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Objectives

• What are Carbapenemase Producing Organisms?
• Overview of global and national activities
• Update on BC activities
• Challenges and next steps
Carbapenemases are a class of enzymes that inactivate carbapenem antibiotics by hydrolysing them.

Carbapenem antibiotics, often referred to as “last resort antibiotics”:
- Imipenem
- Meropenem
- Ertapenem

Carbapenemases most commonly in E. coli and Klebsiella spp., (Enterobacteriaceae) but have also been found in other Gram-negative species.
Terminology

- **CRE**: Carbapenem resistant Enterobacteriaceae (mechanism unknown)
- **CPE**: Carbapenemase producing Enterobacteriaceae (mechanism known)
- **CPO**: Carbapenemase producing organisms (Enterobacteriaceae plus other non-fermentors)
- **Carbapenem**: A broad-spectrum class of antibiotics
- **Enterobacteriaceae**: A family of Gram-Negative bacteria (e.g. E. coli, Klebsiella pneumoniae, etc)
- **Non-fermentors**: Pseudomonas sp, Acinetobacter sp, etc
We are loosing are miracle drugs and research/industry are not rising up to the challenge.
ANTIBIOTIC APPROVALS: 1983-2011

Infectious Disease Society of North America, 2011
Antibiotic Timeline and Emergence of Resistant Bacteria

Molton et al., CID 2013
### eta-lactamase Family

<table>
<thead>
<tr>
<th>Molecular Class</th>
<th>Types</th>
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<tr>
<td>A</td>
<td>TEM, SHV, CTX-M, KPC, GES, SMC, IMI, PER, NMC-A, SFO, SFC, BIC, IBC</td>
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<tr>
<td>B</td>
<td>NDM-1, IMP, VIM, GIM, SPM, SIM, DIM, AIM, KHM</td>
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<tr>
<td>C</td>
<td>CMY, ACT, FOX, MOX</td>
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<tr>
<td>D</td>
<td>OXA, PSE, OXA-48</td>
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</table>
New metallo-$\beta$-lactamase (Ambler Class B), shares little with others in the same class

NDM-1 found on plasmid therefore, transferable

Other broad resistance genes carried on plasmid

NDM resistant to all $\beta$-lactams and many other antibiotics
Transferable Carbapenemase genes (on plasmid)

- highly transmissible: Serious Infection Control implications

- Can be shared between different species (Enterobacteriaceae, other gram-negative bacilli)
New Delhi Metallo-beta-lactamase (NDM-1)

- Reports in 2008 of Swedish and UK travelers to Indian subcontinent
- Since then, reports of high endemicity in Indian, Pakistan and Bangladesh hospitals
- NDM-1 genes in sewage and water reservoirs in some Indian cities
  - 51/171 (30%) waste water seepage
  - 2/50 (4%) communal drinking water samples

Walsh et al. The Lancet Infectious Diseases, 2011, 11: 355-62

CRE in UK 2003-2009

Total of 70 isolates in 2009
With 35 NDM
Global Distribution NDM-1

29 countries
First introductions of NDM-1 to Canada

- 76 yo female (E. coli, K. pneumoniae UTI) was hospitalized in India, direct transfer to a BC Hospital early 2010. First BC case. Mulvey et al. 2011. EID 17:103-6.


NDM in Canada: 2012-2013 Several reports on CRE outbreaks

- **Borgia et al.**, Clinical Infectious Diseases
  - 5 K. pneumoniae and E. coli all epi linked in a tertiary care community hospital in Brampton, Ont. No travel history.

- **Chris Lowe et al.**, Infect Control Hosp Epidemiol.
  - Transmission in a Toronto Hospital
  - 2 index cases with NDM1 K. pneumoniae
  - Transmission to 7 patients was identified

  - Outbreak in a Calgary Hospital
  - Index case with hospitalization Hx in India
  - Several MDR GNR organisms
  - Transmission to 5 patients was identified; resulted in death of 1 patient from sepsis
Notes from the Field


Transmission via medical devices
- reviewed cleaning and disinfection process
- no lapse in protocol
NDM and KPC World-Wide

Molton et al., CID 2013
Global Dissemination of KPC

• United States
  - KPC first reported in North Carolina in 2001—subsequent outbreaks and transmission of KPC-producing organisms reported in northeastern U.S
  - KPCs now in 42 states Dominant clone ST258 accounts for 70% of KPC isolates sent to CDC
  - KPC increased from 1.2% in 2001 to 4.2% in 2011
  - 2012, 4.6% of acute-care hospitals reported at least one CPE HAI

• Israel
  - Increased reports of KPC cases started in 2006
  - 8 hospitals and 5 long-term care centers with similar PFGE fingerprints
  - Genetic relation to U.S strains suggested strain exchange

First introductions of KPC to Canada

• 1st report KPC in Ottawa (3 cases), 2008
  – 2 cases had travel history to USA
  – possible transmission
    Goldfarb et al. (2009) JCM 47:1920–1922

• KPC strains and plasmids similar between NYC and Toronto
KPC Outbreaks in Canada

1 case from Toronto in 2008, no travel history

**Outbreak 1**
- ICU 9 cases (3 pneumonia, 1 UTI, 1 SSI)
- E. coli (5), K. oxytoca (2), S. marcescens (2), and C. freundii (1)
- 4 deaths none attributed entirely to infection
  - 2012 Leung et al, Can J Infect Dis Med Micro

**Outbreak 2**
- 16 patients with KPC producing Enterobacter cloacae
- $\text{bla}_{\text{KPC}}$ localized on multiple plasmids in a diverse non-clonal genetic background of E. cloacae
  - 2013 Haraoui, J Clin Micro

Now seeing outbreaks in Montreal

Slide courtesy of Mike Mulvey, NML
First described in Turkey in 2004

Focused around Mediterranean countries

Outbreak of OXA-48 *K. pneumoniae* in France in 2010. 10 ICU patients in 2 months. 5 died.

Found in 2/4 “puddles” sampled in Morocco

Most difficult to detect of the carbapenemases
- Low MICs to carbapenem and cephalosporins
- Under reporting?
5 patients with healthcare outside of Canada
  - Syria, Egypt, St Lucia, Saudi Arabia, Australia and India

No reports of outbreaks in Canada
CPE in Canada: CPHLN Data

- KPC
- NDM
- OXA-48
- SME
- Other

(n=590)

Year

2008 (n=5)
2009 (n=5)
2010 (n=68)
2011 (n=141)
2012 (n=140)
2013 (n=222)

* One isolate contained NDM and OXA
CPE by Region in Canada: CPHLN Data

- West (n=141)
- Central (n=357)
- East (n=6)

* One isolate contained NDM and OXA
Enterobacteriaceae Producing Carbapenemases in Canada (n=324) As of August 31, 2012

- **West (n=65)**
  - 36 NDM
  - 8 KPC
  - 1 OXA-48
  - 20 Other

- **Central (n=255)**
  - 50 NDM
  - 174 KPC
  - 20 OXA-48
  - 11 Other

- **East (n=4)**
  - 3 NDM
  - 0 KPC
  - 0 OXA-48
  - 1 Other

- **North (n=0)**
Treatment Options
Enterobacteriaceae

- Carbapenems
  - e.g. Imipenem, Meropenem, etc
- β-lactams (Ampicillin, Amoxicillin/Clavulanic, Cephalosporins)
- Fluoroquinolones
- Aminoglycosides
- Tetracyclines
- Nitrofurantoin

- Colistin
- Chloramphenicol
- Tigecycline

Kus et al CMAJ 2010
Treatment Options for CPE

- Carbapenems
  - e.g. Imipenem, Meropenem, etc
- β-lactams (Ampicillin, Amoxicillin/Clavulanic, Cephalosporins)
- Fluoroquinolones
- Aminoglycosides
- Tetracyclines
- Nitrofurantoin

- Colistin
- Chloramphenicol
- Tigecycline

Kus et al CMAJ 2010
BC’s Response to this Emerging Pathogen

- Collaboration for Surveillance in BC since 2010
  - BC Public Health Microbiology and Reference Laboratory (PHMRL)
  - BC Association of Medical Microbiologists (BCAMM) and associated labs
  - National Microbiology Laboratory (NML)

- PICNet
  - Carbapenem-resistant Gram-negative Bacilli (CRGNB) Toolkit 2011
Frontline Laboratories

• Patient screening program as appropriate to the patient population and risk factors
  - Returning travelers from endemic regions
  - Patients with healthcare exposures in endemic regions
  - In-hospital contacts to known cases

• Specimen isolate screening methods
  - Follow up all carbapenem intermediate or resistant isolates with additional phenotypic tests (e.g. Etests, ROSCO disc tests, MAST disc tests, etc)
  - Send all potential CPO’s to BCCDC lab
Laboratory surveillance in BC (cont’d)

**BC Public Health Lab**

- Implemented molecular detection tools to confirm suspicious isolates
- Called positive results to submitting lab
  - travel history?
  - infection control interventions
- Repository for all identified isolates in BC
- Regular communications to update BC scenario via LabTrends
  [http://www.bccdc.ca/PHSALaboratories/PublicationsandReports/default.htm](http://www.bccdc.ca/PHSALaboratories/PublicationsandReports/default.htm)
Laboratory surveillance in BC

• Isolates submitted to BC Public Health Lab since Oct 2010 (2008 by collection date)
  • Carbapenem intermediate and resistant isolates

• Multiplex PCR (NML and Hanson et al)
  • CPO
    • KPC, NDM, IMP, VIM, OXA-48, (SME)
  • ESBL
    • SHV, TEM, CTX-M, OXA-1, CMY-2
  • AmpC
    • CMY/MOX, CMY-2/LAT, DHA, ACC, MIR/ACT, FOX
>1000 isolates submitted to BCCDC from 2010 to December 2013 for testing.
### All CPO, 2008-Current*

**N=145**

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<th>Year</th>
<th>IMP (3)</th>
<th>KPC (9)</th>
<th>VIM (11)</th>
<th>SME (24)</th>
<th>OXA-48 (17)</th>
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Carbapenemase Producing Organisms by Species, 2008-Current*

- **Klebsiella pneumoniae**: NDM
- **Escherichia coli**: NDM, KPC
- **Citrobacter freundii**: NDM, KPC
- **Enterobacter spp.**: NDM, KPC
- **Morganella morganii**: NDM, KPC
- **Raoultella planticola**: NDM, KPC
- **Serratia spp.**: VIM
- **Acinetobacter baumannii**: IMP
- **Pseudomonas aeruginosa**: OXA-48, SME

*Note: NDM, KPC, VIM, IMP, OXA-48, SME refer to specific types of carbapenemases.*
Enterobacteriaceae with NDM

- **Klebsiella pneumoniae**
- **Enterobacter spp.**
- **Escherichia coli**
- **Citrobacter freundii**
- **Morganella morganii**

Number of Cases

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Years: 2008-2014
CPE by Health Authority

- FHA
- VCHA
- IHA
- IH
- NHA
- Community

Number of Cases

- NDM
- KPC
- VIM
- OXA-48
NDM+ Cases with Travel History

Cases with K. pneumoniae

Cases with Enterobacter

Cases with E.coli, Citrobacter and Acinetobacter

- K. pneumoniae and Enterobacter
  - Combination of nosocomial transmission and travel related
- E.coli, Citrobacter and Acinetobacter
  - Mostly travel related

From 2008-Sept 2013
1) NDM: antibiogram comparisons

• Can the comparison of isolate antibiograms be predictive of “clonality”
2) NDM: genotype comparison

- Can the presence of other resistance genes detected by PCR predictive of “clonality”?

<table>
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<th>KPC</th>
<th>NDM</th>
<th>IMP</th>
<th>VIM</th>
<th>SHV</th>
<th>TEM</th>
<th>CTX-M</th>
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PFGE of Enterobacter cloacae

PFGE-XbaI

2008 2009 2010 2011 2012 2013 2014

Travel
**Enterobacter cloacae** genotype predicts clonality
PFGE of *K. pneumoniae*

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## Plasmid-mediated transmission

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B.C. steps up battle with ‘nightmare bacteria’ cluster

WENDY STUECK
VANCOUVER — The Globe and Mail
Published Thursday, Jan. 23 2014, 9:00 AM EST
Last updated Friday, Jan. 24 2014, 9:31 PM EST
How are these organisms transmitted?

1. Patient-to-patient
2. Shared Health Care equipment
3. Environmental Contact (environmental reservoirs)
4. Health care workers (Primarily hands)
How to prevent spread

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

Screening, Testing and Surveillance for Antibiotic-Resistant Organisms (AROs)

In All Health Care Settings

Guidance for Control of Carbapenem-resistant Enterobacteriaceae (CRE)

2012 CRE Toolkit

Management of Carbapenem Resistant Gram-Negative Bacilli (CRGNB)

Provincial Infectious Diseases Advisory Committee (PIDAC)
### Risk factors for Colonization and Infection with CPE

#### Risk factors for acquisition of CPE
- prolonged hospitalization
- Poor functional status
- ICU stay
- invasive devices
- Immunosuppression
- multiple antibiotic agents

#### Risk factors for infection once colonized with CPE
- Previous invasive procedure
- Diabetes mellitus
- Solid organ tumor
- Tracheostomy
- Urinary catheter
- Prior exposure to antipseudomonal penicillin

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If colonized with CPE, 9-47% of patients may develop infection
CPE Measures Implemented at Affected Units

- **Screening/Active surveillance**
  - On admission to Unit
  - Weekly point prevalence
  - All contacts of suspect or confirmed cases, at 0, 7 and 21 days

- **Precautions**
  - Private room and staff cohorting and dedicated equipment

- **Cohorting of patients and staff**
  - “CPE” nursing assignments & dedicated ward
  - Hand hygiene & PPE (goal: 100%)
  - Weekly audits

- **Antimicrobial stewardship**
CPE Measures Implemented at Affected Units (2)

- Avoid discarding any bodily fluids in sinks
- Cleaning
  - Enhanced cleaning including daily 2\textsuperscript{nd} clean of high touch surfaces in affected rooms/units
  - Use hydrogen peroxide
  - Terminal clean on discharge of colonized patients:
    - Discard all supplies, terminal clean, audit of clean
- Daily CHG baths for all colonized patients.
NDM-positive Isolates from Location X in FHA facility 2013

By Location

- Other
- Location X

By Specimen Type

- Screen
- Clinical

Courtesy of FHA
Enterobacteriaceae with NDM in 2013 (Total=52)

Enhanced Screening

Month

Jan  2
Feb  1
Mar  2
Apr  4
May  4
Jun  2
Jul  5
Aug  9
Sep  4
Oct  7
Nov  9
Dec  7

Number of Cases
Infection Control Processes “in the works”

• Region-wide screening for all admitted patients
  – Question: “Have you been hospitalized or had renal dialysis outside of Canada anytime in the previous 6 months?”
  – If yes: patient will have rectal screen for CPE

• Flagging of contacts who leave hospital before 21 days of CRE screening for screening on re-admission
FHA CPE Activity

• No new cases since mid-January

• Increase specimen volume for the lab
Next Steps and Challenges

• Better and faster testing
  – Develop Real-time PCR method for screening specimens directly

• Maintain aggressive infection control state & CPE alerts between facilities

• Continued Provincial level surveillance with infection control data
  – Collaboration with PICNet

• Further explore genomic characteristics of BC strains and transmission behaviour
  – Whole Genome Sequencing
Summary

• CPE are an emerging pathogen with global spread, now in Canada
• CPE can spread within institutions
• The most vulnerable patients are the most at risk to become colonized and infected
• Treatment of infections is complex
• Control of spread requires full compliance with precautions and antibiotic stewardship
Summary- BC specific

- CPE present in BC. Most commonly NDM and OXA-48
  - Most are identified in hospital setting
- CPE initially introduced to BC facilities from returning travelers to endemic:
  Evidence of nosocomial transmission in BC. Mostly due to NDM+ K. pneumoniae and Enterobacter cloacae
- Characterization of BC strains suggests clonal nature of Enterobacter cloacae spread, but also plasmid-mediated for K. pneumoniae.
- Use of “genotypic” patterns predictive of clonality for Enterobacter cloacae, but not for K. pneumoniae
- Clusters of CPE cases in facilities responding to enhanced screening and infection control interventions
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  Dr. Manal Tadros

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  Dr. Michael Mulvey
Thank you!
Age Distribution for CPE

<table>
<thead>
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<th>Age Group (years)</th>
<th>Number of Cases</th>
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<td>90-99</td>
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Identified Organisms Harbouring NDM-1

- Achromobacter spp
- Aeromonas caviae
- Acinetobacter baumannii
- Kingella denitrificans
- Pseudomonas aeruginosa, P. putida, P. pseudoalcaligenes, P. oryzihabitans
- Stenotrophomonas maltophilia
- Sutonella indologenes
- Vibrio cholerae
- Shigella boydii

Courtesy of Mike Mulvey, NML