Carbapenem-Resistant Enterobacteriaceae Management and Treatment Options

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Overview

• Increase in ESBLs
• Epidemiology of CRE
• Infection control approaches
• Antimicrobial stewardship
• Treatment options
Extended-spectrum β-lactamases (ESBLs): The Forgotten (and Underrated) MDR GNB

- Most commonly identified in enterobacteriaceae
- Plasmid-mediated
- Impart decreased susceptibility to β-lactam antimicrobials
  - Often co-resistance to aminoglycosides, fluoroquinolones
- Carbapenemems are drugs of choice for invasive infections due to ESBL-producers
CTX-M: ESBL Epidemic

- Common ESBL worldwide, often produced by *Escherichia coli*

- Often causes UTI

- Now reported in US
  - Healthcare associated
  - Some community

- Community-based ESBL infection raise concern for continued increases in carbapenem use

Urban, Diag Micro Infect Dis, 2010; Sjölund-Karlsson, EID, 2011
FIG 1 ESBL carriage rates in the community, according to their geographical and temporal distribution. Each bubble area is proportional to the size of the study sample. The lines represent the prevalence of ESBL carriage.
The CTX-M Detroit Experience

• From 2006-2011, total number of ESBL-producing E. coli increased from
  – 1.9% of all *E. coli* tested to 13.8% of all *E. coli* tested
• From 2/11-7/11 at Detroit Medical Center, 575 cases of ESBL-producing *E. coli* were identified
  – 82% urine
  – 8% wound
  – 5% blood
• 491 (85%) were CTX-M producers (predominantly CTX-M 15)
• CTX-M production was associated with increased resistance to other antibiotic classes
• Notable characteristics of ESBL-producing E. coli
  – > 75% POA
  – ~ 15% community-acquired
  – Prior B-lactam, TMP-SMX exposure common
Hayakawa et al, AAC, 2012
Unintended Consequences of Carbapenem Use

In attempt to reduce ESBL rate, imipenem became preferred empiric antimicrobial instead of 3\textsuperscript{rd} 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 <em>Pseudomonas aeruginosa</em> (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

- Emerging problem in *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, Enterobacteriaceae (CRE)

- Risk factors include ICU stay, prolonged exposures to healthcare, indwelling devices, antibiotic exposures
  - Long-term acute care centers (LTACs)

- Severely limits treatment options
  - Increased use of older, toxic agents such as colistin
**Klebsiella pneumoniae** Carbapenemases (KPCs)

- Plasmid-mediated carbapenemase
- KPC-producing strains of *Klebsiella pneumonia* and other enterobacteriaceae
  - KPC-2, KPC-3
- Endemicity in many locales in the US
  - Hyperendemicity in NYC
- Country-wide outbreak ongoing in Israel, Greece, Columbia and others

*Bratu, AAC, 2005; Quale, CID, 2004; Leavitt, AAC, 2007; Carmeli, Clin Micro Infect, 2010*
Clinical epidemiology of the global expansion of *Klebsiella pneumoniae* carbapenemases

Munoz-Price, Lancet ID, 2013
Dramatic Rise in CRE Incidence - US Hospital Reports to CDC

CRE may cause variety of nosocomial infections
- cIAI
- cUTI
- HABP/VABP
- Bacteremia

Mortality up to 35 – 50%

Percentage of carbapenem-resistant *Klebsiella* isolates reported to CDC has steadily increased since 2000

Carbapenemase-producing CRE in the United States

Below is a map showing states with carbapenemase-producing CRE confirmed by CDC.

http://www.cdc.gov/hai/organisms/cre/TrackingCRE.html
CRE

• Risk Factors
  – Prolonged length of stay
  – Long term acute care (LTAC) facility exposure*
  – Mechanical ventilation
  – Intensive Care Unit stay
  – Antimicrobial exposures
  – Poor functional status

• Outcomes
  – Carbapenem-resistance independently increases mortality
  – Overall mortality has ranged from 22-59%

Chen LF et.al. Infect Drug Resist. 2012; 5:133-41
Long-term Care Facilities (LTCFs) and CRE

- Not all LTCFs are created equally
- Long-term acute care centers (LTACs) are associated with CRE to much a greater degree then other types of LTCFs
  - In one study from the midwest, more than 30% of LTAC residents were colonized with CRE
    - ~ 1% of residents in skilled nursing facilities

Transfer from High-Acuity Long-Term Care Facilities Is Associated with Carriage of *Klebsiella pneumoniae* Carbapenemase–Producing *Enterobacteriaceae*: A Multihospital Study

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for the Centers for Disease Control and Prevention (CDC) Prevention Epicenters Program

**FIGURE 1.** Average prevalence and 95% confidence limits of carriage of *Klebsiella pneumoniae* carbapenemase–producing *Enterobacteriaceae* among patients from specific long-term care facility (LTCF) subtypes, at the time of acute care hospital admission. SNF, skilled nursing facility without a ventilator unit; VSNF, skilled nursing facility with a ventilator unit; LTACH, long-term acute care hospital.
Prevention of CRE

• Infection control
  – Contact precautions
  – Source control
  – Environmental hygiene
  – Screening high risk patients

• Antimicrobial stewardship

• Bundle approaches
Active Surveillance

- Use of “screening” cultures to identify patients colonized with pathogens (usually MDR) of interest

- Goal is to prevent spread in the hospital by identifying patients who are colonized and intervening to prevent spread

- Universal vs targeted strategies

- Rectal swabs or stool specimens
  - Selective media
  - Rapid diagnostics such as PCR

- Screening alone does nothing
  - Need process in place to act upon screening results

Munoz-Price, Lancet ID, 2013
Chlorhexidine: Mechanism of Action

• Broad spectrum (Gram-positive, Gram-negative bacteria, fungi)
• Bactericidal and/or bacteriostatic depending on concentration
• Works rapidly (can kill 100% of bacteria within 30 seconds)
• Can kill all categories of microbes
  – Little risk for development of resistance
Role of CHG Bathing With Regards to Hospital Infection and MDRO

• Protect the patient
  – Decrease the degree of colonization/burden of pathogens on skin of individual patient
  – By doing so, decrease risk for device-related infection (ie CLABSI)

• Protect other patients
  – By decreasing the burden of pathogens on an individual patient, the likelihood of spread to other patients (via contaminated healthcare workers and/or environment) is decreased

• Success in preventing infections CLABSI and infections due to MRSA, VRE, Acinetobacter

Environmental Cleaning

• Environmental sources of contamination/infection
  – Increasingly recognized as sources of infection
• Adequacy of cleaning of patients’ rooms suboptimal
• Improve monitoring and feedback of efficacy of cleaning
  – Direct observation and culturing not efficient, time-consuming and expensive
• Other options: ATP bioluminescence and fluorescent dyes
  – Monitor process, efficacy of cleaning
Previously Contaminated Rooms Increase Transmission Risk

Seven studies as of February 2011

- Acinetobacter
- Pseudomonas
- MRSA
- C. difficile

Bar chart showing increased risk of acquisition (%) for different studies:

- Huang: MRSA, VRE
- Hardy: MRSA
- Drees: VRE
- Shaughnessy: C. difficile
- Datta: MRSA
- Nseir: Pseudomonas
- Nseir: Acinetobacter

Mean = 120%

Slide courtesy of Dr. Philip Carling, Boston University School of Medicine
Used fluorescent dyes as part of quality improvement process for environmental cleaning
Figure 2. The percentage of high-touch objects cleaned prior to (A) and after (B) educational interventions in 3 hospitals (A, B, and C).
Bundles

• A bundle is a structured way of improving the processes of care and patient outcomes: a small, straightforward set of evidence-based practices (e.g. 3-5) that, when performed collectively and reliably, have been proven to improve patient outcomes.

Infection control successes for CRE

• Montefiore Medical Center
  – ICU based initiative
  – Active surveillance for detection of CRE coupled with contact precautions for all colonized patients
  – Led to 53% reduction in prevalence of CRE colonization in the unit

• Israeli experience
  – Nationwide intervention
  – Ministry of Health mandated reporting of CRE, isolation of patients with CRE, and other contact measures to decrease transmission
  – Self-contained nursing units for patients

Figure 1. Monthly incidence of carbapenem-resistant Enterobacteriaceae detected by clinical culture per 100,000 patient-days, January 2005–May 2008. The intervention was gradually implemented nationwide from March through May 2007. Data through May 2007 were assembled retrospectively. Data from 1 June 2007 through 31 May 2008 were collected prospectively. The intervention led to a reduction in monthly incidence from a pre-intervention peak of 55.5 cases per 100,000 patient-days in March 2007 to 11.7 cases per 100,000 patient-days in May 2008 ($P < .001$).
What About Antimicrobial Stewardship?

• Antimicrobial stewardship is relatively new discipline in the US
• Attempts to create processes to ensure good, routine antimicrobial care
  – Effective empiric therapy
  – Limiting unnecessary broad spectrum antibiotics
  – Minimize adverse events
Antimicrobial Stewardship - Goals

• Optimize appropriate use of antimicrobials
  – The right agent, dose, timing, duration, route
• Optimize clinical outcomes
  – Reduce emergence of resistance
  – Limit drug-related adverse events
  – Minimize risk of unintentional consequences
• Help reduce antimicrobial resistance
  – The combination of effective antimicrobial stewardship and infection control has been shown to limit the emergence and transmission of antimicrobial-resistant bacteria
• Strategies for controlling MDR GNB
  – De-escalation, shorter durations of therapy, limiting carbapenem use

A “Rational” Stewardship Strategy

• Broad spectrum therapy for empiric treatment of suspected invasive nosocomial infection
• Rapid de-escalation by day 3-4
• When possible, short durations of in-hospital antibiotics for selected populations
• Avoid anti-pseudomonal agents when possible
• “Hit hard, de-escalate, get out”

Correlation of CRE with carbapenem usage

It’s Not Just Carbapenems!
Risk for Overall Antimicrobial Exposures and CRE

<table>
<thead>
<tr>
<th>Antibiotic exposure in previous 3 months</th>
<th>CRE vs Uninfected OR (95% CI)</th>
<th>CRE vs ESBL OR (95% CI)</th>
<th>CRE vs Susceptible OR (95% CI)</th>
<th>CRE vs all controls combined OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>11.4 (2-64.3)</td>
<td>5.2 (1.4 19.4)</td>
<td>12.3 (3.3-45)</td>
<td>7.1 (1.9-25.8)</td>
<td></td>
</tr>
</tbody>
</table>

91 unique patients with CRE were included. Exposure to antibiotics within 3 months was an independent predictor that characterized patients with CRE isolation in all analyses.

Proposed CRE Bundle

• Limit use of broad-spectrum antimicrobials via de-escalation and decreasing duration of therapy
  – Limit carbapenem use
  – Limit overall antimicrobial use (de-escalation, duration)

• Infection control
  – Contact precautions
  – Selective screening (CRE)
  – CHG Bathing
Newer Treatment Options for CRE

• Tigecycline – good in vitro activity;
  – Concerns regarding emergence of resistance during treatment
  – Poor track record in critically ill patients

• Ceftazidime-avibactam – good in vitro activity vs KPCs
  – No clinical experience in treating CRE
  – ? Emergence of resistance concerns
  – Concern over avibactam’s ability to inhibit ESBL + carbapenemase
Older Agents for CRE

- Fosfomycin – most reports indicate good in vitro activity vs CRE
  - IV formulation not available in the US
  - Paucity of favorable clinical data
  - Rapid emergence of resistance during therapy has been reported
  - Some reports of declining activity

- Aminoglycosides - amikacin and gentamicin both have activity against CRE; amikacin usually more potent
  - Aminoglycosides should be not be used outside of urinary tract as monotherapy for invasive GNB infections, CRE

- Polymyxins – excellent in vitro activity
  - Nephrotoxicity
  - PK/PD limitations (particularly for colistin) and unknowns
  - Majority of clinical data retrospective, not controlled, biased

Strategies for Treating XDR-GNB

• Little if any controlled data
• Mortality rates are high
• For invasive infections, if no first line agent is active, then combination therapy is preferred
  – Agents with activity traditionally limited to polymyxins, aminglycosides, tigecycline
  – Carbapenems often used in combination for synergy
    • Better effect when carbapenem MICs are lower
  – Clinical impact of combination therapy for XDR-GNB unknown
    • Some retrospective studies suggest mortality advantage when using 2 or more drugs with in vitro activity*
    • Concerns re: unnecessary overuse of carbapenems
  – Efficacy of newer agents (ceftazidime-avibactam) unknown

Tumbarello et al, JAC, 2015, 2133-43; Tumbarello et al, Clin Infect Dis, 2012, 943-50
## Agents in the Pipeline

<table>
<thead>
<tr>
<th>Agent</th>
<th>Class</th>
<th>Status</th>
<th>Notable activity against CRE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aztreonam-avibactam</td>
<td>Monobactam-BLI</td>
<td>Phase I</td>
<td>Aztreonam active against MBLs</td>
</tr>
<tr>
<td>Plazomicin</td>
<td>Aminoglycoside</td>
<td>Phase III</td>
<td>More potent against KPC</td>
</tr>
<tr>
<td>Eravacycline</td>
<td>Fluorocycline</td>
<td>Phase III</td>
<td>Not inhibited by carbapenemases</td>
</tr>
<tr>
<td>Carbavance</td>
<td>Carbapenem +borate inhibitor</td>
<td>Phase III</td>
<td>Some metallo activity?</td>
</tr>
<tr>
<td>Relebactam</td>
<td>Carbapenem-BLI</td>
<td>Phase II</td>
<td>Active against KPC</td>
</tr>
<tr>
<td>BAL30072</td>
<td>Monosulfactam</td>
<td>Phase I</td>
<td>KPC, MBL, OXA</td>
</tr>
</tbody>
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Doi et al, Semin Respir Crit Care Med 2015; 36(01): 074-084
Conclusions

• CRE is a growing threat in many regions around the world
  – Frequency is increasing

• Major infection control challenge
  – Regional approaches, bundled approaches
  – Importance of antimicrobial stewardship

• Treatment options limited
Questions?