>50 (9.9)</td>
<td>13 (12)</td>
<td>15 (14)</td>
<td>1 (1)</td>
<td>15 (23)</td>
<td>4 (8)</td>
</tr>
<tr>
<td>Escherichia coli</td>
<td>47 (9.3)</td>
<td>3 (3)</td>
<td>14 (13)</td>
<td>1 (1)</td>
<td>18 (28)</td>
<td>5 (10)</td>
</tr>
<tr>
<td>Enterococcus</td>
<td>44 (8.7)</td>
<td>2 (2)</td>
<td>16 (15)</td>
<td>5 (6)</td>
<td>11 (17)</td>
<td>6 (12)</td>
</tr>
<tr>
<td>Pseudomonas aeruginosa</td>
<td>36 (7.1)</td>
<td>14 (13)</td>
<td>7 (6)</td>
<td>1 (1)</td>
<td>7 (11)</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Candida spp.</td>
<td>32 (6.3)</td>
<td>4 (4)</td>
<td>3 (3)</td>
<td>3 (4)</td>
<td>3 (5)</td>
<td>11 (22)</td>
</tr>
</tbody>
</table>


<table>
<thead>
<tr>
<th>Gram-negative</th>
<th>% Resistance (n) in Nonurinary Isolates</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Intensive Care Unit (ICU)</td>
</tr>
<tr>
<td></td>
<td>Ceftazidime-Resistant</td>
</tr>
<tr>
<td>E. coli</td>
<td>11.0 (3084)</td>
</tr>
<tr>
<td>K. pneumoniae</td>
<td>26.8 (1780)</td>
</tr>
<tr>
<td>A. baumannii</td>
<td>60.1 (550)</td>
</tr>
<tr>
<td>P. aeruginosa</td>
<td>18.6 (2615)</td>
</tr>
</tbody>
</table>


Oregon Health & Science University Antibiogram, 2014

Serious Bacterial Infections: A Focus on Clostridium difficile and Gram-Negative Infections
The hidden epidemic of Escherichia coli

Nabet C, Raoult D.

- Lifetime probability of a woman having a symptomatic UTI = 40%–50%
- Billions of resistance genes enter waste water from hospitals
- Waste water plants loaded with E. coli with numerous resistance genes – the bugs die, but the genes move on
- 92% of outpatient OHSU E. coli ceftriaxone S – 2015
- 81% of inpatient OHSU E. coli ceftriaxone S – 2015

Ceftolozane-Tazobactam vs. Levofloxacin for Complicated UTIs – Resistance Matters!


Gram-negative Resistance Mechanisms

Mechanisms of Resistance in *P. aeruginosa*

- Quinolones
  - Reduced affinity to topoisomerase 2
  - Reduced affinity to topoisomerase 4
- Aminoglycosides
  - Reduced transport
  - Methylase genes
  - Modifying enzymes
- Up-regulation of efflux systems – beta-lactams
  - MexAB-OprM
  - MexCD-OprJ
  - MexEF-OprN
  - MexXY-OprM
- Porin Deletion – Carbapenems
  - OprD
- Membrane charge changes – Polymyxins
- Beta-lactamases
  - De-repression of AmpC
  - VIM/IMP/NDM metallo enzymes
  - OXA enzymes
- And the list goes on...


Carbapenem Resistance in Enterobacteriaceae

<table>
<thead>
<tr>
<th>Enzyme</th>
<th>Corese genetic platform</th>
<th>Species distribution in Enterobacteriaceae</th>
<th>Geographic distribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>RPC</td>
<td>K pneumoniae sequence type 75A, various plasmid types, transposon Tn4401</td>
<td>K pneumoniae, <em>Enterobacteriaceae</em>, diverse <em>Enterobacteriaceae</em></td>
<td>Endemic in the United States, Germany, Brazil, Italy, Puerto Rico, China, and South America</td>
</tr>
<tr>
<td>NDM</td>
<td>Various plasmid types</td>
<td>K pneumoniae and T eosinophila predominant, diverse Enterobacteriaceae</td>
<td>India subcontinent and the Balkan region, and around the world</td>
</tr>
<tr>
<td>OXA-48</td>
<td>IncF1-type plasmid</td>
<td>K pneumoniae, <em>Enterobacteriaceae</em>, diverse Enterobacteriaceae</td>
<td>Southern and Western Europe, China, and South Africa</td>
</tr>
<tr>
<td>VIM</td>
<td>Gene cassette in class 1 integrons</td>
<td>K pneumoniae predominant</td>
<td>Common in Italy, Germany, and the Far East, sporadically globally</td>
</tr>
<tr>
<td>IMP</td>
<td>Gene cassette in class 1 integrons</td>
<td>K pneumoniae predominant</td>
<td>Common in the Far East, and South America, sporadically globally</td>
</tr>
<tr>
<td>SME</td>
<td>Chromosone</td>
<td><em>Enterobacteriaceae</em></td>
<td>Sporadic in North America and South America</td>
</tr>
</tbody>
</table>


Who is at Risk for Colonization and Subsequent Infections with MDR Gram-negatives?

- Previous exposure to broad-spectrum antibiotics
  - Including vancomycin
- Exposure to an increasing number of antibiotics
- Increasing age (>60 yo)
- Increasing chronic disease score
- Previous ICU stay
- COPD
- Increasing duration of hospitalization

Time to Effective Antibiotics & Mortality


What Happens When You Run Out of Options

- KPC-producing bacteria
- 111 ICU patients in Italy, single center, septic shock
- Overall mortality: 40%
- Predictors of survival
  - Initial therapy (w/in 24h) - 2 antibiotics with in vitro activity
  - Removal of source of infection
  - Use of colistin
- Predictors of mortality
  - Colistin resistance
  - Intra-abdominal source


Compromise of the Last Line

Emergence of plasmid-mediated colistin resistance mechanism MCR-1 in animals and human beings in China: a microbiological and molecular biological study

- Gene easily mobilized to E. coli, K. pneumoniae and P. aeruginosa
- Adds a phosphoethanolamine to lipid A = no binding of colistin
- 78 (15%) of 523 samples of raw meat
- 166 (21%) of 804 animals during 2011–14
- 16 (1%) of 1322 samples from inpatients with infection


Conclusions

- The challenge of resistant Gram-negative bacteria is substantial
- The bugs don’t stop, and they have a variety of weapons
- Antibiotic development has not kept pace, but is improving?
- Resistance often = clinical failure
- Clinical failure often = increased mortality
Current Therapeutic Options for Antimicrobial-Resistant Gram-Negative Infections

Keith A. Rodvold, PharmD, FCCP, FIDSA
Professor of Pharmacy Practice and Medicine
 Colleges of Pharmacy and Medicine
 University of Illinois at Chicago
 Chicago, IL
Antibiotic Treatment of Resistant Gram-negative Organisms

- Infections caused by resistant Gram-negative organisms are associated with increased morbidity and mortality compared to susceptible counterparts.
- Choice of empiric therapy has become more difficult for serious infections because of antimicrobial resistance to first-line agents.
- Clinicians also have the dilemma between choosing:
  - an agent that is inactive versus broad-spectrum agent
  - monotherapy versus combination therapy
  - determining the role of adjunctive therapy

Antibiotic Resistance Threats in the United States, 2013

<table>
<thead>
<tr>
<th>Gram-negative Organism</th>
<th>Cases (%)</th>
<th>Deaths (%)</th>
<th>Threat Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESBL-producing Enterobacteriaceae</td>
<td>26,000</td>
<td>1700</td>
<td>Serious</td>
</tr>
<tr>
<td></td>
<td>(1.93)</td>
<td>(7.44)</td>
<td></td>
</tr>
<tr>
<td>Carbapenem-resistant Enterobacteriaceae</td>
<td>9300</td>
<td>610</td>
<td>Urgent</td>
</tr>
<tr>
<td></td>
<td>(0.69)</td>
<td>(2.67)</td>
<td></td>
</tr>
<tr>
<td>Multidrug-resistant <em>Pseudomonas aeruginosa</em></td>
<td>6700</td>
<td>440</td>
<td>Serious</td>
</tr>
<tr>
<td></td>
<td>(0.5)</td>
<td>(1.92)</td>
<td></td>
</tr>
<tr>
<td>Multidrug-resistant <em>Acinetobacter</em> spp.</td>
<td>7300</td>
<td>500</td>
<td>Serious</td>
</tr>
<tr>
<td></td>
<td>(0.54)</td>
<td>(2.18)</td>
<td></td>
</tr>
</tbody>
</table>

Estimated annual incidence of infection due to notable antimicrobial-resistant organisms:
Total: 1,349,766 cases and 22,840 deaths
ESBL, extended-spectrum beta-lactamase

Which one of the following statements best describes the availability of colistin and/or polymyxin B at your institution?

1. Colistin only and anyone can prescribe it
2. Colistin only but with restrictions who can prescribe it
3. Polymyxin B only and anyone can prescribe it
4. Polymyxin B only but with restrictions who can prescribe it
5. Both agents and anyone can prescribe it
6. Both agents but with restrictions who can prescribe it
7. I don’t know
Colistin and Polymyxin B

- Assumed an important role as “salvage therapy” for otherwise untreatable Gram-negative infections
- Emerging pharmacokinetic/pharmacodynamic data indicate that monotherapy is unlikely to generate plasma concentrations that are reliably efficacious
- Regrowth and the emergence of resistance with monotherapy are commonly reported even when concentrations exceed those achieved clinically
- Combination therapy has been suggested as a possible means of increasing antimicrobial activity and reducing the development of resistance


Combination Antibiotic Treatment of Resistant Gram-negative Organisms

- Choice of agents often involves:
  - Aminoglycosides
  - Beta-lactam/beta-lactamase inhibitors
  - Carbapenems
  - Fosfomycin
  - Polymyxins
  - Rifampin
  - Tetracyclines
  - Tigecycline
- Clinical evidence regarding effectiveness of different treatment regimens is principally derived from retrospective studies, case reports or small prospective studies; no randomized clinical trials
- Need for new antimicrobial agents to treat resistant Gram-negative organisms is inevitably important

Agents Being Developed to Treat Resistant Gram-negative Bacteria

<table>
<thead>
<tr>
<th>Agent</th>
<th>Related-Class</th>
<th>Developer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ceftolozane-Tazobactam</td>
<td>BLBLI</td>
<td>Merck</td>
</tr>
<tr>
<td>Ceftazidime-Avibactam</td>
<td>BLBL</td>
<td>Allergan</td>
</tr>
<tr>
<td>Meropenem-RPX7009</td>
<td>BLBLI</td>
<td>Medicines Company</td>
</tr>
<tr>
<td>Imipenem-Relebactam</td>
<td>BLBLI</td>
<td>Merck</td>
</tr>
<tr>
<td>Aztrenam-Avibactam</td>
<td>BLBLI</td>
<td>AstraZeneca</td>
</tr>
<tr>
<td>S649266</td>
<td>Cephalosporin</td>
<td>Shionogi</td>
</tr>
<tr>
<td>Eravacycline</td>
<td>Tetracycline</td>
<td>Tetraphase</td>
</tr>
<tr>
<td>Plazomicin</td>
<td>Aminoglycoside</td>
<td>Achaogen</td>
</tr>
<tr>
<td>POL7080</td>
<td>Macrocycle LptD Inhibitor</td>
<td>Roche / Polyphor</td>
</tr>
</tbody>
</table>

BLBLI, Beta-lactam/beta-lactamase inhibitor combinations
Beta-lactamase Inhibitor Revival
New Hope for Old Antibiotics

- Tazobactam
  - 2:1 ratio ceftolozane:tazobactam (FDA approval)
- Avibactam (NXL-104) and Relebactam (MK-7655)
  - Novel diazabicyclooctane class
  - 4:1 ratio ceftazidime:avibactam (FDA approval)
  - 2:1 and 4:1 imipenem:relebactam
- RPX7009
  - Boron-containing serine beta-lactamase inhibitor
  - 1:1 ratio meropenem:RPX7009


Ambler Classification (Beta-lactamases)

<table>
<thead>
<tr>
<th>Ambler Class</th>
<th>Beta-lactamase Type</th>
<th>Preferred Substrates</th>
<th>Representative Enzymes</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Narrow-spectrum</td>
<td>Penicillins, narrow-spectrum cephalosporins</td>
<td>TEM-1, TEM-2, SHV-1</td>
</tr>
<tr>
<td>A</td>
<td>Extended-spectrum</td>
<td>Narrow and extended-spectrum beta-lactams</td>
<td>SHV-2, CTX-M-15, PER-1, VEB-1</td>
</tr>
<tr>
<td>A</td>
<td>Serine-carbapenemase</td>
<td>Carbapenems</td>
<td>KPC-1, IMP-1, SME-1</td>
</tr>
<tr>
<td>B</td>
<td>Metallo-beta-lactams</td>
<td>Most beta-lactams, including carbapenems</td>
<td>VIM-1, IMP-1, NDM-1</td>
</tr>
<tr>
<td>C</td>
<td>Cephalosporinases</td>
<td>Cephalosporins</td>
<td>AmpC, P99, ACT-1, CMY-2, FOX-1, MIR-1</td>
</tr>
<tr>
<td>D</td>
<td>OXA-type enzymes</td>
<td>Penicillins, oxacillins, carbapenems</td>
<td>OXA enzymes</td>
</tr>
</tbody>
</table>


Spectrum of Beta-lactamase Inhibitors

<table>
<thead>
<tr>
<th>Spectrum</th>
<th>Beta-lactamase Inhibitor</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Tazobactam</td>
</tr>
<tr>
<td>Class A narrow-spectrum</td>
<td>X</td>
</tr>
<tr>
<td>Class A ESBLs</td>
<td>X</td>
</tr>
<tr>
<td>Class A carbapenemases</td>
<td>X</td>
</tr>
<tr>
<td>Some class C enzymes</td>
<td>X</td>
</tr>
<tr>
<td>Some class D enzymes</td>
<td>X</td>
</tr>
</tbody>
</table>

Agents Being Developed to Treat Resistant Gram-negative Bacteria

<table>
<thead>
<tr>
<th>Agent</th>
<th>Related-Class</th>
<th>Developer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ceftolozane-Tazobactam</td>
<td>BLBLI</td>
<td>Merck</td>
</tr>
<tr>
<td>Ceftazidime-Avibactam</td>
<td>BLBLI</td>
<td>Allergan</td>
</tr>
<tr>
<td>Meropenem-RPX7009</td>
<td>BLBLI</td>
<td>Medicines Company</td>
</tr>
<tr>
<td>Imipenem-Relebactam</td>
<td>BLBLI</td>
<td>Merck</td>
</tr>
<tr>
<td>Aztreonam-Avibactam</td>
<td>BLBLI</td>
<td>AstraZeneca</td>
</tr>
<tr>
<td>S649266</td>
<td>Cephalosporin</td>
<td>Shionogi</td>
</tr>
<tr>
<td>Eravacycline</td>
<td>Tetracycline</td>
<td>Tetraphase</td>
</tr>
<tr>
<td>Plazomicin</td>
<td>Aminoglycoside</td>
<td>Achaogen</td>
</tr>
<tr>
<td>POL7080</td>
<td>Macrocycle LptD Inhibitor</td>
<td>Roche / Polyphor</td>
</tr>
</tbody>
</table>

Which one of the following statements best describes the availability of ceftolozane-tazobactam (Zerbaxa™) and/or ceftazidime-avibactam (Avycaz™) at your institution?

1. Ceftolozane-tazobactam only and anyone can prescribe it
2. Ceftolozane-tazobactam only but with restrictions who can prescribe it
3. Ceftazidime-avibactam only and anyone can prescribe it
4. Ceftazidime-avibactam only but with restrictions who can prescribe it
5. Both agents, and anyone can prescribe it
6. Both agents but with restrictions who can prescribe it
7. I don’t know

Ceftolozane-Tazobactam

- Antipseudomonal cephalosporin plus beta-lactamase inhibitor
- Spectrum of activity: Gram-negatives, including MDR Pseudomonas aeruginosa and ESBL-producing strains
- FDA approval in December 2014
  - Complicated Urinary Tract Infections, including Pyelonephritis
  - Complicated Intraabdominal Infections (plus metronidazole)
  - IV dose: 1.5 g (1 g ceftolozane; 0.5 g tazobactam) q8h (1-h infusion)
- Dosage adjustment in patients with renal impairment (CrCl ≤50 mL/min) or ESRD on hemodialysis
- Most common adverse reactions are nausea, diarrhea, headache, and pyrexia

Ceftolozane-Tazobactam

- Demonstrated in vitro activity against *Pseudomonas aeruginosa* isolates tested that had:
  - Chromosomal AmpC
  - Loss of outer membrane porin (OprD) or
  - Up-regulation of efflux pumps (MexXY, MexAB)
- Not active against bacteria producing metallo-β-lactamases
- Current FDA susceptibility interpretive criteria:

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Susceptible (S)</th>
<th>Intermediate (I)</th>
<th>Resistant (R)</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Pseudomonas aeruginosa</em></td>
<td>≤4 / 4*</td>
<td>8 / 4*</td>
<td>≥16 / 4*</td>
</tr>
</tbody>
</table>

*Ceftolozane and tazobactam susceptibility testing performed with a fixed 4 µg/mL concentration of tazobactam*

Ceftolozane and tazobactam for injection, for intravenous use - prescribing information, July 2015.

**Ceftolozane-Tazobactam**

Antimicrobial susceptibility patterns of *Pseudomonas aeruginosa* isolates from patients hospitalized with pneumonia stratified by geographic region (2012):

<table>
<thead>
<tr>
<th>% Susceptible</th>
<th>USA (CLSI) n = 500</th>
<th>Europe (EUCAST) n = 519</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ceftolozane–tazobactam*</td>
<td>99.4</td>
<td>89.0</td>
</tr>
<tr>
<td>Ceftazidine</td>
<td>82.0</td>
<td>65.5</td>
</tr>
<tr>
<td>Piperacillin–tazobactam</td>
<td>76.2</td>
<td>63.0</td>
</tr>
<tr>
<td>Meropenem</td>
<td>80.6</td>
<td>67.1</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>76.6</td>
<td>54.7</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>87.0</td>
<td>74.6</td>
</tr>
<tr>
<td>Amikacin</td>
<td>97.4</td>
<td>82.3</td>
</tr>
</tbody>
</table>

* Percentage inhibited at ceftolozane-tazobactam MICs ≤8 µg/mL; for comparison purposes only

*Ceftolozane-Tazobactam activity tested against *Pseudomonas aeruginosa* isolates from patients hospitalized with pneumonia (USA - 2012)*

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Cumulative (%) inhibited at MIC in µg/mL of:</th>
<th>MIC&lt;sub&gt;50&lt;/sub&gt; / MIC&lt;sub&gt;90&lt;/sub&gt; (µg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pseudomonas aeruginosa&lt;sup&gt;SR&lt;/sup&gt; (n=1518)</td>
<td>92.6 / 91.1 / 94.6</td>
<td>8 / 8 / 8</td>
</tr>
<tr>
<td>Ceftazidine-non-S&lt;sup&gt;SR&lt;/sup&gt; (n=269)</td>
<td>72.1 / 77.7 / 79.6</td>
<td>4 / &gt;32</td>
</tr>
<tr>
<td>Ceftazime-non-S&lt;sup&gt;SR&lt;/sup&gt; (n=230)</td>
<td>70.7 / 77.0 / 79.1</td>
<td>4 / &gt;32</td>
</tr>
<tr>
<td>Meropenem-non-S&lt;sup&gt;SR&lt;/sup&gt; (n=268)</td>
<td>75.7 / 78.0 / 79.9</td>
<td>2 / &gt;32</td>
</tr>
<tr>
<td>Piperacillin-tazobactam-non-S&lt;sup&gt;SR&lt;/sup&gt; (n=215)</td>
<td>76.5 / 81.4 / 83.0</td>
<td>2 / &gt;32</td>
</tr>
<tr>
<td>CAZ &amp; MEM &amp; P/T-non-S&lt;sup&gt;SR&lt;/sup&gt; (n=138)</td>
<td>60.1 / 63.9 / 67.1</td>
<td>4 / &gt;32</td>
</tr>
<tr>
<td>Levofloxacin-non-S&lt;sup&gt;SR&lt;/sup&gt; (n=257)</td>
<td>81.4 / 82.7 / 84.4</td>
<td>2 / &gt;32</td>
</tr>
<tr>
<td>Gentamicin-non-S&lt;sup&gt;SR&lt;/sup&gt; (n=189)</td>
<td>71.6 / 75.1 / 76.1</td>
<td>2 / &gt;32</td>
</tr>
<tr>
<td>Multidrug-resistant (MDR)-non-S&lt;sup&gt;SR&lt;/sup&gt; (n=158)</td>
<td>72.4 / 75.6 / 77.6</td>
<td>2 / &gt;32</td>
</tr>
<tr>
<td>Extensively drug-resistant (XDR)-non-S&lt;sup&gt;SR&lt;/sup&gt; (n=174)</td>
<td>63.2 / 66.1 / 69.9</td>
<td>4 / &gt;32</td>
</tr>
</tbody>
</table>

Ceftolozane-Tazobactam

- Isolates displaying derepressed AmpC had ceftolozane-tazobactam MIC values ranging from 1 to 16 µg/mL.

- The development of high-level resistance to ceftolozane-tazobactam appears to occur efficiently only in a *Pseudomonas aeruginosa* mutator background, in which multiple mutations lead to overexpression and structural modifications of AmpC.

- *Pseudomonas aeruginosa* is able to adapt to efficacious beta-lactams, including newer cephalosporin ceftolozane, through a variety of mutations affecting its intrinsic beta-lactamase, AmpC.

---

Ceftolozane-Tazobactam

- Spectrum of activity: Gram-negatives, including MDR *Pseudomonas aeruginosa* and ESBL-producing strains

- FDA approval in December 2014
  - Complicated Urinary Tract Infections, including Pyelonephritis
  - Complicated Intraabdominal Infections (plus metronidazole)
  - IV dose: 1.5 g (1 g ceftolozane; 0.5 g tazobactam) q8h (1-h infusion)

- Ongoing Phase 3 Trial: Ventilated nosocomial pneumonia; 
  **increased dose**: 3.0 g (2 g ceftolozane; 1 g tazobactam) q8h
  - For 8 days; however 14 days for *Pseudomonas aeruginosa*

- Plasma-to-epithelial lining fluid penetration ~50%

---

Ceftolozane–Tazobactam Therapy* of Respiratory Infections due to MDR *Pseudomonas aeruginosa*

<table>
<thead>
<tr>
<th>Age; Sex</th>
<th>Prior Antibiotics</th>
<th>Clinical / Microbiologic Outcomes</th>
<th>Susceptibilities (MIC, µg/mL)</th>
</tr>
</thead>
</table>
| 69 y; male | Ciprofloxacin | Cure / Eradication | Ceftolozane–Tazobactam (0.25)  
  Meropenem (>4)  
  Ceftazidime (8)  
  Ciprofloxacin (2)  
  Tobramycin (2)  
  Piperacillin-Tazobactam (1/4) |
| 63 y; male | Meropenem, Ciprofloxacin | Cure / Eradication | Ceftolozane–Tazobactam (1)  
  Meropenem (>4)  
  Cefepime (≤16)  
  Ciprofloxacin (2)  
  Tobramycin (8)  
  Piperacillin-Tazobactam (≤8)  
  Colistin (susceptible)  
  Polymyxin (susceptible) |
| 52 y; Male | Meropenem, Linezolid | Cure / Eradication | Ceftolozane–Tazobactam (1)  
  Meropenem (>4)  
  Cefepime (≤16)  
  Ciprofloxacin (≤0.5)  
  Tobramycin (≤2)  
  Piperacillin-Tazobactam (≤16) |

*Ceftolozane–tazobactam 3 g IV every 8 hours for 14 days

Gelfand MS & Cleveland KO. Clin Infect Dis. 2015;61:853-855 [letter to editor].

---

Serious Bacterial Infections: A Focus on *Clostridium difficile* and Gram-Negative Infections
Ceftazidime-Avibactam

- **Antipseudomonal cephalosporin plus beta-lactamase inhibitor**
- **Spectrum of activity:** Gram-negatives, including MDR *Pseudomonas aeruginosa*, ESBL-producing strains, KPCs
- **FDA approval in February 2015** (based on Phase 2 data)
  - Complicated Urinary Tract Infections, including Pyelonephritis
  - Complicated intraabdominal Infections (plus metronidazole)
  - IV dose: 2.5 g (2 g ceftazidime; 0.5 g avibactam) q8h (2-h infusion)
  - For patients with limited or no alternative treatment options
- **Dosage adjustment in patients with CrCl ≤50 mL/min**
- **Most common adverse reactions are vomiting, nausea, constipation, and anxiety**

**Dosage Adjustment**

- **IV dose:** 2.5 g (2 g ceftazidime; 0.5 g avibactam) q8h (2-h infusion)

**Common Adverse Reactions**

- Vomiting
- Nausea
- Constipation
- Anxiety


---

Ceftazidime-Avibactam

- **Demonstrated in vitro activity** against *Pseudomonas aeruginosa* in the presence of:
  - Some AmpC beta-lactamases or
  - Certain strains lacking outer membrane porin (OprD)
- **Not active** against bacteria producing metallo-β-lactamases and may not have activity against Gram-negative bacteria that overexpress efflux pumps or have porin mutations
- **Current FDA susceptibility interpretive criteria:**

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Minimum Inhibitory Concentrations (µg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Susceptible (S)</td>
</tr>
<tr>
<td><em>Pseudomonas aeruginosa</em></td>
<td>≤8 / 4*</td>
</tr>
<tr>
<td>Enterobacteriaceae</td>
<td></td>
</tr>
</tbody>
</table>

* Ceftazidime/avibactam susceptibility testing performed with a fixed 4 µg/mL concentration of avibactam

Ceftazidime and avibactam for injection, for intravenous use - prescribing information, September 2015.

---

Ceftazidime-Avibactam

**Antimicrobial susceptibility patterns of *Pseudomonas aeruginosa* isolates from intensive care unit (ICU) and non-ICU patients from US Hospital (2012–2013):**

<table>
<thead>
<tr>
<th></th>
<th>% Susceptible</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ICU n = 542</td>
</tr>
<tr>
<td>Ceftazidime-avibactam*</td>
<td>95.6</td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>77.7</td>
</tr>
<tr>
<td>Cefepime</td>
<td>79.8</td>
</tr>
<tr>
<td>Piperacillin–tazobactam</td>
<td>71.2</td>
</tr>
<tr>
<td>Meropenem</td>
<td>76.6</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>76.4</td>
</tr>
<tr>
<td>Amikacin</td>
<td>98.6</td>
</tr>
<tr>
<td>Colistin</td>
<td>100.0</td>
</tr>
</tbody>
</table>

*Percentage inhibited at ceftazidime-avibactam MICs ≤8 µg/mL
### Ceftazidime-Avibactam

Ceftazidime-avibactam activity tested against *Pseudomonas aeruginosa* isolates from patients hospitalized in USA (2012–2013):

<table>
<thead>
<tr>
<th></th>
<th>Cumulative (%) inhibited at MIC in µg/mL of:</th>
<th>MIC₅₀ / MIC₉₀ (µg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td><em>Pseudomonas aeruginosa</em> (n=3082)</td>
<td>91.7</td>
<td>97.0</td>
</tr>
<tr>
<td>non-ICU (n=2240)</td>
<td>93.2</td>
<td>97.5</td>
</tr>
<tr>
<td>ICU (n=842)</td>
<td>87.9</td>
<td>95.6</td>
</tr>
<tr>
<td>VAP (n=185)</td>
<td>92.4</td>
<td>97.3</td>
</tr>
<tr>
<td>Ceftazidime-non-S (n=482)</td>
<td>60.2</td>
<td>80.7</td>
</tr>
<tr>
<td>Meropenem-non-S (n=537)</td>
<td>67.8</td>
<td>87.0</td>
</tr>
<tr>
<td>Multidrug-resistant (MDR) (n=436)</td>
<td>57.3</td>
<td>80.7</td>
</tr>
<tr>
<td>Extensively drug-resistant (XDR) (n=247)</td>
<td>46.6</td>
<td>74.5</td>
</tr>
</tbody>
</table>


### Resistance to Ceftazidime-Avibactam

- β-lactam-resistant *Pseudomonas aeruginosa* clinical isolates
  - 18.5% of archived isolates (n = 54) from a decade ago were resistant to ceftazidime-avibactam with MIC of ≥16 µg/mL
- Acquired resistance, which may be driven by altered outer membrane permeability or overexpressed efflux pumps
- Combination poses a potential advantage
  - Addition of colistin reduced resistance to 7% of strains
  - Addition of fosfomycin reduced resistance to 1.9% of strains
- Resistance was not due to changes in penicillin-binding-protein (PBP) sequence or changes to β-lactamase sequence or expression level


### Ceftazidime-Avibactam

- Spectrum of activity: Gram-negatives, including MDR *Pseudomonas aeruginosa*, ESBL-producing strains, KPCs
- FDA approval in February 2015 (based on Phase 2 data)
  - Complicated Urinary Tract Infections, including Pyelonephritis
  - Complicated Intraabdominal Infections (plus metronidazole)
  - For patients with limited or no alternative treatment options
  - IV dose: 2.5 g (2 g ceftazidime; 0.5 g avibactam) q8h (2-h infusion)
- Clinical trials: Nosocomial pneumonia - Dose of 2.5 g q8h
- Plasma-to-epithelial lining fluid penetration ~30%
Agents Being Developed to Treat Resistant Gram-negative Bacteria

<table>
<thead>
<tr>
<th>Agent</th>
<th>Related-Class</th>
<th>Developer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ceftolozane-Tazobactam</td>
<td>BLBLI</td>
<td>Merck</td>
</tr>
<tr>
<td>Ceftazidime-Avibactam</td>
<td>BLBLI</td>
<td>Allergan</td>
</tr>
<tr>
<td>Meropenem-RPX7009</td>
<td>BLBLI</td>
<td>Medicines Company</td>
</tr>
<tr>
<td>Imipenem-Relebactam</td>
<td>BLBLI</td>
<td>Merck</td>
</tr>
<tr>
<td>Aztreonam-Avibactam</td>
<td>BLBLI</td>
<td>AstraZeneca</td>
</tr>
<tr>
<td>S649266</td>
<td></td>
<td>Shionogi</td>
</tr>
<tr>
<td>Eravacycline</td>
<td>Tetracycline</td>
<td>Tetraphase</td>
</tr>
<tr>
<td>Plazomicin</td>
<td>Aminoglycoside</td>
<td>Achaogen</td>
</tr>
<tr>
<td>POL7080</td>
<td>Macrolide</td>
<td>Roche / Polyphor</td>
</tr>
</tbody>
</table>

BLBLI, Beta-lactam/beta-lactamase inhibitor combinations

In Vitro Activity of Meropenem–RPX7009

4,500 isolates collected from 11 hospitals in Brooklyn and Queens, NY from November 2013 to January 2014

<table>
<thead>
<tr>
<th>Species (n)</th>
<th>Meropenem</th>
<th>Meropenem-RPX7009 (4 µg/mL)</th>
<th>Meropenem-RPX7009 (8 µg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MIC50</td>
<td>MIC90</td>
<td>MIC50</td>
</tr>
<tr>
<td>Klebsiella pneumoniae (KPC+) (121)</td>
<td>0.06/4</td>
<td>2/4</td>
<td>0.03/8</td>
</tr>
<tr>
<td>Pseudomonas aeruginosa (98)</td>
<td>32/4</td>
<td>8/8</td>
<td>32/8</td>
</tr>
<tr>
<td>Acinetobacter baumannii (84)</td>
<td>32/64</td>
<td>32/4</td>
<td>32/8</td>
</tr>
</tbody>
</table>

MIC values in µg/mL.

- Addition of RPX7009 resulted in a 64- to 512-fold decrease in meropenem MIC in majority of KPC-positive isolates
- All but 2 of these isolates (98.3%) were inhibited by 1 µg/mL meropenem combined with RPX7009 at 8 µg/mL


Meropenem-RPX7009

- In vitro hollow-fiber model (simulating human exposure of 2 g meropenem plus 2 g RPX7009 dose q8h and infused over 3 hours) demonstrated bactericidal activity against KPC-producing isolates of Enterobacteriaceae
- In vivo efficacy in murine thigh infection model against KPC-producing isolates of K. pneumoniae, E. coli, and E. cloacae (MICs ranging from ≤0.06 to 8 µg/mL)
- Agents display identical concentration-time profiles with each other in plasma and in epithelial lining fluid
- Clinical trials evaluating the efficacy, safety, and tolerability in adults with serious infections due to carbapenem-resistant Enterobacteriaceae are ongoing

ICAAC 2014 (abstr. F-958 & F-959).
Clinicaltrials.gov: NCT02166476 & NCT02168946.
### In Vitro Activity of Imipenem-Relebactam

4,000 isolates collected from 11 hospitals in Brooklyn and Queens, NY from November 2013 to January 2014

<table>
<thead>
<tr>
<th>Species</th>
<th>Imipenem</th>
<th>Imipenem-Relebactam</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MIC&lt;sub&gt;50&lt;/sub&gt;</td>
<td>MIC&lt;sub&gt;90&lt;/sub&gt;</td>
</tr>
<tr>
<td>Escherichia coli (2778)</td>
<td>0.25</td>
<td>0.25</td>
</tr>
<tr>
<td>Klebsiella pneumoniae (891)</td>
<td>0.25</td>
<td>4</td>
</tr>
<tr>
<td>bl&lt;sub&gt;KPC&lt;/sub&gt;-possessing K. pneumoniae (111)</td>
<td>16</td>
<td>&gt;16</td>
</tr>
<tr>
<td>Enterobacter spp. (211)</td>
<td>0.5</td>
<td>1</td>
</tr>
<tr>
<td>Pseudomonas aeruginosa (490)</td>
<td>2</td>
<td>16</td>
</tr>
<tr>
<td>Imipenem-resistant P. aeruginosa (144)</td>
<td>8</td>
<td>&gt;16</td>
</tr>
<tr>
<td>Acinetobacter baumannii (158)</td>
<td>4</td>
<td>&gt;16</td>
</tr>
<tr>
<td>bl&lt;sub&gt;OXA-23&lt;/sub&gt;-possessing A. baumannii (58)</td>
<td>&gt;16</td>
<td>&gt;16</td>
</tr>
</tbody>
</table>

MIC values in µg/mL


---

### Plazomicin (ACHN-490)

- Next-generation aminoglycoside (“neoglycoside”) synthetically derived from sisomicin
- Inhibits bacterial protein synthesis and exhibits dose-dependent bactericidal activity
- In vitro activity against both Gram-positive and Gram-negative organisms, including isolates harboring any of clinically relevant aminoglycoside-modifying enzymes (e.g., acetyltransferases, nucleotidyltransferases, and phosphotransferases)
- In vitro synergy activity when combined with cefepime, doripenem, imipenem or piperacillin-tazobactam against Pseudomonas aeruginosa
- After IV 15 mg/kg dose, maximum plasma concentration ~113 µg/mL, AUC<sub>0-24</sub> of 235 µg•h/mL, t<sub>1/2</sub> of 4 hours, and apparent V<sub>ss</sub> of 0.25 L/kg
- Human studies have not reported nephrotoxicity or ototoxicity, and lack of ototoxicity in the guinea pig model


---

### Plazomicin

In vitro activity of plazomicin against aminoglycoside-susceptible and non-susceptible Pseudomonas aeruginosa:

<table>
<thead>
<tr>
<th>Cumulative (%) inhibited at MIC in µg/mL of:</th>
<th>≤0.25</th>
<th>0.5</th>
<th>1</th>
<th>2</th>
<th>4</th>
<th>8</th>
<th>16</th>
<th>32</th>
<th>64</th>
<th>&gt;64</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amikacin-S (n=547)</td>
<td>2.7</td>
<td>4.1</td>
<td>10.7</td>
<td>38.3</td>
<td>71.1</td>
<td>90.6</td>
<td>98.8</td>
<td>100</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gentamicin-S (n=529)</td>
<td>2.6</td>
<td>4.2</td>
<td>11.2</td>
<td>40.6</td>
<td>74.5</td>
<td>93.6</td>
<td>99.6</td>
<td>100</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tobramycin-S (n=550)</td>
<td>2.5</td>
<td>3.9</td>
<td>10.5</td>
<td>38.0</td>
<td>70.0</td>
<td>88.2</td>
<td>95.7</td>
<td>98.6</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>Amikacin-non-S (n=32)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>6.3</td>
<td>6.3</td>
<td>12.5</td>
<td>15.6</td>
<td>46.9</td>
<td>75.0</td>
<td>100</td>
</tr>
<tr>
<td>Gentamicin-non-S (n=44)</td>
<td>1.6</td>
<td>1.6</td>
<td>1.6</td>
<td>3.1</td>
<td>10.9</td>
<td>26.6</td>
<td>50.0</td>
<td>73.4</td>
<td>87.5</td>
<td>100</td>
</tr>
<tr>
<td>Tobramycin-non-S (n=22)</td>
<td>3.0</td>
<td>3.0</td>
<td>3.0</td>
<td>12.1</td>
<td>27.3</td>
<td>54.5</td>
<td>69.7</td>
<td>72.7</td>
<td>75.8</td>
<td>100</td>
</tr>
</tbody>
</table>

- Landman et al: plazomicin MIC<sub>90</sub> = 8 µg/mL and MIC<sub>90</sub> = 32 µg/mL for 679 isolates of P. aeruginosa (amikacin: MIC<sub>90</sub> = 8 µg/mL and MIC<sub>90</sub> = 16 µg/mL)
- Mechanisms resulting in elevated MICs poorly defined; likely that reduced permeability and/or efflux are contributing factors

Plazomicin

- A Phase 3, Multicenter, Randomized, Open-Label Study to Evaluate the Efficacy and Safety of Plazomicin Compared with Colistin in Patients with Infection Due to Carbapenem-Resistant Enterobacteriaceae (CRE) [CARE]
  - Plazomicin in combination with meropenem or tigecycline
  - Colistin in combination with meropenem or tigecycline
  - Treatment of patients with bloodstream infection, hospital-acquired or ventilator-associated bacterial pneumonia

- A Phase 3, Randomized, Multicenter, Double-Blind Study to Evaluate the Efficacy and Safety of Plazomicin Compared with Meropenem Followed by Optional Oral Therapy for the Treatment of Complicated Urinary Tract Infection, including Pyelonephritis, in Adults

ClinicalTrials.gov: NCT01970371
ClinicalTrials.gov: NCT02468827

Combination Antibiotic Treatment of Resistant Gram-negative Organisms

- Choice of agents often involves:
  - Aminoglycosides
  - Beta-lactam/beta-lactamase inhibitors
  - Carbapenems
  - Fosfomycin
  - Polymyxins
  - Rifampin
  - Tetracyclines
  - Tigecycline

- Clinical evidence regarding effectiveness of different treatment regimens is principally derived from retrospective studies, case reports or small prospective studies; no randomized clinical trials

- Need for new antimicrobial agents to treat resistant Gram-negative organisms is inevitably important

Generations of Tetracycline Antibiotics

- Doxycycline and Minocycline
  - Discovery of “glycylcyclines” in the early 1990s
    - Evade most bacterial efflux pumps
    - Not affected by TetM ribosomal protection mechanism
  - Tigecycline approved by FDA in 2005 as an intravenous broad-spectrum antibacterial agent

Tigecycline Treatment of Resistant Gram-negative Organisms

- Carbapenemase-producing Enterobacteriaceae and MDR *Acinetobacter* spp.
- Tigecycline has a large volume of distribution and low concentrations in blood, epithelial lining fluid of the lungs, and urinary tract
- Higher intravenous doses of tigecycline (100 mg every 12 hours) has resulted in better clinical cure rate, especially in critically ill patients with severe infections, including MDR bacteria

Doi Y and Paterson DL. Semin Respir Crit Care Med. 2015;36:74-84.

Eravacycline: A Fluorocycline

- Fully synthetic fluorocycline with broad-spectrum activity including MDR Gram-positive, Gram-negative, aerobic and anaerobic organisms (reduced activity against *Pseudomonas aeruginosa* and *Burkholderia cenocepacia*)
- Active against isolates containing tigecycline-specific efflux (TetA and TetB) and ribosomal protection proteins (TetM and TetO)
- Active against Enterobacteriaceae harboring ESBLs and carbapenemases
- Intravenous and oral formulations

Fucci NA and Bush K. Clin Microbiol Rev 2013; 26: 792-821

In Vitro Activity of Eravacycline

- 4,000 isolates collected from 11 hospitals in Brooklyn and Queens, NY from November 2013 to January 2014
- Broth microdilution (eravacycline, tigecycline) and agar dilution (all other agents) using CLSI standards

<table>
<thead>
<tr>
<th>Species (n)</th>
<th>ESBL</th>
<th>mIC50</th>
<th>mIC90</th>
<th>Eravacycline MIC50/MIC90</th>
<th>Tigecycline MIC50/MIC90</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>E. coli</em> (2,866)</td>
<td>13%</td>
<td>0.17</td>
<td>-</td>
<td>0.12/0.5</td>
<td>4/or &gt;</td>
</tr>
<tr>
<td><em>E. pneumoniae</em> (364)</td>
<td>33%</td>
<td>0.13</td>
<td>-</td>
<td>0.25/1.0</td>
<td>0.5/2.0</td>
</tr>
<tr>
<td><em>Enterobacter aerogenes</em> (98)</td>
<td>22%</td>
<td>3.2</td>
<td>-</td>
<td>0.25/1.0</td>
<td>0.5/2.0</td>
</tr>
<tr>
<td><em>Enterobacter cloacae</em> (124)</td>
<td>25%</td>
<td>3.2</td>
<td>-</td>
<td>0.5/1.0</td>
<td>0.5/2.0</td>
</tr>
<tr>
<td><em>Acinetobacter baumannii</em> (158)</td>
<td>67%</td>
<td>0.02</td>
<td>36%</td>
<td>0.5/1.0</td>
<td>2.0/6.0</td>
</tr>
</tbody>
</table>

MIC values in µg/mL

How Useful Will These New Agents be in the Future?

- New agents for treatment of Gram-negative infections are promising and could help preserve and enhance our antibiotic armamentarium
- These agents may provide opportunities for monotherapy of resistant Gram-negative organisms
- These advantages will need to be evaluated and compared to older and generic agents in regards to the use of healthcare resources and patient outcomes
- Results from randomized controlled trials are needed in severely ill patients with resistant Gram-negative infections for both older and newer agents and as monotherapy and combination therapy

Serious Bacterial Infections: A Focus on *Clostridium difficile* and Gram-Negative Infections