Carbapenem Resistant Enterobacteriaceae (CRE)

Gregory Weston MD, MS
Physician Director of Infection Prevention and Control
Montefiore Medical Center
APIC Greater New York Chapter Meeting
1/15/20
Disclosure

- I have received funding for research through a subcontract that originated with Allergan

- I will briefly mention antibiotics that treat CRE
Objectives

- Know the definition of CRE – and recent changes to it
- Understand the mechanisms of carbapenem resistance
- Know that the most likely mechanism of resistance varies in different parts of the world
- Understand the implications of CRE for patient care
- Recognize risk factors for carbapenem resistance
- Discuss infection control interventions against CRE organisms
- Discuss screening for CRE organisms
Carbapenem-resistant Enterobacteriaceae (CRE) are a major concern for patients in healthcare facilities. Some bacteria in this family are resistant to nearly all antibiotics, leaving more toxic or less effective treatment options.
**CRE Are Tough to Treat**

**Blood, Bacteriology Culture (2nd Set, Post-Antibiotic)**

Status: Final result  Visible to patient: No (Not Released) Next app't: None

Specimen Information: Blood

### Blood, Bacteriology Culture

#### Gram Stain

From Aerobic and Anaerobic Bottles: Gram negative bacilli

This is an appended report. These results have been appended to

#### Susceptibility

<table>
<thead>
<tr>
<th>Susceptibility</th>
<th>CRE - Klebsiella pneumoniae ssp pneumoniae</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MIC/INTERPRETATION</td>
</tr>
<tr>
<td>Amikacin</td>
<td>32 ug/ml Intermediate</td>
</tr>
<tr>
<td>Ampicillin</td>
<td>&gt; 16 ug/ml Resistant</td>
</tr>
<tr>
<td>Ampicillin/Sulbactam</td>
<td>&gt;16/8 ug/ml Resistant</td>
</tr>
<tr>
<td>Aztreonam</td>
<td>&gt; 16 ug/ml Resistant</td>
</tr>
<tr>
<td>Cefazolin</td>
<td>&gt; 16 ug/ml Resistant</td>
</tr>
<tr>
<td>Cefepime</td>
<td>&gt; 16 ug/ml Resistant</td>
</tr>
<tr>
<td>Cefotaxin</td>
<td>&gt; 16 ug/ml Resistant</td>
</tr>
<tr>
<td>Ceftriaxime/Avibactam</td>
<td>3 ug/ml Sensitive</td>
</tr>
<tr>
<td>Ceftriaxime</td>
<td>&gt; 32 ug/ml Resistant</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>&gt;2 ug/ml Resistant</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>&gt;8 ug/ml Resistant</td>
</tr>
<tr>
<td>Identification</td>
<td>Identification</td>
</tr>
<tr>
<td>Meropenem</td>
<td>&gt;8 ug/ml Resistant</td>
</tr>
<tr>
<td>Piperacillin/Tazobactam</td>
<td>&gt;64/4 ug/ml Resistant</td>
</tr>
<tr>
<td>Polymyxin B</td>
<td>0.38 ug/ml Resistant</td>
</tr>
<tr>
<td>Tigecycline</td>
<td>1.5 ug/ml Sensitive</td>
</tr>
<tr>
<td>Tobramycin</td>
<td>&gt;8 ug/ml Resistant</td>
</tr>
<tr>
<td>Trimethoprim/Sulfamethoxazole</td>
<td>&gt;2/38 ug/ml Resistant</td>
</tr>
<tr>
<td>a THIS ORGANISM IS A MDR</td>
<td>Resistant</td>
</tr>
<tr>
<td>a THIS ORGANISM IS A XDR</td>
<td>Resistant</td>
</tr>
</tbody>
</table>

1 Testing done for research purposes only

---

**Montefiore**

Albert Einstein College of Medicine

**EINSTEIN**

Doing More

---
Enterobacteriaceae Are Gram Negative Gut Bacteria

<table>
<thead>
<tr>
<th>Enterobacteriaceae</th>
<th>Not Enterobacteriaceae</th>
</tr>
</thead>
<tbody>
<tr>
<td>Klebsiella pneumoniae</td>
<td>Pseudomonas aeruginosa</td>
</tr>
<tr>
<td>E. Coli</td>
<td>Acinetobacter baumanii</td>
</tr>
<tr>
<td>Enterobacter species</td>
<td>Stenotrophomonas maltophilia</td>
</tr>
<tr>
<td>Citrobacter species</td>
<td>Burkholderia cepacia</td>
</tr>
<tr>
<td>Serratia marcescens</td>
<td>Enterococcus faecium</td>
</tr>
<tr>
<td>Proteus species</td>
<td></td>
</tr>
</tbody>
</table>

Other types of resistant bacteria are important but this lecture and the label “CRE” deals with Enterobacteriaceae
CDC Uses a Sensitive Definition for CRE

- Current CDC definition for CRE (post 2015):
  - Resistance to any Carbapenem (includes Ertapenem)
    OR
  - Detection of a Carbapenemase Enzyme

- Prior (2015) CDC definition for CRE:
  - Resistance or Intermediate susceptibility to Meropenem, Imipenem or Doripenem
    AND
  - Resistance to 3rd Generation Cephalosporins (Ceftriaxone)

- The newer definition includes more organisms

- The older definition was more specific to identify organisms with a carbapenemase enzyme
Beta Lactamases Destroy Beta Lactams in Between the Gram Negative Bacteria Double Membrane

By Jeff Dahl - Own work, GFDL, https://commons.wikimedia.org/w/index.php?curid=3647374
Carbapenemases are a Subset of Beta Lactamases

There Are A Few Types of Carbapenemases

- **KPC** – *Klebsiella pneumoniae* Carbapenemase
  - KPC-2 and KPC-3 are the most common in NYC and USA
  - Any species can have it (not just *Klebsiella*)

- **Oxa Carbapenemases**
  - Seen more often in Europe, Turkey, North Africa

- **Metallo Beta Lactamases**
  - New Delhi (NDM-1) – From Pakistan, India, China, Mid-East
  - VIM - Europe
  - IMP – Europe, Japan
  - The Metallo Beta Lactamases are resistant to some of the new antibiotics that work against KPC carbapenemases
Carbapenemase Distribution World Wide

KPC-2 and KPC-3 are the Most Common Carbapenemases in NYC

<table>
<thead>
<tr>
<th>CRE pathogen</th>
<th>KPC-2</th>
<th>KPC-3</th>
<th>NDM</th>
<th>OXA-48</th>
<th>TEM non-ESBL</th>
<th>SHV non-ESBL</th>
<th>SHV ESBL</th>
<th>CTX-M</th>
<th>AmpC</th>
<th>ompK35 mutation</th>
<th>ompK36 mutation</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>K. pneumoniae</em> (n = 97)</td>
<td>44 (45)</td>
<td>48 (49)</td>
<td>1 (1)</td>
<td>82 (85)</td>
<td>62 (64)</td>
<td>31 (32)</td>
<td>8 (8)</td>
<td>81 (84)</td>
<td>33 (34)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>KPC-2 (n = 44)</td>
<td>44 (100)</td>
<td></td>
<td></td>
<td></td>
<td>37 (84)</td>
<td>27 (61)</td>
<td>17 (39)</td>
<td>2 (5)</td>
<td>35 (80)</td>
<td>10 (23)</td>
<td></td>
</tr>
<tr>
<td>KPC-3 (n = 48)</td>
<td></td>
<td>48 (100)</td>
<td></td>
<td>43 (90)</td>
<td>31 (65)</td>
<td>13 (27)</td>
<td>2 (4)</td>
<td>42 (88)</td>
<td>21 (45)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other (n = 5)</td>
<td>1 (20)</td>
<td>2 (40)</td>
<td></td>
<td>4 (80)</td>
<td>1 (20)</td>
<td>4 (80)</td>
<td></td>
<td>4 (80)</td>
<td>2 (40)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Enterobacter</em> spp. (n = 5)</td>
<td>1 (20)</td>
<td>3 (60)</td>
<td></td>
<td>4 (80)</td>
<td>1 (20)</td>
<td>4 (80)</td>
<td></td>
<td>N/A</td>
<td>N/A</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Escherichia coli</em> (n = 3)</td>
<td>1 (33)</td>
<td>1 (33)</td>
<td></td>
<td>1 (33)</td>
<td>2 (67)</td>
<td>1 (33)</td>
<td></td>
<td>N/A</td>
<td>N/A</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Morganella morganii</em> (n = 1)</td>
<td>1 (100)</td>
<td></td>
<td></td>
<td></td>
<td>1 (100)</td>
<td></td>
<td></td>
<td>N/A</td>
<td>N/A</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Satlin et al. Multicenter Clinical and Molecular Epidemiological Analysis of Bacteremia Due to Carbapenem-Resistant Enterobacteriaceae (CRE) in the CRE Epicenter of the United States. Antimicrobial Agents and Chemotherapy. 2017; 61: e02349-16
Carbapenemases on Plasmids can Spread

- Plasmids contain genes but are separate from the bacterial chromosome
- It is easier for a gene on a plasmid to get shared with other bacteria, even across species

Carbapenem Resistance without Carbapenemases May involve Porin mutations combined with other resistance elements

By Jeff Dahl - Own work, GFDL, https://commons.wikimedia.org/w/index.php?curid=3647374
Species of CRE affects Likelihood of Carbapenemase Production

<table>
<thead>
<tr>
<th>Carbapenemase Producing CRE N=37</th>
<th>Non-Carbapenemase Producing CRE N = 46</th>
</tr>
</thead>
<tbody>
<tr>
<td>Klebsiella pneumoniae 28 (76 %)</td>
<td>Enterobacter species 27 (59 %)</td>
</tr>
<tr>
<td>Enterobacter species 7 (19 %)</td>
<td>Klebsiella pneumoniae 14 (30 %)</td>
</tr>
<tr>
<td>E coli 1</td>
<td>E coli 3 (6.5 %)</td>
</tr>
<tr>
<td>Citrobacter species 1</td>
<td>Serratia 1</td>
</tr>
<tr>
<td></td>
<td>Proteus 1</td>
</tr>
</tbody>
</table>
Carbapenemase Production May Affect Patient Outcome in CRE Infection

Table 4. Fourteen-Day Mortality for Patients With Carbapenemase-Producing Carbapenem-Resistant Enterobacteriaceae (CP-CRE) Compared With non-CP-CRE Bacteremia

<table>
<thead>
<tr>
<th>Covariate</th>
<th>Odds Ratio (95% CI)</th>
<th>PValue</th>
<th>Adjusted Odds Ratio (95% CI)</th>
<th>PValue</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbapenemase-producing carbapenem-resistant Enterobacteriaceae bacteremia</td>
<td>3.20 (1.06–9.61)</td>
<td>.04</td>
<td>4.92 (1.01–24.81)</td>
<td>.05</td>
</tr>
<tr>
<td>Pitt bacteremia score ≥4</td>
<td>9.13 (2.39–34.86)</td>
<td>.001</td>
<td>11.89 (2.38–59.30)</td>
<td>.005</td>
</tr>
<tr>
<td>Active empiric antibiotic therapy</td>
<td>.79 (0.27–2.29)</td>
<td>.67</td>
<td>2.46 (0.53–11.48)</td>
<td>.25</td>
</tr>
<tr>
<td>Active directed antibiotic therapy</td>
<td>.17 (0.04–0.72)</td>
<td>.01</td>
<td>0.10 (0.004–2.22)</td>
<td>.14</td>
</tr>
<tr>
<td>Days of combination antibiotic therapy</td>
<td>.89 (0.79–1.00)</td>
<td>.07</td>
<td>0.73 (0.59–0.93)</td>
<td>.01</td>
</tr>
<tr>
<td>Polymixin therapy administered</td>
<td>4.61 (1.16–18.3)</td>
<td>.03</td>
<td>5.57 (1.07–28.96)</td>
<td>.04</td>
</tr>
<tr>
<td>Diabetes</td>
<td>3.12 (0.99–9.84)</td>
<td>.05</td>
<td>3.42 (0.62–19.07)</td>
<td>.16</td>
</tr>
<tr>
<td>Immunocompromised</td>
<td>.45 (0.14–1.40)</td>
<td>.17</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Carbapenem therapy administered</td>
<td>.82 (0.27–2.52)</td>
<td>.74</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Meropenem minimum inhibitory concentration ≥16 μg/mL</td>
<td>1.40 (0.38–5.01)</td>
<td>.61</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

14 Day Mortality: 12 (32 %) in the CP group and 6 (13 %) in the Non CP group

Tamma et al. Comparing the Outcomes of Patients with Carbapenemase-Producing and Non-Carbapenemase-Producing Carbapenem-Resistant Enterobacteriaceae Bacteremia. Clinical Infectious Diseases. 2017; 64: 257-64
Patient Outcomes in CRE Infections are Poor

- 50% Mortality for Bloodstream Infection – likely improved with newer antibiotics

- Patients are often started on ineffective antibiotics
  - Median time to appropriate therapy 47 hours

- Patients often have multiple comorbidities prior to CRE infection

- Available antibiotics until recently have been poorly effective
  - Polymyxin/Colistin and Aminoglycosides are toxic
  - Tigecycline is associated with failure in bloodstream infection
Newer Anti-CRE Drugs Are an Improvement, But Not Perfect

<table>
<thead>
<tr>
<th>Infection Type</th>
<th>Bloodstream</th>
<th>UTI</th>
<th>Skin/Soft Tissue</th>
<th>Pneumonia</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 Day Clinical Success</td>
<td>75 %</td>
<td>88 %</td>
<td>67 %</td>
<td>36%</td>
</tr>
</tbody>
</table>

- Ceftazidime-Avibactam has shown improved results for bloodstream infection – concern about pneumonia results
  - Resistance has begun to emerge

- Meropenem-Vaborbactam and Eravacycline are other new options

- None of these drugs are effective against NDM-1

Shields et al. Pneumonia and renal replacement therapy are risk factors for ceftazidime-avibactam treatment failures and resistance among patients with carbapenem-resistant Enterobacteriaceae infections. Antimicrobial Agents and Chemotherapy. 2018; 62: e02497-17
CDC CRE Tool Kit – Basic Interventions

- Hand Hygiene
  - acquisition from the environment

- Appropriate use of PPE
  - acquisition from the environment

- Antimicrobial Stewardship
  - develop resistance from antibiotic exposure

- Environmental Cleaning
  - close attention to sink drains and splash areas around sink drains
CDC CRE Tool Kit – Specific Interventions

- Contact precautions for all Carbapenemase producing CRE
  - Might use surveillance cultures or a long duration of time without positive culture to stop contact precautions

- Notification system to alert clinicians when a CRE patient returns to the facility, or a new CRE result is identified

- Notify receiving facilities when transferring CRE patient

- Patient and staff cohorting
  - But might want to know mechanism of resistance before cohorting
CDC CRE Tool Kit – Advanced Interventions

- Screening contacts of CRE patients – for new introduction of CRE or a new carbapenemase

- Point prevalence survey – testing an entire unit in a suspected cluster or outbreak

- Active surveillance testing
  - For facility or a high risk unit or population
  - Patients admitted from outside the US

- Chlorhexidine bathing
Components of Successful Anti-CRE Interventions From Quasi Experimental Studies

- Contact Precautions
- Active Screening
- Isolation and Cohorting of Staff
- Monitoring and Feedback for Infection Control Practices
- Hand Hygiene Campaign

Active Screening in National Israeli Intervention Outbreak Setting

- **Acute Care**
  - Ward contacts of CRE cases
  - Patients recently admitted to or transferred from other facilities
  - Patients on wards with high incidence of CRE

- **Post Acute Care Hospitals**
  - Serial point prevalence surveys

Active Screening in a CRE Endemic US City (Chicago)

- Started with Screening of ICU patients and transfers from other facilities (including LTACH, where CRE prevalence 30%)
  - Screened more than 100 patients for each CRE found

- Stopped ICU screening and continued screening of transfers from other facilities
  - In Medical and Surgical ICU they screened approximately 30 patients per CRE found
  - 10 of 21 patients identified during the first screening period would have been missed

Shimasaki T et al. Active screening and interfacility communication of carbapenem-resistant enterobacteriaceae (CRE) in a tertiary care hospital. Infection Control and Hospital Epidemiology. 2018: 39; 1058-1062
Regional Coordination to Slow the Rise of CRE


Take Home Points

- Implementation of 2015 CDC definition of CRE may cause misleading rise in CRE rate. The 2015 definition identifies a higher percentage of non-carbapenemase producing CRE.

- Carbapenemase producing CRE might more easily spread resistance to other bacteria, and may be associated with worse patient outcomes.

- KPC is the most common carbapenemase in NY/USA but other parts of the world are different, and other carbapenemases are coming to NY.

- Invasive CRE infections are associated with poor patient outcomes – newer antibiotics may not fully solve this problem.
Take Home Points

- Prior cultures with CRE, residence in SNF, mechanical ventilation, other healthcare exposures are associated with CRE infection – epidemiology in your own institution may determine which patients are more likely to have CRE.

- Infection control interventions against CRE include the fundamentals of IPC (hand hygiene, isolation) as well as advanced interventions (ie screening).

- Active screening of CRE has been used in outbreak and endemic settings but the optimal approach is not clear.

- Coordination among facilities in the same region can magnify individual infection prevention interventions.