Applying the Latest Approaches in the Management of *C. difficile* Infection and Recurrence

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Objectives

• Assess the role of newer antimicrobial agents as part of the armamentarium in the management of infections caused by *C. difficile*

• Evaluate the utility of novel approaches that reduce the risk of recurrent *C. difficile* infection in high-risk patients

The Impact of *Clostridium difficile* Infections (CDI)


Of patients with CDI given metronidazole or oral vancomycin, 25% will experience recurrent CDI


Inflammation

Antibody response

Therapeutic Goals for CDI

**Essential:**
- Correct dysbiosis
- Kill the organism
- Adaptive immunity

**Optional but nice:**
- Safe and convenient
- Also affects toxins and spores
- Short vs. long-term
There has Been an Explosion in Treatment Possibilities for CDI

Current: Probiotics  
FMT  
Use narrow-spectrum antibiotics

Metronidazole  
Vancomycin  
Fidaxomicin

IVIG  
Monoclonal antibodies vs. C. difficile toxins

Future: 2nd-generation FMT  
non-tox C. difficile M3  
Ecobiotics

Surotomycin  
Cadazolid  
Ridinilazole

Toxoid vaccines

Current European CDI guidelines

CDI  
Non-severe CDI  
(Risk of) first recurrence  
Severe disease or complicated course

Metronidazole  
Vancomycin  
Fidaxomicin

Vancomycin  
Fidaxomicin  
Metronidazole

Green: strongly supports use; Blue: moderately supports use; Grey: Minimally supports use; Red: recommend to not use

More Recently, Metronidazole has been Shown to be Globally Inferior to Vancomycin (Tolevamer Phase III RCT)

Clinical success  
Recurrence

Tolevamer  
Metronidazole (n=278)  
Vancomycin (n=259)

0.73  
0.81  
0.23  
0.21

P=0.02  
P=0.045

P=0.004

Increased Failure Rate of Metronidazole also Associated with Increased 30-day Mortality

30-day mortality (%)

Any severity  
Mild-moderate CDI severity  
Severe

Vancomycin  
Metronidazole

8.6%  
6.9%  
19.8%

10.6%  
6.9%  
15.3%

5.9%  
10.6%  
8.6%

Any severity: 30-day mortality was significantly greater with metronidazole (RR: 1.58, 95% CI: 1.49-1.68). Risk of CDI recurrence was similar across treatment groups (16.3-22.8%).


Explosion in Treatment Possibilities for CDI Minus 1

Current: Probiotics  
FMT  
Use narrow-spectrum antibiotics

Vancomycin  
Fidaxomicin

IVIG  
Monoclonal antibodies vs. C. difficile toxins

Future: 2nd-generation FMT  
non-tox C. difficile M3  
Ecobiotics

Surotomycin  
Cadazolid  
Ridinilazole

Toxoid vaccines

Fidaxomicin: Equal Efficacy as Vancomycin to Cure Patients and Lessens the Risk of Recurrence

Response rate (%)

Clinical cure  
Recurrence  
Global cure

Fidaxomicin  
Vancomycin

92.1  
92.1  
92.1  
77.7

89.8  
89.8  
89.8  
67.1

P=0.004

The second phase III study showed similar results (Crook et al. Lancet ID)

Impact of Concomitant Antibiotics on Response to CDI Treatment

No CA

Fidaxo: N=391

Vanco: N=416

P

Clinical cure 92% 93% 0.80

Recurrence 12% 23% <0.00

Sustained response 81% 69% <0.00

CA

Fidaxo: N=90

Vanco: N=102

P

Clinical cure 90% 79% 0.04

Recurrence 17% 29% 0.05

Sustained response 72% 59% 0.02


CA = concomitant antibiotics

However, this Drug is Quite Costly:

Fidaxomicin Use By Region

We Really Have to Do a Better Job of Using Fidaxomicin Correctly

Appropriate Use of Fidaxomicin

• Because of high acquisition cost, fidaxomicin has been reserved for a very select patient population almost always in combination with other anti- C. difficile or other antibiotics

• Remember: fidaxomicin’s primary MOA is its narrow spectrum of activity preserving host microbiota

• Can the anti-recurrence effect of fidaxomicin offset its high acquisition cost?


Recurrent CDI is Costly:

Healthcare Utilization for Recurrent CDI

Increased Healthcare Utilization = Increased Healthcare Costs

<table>
<thead>
<tr>
<th>Disease</th>
<th>Without recurrent CDI</th>
<th>With recurrent CDI</th>
</tr>
</thead>
<tbody>
<tr>
<td>CDI-attributable LOS</td>
<td>$60 (23 – 200)</td>
<td>$140 (30 – 260)</td>
</tr>
<tr>
<td>CDI-attributable hospitalization*</td>
<td>$13,168</td>
<td>$28,218 (15,049 – 47,030)</td>
</tr>
<tr>
<td>Total hospitalization*</td>
<td>$20,093 (11,287 – 41,386)</td>
<td>$45,148 (20,480 – 82,772)</td>
</tr>
</tbody>
</table>

Any Evidence that Fidaxomicin may Reduce these Costs?

Patients who received oral vancomycin (n=46) or fidaxomicin (n=49) for the treatment of CDI via a protocol that encouraged fidaxomicin for select patients. CDI-related re-admissions: Fidaxo: 20.4%; Vanc: 41.3%

Real-world Evidence that Fidaxomicin may Reduce these Costs?


It’s Important to Remember that Recurrent CDI is More than about Cost

The Microbiome “Organ” Continues to be Damaged with Recurrent CDI

What Else do We have in our Damaged Microbiome?
And Last But not Least, the Patient Perspective

The Driver for Decreased QOL is not so Much Physical as a Worry/Anxiety of Transmissibility or Symptom Persistence

Quality of Life (QOL) Goes Down Considerably with Recurrent CDI

Patient Perspective

"It was a little over a year ago I was diagnosed and treated with metronidazole, then treated again in April with vancomycin for it as tested positive again, and am 50 years old and otherwise healthy except for hypertension issues. I think I acquired it as a caretaker for my elderly mother (who has since passed away), and having antibiotics for dental issues. I wouldn't wish this illness on my worst enemy, and it's been a life changer for me."

Explosion in Treatment Possibilities for CDI: Augment Immune Response!

Serum Concentrations of IgG Antibodies Against Toxin A, Toxin B, and Non-toxin Antigens
**Monoclonal Antibody: Phase II Study**

<table>
<thead>
<tr>
<th>Recurrence at 12 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monoclonal antibodies (n=101)</td>
</tr>
<tr>
<td>Rate (%)</td>
</tr>
<tr>
<td>0</td>
</tr>
<tr>
<td>7</td>
</tr>
</tbody>
</table>

Recurrence at 12 weeks: Placebo vs. Monoclonal antibodies (n=101).


**Phase III Studies of Bezlotoxumab: CDI Recurrence**

<table>
<thead>
<tr>
<th>Recurrence at 12 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
</tr>
<tr>
<td>Rate (%)</td>
</tr>
<tr>
<td>17</td>
</tr>
</tbody>
</table>

Recurrence at 12 weeks: Placebo vs. Bezlotoxumab Load vs. Bezlotoxumab Full vs. Pooled Data.


**Bezlotoxumab was also Shown to Reduce Hospital Re-admissions (European Population)**

<table>
<thead>
<tr>
<th>Re-admission type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospital 30-d re-admission rate</td>
</tr>
<tr>
<td>CDI-associated</td>
</tr>
<tr>
<td>Bezlo+SOC (n=265)</td>
</tr>
<tr>
<td>Rate (%)</td>
</tr>
<tr>
<td>4.5</td>
</tr>
</tbody>
</table>

Re-admission type: Hospital 30-d re-admission rate:
- Bezlotoxumab vs. Placebo.


**Explosion in Treatment Possibilities for CDI: Correct Dysbiosis!**

- **Current:**
  - Probiotics
  - FMT
  - Use narrow-spectrum antibiotics
  - Vancomycin
  - Fidaxomicin

- **Future:**
  - 2nd-generation FMT
  - non-tox C. difficile M3
  - Ecobiotics
  - Suemotocins
  - Cadazolid
  - Ridinilazole
  - Toxoid vaccines

**Duodenal Infusion of Donor Feces for Recurrent C. difficile Infection**

<table>
<thead>
<tr>
<th>CDI resolution (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PO vanco + FMT</td>
</tr>
<tr>
<td>Rate (%)</td>
</tr>
<tr>
<td>90</td>
</tr>
</tbody>
</table>

Resolution: no diarrhea without relapse after 10 weeks.

Correction of Dysbiosis will Likely Become Standard Practice in CDI (and beyond). We Will Always Need to Kill the Bug Though!


25 patients with recurrent CDI that were not able to perform FMT. Twenty-one of the 25 patients (84%) remained free of diarrhea during the following 9 months. The 4 patients who relapsed permanently resolved their diarrhea after a conventional 3-week course of oral vancomycin 125 mg 4 times daily followed by a 2-week course of rifaximin 200 mg twice daily. All 4 patients remained symptom-free at 12 months of follow-up.

Conclusion

• As long as we live in a world of elderly, hospitalized patients given broad-spectrum antibiotics, CDI is here to stay.
• With a coordinated effort and contemporary epidemiologic techniques, we can likely control and respond to future changes in the pathogenesis of CDI.
• With a little luck and good science, we may also be able to discover new insights into strategies to prevent and control CDI.

Antimicrobial Resistance

• In USA:
  - AMR organisms cause >2 million infections
  - 23,000 deaths each year (~25,000 in Europe)
  - Estimated $20 billion in excess medical spending each year

• Full global effect of AMR is difficult

• Recent global emergence:
  - USA (carbapenem-resistant *Klebsiella pneumoniae*)
  - India (bacteria with the plasmid-mediated *bla* NDM-1 gene that confers resistance to carbapenems)
  - *Escherichia coli* with plasmid-mediated *mcr-1* gene that confers resistance to colistin (originally described in China)

Current Therapeutic Options for Antimicrobial-Resistant Gram-Negative Infections

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Colleges of Pharmacy and Medicine
University of Illinois at Chicago
Chicago, IL

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 <em>Enterobacteriaceae</em></td>
<td>26,665</td>
<td>1,786</td>
<td>Serious</td>
</tr>
<tr>
<td>Multidrug-resistant <em>Pseudomonas aeruginosa</em></td>
<td>670</td>
<td>640</td>
<td>Serious</td>
</tr>
<tr>
<td>Carbapenem-resistant <em>Enterobacteriaceae</em></td>
<td>930</td>
<td>610</td>
<td>Urgent</td>
</tr>
<tr>
<td>Multidrug-resistant <em>Acinetobacter baumannii</em></td>
<td>730</td>
<td>560</td>
<td>Serious</td>
</tr>
</tbody>
</table>

Estimated annual incidence of infection due to notable antimicrobial-resistant organisms.

Total: 1,245,784 cases and 22,840 deaths.
ESBL, extended-spectrum beta-lactamase

WHO Priority Pathogen List for R&D of New Antibiotics

• Priority 1: Critical
  - *Enterobacteriaceae*, carbapenem-resistant, ESBL-producing
  - *Pseudomonas aeruginosa*, carbapenem-resistant
  - *Acinetobacter baumannii*, carbapenem-resistant

  - Includes multidrug-resistant bacteria that pose a particular threat in hospitals, nursing homes, and among patients whose care requires devices such as ventilators and blood catheters
  - Can cause severe and often deadly infections such as bloodstream infections and pneumonia
  - Resistant to a large number of antibiotics, including the best available antibiotics for treating multidrug-resistant bacteria

Revised February 27, 2017
Bloodstream Infections Caused by MDR Gram-Negative Bacteria

- 891 patients with monomicrobial MDR BSI at Duke University
  - 292 patients (33%) had BSI due to MDR pathogens and more likely to have:
    - History of transplant (15% versus 13%; P = 0.02)
    - Prior Gram-negative infection (46% versus 31%; P = 0.0003)
    - Hospital-acquired infection (35% versus 28%; P = 0.05)
- Most commonly isolated Gram-negative bacteria were:
  - Escherichia coli (37%; 130/351)
  - Klebsiella pneumoniae (19%; 66/351)
  - Pseudomonas aeruginosa (13%; 119/351)
- MDR phenotype was most common in Escherichia coli (50%) and Citrobacter freundii (44%)

MDR, multidrug-resistant (resistant to at least one agent in greater than or equal to 3 antimicrobial categories);
BSI, bloodstream infections


Ceftolozane-Tazobactam

- Demonstrated potent in vitro activity against Pseudomonas aeruginosa isolates tested that had:
  - Chromosmal AmpC or
  - Loss of outer membrane porin (OprD) or
  - Up-regulation of efflux pumps (MexXY, MexAB)
  - Loss of outer membrane porin (OprD)
- Not active against bacteria producing metallo-β-lactamases
- Current FDA susceptibility interpretive criteria:
  - Pathogen
  - Susceptible (S) Intermediates (I) Resistant (R)
  - Pseudomonas aeruginosa
    - 8/4 ≤2 ≤21
  - *Ceftolozane-tazobactam susceptibility testing performed with a fixed 4 µg/mL concentration of tazobactam

ZERBAXA® (ceftolozane and tazobactam) for injection, for intravenous use. Prescribing Information, Merck & Co., Inc., Whitehouse Station, NJ. October 2016.

Ceftolozane-Tazobactam Current Availability of Susceptibility Tests

- Disks
  - MAST Disk: Hardy Diagnostics, commercially-available FDA-approved diameters:
    - Enterobacteriaceae: >21mm (S), 18-20mm (I), and <17mm (R)
    - P. aeruginosa: >21mm (S), 17-20mm (I), and <16mm (R)
- Gradient Strips
  - Breakpoints published in the package insert and latest CLSI M100 document
  - Etest (Biomerieux) can be ordered from http://www.biomerieux-diagnostics.com/lest-ceftolozane-tazobactam-c-t-256 (FDA clearance pending) and Liofilchem (<http://www.liofilchem.net/pdf/html/brochure_pdf/.>) Approved in USA, Europe, Canada
- Panels
  - Vitek 2 (Biomerieux) card approved and will undergo beta-testing; not yet commercially available, software updates started in March 2017
  - Microscan (Beckman Coulter) expect commercial availability in late 2017/2018
  - Trek Panel (ThermoFisher Scientific) commercially available since Q1 2016


Ceftazidime-Avibactam

- 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 (cUTI), including pyelonephritis
  - Complicated Intrabdominal Infections (cIAI) plus metronidazole
  - IV dose: 1.5 g (1g ceftazidime; 0.5 g avibactam) q8h (1-h infusion)
- Dosage adjustment in patients with renal impairment (CrCl ≤50 mL/min) or ESRD on hemodialysis
- Most common adverse reactions (≥5%) in both cUTI patients are:
  - Nausea, diarrhea, headache, and pyrexia


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>
<th>Susceptible</th>
<th>Intermediates</th>
<th>Resistant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pseudomonas aeruginosa</td>
<td>8 ≤ 16 ≤ 25</td>
<td>≤ 8</td>
<td>≤ 16</td>
<td>≥ 25</td>
</tr>
</tbody>
</table>

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

ZERBAXA® (ceftolozane and tazobactam) for injection, for intravenous use. Prescribing Information, Merck & Co., Inc., Whitehouse Station, NJ. October 2016.
**Ceftazidime-Avibactam**

**Current Availability of Susceptibility Tests**

- **Approved Tests**
  - KB Disks from Hardy Diagnostics and BD
  - Custom Sensititre (ThermoFisher)
- **Tests in Development**
  - Etest (Biomérieux) can be ordered from [http://www.biomerieux-diagnostics.com/estest-ceftazidime-avibactam-cza-256](http://www.biomerieux-diagnostics.com/estest-ceftazidime-avibactam-cza-256) (FDA clearance pending)
  - MIC test strip (Liofilchem) can be ordered directly from Liofilchem [http://www.liofilchem.net/en/pdf/mic_brochure.pdf](http://www.liofilchem.net/en/pdf/mic_brochure.pdf) (Not cleared by FDA)
- **Automated Tests**
  - Phoenix (BD): FDA-approved, but not available yet
  - Vitek 2: Software validation Q1 2017, expected approval Q2 2018
  - MIC test strip (Liofilchem) can be ordered directly from Liofilchem
  - Etest (Biomérieux) can be ordered from [http://www.biomerieux-diagnostics.com/estest-ceftazidime-avibactam-cza-256](http://www.biomerieux-diagnostics.com/estest-ceftazidime-avibactam-cza-256) (FDA clearance pending)
  - Custom Sensititre (ThermoFisher)
  - KB Disks from Hardy Diagnostics and BD

**Decreased Clinical Cure Rates in cIAI**

**Patients with Baseline CrCl of 30 to ≤50 mL/min**

<table>
<thead>
<tr>
<th>Renal Function</th>
<th>Ceftazidime-Avibactam (Avycaz®)</th>
<th>Piperacillin-Tazobactam</th>
<th>Meropenem</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal / Mild impairment (CrCl: &gt;50 mL/min)</td>
<td>85% (32/37)</td>
<td>86% (35/41)</td>
<td>89% (32/37)</td>
</tr>
<tr>
<td>Moderate impairment (CrCl: 30 to ≤50 mL/min)</td>
<td>48% (11/23)</td>
<td>69% (19/28)</td>
<td>81% (24/30)</td>
</tr>
</tbody>
</table>

**Use of Non-carbapenem Beta-Lactams for the Treatment of ESBL Infections**

- **Cefepime**
  - Do not favor use for serious ESBL infections
  - Non-severe ESBL-producing infections (e.g., UTIs with cefepime MICs ≥2 mg/L) so pharmacodynamic targets are met
  - Non-severe ESBL-producing infections with MICs of 4–8 mg/L, recommend 2 g qdh, possibility as a continuous infusion
- **Piperacillin-Tazobactam**
  - Reasonable options for low- to moderate-severity infections resulting from urinary or biliary sources, and infections with piperacillin MICs <4 mg/L
  - Carbapenem may be more appropriate first in critically ill patients, patients with high inoculum infections, and elevated piperacillin MIC values
  - Regardless, recommend administering 4.5 g qdh (or 4.5 g qdh as extended infusion) for patients with invasive ESBL infections

**ESBL Phenotype Among Enterobacteriaceae Isolates in United States Hospitals – 2014**

<table>
<thead>
<tr>
<th>Region</th>
<th>% ESBL Positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>West North Central</td>
<td>13.3%</td>
</tr>
<tr>
<td>East North Central</td>
<td>15.5%</td>
</tr>
<tr>
<td>Midwest</td>
<td>16.3%</td>
</tr>
<tr>
<td>Mid-Atlantic</td>
<td>17.9%</td>
</tr>
<tr>
<td>East South Central</td>
<td>19.7%</td>
</tr>
<tr>
<td>West South Central</td>
<td>23.7%</td>
</tr>
<tr>
<td>South Atlantic</td>
<td>24.0%</td>
</tr>
<tr>
<td>New England</td>
<td>24.8%</td>
</tr>
<tr>
<td>New England</td>
<td>25.1%</td>
</tr>
<tr>
<td>Pacific</td>
<td>30.6%</td>
</tr>
</tbody>
</table>

Use of Newer Beta-Lactam/Beta-Lactamase Inhibitors for the Treatment of ESBL Infections

**Ceftolozane-Tazobactam**
- Efficacy of ceftolozane-tazobactam (C-T), pooled analysis Phase 3 cUTI & cIAI trials
- 150 patients (11%) had ESBL-producing Enterobacteriaceae (pooled MI population)
  - MIC<sub>90</sub> / MIC<sub>90</sub> for ESBL-producing strains of:
    - Escherichia coli: 8 / 16 mg/L
    - Pseudomonas aeruginosa: 8 / 16 mg/L
- Clinical cure rates for mMITT population Phase 3 cIAI trials:
  - 90.5% (349/387) all patients for Meropenem
  - 92.5% (45/49) ESBL-ENT for Meropenem
  - 87.5% (49/56) MIC-screen positive for Meropenem
- Evidence suggests a potential role, however clinical data are needed and significant-expense is a limiting factor

**Ceftazidine-Avibactam**
- Tends to be more active in vitro against ESBL-producers than ceftolozane-tazobactam
- MIC<sub>90</sub> / MIC<sub>90</sub> for ESBL-producing strains of:
  - Escherichia coli: 0.5 / 8 mg/L
  - Pseudomonas aeruginosa: 8 / 16 mg/L
- Clinical cure rates for mMITT population:
  - 87.5% (49/56) MIC-screen positive for Cef-Av
  - 85.5% (344/404) MIC-screen positive for Meropenem
  - 84.8% (45/53) ESBL-ENT for Cef-Av
  - 81.6% (337/413) all patients for Cef-Av
  - 88.5% (23/26) for meropenem
  - 82.6% (38/46) for levofloxacin
  - 94.4% (17/18) ESBL-K. pneumoniae
- Evidence suggests a potential role, however more clinical data are needed and significant expense is a limiting factor

**Multidrug-Resistant Pseudomonas aeruginosa Isolates in United States Hospitals: 2011–2014**

- Isolates displaying derepressed AmpC had ceftolozane-tazobactam MIC values ranging from 1 to 16 mg/L<sup>1</sup>
- 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<sup>2</sup>
- 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<sup>2</sup>

**“Real World” Treatment Reports Ceftolozane-Tazobactam for MDR Pseudomonas aeruginosa**
- Treatment outcomes for 15 patients with XDR infections: Clinical cure 67%; All-cause in-hospital mortality 27%; 6/8 microbiological cure; 2 microbiological failures; combination therapy in 10 of 15: 4 failures at end of therapy<sup>3</sup>
- Multicenter, retrospective study of 35 patients infected with carbapenem-resistant P. aeruginosa; pneumonia most common indication (n=18); treatment success rate was 74% (n=26); treatment failure in all cases where MIC 38 mg/L<sup>2</sup>
- Multicenter, retrospective study of 12 patients; salvage therapy for severe MDR infections (83% presented as septic shock; 3 deaths); pneumonia in 6 patients (50%); microbiological eradication in 10 patients (83.3%); however 2 patients had late recrrecurrence with C-T resistant MDR-PA<sup>2</sup>

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**Use of Newer Beta-Lactam/Beta-Lactamase Inhibitors for the Treatment of ESBL Infections**

**Ceftolozane-Tazobactam**
- Ceftolozane has good activity against Enterobacteriaceae, but limited activity against ESBLs
- Tazobactam is a potent, irreversible inhibitor of most ESBLs
- MIC<sub>90</sub> / MIC<sub>90</sub> for ESBL-producing strains of:
  - Escherichia coli: 0.5 / 4 mg/L
  - Klebsiella pneumoniae: 4 / 12 mg/L
- Evidence suggests a potential role, however more clinical data are needed and significant expense is a limiting factor

**Ceftazidine-Avibactam**
- Efficacy of ceftazidine-avibactam (Cef-Avi) among mMITT population Phase 3 cIAI trials
- 124 patients had Enterobacteriaceae after testing MIC screen positive (avibactam and/or ceftazidine MIC ≥2 mg/L)
- Clinical cure rates for mMITT patients:
  - 87.5% (49/56) MIC-screen positive for Cef-Avi
  - 85.5% (344/404) MIC-screen positive for Meropenem
  - 84.8% (45/53) ESBL-ENT for Cef-Avi
  - 81.6% (337/413) all patients for Cef-Avi
  - 88.5% (23/26) for meropenem
  - 82.6% (38/46) for levofloxacin
  - 94.4% (17/18) ESBL-K. pneumoniae
- Evidence suggests a potential role, however more clinical data are needed and significant expense is a limiting factor

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**Ceftolozane-Tazobactam susceptibility patterns of 3851 Pseudomonas aeruginosa isolates from United States hospitals (PACTS, 2012–2015):**

<table>
<thead>
<tr>
<th>MIC&lt;sub&gt;90&lt;/sub&gt;</th>
<th>Susceptible</th>
<th>MIC&lt;sub&gt;90&lt;/sub&gt;</th>
<th>MIC&lt;sub&gt;90&lt;/sub&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>All isolates (n=3851)</td>
<td>97.0</td>
<td>0.5</td>
<td>2</td>
</tr>
<tr>
<td>Meropenem - Nonsusceptible (n=699)</td>
<td>87.6</td>
<td>1</td>
<td>8</td>
</tr>
<tr>
<td>Multidrug-resistant (MDR) (n=607)</td>
<td>84.0</td>
<td>2</td>
<td>8</td>
</tr>
<tr>
<td>Extensively drug-resistant (XDR) (n=363)</td>
<td>76.9</td>
<td>2</td>
<td>16</td>
</tr>
<tr>
<td>Nonsusceptible to cefepime, ceftazidime, meropenem, and piperacillin-tazobactam (n=124)</td>
<td>68.0</td>
<td>4</td>
<td>&gt;2</td>
</tr>
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**Real World” Treatment Reports Ceftolozane-Tazobactam for MDR Pseudomonas aeruginosa**
- Treatment outcomes for 15 patients with XDR infections: Clinical cure 67%; All-cause in-hospital mortality 27%; 6/8 microbiological cure; 2 microbiological failures; combination therapy in 10 of 15: 4 failures at end of therapy<sup>3</sup>
- Multicenter, retrospective study of 35 patients infected with carbapenem-resistant P. aeruginosa; pneumonia most common indication (n=18); treatment success rate was 74% (n=26); treatment failure in all cases where MIC 38 mg/L<sup>2</sup>
- Multicenter, retrospective study of 12 patients; salvage therapy for severe MDR infections (83% presented as septic shock; 3 deaths); pneumonia in 6 patients (50%); microbiological eradication in 10 patients (83.3%); however 2 patients had late recrrecurrence with C-T resistant MDR-PA<sup>2</sup>
Ceftazidime-Avibactam

- Ongoing Phase 3 Trial: Ventilated nosocomial pneumonia (NCT02070757)
- Increased dose: 3.0 g q 8 h ceftazidime; 1 g (avibactam) q 8 h
- Initial report on treating respiratory infections caused by MDR Pseudomonas aeruginosa

Resistance to Ceftazidime-Avibactam

- β-lactam-resistant Pseudomonas aeruginosa clinical isolates
  - 18.5% of archival isolates (n=216) from a decade ago were resistant to ceftazidime-avibactam with MIC of 216 µg/mL
  - Acquired resistance, which may be driven by altered outer membrane permeability or overexpressed efflux pumps
  - Combination poses a potential advantage
  - Addition of fosfomycin reduced resistance to 1.9% of strains
  - Addition of colistin reduced resistance to 7% of strains
  - 18.5% of archived isolates (n=54) from a decade ago were resistant to ceftazidime-avibactam with MIC of ≥16 µg/mL


- REPRISE Study¹
  - Ceftazidime-avibactam or best-available therapy in patients with carbapenem-resistant Enterobacteriaceae and Pseudomonas aeruginosa cUTI or cIAI
- Case Series from Compassionate-use ²
  - Carbapenem-resistant Enterobacteriaceae or Pseudomonas aeruginosa
- Ceftazidime-avibactam was superior to other treatment regimens against carbapenem-resistant Klebsiella pneumoniae bacteremia ³
  - Higher rates of clinical success (P=0.005) and survival (P=0.01) and less nephrotoxicity than amingoglycoside and colistin-containing regimens
- Ceftazidime-avibactam had a 23% reduced risk for death compared to colistin for carbapenem-resistant Enterobacteriaceae ⁴
  - Ceftazidime-avibactam also had 64% probability of a better outcome

Notes:


References:

**Ceftazidime-Avibactam**

Emergence of Resistance among Enterobacteriaceae

- First clinical case of a ceftazidime-avibactam-resistant Klebsiella pneumoniae, in a patient with no previous exposure
- Resistance due to porin mutations and the increased expression of KPC-3
- 37 CRE-infected patients treated with ceftazidime-avibactam
  - Clinical success was 59% (22/37) and 30-day survival was 76% (28/37)
  - CRE infections recurred within 90 days in 23% (9/22)
  - Resistance detected in 30% (3/10) of microbiologic failures
- Development of resistance conferring $b_{lux}$ mutations in K. pneumoniae within 15 to 19 days of ceftazidime-avibactam exposure, but may be ameliorated if carbapenem susceptibility is restored
- Surveillance studies continue to document low frequency of ceftazidime-avibactam resistance among Enterobacteriaceae isolates carrying $b_{lux}$


**Meropenem-Vaborbactam**

- Carbapenem plus beta-lactamase inhibitor
- Spectrum of activity: Gram-positives and Gram-negatives (is stable to hydrolysis by most beta-lactamases, including penicillinases and cephalosporinases) and vaborbactam protects meropenem from degradation by certain serine beta-lactamases (i.e., KPCs)
- FDA approval in August 2017
- Complicated Urinary Tract Infections (cUTI), including Acute Pyelonephritis
  - IV dose: 4 g (2 g meropenem; 2 g vaborbactam) q8h (3-h infusion)
- Dosage adjustment in patients with an estimated glomerular filtration rate (eGFR <50 mL/min/1.73m²) or ESRD on hemodialysis
- Most common adverse reactions (23%) were headache, phlebitis/infusion site reactions, and diarrhea

Vabomere™ Prescribing Information, August 2017.

**Monotherapy vs Combination Therapy**

Carbapenem-Resistant Enterobacteriaceae (CRE) Infections

- Empirical monotherapy usually appropriate
- Choice of antibiotics should be based on local resistance epidemiology

**Complicated Urinary Tract Infections, including Acute Pyelonephritis**

- m-MITT Population
- EORTT Eradication Rate at TOC
- Composite Cure Rates
- Levofloxacin Resistance

**Meropenem-Vaborbactam**

- Efficacy, Safety, Tolerability of Carvabance Compared to Best Available Therapy in Serious Infections Due to Carbapenem-Resistant Enterobacteriaceae in Adults (TANGO-2) (NCT02168946; clinicaltrials.gov)
- Data Safety and Monitoring Board's recommendation to discontinue randomization into the TANGO-2 trial was based on the results of an interim analysis of data
  - Efficacy: Statistically-significant differences favor meropenem-vaborbactam over best available therapy for clinical cure at the test of cure visit in the protocol-specified primary population (all patients with microbiologically-eligible CRE)
  - Mortality rate: Lower among patients treated with meropenem-vaborbactam
  - Renal toxicity: Lower rates of renal adverse events and serum creatinine increases among patients treated with meropenem-vaborbactam than best available therapy – particularly among patients receiving colistin and aminoglycosides


**Antibiotic Treatment of Multidrug-Resistant Gram-Negative Organisms**

- Multidrug-resistant Gram-negative bacteria have become widespread and increasing worldwide
- New agents for treatment of Gram-negative infections are promising and could help preserve and enhance our antibiotic armamentarium
- 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 a broad-spectrum agent
  - monotherapy versus combination therapy
  - determining the role of adjunctive therapy