NEXT GENERATION ANTIBIOTICS
NEXT GENERATION CHALLENGES

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WHY THE FUSS?

DEADLY GERMS, LOST CURES

A Mysterious Infection, Spanning the Globe in a Climate of Secrecy

The rise of Candida auris embodies a serious and growing public health threat: drug-resistant germs.

April 6 2019

Pan-Resistant New Delhi Metallo-Beta-Lactamase-Producing Klebsiella pneumoniae
— Washoe County, Nevada, 2016

MMWR / January 13, 2017 / Vol. 66 / No. 1

In world first, UK reports high-level gonorrhea resistance

Lisa Schnirring | News Editor | CIDRAP News | Mar 28, 2018
WHY THE FUSS?

ANTIBIOTIC RESISTANCE THREATS in the United States, 2013

Estimated minimum number of illnesses and deaths caused by antibiotic resistance*:

At least 2,049,442 illnesses, 23,000 deaths

*bacteria and fungus included in this report
WHY THE FUSS?

Antibiotic Resistance of *Klebsiella pneumoniae* in United States

% Resistant (invasive isolates)

- Aminoglycosides
- Carbapenems
- Cephalosporins (3rd gen)
- Fluoroquinolones
- Piperacillin–tazobactam

Center for Disease Dynamics, Economics & Policy (cddep.org)
WHY THE FUSS?

Antibiotic Resistance of *Pseudomonas aeruginosa* in United States

% Resistant (Invasive Isolates)

- Carbapenems
- Piperacillin-tazobactam
- Polymyxins

Center for Disease Dynamics, Economics & Policy (cddep.org)
**THE GAIN ACT (2012)**

- **Generating Antibiotic Incentives Now Act**
- Grants special status to drugs that are ‘Qualified Infectious Disease Product’ (QIDP)
  - Fast track designation
  - Priority review
  - Possible 5 year extension of exclusivity
- To date, 147 QIDP designations
  - 74 for novel drugs
  - Approved 12 new anti-infectives
21ST CENTURY CURES ACT

- Limited Population Antibacterial Drug (LPAD) pathway
  - Provides flexibility for drugs intended for multidrug resistant infections
  - Allows for smaller, descriptive datasets supplemented by robust non-clinical data
- Improves surveillance of AMR
- Incorporation of CLSI data into FDA breakpoints
  - Commercial AST devices are required to update their breakpoints within 90 days of any FDA breakpoint update
Up to 50% mortality in bloodstream and other serious infections
CARBAPENEM RESISTANCE

- 2 mechanisms
  - Carbapenemase
    - High level resistance (MIC $\geq 32$ mcg/ml)
  - Hyperproduction of an ESBL enzyme combined with mutations in outer membrane porins
    - Occurs in the setting of prolonged exposure to $\beta$-lactams
    - Can have moderate level resistance (MIC $\leq 16$ mcg/ml) in certain cases
### CARBAPENEMASES

<table>
<thead>
<tr>
<th>Enzyme</th>
<th>Typical pathogen hosts</th>
<th>Type</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>KPC</td>
<td>Enterobacteriaceae</td>
<td>Serine protease (Ambler class A)</td>
<td>Most common carbapenemase in the US</td>
</tr>
<tr>
<td>NDM-1</td>
<td>K. pneumoniae E. cloacae</td>
<td>Metallo-β-lactamase (Ambler class B)</td>
<td>Not active against aztreonam</td>
</tr>
<tr>
<td>OXA-48</td>
<td>A. baumannii, Enterobacteriaceae</td>
<td>Serine protease (Ambler class D)</td>
<td>No cephalosporinase activity</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Less active than KPC or NDM-1</td>
</tr>
</tbody>
</table>
| L1 / L2 | S. maltophilia        | L1: Metallo-β-lactamase (Class B)  
|        |                        | L2: Extended spectrum cephalosporinase | L1 confers resistance to carbapenems  
|        |                        |      | L2 confers resistance to cephalosporins |

- Most organisms with carbapenemases also carry wide range of ESBL enzymes
CARBAPENEM RESISTANCE THROUGH COMBINATION PATHWAYS

- Occurs through
  - Mutations in outer membrane porins leading to decreased permeability
  - Upregulation of efflux pumps
  - Upregulation of lower level β-lactamases (ie AmpC or other ESBLs)
- Most common in non-fermenting GNRs (*Pseudomonas*, *Acinetobacter*, *Stenotrophomonas*) with a fixed source / biofilm (GU stents, CF pts)
NEXT GENERATION ANTIBIOTICS

β-lactam combinations

- Ceftazidime-avibactam
- Ceftolozane-tazobactam
- Meropenem-vaborbactam

β-lactams

- Cefiderocol

β-lactams

- Cefiderocol

Tetracyclines

- Eravacycline
CEFTAZIDIME-AVIBACTAM
CAZ-AVI: OVERVIEW

• Ceftazidime
  • Broad Gram negative coverage, particularly for *Pseudomonas*
• Avibactam
  • Novel non-β-lactam β-lactamase inhibitor
  • Reversible binding of β-lactamase, allowing for recycling
• Approved in 2015
• Indications
  • Complicated intra-abdominal infection (cIAI)
  • Complicated UTI (cUTI)
  • Hospital-acquired / ventilator-associated pneumonia (HAP/VAP)
CAZ-AVI: ACTIVITY

• High activity
  • KPC Enterobacteriaceae
    • Superior to colistin, carbapenem + colistin, colistin + aminoglycoside
  • AmpC / CTX-M
  • OXA-48

• Moderate activity
  • *Pseudomonas*

• No activity
  • MBLs
  • *Acinetobacter*-type OXA enzymes
  • *Stenotrophomonas*

[https://www.avycaz.com/inform-surveillance-study](https://www.avycaz.com/inform-surveillance-study)
Clinical Outcomes, Drug Toxicity, and Emergence of Ceftazidime-Avibactam Resistance Among Patients Treated for Carbapenem-Resistant Enterobacteriaceae Infections

Ryan K. Shields,1,3,4,a Brian A. Potoski,1,2,3,a Ghady Haidar,1 Binghua Hao,4 Yohei Doi,1 Liang Chen,6 Ellen G. Press,7 Barry N. Kreiswirth,6 Cornelius J. Clancy,1,6,5 and M. Hong Nguyen1,3,4

CAZ-AVI: RESISTANCE

- Mediated through
  - Mutations in the active site of KPC (D179Y)
  - Mutations in outer membrane proteins (OmpK35/K36)
- Multiple *in vivo* and *in vitro* reports with the identical mutations arising independently
- Can occur while on treatment

Shields, CID, 2016
MEROPENEM-VABORBACTAM
MEM-VAB: OVERVIEW

- Meropenem
  - Broad spectrum carbapenem
- Vaborbactam
  - Novel cyclic boronic acid compound designed specifically to inhibit KPCs
  - Reversible inhibition, similar to avibactam
- Approved 2017
- Indications
  - cUTI
MEM-VAB: ACTIVITY

- **High activity**
  - KPC Enterobacteriaceae
  - AmpC / CTX-M

- **Moderate activity**
  - *Pseudomonas*
    - But not above that conferred by MEM monotherapy

- **No activity**
  - MBLs
  - OXA-48
  - *Acinetobacter*
  - *Stenotrophomonas*

<table>
<thead>
<tr>
<th>Bacterium</th>
<th>Meropenem-vaborbactam</th>
<th>Meropenem</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Enterobacteriaceae</em> (10,426)</td>
<td>≤0.015</td>
<td>0.06</td>
</tr>
<tr>
<td>CRE (265)</td>
<td>Meropenem-vaborbactam</td>
<td>0.5</td>
</tr>
<tr>
<td>KPC producers (135)</td>
<td>Meropenem-vaborbactam</td>
<td>0.12</td>
</tr>
<tr>
<td>Non-KPC-producing CRE (129)</td>
<td>Meropenem-vaborbactam</td>
<td>4</td>
</tr>
<tr>
<td><em>P. aeruginosa</em> (2,604)</td>
<td>Meropenem-vaborbactam</td>
<td>0.5</td>
</tr>
<tr>
<td></td>
<td>Meropenem</td>
<td>0.5</td>
</tr>
</tbody>
</table>

Castanheira, AAC, 2017
<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Phenotype</th>
<th>CAZ-AVI</th>
<th>MEM-VAB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enterobacteriaceae</td>
<td>ESBL</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td></td>
<td>AmpC</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td></td>
<td>KPC</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td></td>
<td>MBL</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>OXA-48 like</td>
<td>+++</td>
<td>*</td>
</tr>
<tr>
<td>Acinetobacter baumannii</td>
<td>Carbapenem-resistant</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Pseudomonas aeruginosa</td>
<td>Carbapenem-resistant</td>
<td>++</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Pan-β-lactam resistant</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Stenotrophomonas maltophilia</td>
<td>Ceftazidime-resistant</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

* Driven by activity of meropenem; no additional benefit from vaborbactam

Pogue, CID, 2019
CEFTOLOZANE-TAZOBACTAM
Ceftolozane is similar to ceftazidime but
- Has higher affinity for PBPs produced by Pseudomonas
- Has better outer membrane permeability
- Is more stable to AmpC
- Retains activity in the presence of efflux pumps or loss of porins

Tazobactam
- Confers extended activity to ESBL Enterobacteriaceae
- Approved in 2015

Indications
- cIAI
- cUTI
C/T: ACTIVITY

- **High activity**
  - *Pseudomonas*
  - AmpC / CTX-M (ESBL) *E. coli*
- **Moderate activity**
  - ESBL *K. pneumoniae*
- **No activity**
  - Class A, B or D carbapenemases
  - Carbapenem-resistant *Acinetobacter*
  - *Stenotrophomonas*
<table>
<thead>
<tr>
<th>BLC</th>
<th>Disk Diffusion (Vendor)</th>
<th>Gradient Diffusion (Vendor)</th>
<th>BMD (Vendor)</th>
<th>Automated US AST Systems (Vendor*)</th>
<th>Isolates Available from CDC AR Bank</th>
</tr>
</thead>
<tbody>
<tr>
<td>C/T</td>
<td>Y (Hardy)</td>
<td>Y (bioMerieux, Liofilchem)</td>
<td>Y (Thermo-Fisher)</td>
<td>Y (BD, Beckman Coulter)</td>
<td>Y</td>
</tr>
<tr>
<td>CZA</td>
<td>Y (BD, Hardy)</td>
<td>Y (bioMerieux)</td>
<td>Y (Thermo-Fisher)</td>
<td>Y (BD, Beckman Coulter)</td>
<td>Y</td>
</tr>
<tr>
<td>MEV</td>
<td>Y (Hardy)</td>
<td>Y (Liofilchem)</td>
<td>Y (Thermo-Fisher)</td>
<td>Y (BD)</td>
<td>N</td>
</tr>
</tbody>
</table>

C/T, ceftolozane-tazobactam; CDC AR Bank, Centers for Disease Control and Prevention Antimicrobial Resistance Bank; CZA, ceftazidime-avibactam; FDA, Food and Drug Administration; MEV, meropenem-vaborbactam; N, no; Y, yes.
Performance of ceftazidime/avibactam susceptibility testing methods against clinically relevant Gram-negative organisms

E. Wenzler 1*, M. Lee 1, T. J. Wu 1, K. A. Meyer 1, R. K. Shields 2,3, M. H. Nguyen 2,3, C. J. Clancy 2−4, R. M. Humphries 5 and A. T. Harrington 6


Conclusions: Our data indicate that the Etest is a suitable alternative to BMD for testing ceftazidime/avibactam against ceftazidime- and meropenem-resistant K. pneumoniae. The 30/20 μg discs overestimate resistance and may lead to the use of treatment regimens that are more toxic and less effective.
TREATMENT OF PATHOGENS WITH A METALLO-B-LACTAMASE

- Amikacin
- Colistin / polymyxin B
- Tigecycline

None of the newer β-lactam combination agents are effective against MBLs
TREATMENT OF PATHOGENS WITH A METALLO-\(\beta\)-LACTAMASE

Can Ceftazidime-Avibactam and Aztreonam Overcome \(\beta\)-Lactam Resistance Conferred by Metallo-\(\beta\)-Lactamases in Enterobacteriaceae?

Avibactam Restores the Susceptibility of Clinical Isolates of Stenotrophomonas maltophilia to Aztreonam

Marshall, AAC, 2017

Mojica, AAC, 2017
Stacked disk testing is a cheap but (probably) accurate way to assess for synergy

- Very little clinical experience
- No optimal dosing regimen
CEFIDEROCOL: OVERVIEW

- Novel cephalosporin with an attached siderophore moiety
  - High stability to serine and zinc proteases
  - High penetration through the outer membrane
- Trojan horse mechanism
  - Siderophore moiety chelates extracellular iron
  - Iron-antibiotic combination transported back through outer membrane iron transporter
  - Antibiotic able to then bind target PBP
- Not yet FDA approved (but likely will be soon)
CEFIDERO COL: ACTIVITY

- High activity
  - KPC (class A), NDM-1 (class B), OXA-type enzymes (class D)
  - MDR non-fermenters

https://www.escmid.org/escmid_publications/escmid_elibrary/material/?mid=52612
Very few cases of resistance have been described, but it has been shown *in vitro* and in animal models with a pre-clinical analog.
CLSI has approved "investigational breakpoints" in M100 S-29.

<table>
<thead>
<tr>
<th></th>
<th>Broth dilution</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>S</td>
</tr>
<tr>
<td>Enterobacteriaceae</td>
<td>&lt;=4</td>
</tr>
<tr>
<td><em>P. aeruginosa</em></td>
<td>&lt;=4</td>
</tr>
<tr>
<td><em>Acinetobacter spp</em></td>
<td>&lt;=4</td>
</tr>
<tr>
<td><em>S. maltophilia</em></td>
<td>&lt;=4</td>
</tr>
</tbody>
</table>
CEFIDEROCOL: AST

• For broth testing:

(24) Testing cefiderocol requires iron-depleted CAMHB. Chelation is used for iron depletion, which also removes other cations (ie, calcium, magnesium, and zinc). Following this process, cations are added back to concentrations of calcium 20–25 mg/L, magnesium 10–12.5 mg/L, and zinc 0.5–1.0 mg/L.

• But MH agar does not need adjustment...
ERAVACYCLINE
ERAVACYCLINE: OVERVIEW

- Next generation fluorocycline (tetracycline analog)
  - Blocks elongation by inhibiting 30S ribosomal subunit
  - Generally bacteriostatic but can be -cidal in certain strains
- Approved 2018
- Indications
  - cIAI
  - Failed in trial for cUTI
ERAVACYCLINE: ACTIVITY

- High activity
  - MSSA / MRSA
  - CoNS
  - All Streptococci
  - VSE / VRE
  - Anaerobes
  - ESBL Enterobacteriaceae
  - CRE
  - Carbapenem resistant *Acinetobacter* spp (except those with OXA-48 or NDM-1)
ERAVACYCLINE: RESISTANCE

- Stable to the most common resistance mechanisms that affect earlier generation tetracyclines except tigecycline
  - Efflux pumps (tetA / tetB / tetK)
  - Ribosomal protection proteins (tetM)
- Hopefully better tolerated than tigecycline

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In Vitro MIC (mcg/mL)

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Control</th>
<th>tet(M)</th>
<th>tet(K)</th>
<th>tet(A)</th>
<th>tet(B)</th>
</tr>
</thead>
<tbody>
<tr>
<td>XERAVA</td>
<td>0.063</td>
<td>0.063</td>
<td>0.031</td>
<td>0.25</td>
<td>0.063</td>
</tr>
<tr>
<td>Tigecycline</td>
<td>0.063</td>
<td>0.13</td>
<td>0.063</td>
<td>1</td>
<td>0.063</td>
</tr>
<tr>
<td>Doxycycline</td>
<td>2</td>
<td>64</td>
<td>4</td>
<td>32</td>
<td>32</td>
</tr>
<tr>
<td>Minocycline</td>
<td>0.5</td>
<td>64</td>
<td>1</td>
<td>8</td>
<td>16</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>2</td>
<td>128</td>
<td>128</td>
<td>&gt;128</td>
<td>&gt;128</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>0.063</td>
<td>0.13</td>
<td>0.063</td>
<td>0.13</td>
<td>0.13</td>
</tr>
</tbody>
</table>

https://www.xerava.com/differentiation
ERAVACYCLINE: AST

- Liofilchem MIC test strips
- Hardy disks
- No CLSI breakpoints (yet)
THANK YOU!

- Rebecca Zaffini
- NACMID
- ASM