CPE Epidemiology in Ontario

Gary Garber MD FRCP FACP FIDSA
September 21 2018
Kingston Ontario
Objectives

• To show the trends of CPE in Ontario
• To define the changes in reporting of CPE
• Future directions in monitoring of CPE
• To identify the importance of linking IPAC to Antimicrobial stewardship
CPE – What is it?

- **Carbapenems**: A class of broad spectrum antibiotics that are used for treating infection caused by resistant bacteria (e.g., ertapenem, meropenem, imipenem, doripenem)

- **Carbapenemase Genes**: Genes, made up of DNA, that instruct the bacteria to make protein or enzyme called carbapenemase (genes: KPC, NDM, OXA, VIM, etc.)

- **Carbapenemase**: Enzymes that break down most antibiotics including carbapenems

- **Enterobacteriaceae**: A large family of bacteria present normally (part of gut flora) or pathogenically in the human intestinal tract (e.g., E.coli, Enterobacter, Klebsiella, etc.)
Acronyms: CPO, CPE, CRE, CRO

- C ➔ Carbapenems (antibiotics)
- R ➔ Resistant
- P ➔ Producing (carbapenemase enzyme)
- O ➔ Organisms
- E ➔ Enterobacteriaceae

- CPE is most worrisome – with ~ 50% mortality (infections)
Resistant Bacteria-CPE

- These bacteria have resistance against our most potent antimicrobials, the Carbapenems, and usually also resistant to the B-lactams and Quinolones
- Patients die of serious infections with CPE due to lack of effective therapy
- Rates of CPE are rising in many settings
- NDM-1, outbreaks in NYC and Israel, and more recently across Canada
How is CPE Spread?

- Most with CPE are colonized in the lower GI tract
- Direct contact: Unwashed hands
- Indirect Contact: Contaminated equipment and surfaces including sinks, shower drains, and endoscopes
- Infection: Enters at specific site and causes symptoms, e.g., pneumonia and UTI
CPE

• Most isolates are from patients screened for colonization
• Most infections have been urinary track infections
• Majority of patients have either visited SE Asia or India subcontinent
• Associated with medical care overseas
• Some cases source is unknown
• Possible nosocomial spread
CPE in Canada: CPHLN Data

<table>
<thead>
<tr>
<th>Year</th>
<th>KPC</th>
<th>NDM</th>
<th>OXA-48</th>
<th>SME</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>2008 (n=5)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2009 (n=5)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2010 (n=69)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2011 (n=146)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2012 (n=146)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2013 (n=219)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Total: (n=590)
The bar chart shows the number of isolates by region and year. The total number of isolates is 590. The breakdown is as follows:

- **West** (n=174):
  - 2008: 5
  - 2009: 5
  - 2010: 3
  - 2011: 2
  - 2012: 1
  - 2013: 1

- **Central** (n=409):
  - 2008: 1
  - 2009: 1
  - 2010: 5
  - 2011: 10
  - 2012: 20
  - 2013: 30

- **East** (n=7):
  - 2012: 1
  - 2013: 1

The chart indicates a significant increase in isolates in the Central region, particularly in the years 2010, 2011, and 2012.
Total Number of Submitted Isolates Received by the CPE Surveillance Program, 2012–2016.
CPE is a growing problem in Ontario?

Incidence of CPE in Ontario

2016 Report

2017 Report

*Note: Number of CPE positive isolates submitted to PHOL for confirmatory testing from unique patients
Better Ontario Data in 2018

- CPE is added to the reportable disease list
- To examine the descriptive epidemiology of reported CPE cases since May 2018
CPE is now reportable

Effective May 1, 2018:

• CPE colonization and infection are now included in the regulations for reporting diseases of public health significance (DOPHS) and reportable to the local public health unit

• First isolate only

• All confirmed cases of CPE require investigation to determine if nosocomial transmission of CPE has occurred and to identify the source of transmission
Methods

• Confirmed CPE cases with specimen collection dates between May 1\textsuperscript{st} 2018 & Aug 31\textsuperscript{st} 2018
• Data extracted Sept 6\textsuperscript{th} 2018 from iPHIS
• iPHIS is a dynamic disease reporting system which allows ongoing updates to data previously entered. As a result, data extracted from iPHIS represents a snapshot at the time of extraction and may differ from previous or subsequent reports.
Ontario Reports Since May 1, 2018

- 106 cases reported in 101 patients
- 53% male
- 58% age 65+
- 72% identified on hospital admission
- 16% associated with reporting facility
- Most (38%) NDM E.coli
- 60% colonization
- 51% rectal swab; 36% urine

Source: Ontario Ministry of Health and Long-Term Care, integrated Public Health Information System (iPHIS) database, extracted by Public Health Ontario [2018/09/06].
Number of reported CPE cases by specimen type
May 2018 to Aug 2018

<table>
<thead>
<tr>
<th>Specimen type</th>
<th>Number of cases (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Swab</td>
<td>54 (51)</td>
</tr>
<tr>
<td>Urine</td>
<td>38 (36)</td>
</tr>
<tr>
<td>Blood</td>
<td>6 (6)</td>
</tr>
<tr>
<td>Other Specimen</td>
<td>5 (5)</td>
</tr>
<tr>
<td>Sputum</td>
<td>3 (3)</td>
</tr>
<tr>
<td>Total</td>
<td>106</td>
</tr>
</tbody>
</table>

Source: Ontario Ministry of Health and Long-Term Care, integrated Public Health Information System (iPHIS) database, extracted by Public Health Ontario [2018/09/06].
## Risk Factors for Reported CPE Cases
### May 2018 to Aug 2018, Ontario

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic illness</td>
<td>88</td>
</tr>
<tr>
<td>Hospitalization in Canada in last 12 months</td>
<td>69</td>
</tr>
<tr>
<td>Travel outside Canada in last 12 months</td>
<td>58</td>
</tr>
<tr>
<td>Other medical risk factors</td>
<td>50</td>
</tr>
<tr>
<td>Previous CPE colonization</td>
<td>40</td>
</tr>
<tr>
<td>Hospitalization outside of Canada in last 12 months</td>
<td>37</td>
</tr>
<tr>
<td>ICU admission in Canada in last 12 months</td>
<td>32</td>
</tr>
<tr>
<td>Medical/surgical procedure outside of Canada in last 12 months</td>
<td>27</td>
</tr>
<tr>
<td>Endoscopic procedure in Canada in last 12 months</td>
<td>20</td>
</tr>
<tr>
<td>Other behavioural risk factors</td>
<td>14</td>
</tr>
<tr>
<td>Known contact with confirmed case in last 12 months</td>
<td>3</td>
</tr>
<tr>
<td>Medical/surgical procedure in Canada in last 12 months – excluding endoscopic</td>
<td>0</td>
</tr>
</tbody>
</table>

Source: Ontario Ministry of Health and Long-Term Care, integrated Public Health Information System (iPHIS) database, extracted by Public Health Ontario [2018/09/06].
Proportion of Reported CPE cases by Diagnosing Health Unit
May 2018 to August 2018, Ontario

Source: Ontario Ministry of Health and Long-Term Care, integrated Public Health Information System (iPHIS) database, extracted by Public Health Ontario [2018/09/06].
Prevalence:
Percentage of Ontario CPE Isolates in Peel LHINs (CW & MH) by year of report

- 28% in 2008-2012
- 35% in 2013
- 43% in 2014
- 44% in 2015
- 50% in 2016
- 55.7% in 2017

Of 276 positive isolates

Peel Data: Disease Status – from May 1, 2018

- Colonized: 53%
- Infected: 44%
- Unspecified: 3%

The data shows a significant proportion of the population is colonized with the disease.
Number of reported CPE cases by status
May 2018 to August 2018, Ontario

Source: Ontario Ministry of Health and Long-Term Care, integrated Public Health Information System (iPHIS) database, extracted by Public Health Ontario [2018/09/06].
## Carbapenemases identified in Reported CPE Cases by Aetiologic Agent

<table>
<thead>
<tr>
<th>Aetiologic Agent*</th>
<th>GES</th>
<th>KPC</th>
<th>NDM</th>
<th>GES</th>
<th>NDM/KPC</th>
<th>NDM/OXA-48</th>
<th>OXA-48</th>
<th>SME</th>
<th>VIM</th>
<th>VIM/KPC</th>
<th>OTHER</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESCHERICHIA COLI</td>
<td>0</td>
<td>4</td>
<td>17</td>
<td>1</td>
<td>1</td>
<td>3</td>
<td>15</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>2</td>
<td>44</td>
</tr>
<tr>
<td>KLEBSIELLA PNEUMONIAE</td>
<td>0</td>
<td>4</td>
<td>10</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>11</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>26</td>
</tr>
<tr>
<td>ENTEROBACTER CLOACAE</td>
<td>0</td>
<td>0</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>8</td>
</tr>
<tr>
<td>CPE OTHER</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>KLEBSIELLA OXYTOCA</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>SERRATIA MARCESCENS</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>CITROBACTER FREUNDII</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>CITROBACTER UNSPECIFIED</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>ENTEROBACTER UNSPECIFIED</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>PROTEUS MIRABILIS</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>1</td>
<td>11</td>
<td>34</td>
<td>1</td>
<td>1</td>
<td>4</td>
<td>26</td>
<td>2</td>
<td>6</td>
<td>1</td>
<td>3</td>
<td>90</td>
</tr>
</tbody>
</table>

* Carbapenemases in 16 cases was not reported

Source: Ontario Ministry of Health and Long-Term Care, integrated Public Health Information System (iPHIS) database, extracted by Public Health Ontario [2018/09/06].
Health Care Exposure History of Reported CPE cases
May 2018 to Aug 2018, Ontario

<table>
<thead>
<tr>
<th>Health Care Exposure history</th>
<th>Yes</th>
<th>No</th>
<th>Total (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Was this client admitted to a hospital at the time of CPE diagnosis?</td>
<td>36</td>
<td>14</td>
<td>50 (72)</td>
</tr>
<tr>
<td>Was this client a resident of a long-term care facility at the time of CPE diagnosis?</td>
<td>0</td>
<td>53</td>
<td>53 (0)</td>
</tr>
<tr>
<td>Is there any evidence that this case was associated with the reporting facility?</td>
<td>7</td>
<td>38</td>
<td>45 (16)</td>
</tr>
</tbody>
</table>

Source: Ontario Ministry of Health and Long-Term Care, integrated Public Health Information System (iPHIS) database, extracted by Public Health Ontario [2018/09/06].
Questions

• What is the best approach for counting patients with multiple enzymes diagnosed at different time points?
• Any suggestions to improve capturing risk factors consistently?
• We also need Carbapenem utilization data to define drivers of resistance.
Protection against CPE

• Suggest you don’t get your kidney transplant in India

• The bacteria colonize the GI track so appropriate isolation and screening, proper hand hygiene and environmental cleaning should prevent spread

• Screening policies are not routinely followed so “at risk” patients are not identified

• Unfortunately our hand hygiene compliance and environmental cleaning are not rigorous enough to do the job
“AMR...is a slow-motion tsunami. It is a global crisis that must be managed with utmost urgency”.

AMR is the “greatest and most urgent global risk”.

“AMR is a serious and growing public health threat”
“We’re by no means at an antimicrobial apocalypse. But it’s kind of like global warming. It’s not an immediate catastrophe, but it could become one if we don’t do something soon.”
- Nick Daneman, 2014

Can we Stop the Tsunami?
Antimicrobial Resistance

Figure from: The review on antimicrobial resistance, Tackling drug-resistant infections globally: Final report and recommendations; May 2016. https://amr-review.org/
MCR-1 ; Colistin Resistance

• A plasmid that contains the resistance complex
• The plasmid can pass these resistance genes to other organisms
• The “mobile” plasmid, makes it scary as it can pass easily to “common” organisms. The complex resistance is no longer a rare hospital organism but can be seen widely.
• Found in animal excrement, then in food supply and finally in patients
• Large plasmids often inhibit growth under “normal conditions
Ottawa River: 2017
Ottawa 2017:
How can we control emerging multidrug resistance?

• Don’t let the resistant organisms predominate

• Don’t let the organisms spread
How do we Stop the Spread of Resistance?

“sand bags”

• Prevent the passage of the organism from person to person
  1. Sanitation
  2. Hand hygiene
  3. Infection Control principles and practice
How do we Stop the Spread of Resistance?

“stop the rain”

• Don’t enable the organism to grow:
  1. Restrict the antibiotic environment which gives the organism its survival advantage
  2. Use effective antimicrobial which evades the resistance

  Appropriate use of antibiotics....Antimicrobial Stewardship
Why is antimicrobial utilization important?

• Resistance is natural
• Some bacteria are inherently resistant to some classes of antibiotics
• Many mechanisms of resistance
• Some are inducible
• Some are constitutive
• Some are transferrable
Why is antimicrobial utilization important?

• Bacteria do NOT develop resistance
• Bacteria spontaneously mutate (1/10^5).
• Survival of the fittest; driven by the environment
• Antibiotics act as the environmental stimulus, the selective pressure.
• Selection is of the “fittest”
• In the presence of an antibiotic, a resistance gene will confer a selective advantage
Antimicrobial Use is a Driver of AMR

- Antimicrobial use is linked to antimicrobial resistance
  - Patient
  - Population

- Antimicrobial drugs are unique as they are the only pharmaceutical agents that have “transmissible loss of efficacy over time”
Does prescribing make a difference in preventing resistance?

- Is resistance inevitable?
- Is resistance futile?
- Is the problem a knowledge gap? An education gap?
- Is prescribing a behavior? Based on pattern recognition
- What are the influencers to effect change?
Does prescribing make a difference in preventing resistance?

- Remove the selective pressure, you then remove the survival advantage of the organism.
- Over time, the resistance patterns will change.
Impact of Changing the Choice of Antibiotics

• Finland...’90...macrolides for Group A streptococcus

• Restrict the use of 3\textsuperscript{rd} generation cephalosporins (ceftazidime) reduced ESBL’s

• Rotate antibiotic classes...ICUs
  -cephalosporin, B-lactams (PiP/Tazo), carbapenem, quinolone
Antimicrobial Stewardship is Needed in All Sectors

20% Humans

7% Hospital

93% Community

80% Animals

Reducing the selective antimicrobial pressure

- Reducing use of antimicrobials in animal feed
- Reducing the non-prescription use of antimicrobials
- Reducing the industrial waste of antimicrobial manufacturing
- Improving sewage management to reduce environmental spread of resistant organisms
- Antibiotic impact on an individual patient “micro-environment” vs amplified impact on a community
Large variability in prescribing practice

• 10 fold difference in antibiotic prescribing among nursing homes

• Some LHINs have more antibiotic prescribing per population

• Variability in physician prescribing, number, duration and type of antimicrobial and with similar patient profiles
The Ontario Program To Improve AntiMicrobial USE (OPTIMISE)

- 90% of antibiotics used in the community
- 8.3 Million Rx
  - 621/1000 pop.
- 80% by MDs
  - 25% of Rx by 2% of MDs
Later-career Physicians Prescribe more Prolonged Courses of Antibiotics among Outpatients: A Cohort Study of 10,616 Family Physicians in Ontario, Canada

Cesar Fernandez-Lazaro, PhD, Pharm. D., MPH.
Authors:
Authors

My Thanks to Camille Achonu, Brad Langford, Kevin Schwartz, Madeleine Ashford and Cesar

For their slides and input

Questions??????