Making Sense of Alphabet Soup: Antimicrobial Resistance in Gram-Negative Bacilli

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Sunnybrook Health Sciences Centre
and the University of Toronto

Disclosures

I have received grants, and served as a consultant on Advisory Boards for:

• Merck Canada Inc.

I will not be discussing ESBLs or fluoroquinolone resistance in GNBs
Objectives

- to understand the mechanisms of carbapenem resistance in GNBs
- to appreciate the epidemiology, risks, and clinical significance of carbapenem resistance
- to consider evidence-based infection prevention and control strategies to limit the emergence and spread of carbapenem-resistant GNBs

Why Do We Care (about GNB resistance)?

- GNBs are major causes of infection, especially nosocomial or healthcare-associated
- GNB infections are associated with significant morbidity and mortality
- increasing incidence of multidrug-resistant GNB; treatment options are often limited
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Dr. Andrew Simor, University of Toronto
Broadcast live from the IPAC Canada conference

Antibiotic Resistance Threats

![Image of antibiotic resistance threats]

CDC, 2013

Antimicrobial Susceptibilities

<table>
<thead>
<tr>
<th>Antimicrobial</th>
<th>MIC(_{90}) (mg/L)</th>
<th>% Susceptible</th>
</tr>
</thead>
<tbody>
<tr>
<td>Imipenem</td>
<td>128</td>
<td>0</td>
</tr>
<tr>
<td>Meropenem</td>
<td>32</td>
<td>3</td>
</tr>
<tr>
<td>Pip/Tazo</td>
<td>&gt;64</td>
<td>0</td>
</tr>
<tr>
<td>Cefotaxime</td>
<td>&gt;256</td>
<td>0</td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>&gt;256</td>
<td>0</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>&gt;8</td>
<td>8</td>
</tr>
<tr>
<td>Tobramycin</td>
<td>&gt;32</td>
<td>0</td>
</tr>
<tr>
<td>Amikacin</td>
<td>&gt;64</td>
<td>0</td>
</tr>
<tr>
<td>Tigecycline</td>
<td>4</td>
<td>67</td>
</tr>
<tr>
<td>Colistin</td>
<td>8</td>
<td>100</td>
</tr>
</tbody>
</table>

Kumarasamy, Lancet Infect Dis 2010

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Carbapenems
“The Big Gun”

- ertapenem
- imipenem
- meropenem
- doripenem

Carbapenems

- Active against most:
  Streptococci
  Enterococci
  MSSA
  Enterobacteriaceae
  GNB afermenters (eg. Pseudomonas)
  Anaerobes

- Ertapenem is **not** active against *Pseudomonas*
Carbapenems
Common Indications

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Pathogen</th>
</tr>
</thead>
<tbody>
<tr>
<td>sepsis NYD</td>
<td>polymicrobial (GNB + anaerobes)</td>
</tr>
<tr>
<td>HAP, VAP</td>
<td>ESBLs</td>
</tr>
<tr>
<td>intra-abd sepsis</td>
<td><em>P. aeruginosa</em></td>
</tr>
<tr>
<td></td>
<td><em>Acinetobacter</em> spp.</td>
</tr>
</tbody>
</table>

Carbapenem Resistance in GNB

- *Pseudomonas aeruginosa*
- *Acinetobacter* spp.
- *Enterobacteriaceae*
Carbapenem Resistance in *Pseudomonas* and Acinetobacter

- In the US, 15-22% of *P. aeruginosa* and 21-48% of *Acinetobacter* spp. are carbapenem-resistant
- In Canada, 10-24% of *P. aeruginosa* and <10% of *Acinetobacter* are carbapenem-resistant


Mechanisms of Carbapenem Resistance

- changes in OMPs (permeability barrier: porin loss + ESBL/AmpC β-lactamase); especially in *Pseudomonas*, or if isolate is R only to ertapenem and not to other carbapenems
- carbapenemases
Enzymes that hydrolyze carbapenem antibiotics (and typically also most other \(\beta\)-lactams and \(\beta\)-lactamase inhibitors); may be chromosomally encoded or more commonly plasmid-mediated.

**Class A (serine)**
- SME (Serratia)
- IMI (Enterobacter)
- GES (Pseudomonas)
- KPC (Klebsiella)

**Class B (MBL)**
- VIM (Pseudomonas)
- IMP, SPM, GIM, SIM
- NDM

**Class D carbapenemase**
- OXA (Acinetobacter)
- OXA-48 (Enterobacteriaceae)
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CPE in Europe, 2014

- 455 hospitals in 36 countries
- 402 E. coli: 19% CPE
- 2,301 K. pneumoniae: 3.7% CPE
- mainly KPC, NDM, OXA-48, VIM

Grundmann, Lancet Infect Dis 2017

CPEs in Canada

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CPE Surveillance in Canada: CNISP 2010-2014

- Overall incidence:
  0.07 per 1,000 admissions
  0.09 per 10,000 patient-days
  (about 1/100th of MRSA rates)
  < 1% of E. coli or Klebsiella

Mataseje, Antimicrob Agents Chemother 2017

CPE in Canada: CPHLN Data

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CPE in Canada: CPHLN Data

(n=1675)

CPE by Species: CPHLN Data

(n=1675*)

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Carbapenemases by Region

Travel Related Antibiotic Resistance including Medical Tourism

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CPE in Toronto/Peel, colonized/infected patients

0 5 10 15 20 25 30 35 40
Number of cases

- Healthcare abroad
- Travel Indian subcontinent
- No out of country risk

2013 2014 2015 2016

TIBDN, 2017 (A. McGeer)

CPE Risk Factors

- Similar as for other AROs:
  - recent hospitalization
  - ICU admission
  - invasive medical devices
  - antibiotic exposure
  - chronic wounds

Savard, Infect Control Hosp Epidemiol 2013

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CPE Fecal Carriage

- mean duration of CPE fecal carriage post-hospital discharge: 387 days; 39% still carrying CPE at 1-year post-discharge
- risks associated with prolonged carriage:
  - repeat hospitalization
  - CPE in clinical culture (not just screening cultures)

Zimmerman, Am J Infect Control 2013

Environmental contamination of the hospital environment is common

Lerner, J Clin Microbiol 2013
Contaminated Hospital Sinks

- contaminated handwashing sinks identified as a source/reservoir for ongoing transmission of CPEs

Lowe, Infect Control Hosp Epidemiol 2013
Vergara-Lopez, Clin Microbiol Infect 2013;
Leitner, Antimicrob Agents Chemother 2015

CRE Transmission via Duodenoscopes

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**CRE Transmission via ERCP Scopes**

- A US Senate investigation found 250 scope-related CRE infections reported from 25 hospitals/clinics in the US and Europe, 2012-2015

Promed-mail, Apr. 16, 2016

**Carbapenemase-Producing Enterobacteriaceae**

- **KPC** (*Klebsiella pneumoniae* carbapenemase)
- **NDM-1** (New Delhi metallo-β-lactamase)
K. *pneumoniae* Carbapenemase

- *K. pneumoniae* carbapenemase (Ambler class A serine β-lactamase)
- $\text{bla}_{KPC}$ gene resides on a transposon, Tn4401
- hydrolyzes all β-lactams, and typically multidrug-resistant
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KPC - Epidemiology

- clonal outbreaks in New York, Israel, Greece, Colombia, Brazil, China
- outbreaks in Montreal and Toronto hospitals

KPC in the US

- KPC is the most common carbapenemase in the US, and is endemic in many areas
- NYC: 2% of ICU patients colonized or infected with KPC, and KPC accounted for 26% of all invasive *K. pneumoniae* infections
- Chicago: 3% of ICU patients and 30% of LTACH residents


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KPC in the US

- meropenem-resist *K. pneumoniae* increased from 0.6% in 2004 to 5.6% in 2008\(^1\)
- NHSN surveillance of device-related infections (2006-07): carbapenem-resist in 10.8% *K. pneumoniae* and 4.0% *E. coli* \(^2\)

\(^1\)Rhomberg, Diagn Microbiol Infect Dis 2009; \(^2\)Hidron, Infect Control Hosp Epidemiol 2008

KPC Risk Factors

- prior use of multiple antibiotics, especially a β-lactam or fluoroquinolone
- prolonged hospitalization
- ICU admission


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KPC Outcome

- KPC infection associated with higher mortality than that caused by carbapenem-susceptible organism
- KPC BSI associated with 40%–70% crude mortality, and attributable mortality as high as 50%

NDM-1

- New Delhi metallo-β-lactamase plasmid-mediated
- has been found in many different coliform species
- resistant to all β-lactams and to most other classes of antibiotics
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NDM-1 widespread in tap water and sewage in New Delhi, India
- 2/50 water specimens and 12/170 sewage specimens
- 20 different bacterial species

(can also be found in surface water and sewage in Canada)

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NDM-1 Outcome

- In a case–control study of patients with hospital-acquired NDM-1 infection, adjusting for co-morbidity, NDM-1 infected patients had:
  - longer mean LOS (44 vs. 13 days; p<0.001)
  - higher mortality (55% vs. 15%; aOR 11.3)


Carbapenem Resistance Diagnosis/Detection

- Lab detection challenging due to heterogeneous expression of resistance to β-lactams
KPC Chromagar (Colorex)  
Chromogenic Media

• KPC Chromagar for KPC detection:  
  100% sensitive  
  98% specific  
• less sensitive for other carbapenemases

Perry, J Antimicrob Chemother 2011;  
Wilkinson, J Clin Microbiol 2012;  
Simner, J Clin Microbiol 2016

Tests for Carbapenemases

• Phenotypic tests  
  - Modified Hodge Test (MHT)  
  - Carba NP  
  - Carbapenem Inactivation Method

• Molecular tests  
  - PCR
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**PCR for CPE Screening from Rectal Swabs**

- Routine active surveillance for carbapenemase-producing Enterobacteriaceae from rectal swabs: diagnostic implications of multiplex polymerase chain reaction

*Journal of Hospital Infection*

**CPE Challenges**

- multiresistant (few treatment options)
- lab detection may be difficult (screening media; confirmation of CPE)
- prolonged fecal carriage and easily transmitted (clonal spread or plasmids)
- environmental contamination may be common, unrecognized (sinks, endoscopes)
- lack of data re: effective infection control

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KPC & NDM-1 Outbreaks Controlled with ‘bundles’:

- attention to hand hygiene
- active screening
- contact precautions
- cohorting as required
- enhanced environmental cleaning
- antibiotic stewardship


CPE Infection Control Guidelines

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>CDC\textsuperscript{a}\textsuperscript{b}</th>
<th>HPA\textsuperscript{a}</th>
<th>FHAC\textsuperscript{c}\textsuperscript{d}</th>
<th>CINQ\textsuperscript{e}\textsuperscript{f}</th>
<th>RI\textsuperscript{a}</th>
<th>FB\textsuperscript{a}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Facility/institution engagement</td>
<td>R</td>
<td>S</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ensure that the board and executives make CPE prevention a high priority and are supportive/include all healthcare facilities/providers</td>
<td>R</td>
<td>S</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prepare a containment action plan</td>
<td>...</td>
<td>R</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
</tbody>
</table>

Isolation of patients

- Use preemptive contact precautions for patients transferred from endemic areas S R R ... R
- Use contact precautions for patients colonized with CPE R R R R R
- Use contact precautions for patients infected with CPE R R R R R
- Use contact precautions for patients hospitalized in the same environment/room as a positive case while cultures are pending S ... R ... ...
- Use contact precautions for epidemiologically-linked patients while surveillance cultures are pending S ... ... ...
- Duration of isolation Maintain for the entire length of stay ... ... R R ...

R, Recommended; S, Suggested

Savard, Infect Control Hosp Epidemiol 2013
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CPE Infection Control Guidelines

<table>
<thead>
<tr>
<th>Surveillance</th>
<th>R</th>
<th>R</th>
<th>R</th>
<th>R</th>
<th>R</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screen high-risk patients on admission (known positives and those returning from endemic areas if hospitalised)</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
</tr>
<tr>
<td>Perform point prevalence survey on high-risk units</td>
<td>R</td>
<td>...</td>
<td>R</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Conduct a round of active surveillance cultures on epidemiologically linked patients (same unit/same healthcare workers)</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
</tr>
<tr>
<td>Repeat surveillance cultures</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
</tr>
<tr>
<td>Screen household contacts of patients</td>
<td>...</td>
<td>S</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Follow surveillance cultures to determine whether colonization persists</td>
<td>S</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>R</td>
</tr>
</tbody>
</table>

| Other infection prevention/control measures | R | R | R | R | R |
| Enhanced/better infection control measures | R | R | R | R | R |
| Add droplet precautions if respiratory tract is colonized/infected | ... | ... | ... | R |
| Cohort patients if necessary | R | R | R | R | R |
| Flap patient record | R | R | R | R | R |
| Implement antimicrobial stewardship program | R | R | R | R | R |
| Limit use of devices | R | ... | ... | ... | ... |
| Environment cleaning | ... | ... | R | ... | ... |
| Use same disinfection process as for MRSA | ... | ... | R | ... | ... |

Savard, Infect Control Hosp Epidemiol 2013

Containment of a Country-wide Outbreak of Carbapenem-Resistant Klebsiella pneumoniae in Israeli Hospitals via a Nationally Implemented Intervention

Schwaber, Clin Infect Dis 2011


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KPC Control in Israel
Nationally mandated IP&C “bundle” implemented in 2007-2008:
- active surveillance (rectal swab) for all high-risk patients
- contact precautions in private room or cohorting of all CRE patients; cohorting staff and dedicated equipment
- flag patients on readmission
- mandatory reporting to public health of every CRE patient, and daily census
- national task force to oversee, provide feedback, and advice to individual hospitals

Cohen, ICHE 2011; Borer, ICHE 2011; Schwaber, CID 2011; Schwaber, CID 2014

KPC Decolonization
- RTC: oral gentamicin + polymyxin E vs. placebo X 7 days
  - ↓ KPC rectal carriage for up to 6 weeks
- case series, 50 patients
  - oral gentamicin
  - ↓ KPC colonization
  - ↓ KPC infections
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Colistin

Colistin: The Revival of Polymyxins for the Management of Multidrug-Resistant Gram-Negative Bacterial Infections
Matthew E. Falagas and Sofin K. Kasiakou
Archives of Internal Medicine (AAMC) and Department of Medicine, "Hennin-Overt" Hospital, Athens, Greece, and "Tuma" University School of Medicine, Boston, Massachusetts

The emergence of multidrug-resistant gram-negative bacteria and the lack of new antibiotics to combat them have led to the revival of polymyxins, an old class of cationic, cyclic polypeptide antibiotics. Polymyxin B and polymyxin E (colistin) are the 2 polymyxins used in clinical practice. Most of the reintroduction of polymyxins during the last few years is related to colistin. The polymyxins are active against selected gram-negative bacteria, including Acinetobacter species, Pseudomonas aeruginosa, Klebsiella species, and Enterobacter species. These drugs have been used extensively worldwide for decades for local use. However, parenteral use of these drugs was abandoned ~20 years ago in most countries, except for treatment of patients with cystic fibrosis, because of reports of common and serious nephrotoxicity and neurotoxicity. Recent studies of patients who received intravenous polymyxins for the treatment of serious P. aeruginosa and Acinetobacter baumannii infections of various types, including pneumonia, bacteremia, and urinary tract infections, have led to the conclusion that these antibiotics have acceptable effectiveness and considerably less toxicity than was reported in old studies.

Falagas, Clin Infect Dis 2005

Colistin-Resistant Enterobacteriaceae

Marston, JAMA 2016

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www.webbertraining.com
mcr-1-positive Colistin-Resistance in Canada

- A few reports of mcr resistance in human isolates reported as of Mar. 2017:


Summary

- Although still uncommon in Canadian hospitals, the incidence of CPEs is rising, including increased rates of nosocomial transmission
- Enormous impact on patient mortality and outcome
- IP&C and antimicrobial stewardship are critical to reduce emergence and spread
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www.webbertraining.com/schedulep1.php

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Speaker: Prof. Karen Vickery, Macquarie University Faculty of Medicine, Australia
(South Pacific Teleclass)

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