Emerging Carbapenem Resistance – What Do We Do Now?
Prof. Andrew Simor, University of Toronto
A Webber Training Teleclass

Disclosures
I have no disclosures or conflicts of interest to declare.

Objectives
• to understand the epidemiology, risks, and impact of carbapenem-resistant organisms in hospitals
• to consider effective strategies for preventing the emergence and spread of carbapenem resistance in healthcare settings

We Have a Basic Problem

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

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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>nosocomial pneumonia, VAP</td>
<td>P. aeruginosa</td>
</tr>
<tr>
<td>intra-abd sepsis</td>
<td>Acinetobacter spp.</td>
</tr>
</tbody>
</table>

Carbapenem Resistance

- Pseudomonas aeruginosa
- Acinetobacter spp.
- Enterobacteriaceae (eg. Klebsiella, E. coli)

Carbapenem Resistance

- changes in OMPs (permeability barrier: porin loss + ESBL/AmpC ß-lactamase); especially in Pseudomonas
- carbapenemases:
  - class A (serine)
  - class B (metallo-ß-lactamase)
  - class D (OXA ß-lactamase)

Carbapenemases

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)

Carbapenem Resistance in Gram-Negative Bacilli:

How Common Is This?

Carbapenem-Resistant GNB in Canadian Hospitals (1)

- 1-yr surveillance in 20 hospitals, 2009-2010
- 58,669 GNB
  - 6,260 P. aeruginosa
  - 331 A. baumannii
  - 52,078 coliforms
  - 34,192 E. coli
  - 7,363 Klebsiella

Matusej, J Antimicrob Chemother 2012

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Carbapenem-Resistant GNB in Canadian Hospitals (2)

*P. aeruginosa*

206 (3.3%) carbapenem-resistant; only 11 (5%) had a carbapenemase (*bla*VIM in 8; *bla*GES in 3)

*A. baumannii*

9 (2.7%) carbapenem-resistant; all *bla*OXA

Mataseje, J Antimicrob Chemother 2012

Carbapenem-Resistant GNB in Canadian Hospitals (3)

*Enterobacteriaceae*

59 (0.1%) carbapenem-resistant:

10 (17%) with carbapenemase KPC (7), NDM-1 (2), SME (1), 6 *Klebsiella*, 2 *E. coli*, 2 *Serratia*

Mataseje, J Antimicrob Chemother 2012

Carbapenem-Resistant *Pseudomonas*

*Pseudomonas aeruginosa*

• 2nd most common isolate in US ICUs
• 3rd most common isolate in Canadian ICUs and Canadian wards


Carbapenem-Resistant *P. aeruginosa*

• carbapenem resistance mostly due to: efflux, altered outer membrane proteins (loss of OprD), or increased AmpC expression
• less often due to a carbapenemase, esp. VIM, less often IMP, NDM


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Carbapenem-Resistant Pseudomonas: Risk Factors

- ICU admission (Harris, Clin Infect Dis 2002; Eagye, Infect Control Hosp Epidemiol 2009)
- prior treatment with a carbapenem (Troillet, Clin Infect Dis 1997; Harris, Clin Infect Dis 2002; Magnus, Infect Control Hosp Epidemiol 2006)
- prior treatment with other antibiotics (fluoroquinolones, Vanco, pip/tazo) (Harris, Clin Infect Dis 2002; Lautenbach, Infect Control Hosp Epidemiol 2006)

Carbapenem-Resistant Pseudomonas - Sunnybrook

- increased from 4.1% in 2002 to 15% in 2010 (p=0.001); 80% in ICU
- risk factors: prior carbapenem (OR 6.2, 95% CI 2.1-18.8), fluoroquinolone (OR 2.7, 95% CI 1.2-6.1), ICU admission (OR 2.9, 95% CI 1.3-6.7)
- multiple clones; only 3 (6%) had a carbapenemase by PCR ($bla_{IMP}$)

Carbapenem-Resistant P. aeruginosa - Sunnybrook

- associated with increased in-hospital mortality (26% vs 11%; p=0.01)
- “ineffective” antibiotics initially prescribed in 24%, but not associated with increased mortality (33% vs 22%; p=0.45)

Carbapenem-Resistant P. aeruginosa - Outcome

- Carbapenem resistance in P. aeruginosa is a significant independent risk factor for mortality as compared to susceptible strains (31% vs 17%; RR 1.9, 95% CI 1.4-2.5)
- Carbapenem resistance also associated with longer LOS and increased costs

Carbapenemases

Enzymes that hydrolyze carbapenem antibiotics (and typically also hydrolyze most other β-lactams and β-lactamase inhibitors); may be chromosomally encoded or more commonly plasmid-mediated

Does ertapenem use spare carbapenem resistance in Pseudomonas?

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Carbapenemases

<table>
<thead>
<tr>
<th>Class</th>
<th>Enzyme</th>
<th>Characteristics</th>
</tr>
</thead>
</table>
| B     | Metallo-β-lactamase | - inhibited by EDTA  
- contain a zinc atom at the active site  
- NDM-1, IMI, GES, Sme |
| A     | Serine β-lactamase | - not inhibited by EDTA  
- serine at active site  
- KPC, VIM, IMP |

Class D enzymes

OXA-48 (E. coli, K. pneumoniae)

Carbapenem-Resistant Enterobacteriaceae

Ontario Public Health Lab  

<table>
<thead>
<tr>
<th>Enzyme</th>
<th>Species</th>
</tr>
</thead>
<tbody>
<tr>
<td>NDM-1</td>
<td>34</td>
</tr>
<tr>
<td>KPC</td>
<td>33</td>
</tr>
<tr>
<td>OXA-48</td>
<td>14</td>
</tr>
<tr>
<td>VIM</td>
<td>6</td>
</tr>
</tbody>
</table>

K. pneumoniae 54  
E. coli 13  
E. cloacae 9

Public Health Ontario, CPE  
Surveillance Report, May 2012

KPC

- K. pneumoniae carbapenemase (Ambler class A β-lactamase)
- blaKPC gene resides on a transposon, Tn4401
- hydrolyzes all β-lactams, and typically multidrug-resistant

KPC Risk Factors

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


Carbapenem-Resistant Enterobacteriaceae

- meropenem-resist K. pneumoniae increased from 0.6% in 2004 to 5.6% in 2008 (in the US)¹
- NHSN surveillance device-related infections (2006-07): carbapenem-resist in 10.8% K. pneumoniae and 4.0% E. coli²

¹Rhomberg, Diagn Microbiol Infect Dis 2009; ²Hidron, Infect Control Hosp Epidemiol 2008

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Risk Factors

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- prolonged hospitalization
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Carbapenem-Resistant Enterobacteriaceae

- KPC is the most common carbapenemase in the US
- In NYC:
  - 2% of ICU patients colonized/infected with KPC
  - KPC accounted for 26% of all invasive K. pneumoniae infections


KPC Outcome

- KPC infection associated with higher mortality than that caused by carbapenem-susceptible organism

KPC - Epidemiology

- clonal outbreaks in New York, Israel, Greece, Colombia, Brazil, China, Canada (Montreal)

KPC Outbreak in Montreal Hospital ICU

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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

NDM-1

- endemic in south Asia (India, Pakistan, Bangladesh)
- spread to UK and other European countries; related to “medical tourism”
(Kumarasamy, Lancet Infect Dis 2010)

Medical Tourism

- International travel is an important risk factor for being colonized or infected with resistant organisms (Laupland, J Infect 2008; Tängdén, Antimicrob Agents Chemother 2010)
- NDM-1 producing bacteria have been associated with admission to hospitals in south Asia (Kumarasamy, Lancet Infect Dis 2010)

NDM-1, 2011

- 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

NDM-1, 2011

- Carbatapenem-producing Enterobacteriaceae

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Carbapenem Resistance

Diagnosis & Treatment

- Lab detection challenging due to heterogeneous expression of resistance to β-lactams
- Treatment options limited (tigecycline, colistin)

Carbapenem Resistance

Revised Breakpoints (CLSI 2010)

<table>
<thead>
<tr>
<th>Carbapenem</th>
<th>Breakpoints (Enterobacteriaceae, µg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Susceptible</td>
</tr>
<tr>
<td>Doripenem</td>
<td>≤ 1.0</td>
</tr>
<tr>
<td>Ertapenem</td>
<td>≤ 0.25</td>
</tr>
<tr>
<td>Imipenem</td>
<td>≤ 1.0</td>
</tr>
<tr>
<td>Meropenem</td>
<td>≤ 1.0</td>
</tr>
</tbody>
</table>

Carbapenem Resistance

Lab Detection

- Revised (lower) MIC breakpoints improve sensitivity of detection, but may be missed by automated systems, and may overcall carbapenemases
- Disk approximation tests with inhibitors; Etest with EDTA (MBL)
- PCR

Carbapenem Resistance

Lab Detection

Disk Diffusion Tests for MBL and Class A (serine) Carbapenemases

- a. KPC/VIM+ESBL isolate
- b. KPC + ESBL isolate
- c. VIM isolate
- d. AmpC/ESBL isolate

Tsakris, J Antimicrob Chemother 2010

Modified Hodge Test

- reasonably good for KPC
- may miss NDM-1
- Nonspecific (high-level AmpC-producers)

KPC Chromagar (Colorex)

Chromogenic Media

KPC Chromagar for KPC detection:
- 100% sensitive
- 98% specific

Samra, J Clin Microbiol 2008

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Carbapenem Resistance

- emergence in a previously susceptible strain (antibiotic selective pressure)
- person-to-person transmission (clonal or plasmid)

Nosocomial Carbapenem Resistance (1)

- study to determine roles of antibiotic selection pressure and patient-to-patient transmission of carbapenem-resist \( P. aeruginosa \)
- med/surg ICU in US, 2001-06
- serial perianal swabs on admission and weekly, to look for imipenem-resist \( Pseudo \); PFGE typing

Johnson, J Infect Dis 2009

Nosocomial Carbapenem Resistance (2)

- 7,071 patients; 300 with imipenem-resist \( Pseudo \) (151 on admission; 149 acquired in ICU)
- 46 (31%) had PFGE patterns suggesting transmission
- 38 (26%) had previous imipenem-susceptible \( Pseudo \) and 28 (19%) had same PFGE pattern, suggesting selective pressure

Johnson, J Infect Dis 2009

CDC Guidelines for Control of CRE

For all healthcare facilities
- hand hygiene
- contact precautions
- patient/staff cohorting
- contact screening
- antimicrobial stewardship
For facilities with CRE transmission
- active surveillance
- 2% chlorhexidine bathing

CDC, 2012

KPC – Infection Control

- active screening identified colonized patients who would otherwise have been missed in NYC ICUs
  (Calfee, Infect Control Hosp Epidemiol 2008)
- “bundle” (active surveillance, contact isolation, flagging, environment cleaning)
  (Ben-David, Infect Control Hosp Epidemiol 2010; Borer, Infect Control Hosp Epidemiol 2011)
- nationwide control in Israel
  (Schwaber, Clin Infect Dis 2011)

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Carbapenem Resistance Challenges in Management

- easy plasmid transmission (NDM-1)
- environmental contamination may be common, unrecognized
- lack of good screening media
- difficult algorithms for detecting or confirming resistance
- few treatment options
- lack of data re: effective infection control

Schwaber, Clin Infect Dis 2011

Coming Soon

02 October (FREE WHO Teleclass – Europe) The Role of Education in Low and Middle Income Countries
Speaker: Prof. Shaheen Mehtar, Stellenbosch University, South Africa
Sponsored by WHO First Global Patient Safety Challenge – Clean Care is Safer Care

11 October Evaluating Chlorhexidine Baths for the Prevention of Central Line Associated Bloodstream Infections (CLABSDs)
Speaker: Prof. Silvia Munoz-Price, University of Miami Miller School of Medicine
Sponsored by Sage Products Inc (www.sageproducts.com)

18 October (South Pacific Teleclass) Meningococcal Disease and the New Zealand Experience – Where to From Here
Speaker: Dr. Tony Walls, University of Otago, New Zealand

25 October Critique and Use of the Scientific Evidence – Sharpening Skills
Speaker: Russell Olmstead, St. Joseph Mercy Health System, Ann Arbor, Michigan
Sponsored by Virox Technologies Inc. (www.virox.com)

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