Treatment and Prevention of Multi-Drug Resistant Gram-Negative Infections: A New Age of Opportunities and Challenges for Antimicrobial Stewardship

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Ann Arbor, MI

Overview

• Epidemiology of extremely-drug resistant (XDR) Gram-negative bacilli

• Treatment
  – Newer agents
  – Pipeline

• Rapid diagnostics

• Stewardship strategies and challenges

• Unmet needs and opportunities
CDC: Drug-Resistant Gram-Negative Bacterial Infection Threats

Urgent and Serious

<table>
<thead>
<tr>
<th>Urgent</th>
<th>Carbapenem-resistant <em>Enterobacteriaceae</em> (CRE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serious</td>
<td>ESBL-producing <em>Enterobacteriaceae</em></td>
</tr>
<tr>
<td></td>
<td>Multidrug-resistant <em>Acinetobacter</em></td>
</tr>
<tr>
<td></td>
<td>Multidrug-resistant <em>Pseudomonas aeruginosa</em></td>
</tr>
</tbody>
</table>

WHO Priority Pathogens List For R&D of New Antibiotics

Priority 1: Critical

- *Acinetobacter baumannii*, carbapenem-resistant
- *Pseudomonas aeruginosa*, carbapenem-resistant
- *Enterobacteriaceae*, carbapenem-resistant, 3rd generation cephalosporin-resistant
Extended-Spectrum Beta-Lactamase (ESBL) Producers

• Plasmid-mediated, most commonly produced by *Klebsiella pneumoniae, Escherichia coli*

• Hydrolyze broad-spectrum β-lactams (not carbapenems)

• Often resistant to other antibiotic classes

• Carbapenems are first-line for invasive infection due to ESBL-producers

• Notable increases in ESBL-producers over past several years (CTX-M)

• More ESBLs = more carbapenem use
Unintended Consequences of Carbapenem Use

In attempt to reduce ESBL rate, imipenem became preferred empiric antimicrobial instead of 3rd generation cephalosporins

<table>
<thead>
<tr>
<th></th>
<th>1995</th>
<th>1996</th>
<th>Change (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cephalosporin use*</td>
<td>5508 g</td>
<td>1106 g</td>
<td>-80</td>
</tr>
<tr>
<td>Imipenem use*</td>
<td>197 g</td>
<td>474 g</td>
<td>+140</td>
</tr>
<tr>
<td>Imipenem-resistant P. aeruginosa (number)</td>
<td>67</td>
<td>113</td>
<td>+68.7</td>
</tr>
</tbody>
</table>

*Unpaired median monthly gram use

Rahal, JAMA, 1998, 1233-37
Carbapenem Resistance among Gram-Negative *Bacilli*

- Emerging problem in Pseudomonas, Acinetobacter, Enterobacteriaceae
- Risk factors include ICU stay, prolonged exposures to healthcare, indwelling devices, antibiotic exposures
  - Long-term acute care (LTAC) stay
- Often multi-drug resistant (MDR) or extremely-drug resistant (XDR)
  - Severely limits treatment options
- All can cause pneumonia, bloodstream infection, wound infection
- Outbreaks reported in single and multiple institutions
- Horizontal spread important, but emergence of resistance (susceptible - - - > resistant) can also play a role

*Klebsiella pneumoniae* Carbapenemases (KPCs)

- Plasmid-mediated carbapenemase
- KPC-producing strains of *Klebsiella pneumoniae* and other enterobacteriaceae
  - KPC-2, KPC-3
- Endemicity in many locales in the US
- Country-wide outbreak ongoing in serveral countries including Greece, Italy, Columbia and others
- Easily spread in the hospital - infection control nightmare
- Historically only susceptible to colistin, tigecycline and select aminoglycosides
  - Newer options available

*Bratu, AAC, 2005; Quale, CID, 2004; Leavitt, AAC, 2007; Carmeli, Clin Micro Infect, 2010*
**KPC-Producing K. pneumoniae**

- OXA-48-Producing Enterobacteriaceae
  - Class D carbapenemase
    - Different from the chromosomal oxacillinases in *A. baumannii*
    - Lineage back to narrow spectrum oxacillinases
    - Weakly hydrolyzes carbapenems
  - Originated in Turkey Spread throughout the middle east, Northern Africa
    - Spotty reports in other parts of Europe
  - US - First case report of two patients in Virginia (*K. pneumoniae*) in 2013
    - CDC, 2015: 52 CRE isolates producing OXA-48-like carbapenemases from 43 patients in 19 states 6/10-8/15 - 2/3 with travel in past year; ~ 50 hospitalized outside US; many with no travel history
    - XDR antibiogram

http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6447a3.htm
Metallo-beta-lactamasases (MBLs)

- MBLs differ from other carbapenemases in that they use zinc to facilitate hydrolysis
  - Efficiently hydrolyze all β-lactams, except aztreonam
- Historically, more commonly described in *P. aeruginosa*
- Rare in US, but relatively common mechanism of CRE worldwide
  - Until recently, IMP (active on imipenem) and VIM (Verona integron-encoded MBLs) were most common MBLs seen
  - 2009 - New Delhi MBL came onto scene

New Delhi Metallo-beta-lactamase 1 (NDM-1)

- 2009 identified in an isolate of *K. pneumoniae* in Swedish patient receiving care in India
  - Quick spread was seen in India and United Kingdom
  - Subsequent spread around the world
- Most worldwide cases have some exposure to endemic regions, but not all
- Spread to other enterobacteriaceae, *A. baumannii* has been reported
- ~ 2/3 of states in the US have reported NDM-1

CRE Update from the CDC

CP-CRE by Mechanism, AR Lab Network, January 2017 – December 2018

<table>
<thead>
<tr>
<th>Carbapenemase producing*</th>
<th>8145</th>
</tr>
</thead>
<tbody>
<tr>
<td>KPC</td>
<td>7076 (87)</td>
</tr>
<tr>
<td>NDM</td>
<td>562 (7)</td>
</tr>
<tr>
<td>OXA-48-type</td>
<td>299 (4)</td>
</tr>
<tr>
<td>VIM</td>
<td>62 (1)</td>
</tr>
<tr>
<td>IMP</td>
<td>76 (1)</td>
</tr>
</tbody>
</table>

*Carbapenemase-producing defined as positive by phenotypic carbapenemase activity test or by molecular assay for one of 5 carbapenemases
*US CP-CRE and 3 CP-CREA had >1 carbapenemase identified

Preliminary data; subject to change

Thanks to Snigdha Vallabhaneni, MD, MPH for use of the slide

Antibiotic Resistance of *Klebsiella pneumoniae* in United States

% Resistant (invasive isolates)

<table>
<thead>
<tr>
<th>Year</th>
<th>Carbapenems</th>
<th>Cephalosporins (3rd gen)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1999</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>2000</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>2001</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>2002</td>
<td>8</td>
<td>6</td>
</tr>
<tr>
<td>2003</td>
<td>9</td>
<td>7</td>
</tr>
<tr>
<td>2004</td>
<td>10</td>
<td>8</td>
</tr>
<tr>
<td>2005</td>
<td>11</td>
<td>9</td>
</tr>
<tr>
<td>2006</td>
<td>12</td>
<td>10</td>
</tr>
<tr>
<td>2007</td>
<td>13</td>
<td>11</td>
</tr>
<tr>
<td>2008</td>
<td>14</td>
<td>12</td>
</tr>
<tr>
<td>2009</td>
<td>15</td>
<td>13</td>
</tr>
<tr>
<td>2010</td>
<td>16</td>
<td>14</td>
</tr>
<tr>
<td>2011</td>
<td>17</td>
<td>15</td>
</tr>
<tr>
<td>2012</td>
<td>18</td>
<td>16</td>
</tr>
<tr>
<td>2013</td>
<td>19</td>
<td>17</td>
</tr>
<tr>
<td>2014</td>
<td>20</td>
<td>18</td>
</tr>
</tbody>
</table>

Center for Disease Dynamics, Economics & Policy (cddep.org)
2019 IDAC Advanced ASP Symposium 7/13/19

Keith S. Kaye, M.D.

**Acinetobacter baumannii**

- Mechanisms of resistance multiple, diverse
  - Porin mutations
  - Altered PBPs
  - Metallo-beta-lactamases, serine carbapenemases (OXA)
    - OXA-23-like, OXA-24-like, OXA-51-like, OXA-58-like
  - Carbapenem resistance seen in multiple geographic locales worldwide
- Problem pathogen in ICU patients (particularly in burn units), elderly and combat injuries from middle east
- Can cause hospital outbreaks
- Treatment options: colistin, tigecycline, minocycline
  - Resistance to these agents reported

Pseudomonas aeruginosa

- Increasing resistance to quinolones, cephalosporins, carbapenems particularly in the hospital and long term care settings
- In the outpatient setting, patients with repeated quinolone exposures are at risk for developing resistance (i.e. recurrent UTI)
- “Grand old man” of resistant nosocomial pathogens
- Carbapenem resistance often multiple, diverse
Mechanisms of Acquired Resistance in *P. aeruginosa*

<table>
<thead>
<tr>
<th>Antimicrobial class</th>
<th>Mechanism of resistance</th>
</tr>
</thead>
<tbody>
<tr>
<td>β-lactams</td>
<td>β-lactamases (endogenous and acquired)</td>
</tr>
<tr>
<td></td>
<td>Efflux pumps</td>
</tr>
<tr>
<td></td>
<td>Changes in outer membrane permeability</td>
</tr>
<tr>
<td>Fluoroquinolones</td>
<td>Target site mutations</td>
</tr>
<tr>
<td></td>
<td>Efflux pumps</td>
</tr>
<tr>
<td>Aminoglycosides</td>
<td>Aminoglycoside-modifying enzymes</td>
</tr>
<tr>
<td></td>
<td>Efflux pumps</td>
</tr>
<tr>
<td></td>
<td>16s RNA Methyfases</td>
</tr>
<tr>
<td>Polymyxins</td>
<td>Changes in lipopoly saccharide</td>
</tr>
</tbody>
</table>


Antibiotic Resistance of *Pseudomonas aeruginosa* in United States

[Graph showing antibiotic resistance trends from 1999 to 2016]

- Carbapenems
- Ceftazidime

Center for Disease Dynamics, Economics & Policy (cddep.org)
Older Agents for Extremely Drug Resistant (XDR) Gram-Negative Bacilli (GNB): Polymyxins

- Traditionally, the cornerstone of treatment for infections caused by MDR/XDR Gram-negative bacteria
  - CRE, *Pseudomonas aeruginosa, Acinetobacter baumannii*
  - Still a frequently relied upon agent worldwide
- Colistimethate Sodium (CMS) - administered as prodrug, metabolized to active moiety colistin, *in vivo*
- Polymyxin B – administered as active drug
- Nephrotoxicity major limitation
  - Polymyxin B might be less nephrotoxic than CMS/colistin
- Still learning about how to optimize use given PK/PD profile
  - PK favorable for polymyxin B

Polymyxin Resistance

- Modification of LPS/Lipid A – most common in *P. aeruginosa* and *A. baumannii*; also occurs in enterobacteriaceae
- Overproduction of surface capsular polysaccharides (CPS) also occurs in enterobacteriaceae; limits interaction between polymyxin and lipid A
- Plasmid-mediated – mcr-1
  - First plasmid-mediated mechanism for polymyxin resistance
  - Described in China in 2015
  - Reported in food, animals, humans
  - Has been found in 5 bacterial species to date
    - *Escherichia coli, Salmonella enterica, Klebsiella pneumoniae, Enterobacter aerogenes, Enterobacter cloacae*, Experimentally transferred to *Pseudomonas aeruginosa*
    - Concerns for potential for rapid widespread dissemination

Newly Approved Therapies

<table>
<thead>
<tr>
<th>Agent</th>
<th>MoA</th>
<th>Approved Indications</th>
<th>In Vitro Activity Against*</th>
<th>Major Treatment Niche</th>
</tr>
</thead>
</table>
| Ceftolozane/ tazobactam | Novel cephalosporin/β-lactamase inhibitor | • cIAI with metronidazole                                                            | • E: TEM, SHV, CTX-M, OXA  
• P: AmpC, OprD loss, upreg. efflux pumps                                                   | • Pseudomonas aeruginosa, including XDR strains                                                  |
| Ceftazidime/ avibactam | Cephalosporin/novel β-lactamase inhibitor | • cIAI with metronidazole                                                            | • E: TEM, SHV, CTX-M, KPCs, AmpC, certain OXA  
• P: AmpC, OprD loss                                                                      | • CRE – KPC, OXA-48                                                                             |
| Meropenem/ vaborbactam | Carbapenem/novel β-lactamase inhibitor    | • cUTI including pyelonephritis by *Enterobacteria ceae*                              | • E: KPC, SME, TEM, SHV, CTX-M, CMY, and ACT                                               | • CRE-KPC                                      |


Ceftazidime/Avibactam: Efficacy for CRE Infections

Ceftazidime/Avibactam: Efficacy for CRE Infections (2)

- CRACKLE prospective, observational cohort study (N = 137)
  - In patients with CRE, ceftazidime/avibactam associated with decreased 30-day mortality vs colistin
    - 9% vs 32%, respectively; \( P = .001 \)


Meropenem/Vaborbactam: Key XDR- GNB Efficacy and Safety Data From Phase III Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Comparator</th>
<th>Infection Type</th>
<th>Efficacy vs Comparator</th>
<th>Safety</th>
</tr>
</thead>
</table>
| TANGO II CRE-based trial N=72 | BAT* | cUTI, acute pyelonephritis HAP/VAP Bacteremia cIAI | **Clinical cure:**
  - EOT: 65.6% vs 33.3%, \( p=0.03 \)
  - TOC: 59.4% vs 26.7%, \( p=0.02 \)

**28-day all-cause mortality:**
- 15.6% vs 33.3%, \( p=0.2 \)

**Microbiologic cure:**
- EOT: 65.6% vs 40.0%, \( p=0.09 \);
  - TOC: 53.1% vs 33.3%, \( p=0.19 \)

- M/V is well tolerated
- M/V associated with lower rates of renal failure
- M/V associated with lower rates of SCR increases ≥ 0.5 mg/dL

*Best available therapy (BAT): variable regimens of monotherapy and combination therapy with polymyxins (53%), carbapenems (47%), aminoglycosides (47%) and tigecycline (33%)

Wunderink RG, Infect Dis Ther, 2018:439-455
Meropenem/Vaborbactam: Potent Activity Against KPC-Producers

<table>
<thead>
<tr>
<th>Organism</th>
<th>Sample Size</th>
<th>Meropenem</th>
<th>Meropenem-Vaborbactam</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<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>KPC producers</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enterobacteriaceae</td>
<td>991</td>
<td>32</td>
<td>&gt;32</td>
</tr>
<tr>
<td>Klebsiella pneumoniae</td>
<td>878</td>
<td>&gt;32</td>
<td>&gt;32</td>
</tr>
<tr>
<td>Escherichia coli</td>
<td>35</td>
<td>4</td>
<td>16</td>
</tr>
<tr>
<td>Enterobacter spp.</td>
<td>29</td>
<td>8</td>
<td>&gt;32</td>
</tr>
<tr>
<td>Klebsiella oxytoca</td>
<td>19</td>
<td>4</td>
<td>32</td>
</tr>
<tr>
<td>Serratia marcescens</td>
<td>16</td>
<td>16</td>
<td>&gt;32</td>
</tr>
<tr>
<td>Citrobacter spp.</td>
<td>13</td>
<td>4</td>
<td>8</td>
</tr>
</tbody>
</table>


Newly Approved Therapies (2)

<table>
<thead>
<tr>
<th>Agent</th>
<th>MoA</th>
<th>Approved Indications</th>
<th>In Vitro Activity Against*</th>
<th>Major Treatment Niche</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eravacycline</td>
<td>Novel synthetic tetracycline</td>
<td>cIAI</td>
<td>Not reported in label</td>
<td>CRE - KPC, OXA, MBL</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Acinetobacter</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>? Achromobacter</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>? Burkholderia</td>
</tr>
<tr>
<td>Plazomicin</td>
<td>Aminoglycoside derivative</td>
<td>cUTI including pyelonephritis by Enterobacteriaceae</td>
<td>E: TEM, SHV, CTX-M, OXA, AmpC, KPC</td>
<td>CRE – KPC, OXA-48; some MBLs</td>
</tr>
</tbody>
</table>

*E, Enterobacteriaceae

Eravacycline [package insert]. August 2018; Plazomicin [package insert]. June 2018
Plazomicin: Key XDR- GNB Efficacy and Safety Data From Phase III Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Comparator</th>
<th>Infection Type</th>
<th>Efficacy vs Comparator</th>
<th>Safety</th>
</tr>
</thead>
<tbody>
<tr>
<td>CARE*</td>
<td>Colistin*</td>
<td>Bacteremia, HAP/VAP</td>
<td>28-day all-cause mortality or significant disease related complications**: 24% vs. 50%</td>
<td>Plazomicin-based therapy associated with lower rates of renal failure, Therapeutic drug monitoring recommended</td>
</tr>
</tbody>
</table>

*CARE* CRE-based trial, combination therapy N=37

*Both plazomicin and colistin administered in combination with meropenem or tigecycline

**New/worsening ARDS, new lung abscess or empyema, new-onset septic shock; persistence of bacteremia ≥5 days (BSI only); new-onset bacteremia (HABP/VABP only)

McKinnell JA NEJM, 2019, 791-3

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![Cumulative Probability of Survival and Increase in Serum Creatinine Concentration](attachment:image.png)

McKinnell JA NEJM, 2019, 791-3

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Keith S. Kaye, M.D.
Pipeline: Novel Investigational Agents

<table>
<thead>
<tr>
<th>Agent/Regimen</th>
<th>MoA</th>
<th>Reported in Vitro Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Imipenem/cilastatin/relebactam</td>
<td>Relebactam: novel class A and C (\beta)-lactamase inhibitor</td>
<td>CRE due to KPC; some enhanced PA activity</td>
</tr>
<tr>
<td>Aztreonam/avibactam</td>
<td>Monobactam/(\beta)-lactamase inhibitor</td>
<td>CRE (KPC, OXA, MBL)</td>
</tr>
<tr>
<td>Cefiderocol</td>
<td>Novel siderophore cephalosporin</td>
<td>CRE (KPC, OXA, MBL); enhanced PA, ACB activity</td>
</tr>
</tbody>
</table>

New Age of Antimicrobial Stewardship

- A new type of “diagnostic stewardship”
- Making the “best” choice for treatment of MDR-GNB
Utility of Rapid Diagnostics

- Rapid organism identification
  - Multiple platforms now available: PCR, multiplex PCR, PNA FISH, MALDI-TOF MS
  - Can improve time to effective therapy and clinical outcomes when use of technology is coupled with antimicrobial stewardship intervention
- Rapid genotypic testing: identify select resistance markers
  - Allows for early escalation of antibiotic therapy
  - Key: guidance on interpretation should be provided to clinicians or antimicrobial stewardship should be alerted
- Rapid phenotypic antimicrobial susceptibility testing
  - Accelerate Pheno, others in pipeline
  - Improves ability to rapidly de-escalate, optimize therapy
  - Important when multiple resistance mechanisms present

Rapid Diagnostics Can Be Used to Improve Time to Effective Therapy

Day 0
- Blood Draw
- Conventional Dx

Day 1
- Blood Draw
- Positive Blood Culture
- Gram Stain

Empiric Rx → Broad-spectrum Rx → Targeted Rx

Day 2
- Conventional Species ID

Day 3

Day 4

... Rapid and accurate results on day 1:
- Supports decisions for appropriate and targeted therapy 1-3 days earlier than conventional methods

Thanks to Debbie Goff for use of the slide
The Hook

- Implementation of rapid diagnostics alone, as is the case with most technology, will do nothing if not used appropriately
  - Birth control
  - Parachutes
- Process to alert providers to results and to have results be appropriately interpreted and acted upon in a timely manner is critical – and challenging
  - Often overlooked
  - Cannot be accomplished by clinical microbiology alone or by antimicrobial stewardship alone
  - Successful programs have included stewardship in the process

Pogue, JM et al, CMI, 2015, 302-12

Use of MALDI-TOF Results to Improve Patient Outcomes in Bacteremia

<table>
<thead>
<tr>
<th>Table 3. Clinical and Treatment-Related Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>------------------------------------------</td>
</tr>
<tr>
<td>Outcome</td>
</tr>
<tr>
<td>Clinical outcomes</td>
</tr>
<tr>
<td>30-day all-cause mortality</td>
</tr>
<tr>
<td>Time to microbiological clearance, d</td>
</tr>
<tr>
<td>Length of hospitalization, d</td>
</tr>
<tr>
<td>Length of ICU stay, d</td>
</tr>
<tr>
<td>Recurrence of same BSI</td>
</tr>
<tr>
<td>30-day readmission with same BSI</td>
</tr>
<tr>
<td>Treatment-related outcomes</td>
</tr>
<tr>
<td>Time to effective therapy, h</td>
</tr>
<tr>
<td>Time to optimal therapy, h</td>
</tr>
</tbody>
</table>

Huang, Clin Infect Dis, 2013, 1237-45
Integrating Rapid Diagnostics and Antimicrobial Stewardship at Community Hospitals

- Intervention included implementation of MALDI-TOF and antimicrobial stewardship pharmacist feedback and intervention
- Study population included patients with Gram-negative bacteremia
- Improved time to active treatment
- Mean cost savings of $3,411 per patient

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Pre-intervention (n = 132)</th>
<th>Intervention (n = 214)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surviving LOS, d</td>
<td>6.4 ± 3.5</td>
<td>6.4 ± 4</td>
<td>.3</td>
</tr>
<tr>
<td>Surviving ICU, d^2</td>
<td>2.3 ± 3.6</td>
<td>3.7 ± 3.4</td>
<td>.6</td>
</tr>
<tr>
<td>Mortality</td>
<td>14 (9.4)</td>
<td>11 (4.9)</td>
<td>.07</td>
</tr>
<tr>
<td>Therapy adjusted</td>
<td>95 (63.8)</td>
<td>201 (84.2)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Cost (avg)</td>
<td>$18,664 ± $28,673</td>
<td>$17,294 ± $13,538</td>
<td>.04</td>
</tr>
<tr>
<td>Non-ICU</td>
<td>$11,930 ± $8,527</td>
<td>$10,842 ± $8,079</td>
<td>.3</td>
</tr>
<tr>
<td>ICU^2</td>
<td>$24,116 ± $25,561</td>
<td>$22,675 ± $17,149</td>
<td>.7</td>
</tr>
</tbody>
</table>

Lockwood et al, Infec Contr Hosp Epi, 2016, 425-432

Rapid Diagnostic Results Often Difficult to Interpret
Rapid Diagnostic Results
Often Difficult to Interpret

MALDI-TOF and the Wonderful World of Bacteria I Have Never Heard Of

- Kocuria rhizophila
- Arthrobacter cumminsi
- Veillonella aypica
- Porphyromonas somerae
- Corynebacterium confusum
- Helcococcus kunzii
- Weeksella virosa
Is Genotype Enough Information?

- Most rapid diagnostics are genotypic – based on presence/absence of genes, not on susceptibility
  - Presence or absence of genes does not always equate with susceptibility or resistance

- Example: patient with sepsis treated with vancomycin+ zosyn
  - Blood cultures positive for GNR and GPCs
    - Rapid diagnostics identify *Escherichia coli* and *Staphylococcus aureus*
    - CTX-M negative and MecA positive
    - Interpreted as MRSA and *E. coli* that is not an ESBL-producer

- Vancomycin continued and zosyn discontinued; ceftriaxone started

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### *E. coli* Susceptibility Results

<table>
<thead>
<tr>
<th>Antimicrobial</th>
<th>Test result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cefepime</td>
<td>R</td>
</tr>
<tr>
<td>Piperacillin-tazobactam</td>
<td>R</td>
</tr>
<tr>
<td>Meropenem</td>
<td>S</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>R</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>S</td>
</tr>
</tbody>
</table>

- *E. coli* was CTX-M negative – and was thus, interpreted as being cephalosporin-susceptible
- Other ESBLs such as SHV and TEM types might have been present – not tested for in assay
Genotype vs Phenotype OR Both?

- Rapid genotypic results (negative for resistance genes) might be misinterpreted
- Rapid phenotypic susceptibility testing would be helpful

New Age of Diagnostic Stewardship

- Stewardship needed to
  - Help decide which rapid diagnostics to purchase
  - How to best communicate results to clinicians
  - Effectively interpret results so that optimal recommendations can be made
The “New Age” of Antimicrobial Stewardship: Choosing the Best Antibiotic for a Specific MDR-GNB

Continuum of optimizing antibiotic therapy

- Initiation of effective empiric antibiotic(s)
  - EARLY initiation
  - PD-optimized dosing

- Selection of optimal definitive antibiotic(s)
  - Antibiotic de-escalation
  - PD-optimized dosing

- Evidence-based duration of therapy
  - Limiting exposure by giving shorter courses when appropriate

Same principles, NEW (better) drugs for MDROs

- Which drug do we choose?
- Can we use rapid diagnostics to help us?

Antibiotics for MDR-GNB

2015
- Polymyxins

Today
- Ceftazidime-avibactam
- Ceftolozane-tazobactam
- Meropenem-vaborbactam
- Plazomicin
- Eravacycline
  - More on the way . . .
Picking the Right Antibiotic – Not as Easy as It sounds

Table. Review of improved antimicrobial activity

<table>
<thead>
<tr>
<th>Agent</th>
<th>Carbapenem-resistant Enterobacteriaceae</th>
<th>NDR Pseudomonas aeruginosa</th>
<th>Acinetobacter spp.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>KPC producers</td>
<td>Metallo-beta-lactamase producers</td>
<td></td>
</tr>
<tr>
<td>Ceftolozane/tazobactam</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Ceftazidime/avibactam</td>
<td>+</td>
<td>-</td>
<td>+/-</td>
</tr>
<tr>
<td>Meropenem/vaborbactam</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Cefepime/avibactam</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Pazardizan</td>
<td>+</td>
<td>+/-</td>
<td>+</td>
</tr>
<tr>
<td>Imipenem/relebactam</td>
<td>+</td>
<td>-</td>
<td>+/-</td>
</tr>
<tr>
<td>Eravocycline</td>
<td>+</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Fofoxofin</td>
<td>+</td>
<td>+/-</td>
<td>+/-</td>
</tr>
</tbody>
</table>

*Symbols are used to define the presence or absence of antimicrobial activity for each organism listed: Specifically, +" refers to good activity, +/- refers to some activity, although it may be variable, and "-" refers to poor or no activity.


Ceftazidime/avibactam vs Meropenem/vaborbactam

Concerns with Development of Resistance to Ceftazidime-Avibactam

First Report of Ceftazidime-Avibactam Resistance in a KPC-3-Expressing *Klebsiella pneumoniae* Isolate

Romney M. Humphries,* Shang-yin Yang,* Meera Homarajata, Kevin W. Ward,* Janet A. Hindlen,* Shelley A. Miller,* Avic Gregson*

*In Vitro* Selection of Ceftazidime-Avibactam Resistance in *Enterobacteriaceae* with KPC-3 Carbapenemase

David M. Linehom,* Maximo Warner,* Dorota Jenney,* Shazad Muthig,* Wright W. Nichols,* Nazim Mustafa,* Neil Woodford*

Emergence of Ceftazidime-Avibactam Resistance Due to Plasmid-Borne *bla*<sub>KPC-3</sub> Mutations during Treatment of Carbapenem-Resistant *Klebsiella pneumoniae* Infections

Ryan K. Shields,* Liang Chen,* Sheng Chen, Kalpana D. Chandra,* Ilene G. Price,* Avic Snyder,* Ruth Pandey,* Yafei Dui,* Barry R. Kriewall*,* M. Hong Nguyen,*

Correspondence:

CRE Treatment: Ceftazidime/avibactam vs Meropenem/vaborbactam OR Both?

- Direct comparisons cannot be made due to lack of clinical data
- Overall, resistance to both agents remains low and cross-resistance appears to be infrequent
  - Of 991 KPC-producing isolates, 24 had resistance to either drug and only 5 were resistant to both
- M/V appears to have a lower propensity for resistance development than C/A in CRE and thus could be preferred
  - Caveat: C/A has been available longer, used more in clinics
- C/A has enhanced activity against OXA-48 as well as MDR PSA (M/V does not)
- Bottom line: local epidemiology should be used to guide formulary decisions but both agents are likely needed

Ceftazidime/avibactam and Ceftolozane/tazobactam are Options for *P. aeruginosa*

- 2972 isolates of *P. aeruginosa* from Michigan Medicine: C/A vs C/T

<table>
<thead>
<tr>
<th></th>
<th>C/A</th>
<th>C/T</th>
</tr>
</thead>
<tbody>
<tr>
<td># of Isolates</td>
<td>2972</td>
<td>2972</td>
</tr>
<tr>
<td>% S</td>
<td>96.2</td>
<td>94.2</td>
</tr>
<tr>
<td>MIC&lt;sub&gt;50&lt;/sub&gt; (mg/L)</td>
<td>≤2</td>
<td>≤1</td>
</tr>
<tr>
<td>MIC&lt;sub&gt;90&lt;/sub&gt; (mg/L)</td>
<td>≤4</td>
<td>≤2</td>
</tr>
<tr>
<td>MIC Range (mg/L)</td>
<td>≤2 - &gt;16</td>
<td>≤1 - &gt;32</td>
</tr>
</tbody>
</table>

Patel TS, et al. ID Week 2019. Accepted.

**Ceftazidime/avibactam - For XDR-Pseudomonas?**

<table>
<thead>
<tr>
<th>Medication</th>
<th>MIC Range (mg/L)</th>
<th>Sensitivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amikacin</td>
<td>≥8 mcg/mL</td>
<td>Resistant</td>
</tr>
<tr>
<td>Aztreonam</td>
<td>≥16 mcg/mL</td>
<td>Resistant</td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>≥16 mcg/mL</td>
<td>Resistant</td>
</tr>
<tr>
<td>Ceftolozane</td>
<td>≥8 mcg/mL</td>
<td>Resistant</td>
</tr>
<tr>
<td>Ceftoletrozine</td>
<td>≥8 mcg/mL</td>
<td>Resistant</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>1 mcg/mL</td>
<td>Resistant</td>
</tr>
<tr>
<td>Imipenem</td>
<td>≥8 mcg/mL</td>
<td>Resistant</td>
</tr>
<tr>
<td>Levetimicin</td>
<td>≥8 mcg/mL</td>
<td>Resistant</td>
</tr>
<tr>
<td>Meropenem</td>
<td>16 mcg/mL</td>
<td>Resistant</td>
</tr>
<tr>
<td>Piperacillin/tazobactam</td>
<td>≥64 mcg/mL</td>
<td>Intermediate</td>
</tr>
<tr>
<td>Tobramycin</td>
<td>≥8 mcg/mL</td>
<td>Resistant</td>
</tr>
</tbody>
</table>
Ceftazidime/avibactam Is an Option for *P. aeruginosa*

- 2972 isolates of *P. aeruginosa*
- C/A susceptibility stratified by C/T susceptibility

<table>
<thead>
<tr>
<th></th>
<th>CT-S (n=2799)</th>
<th>CT-R (n=173)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CA-S (n=2859)</td>
<td>2775 (99.1)</td>
<td>84 (48.6)</td>
</tr>
<tr>
<td>CA-R (n=113)</td>
<td>24 (0.9)</td>
<td>89 (51.4)</td>
</tr>
</tbody>
</table>

- Mechanism for CT-R/CA-S phenotype unknown
  - Carbapenemase negative by State Lab
  - Investigation ongoing
    - Clinical characteristics and molecular work ongoing
- BOTH drugs should be routinely tested and considered!

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New Antibiotics: Summary and Unmet Needs

- Newer agents available; attractive agents in pipeline
- Resistance to newer agents concerning
  - Documented with ceftaz/avibactam, ceftolozane/tazobactam
  - Can develop during treatment
- Mono vs combo therapy with new agents – unclear which is preferable
- Unmet treatment needs persist
  - CRE: MBLs
  - ACB
  - XDR PA
New Age of Antimicrobial Stewardship!

- Rapid diagnostics are wonderful new stewardship tools, but are difficult to interpret
  - Important for stewardship personnel to aid clinicians in appropriate interpretation

- Several new agents available for MDR-GNB

- Stewardship personnel needed to help determine
  - Formulary decisions
  - Guidance regarding which agent for which pathogen
    - Activity dependent on pathogen, mechanism of resistance
    - Emergence of resistance potential important to consider

Questions?