CRE Laboratory Detection & Recap of ARO Consensus Conference

SASKPIC CONFERENCE
SEPTEMBER 26TH, 2014

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Outline

- CRE Laboratory Detection
  - What is recommended?
  - Why is this a challenge for labs?
  - What are the implications for infection control?

- Update of ARO Consensus Conference
  - Highlights of Consensus Statement
  - Highlights of Discussions
CRE Introduction

**What are we talking about?**
- “Carbapenem Resistant Enterobacteriaceae”
- “Carbapenemase Producing Organisms”
- Gram negative bacteria which have acquired the ability to produce an enzyme that inactivates carbapenem antibiotics
- E.g. KPC, NDM, OXA-48, SME
CRE Introduction

Why do we care?
- Carbapenems are currently our ‘last line of defense’ for many infections
- We are now facing multidrug resistant bacteria without ANY therapeutic options
- Genes encoding carbapenemase enzymes are carried on mobile plasmids
CPE in Canada: CPHLN Data

Number of Isolates

Year

<table>
<thead>
<tr>
<th>Year</th>
<th>Number of Isolates</th>
<th>KPC</th>
<th>NDM</th>
<th>OXA-48</th>
<th>SME</th>
<th>Other</th>
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<tbody>
<tr>
<td>2008 (n=5)</td>
<td>5</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>2009 (n=5)</td>
<td>5</td>
<td>1</td>
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<td>1</td>
<td>2</td>
<td>1</td>
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<tr>
<td>2010 (n=69)</td>
<td>69</td>
<td>16</td>
<td>18</td>
<td>16</td>
<td>5</td>
<td>1</td>
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<td>2011 (n=143)</td>
<td>143</td>
<td>53</td>
<td>34</td>
<td>34</td>
<td>19</td>
<td>9</td>
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<tr>
<td>2012 (n=150)</td>
<td>150</td>
<td>58</td>
<td>40</td>
<td>40</td>
<td>25</td>
<td>7</td>
</tr>
<tr>
<td>2013 (n=205)</td>
<td>205</td>
<td>89</td>
<td>80</td>
<td>80</td>
<td>40</td>
<td>13</td>
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<tr>
<td>2014 (6 months) (n=173)</td>
<td>173</td>
<td>80</td>
<td>60</td>
<td>60</td>
<td>30</td>
<td>8</td>
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</tbody>
</table>

(n=750)*

*One NDM/OXA-48 (2013) and one VIM/KPC (2013) NOT included

Courtesy of: Mike Mulvey (NML), Canadian Public Health Laboratory Network
Tomorrow’s Antibiotics: The Drug Pipeline

The number of new antibiotics developed and approved has steadily decreased in the past three decades, leaving fewer options to treat resistant bacteria.

Aspergillomarasmine A overcomes metallo-β-lactamase antibiotic resistance

CDC, Antibiotic Resistance Threats 2013
Screening and Detection

- Detection of Clinical Isolates:
  - Routine patient samples are submitted for culture
  - An organism is identified as a pathogen
  - Antimicrobial susceptibility testing is performed
  - Lab recognizes potential CPO phenotype
  - Additional testing +/- confirmatory testing

- Screening for Asymptomatic Carriage:
  - Rectal swab/stool sample submitted
  - Lab looks for organisms with CPO phenotype
  - Additional testing +/- confirmatory testing
What is recommended?

- CDC – HICPAC 2009

  - “Clinical microbiology laboratories should follow CLSI guidelines for susceptibility testing and establish a protocol for detection of carbapenemase production (e.g. modified Hodge test).”

  - “Clinical microbiology laboratories should establish systems to ensure prompt notification of infection prevention staff of all Enterobacteriaceae isolates that are nonsusceptible to carbapenems...”

  - Active surveillance and/or point prevalence surveys are recommended based on prevalence.
What is recommended?

- **CDC 2012**
  - “Screen patients with epidemiologic links to unrecognized CRE colonized or infected patients and/or conduct point prevalence surveys of units containing unrecognized CRE patients”
  - In Facilities with CRE transmission: “Screen high-risk patients at admission or at admission and periodically during their facility stay for CRE. Preemptive contact precautions can be used while results of admission surveillance testing are pending”
  - In Facilities without CRE: “Active surveillance testing and preemptive Contact Precautions to [...]: a) patients admitted from LTC or other facilities with large reservoirs of CRE patients, b) patients with risk factors including open wounds, indwelling devices, antimicrobial usage.”
What is recommended?

- International Working Group, WHO 2013

  “The strategy for screening for CPE – prevalent point cultures, surveillance of related CPE cases, or active surveillance by sending rectal swabs for culture – will depend upon the distinct epidemiological situation of the facility.”
What is recommended?

- PHAC 2010
  - “Ensure that the healthcare laboratory is utilizing appropriate laboratory methods for detection of CRGNB ...”
  - “[If there is evidence of transmission] strongly consider active surveillance culture laboratory testing of other patients...”
  - “Laboratory testing for asymptomatic carriage of CRGNB is not routinely recommended.”
What is recommended?

- PIDAC 2013
  - “...admission screening and pre-emptive Contact Precautions are indicated for individuals with risk factors for CPE. Patients who have received healthcare outside of the country or who are known contact of CPE should be screened.”

  - “Testing bacteria for the presence of carbapenemases is challenging.”
So why is it so challenging?

**Carbapenemase Production ≠ Resistance to Carbapenems**

(necessarily)

**Resistance to Carbapenems ≠ Carbapenemase Production**

(necessarily)
Classic Diagnostic Conundrum

- Set threshold for suspicion very low → Work up of ‘false positive’ growth overwhelming

- Set threshold for suspicion too high → Miss cases of carbapenemase producers
Breakpoints in Brief

- **Minimum Inhibitory Concentration (MIC)**
  - “the lowest concentration of an antibiotic that will inhibit the growth of an organism after overnight incubation”

- **Breakpoints**
  - “interpretation of MIC values for specific drug/bug combinations, meant to assist in the prediction of in vivo activity”
Breakpoints in Brief

- **What Breakpoints *are***
  - Set by international organizations through lengthy, complicated (often controversial) processes. E.g. CLSI, FDA, EUCAST
  - Take into account drug characteristics (pharmacokinetics/dynamics, absorption/distribution, protein binding, excretion, metabolism) AND bacterial characteristics (intrinsic resistance, wildtype phenotypes, resistance mechanisms) AND some patient characteristics (site, penetration, clinical evidence)

- **What Breakpoints *are not***
  - A guarantee that an antibiotic will/won’t work in an infection
  - Diagnostic of the type of resistance
### Breakpoints in Brief

**Pre-2010:**

<table>
<thead>
<tr>
<th></th>
<th>OLD</th>
<th>S</th>
<th>I</th>
<th>R</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ertapenem</td>
<td>≤2</td>
<td>4</td>
<td>≥8</td>
<td></td>
</tr>
<tr>
<td>Meropenem</td>
<td>≤4</td>
<td>8</td>
<td>≥16</td>
<td></td>
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</table>

*If I/R look for carbapenemase production, if + flip susceptible results to resistant

**Post-2010:**

<table>
<thead>
<tr>
<th></th>
<th>NEW</th>
<th>S</th>
<th>I</th>
<th>R</th>
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</thead>
<tbody>
<tr>
<td>Ertapenem</td>
<td>≤0.5</td>
<td>1</td>
<td>≥2</td>
<td></td>
</tr>
<tr>
<td>Meropenem</td>
<td>≤1</td>
<td>2</td>
<td>≥4</td>
<td></td>
</tr>
</tbody>
</table>

*Meant to be reported as is, without confirmation of mechanism of resistance

**What breakpoints do you use?**

- Many labs are not using updated breakpoints because automated instruments follow FDA breakpoints ... which have not changed
When is a CRE not a CRE?

- Not all Enterobacteriaceae that produce carbapenemase enzymes will test resistant to carbapenems
  - E.g. OXA-48 carbapenemase enzymes
    - Imipenem/Meropenem MICs = 0.25 – 1
    - Broad-spectrum cephalosporins MICs = susceptible
  - E.g. expression level of KPC enzyme varies due to differences in the promoter region
When is a CRE not a CRE?

- Resistance to carbapenemems can be due to mechanisms other than carbapenemase production
  - E.g. Coexpression or hyper-production of broad spectrum and ESBL/AmpC enzymes
  - E.g. Porin loss and decreased penetration of antibiotic
Even if we agree on what the screening criteria should be, HOW we screen matters as well.

- More sensitive: broth microdilution, agar dilution
- Less sensitive: disk diffusion, Etests, automated instruments
How does the lab test for CPO?

- #1 – Screening Tests
- #2 – “Tests for Carbapenemase”
- #3 – Confirmatory Testing
Confirmatory Testing

- Molecular detection of carbapenemase genes from isolated bacteria
- Not currently available in Saskatchewan
- Send isolates to National Microbiology Laboratory (NML) in Winnipeg
- Turnaround time 1 – 2 weeks
Screening – PCR

- GeneXpert
- BD Max
- Hyplex
- CheckPoints
- In house panels
- Etc...

**Pros:** rapid, sensitive & specific for targets included

**Cons:** expensive, requires technical expertise, can’t find what it doesn’t look for

...difficult to make a business case for an assay that detects something that we currently don’t have
Alternative Screening Methods

- CDC method
- Chromogenic Agar

Rectal Swab → Grow in presence of carbapenem → Only carbapenem resistant bugs grow!
5mL broth with 10µg meropenem disc

Inoculate rectal swab, incubate overnight

Subculture broth onto MacConkey agar, incubate overnight

Select lactose-fermenting (pink) colonies, subculture to get pure growth, incubate overnight

“Test for Carbapenemase”
Chromogenic Agars

Similar to plates for MRSA, VRE, ESBL screens

Inoculate rectal swab, incubate up to 48 hours

Look for colored colonies

Subculture to get pure growth, incubate overnight

“Test for Carbapenemase”

- E.g. Brilliance CRE, Colorex KPC, ChromID ESBL & ChromID Carba, SuperCarba, in house media
“Test for Carbapenemase”

- [Molecular Testing]
- Modified Hodge Test
- Potentiation Disks
- CarbaNP
- Maldi-Tof
Modified Hodge Test

- Pros: phenotypic, quick-ish
- Cons: mediocre sensitivity, mediocre specificity, difficult to interpret

Photo courtesy of CDC
Indirect Carbapenemase Test

- Pros: phenotypic, quick-ish
- Cons: mediocre sensitivity, mediocre specificity, difficult to interpret

Photo courtesy of Mathers et al. JCM 2013
Potentiation Disks

- C.f. ESBL confirmatory testing

- What inhibits a carbapenemase?
  - NDM-1 metallobetalactamase: EDTA
  - KPC: boronic acid
  - OXA-48: temocillin
  - AmpC: cloxacillin

- Commercial kits: Mast, Rosco
CarbaNP

- Detect activity of carbapenemase

Lyse bacteria & isolate enzymes

Incubate with carbapenem + pH indicator

Carbapenem hydrolyzed → color change!
Detect activity of carbapenemase

- Incubate bacteria with carbapenem
- Run sample on MALDI-TOF
- Analyze peaks: hydrolyzed carbapenem = carbapenemase +!

MALDI-TOF

- Carbapenem
- Site of beta-lactamase action
Why should infection control practitioners care?

- “Ensure that the healthcare laboratory is utilizing appropriate laboratory methods for detection of CRGNB...”

- Are you screening for CREs? Can you screen for CREs if you needed to?

- Lab ability to detect isolates from clinical specimens vs. screening rectal swabs from asymptomatic patients

- How long will it take to get results?

- Should the lab alert you when the 1st screening step is positive? When/if additional tests are positive? Or when confirmatory testing is reported?

- When will you put patients on contact precautions? After initial screening step? If/when additional tests are positive? Only after confirmatory testing is reported?
ARO Consensus Conference

CALGARY, AB
JUNE 2014

SUMMARY & HIGHLIGHTS

HTTP://WWW.IHE.CA/DOCUMENTS/AROS%20-%20CONSENSUS%20STATEMENT%20LONG%20VERSION%20FINAL.PDF
Consensus Conference

- Put on by Institute of Health Economics

- 11 member jury of health professionals, academics, and public representatives

- Considered published studies assembled by the Scientific Committee for the conference; presentations by experts; questions/comments from attendees; private deliberation of jury

- Jury Chair: Dr. Tom Marrie, Scientific Chair: Dr. John Conly

- Funded by the Government of Alberta
Questions

- Overview – What are AROs? What burden do they impose on patients and the health system? Why does control of AROs vary so much?

- Surveillance – Why should we conduct surveillance? What outcomes do we want, and are we achieving them?

- Screening – What is appropriate screening for AROs in various settings? Should we screen for AROs – Pro versus Con.

- What factors can facilitate or hinder effective ARO control in practice? Organizational and cultural factors; Lab capacity.

- Ethical and policy implications – What are the impacts of screening on patients and others? Can screening do harm? What is the economic cost/benefit of screening? What can patients, the public, and health care professionals do to help?

- Research/Evidence – What are the most important gaps in our knowledge? How should we evaluate ARO screening in the future? What are the barriers to effective research and what strategies can address them?
Underlying Guiding Principles

- The problem should be conceived as multi-factorial – there is no single cause or explanation for infection rates and variations among facilities and communities.

- A holistic approach that extends across sectors and includes primary prevention is more likely to yield better and more durable results than treating AROs in isolation in hospitals.

- Simpler and less costly strategies should be pursued before more complex and expensive strategies.

- A higher standard of evidence should be required to support the more costly and time-consuming interventions.

- Policies and practices should be considered provisional and subject to ongoing research and evaluation. AROs and their consequences are a constantly moving target requiring ongoing surveillance.

- It is essential to conduct real-world trials of all interventions to assess their effectiveness.
Overview

1. Develop, implement and evaluate an integrated One Health strategy to minimize the misuse of antibiotics in animals and humans.

- i.e. primary prevention = antimicrobial stewardship
Surveillance – Why should we conduct surveillance? What outcomes do we want, and are we achieving them?

2. Establish comprehensive and standardized information systems for documenting antibiotic use and resistance in humans and animals. Adapt EARS-Net as Canada’s surveillance platform, building on and integrating CNISP, CPARS and other existing surveillance systems to produce timely, relevant and robust surveillance data.

3. Maintain robust standardized surveillance in all health-care facilities for AROs and related infections. Make this information publicly available.

Without good surveillance we’re all just making $%!# up

What is measured, improves
Key Features

- Laboratory-based reporting underpins the system, but should be supplemented as required with additional data.

- Sufficient capacity for data capture, storage and analysis at the local/regional, provincial/territorial and federal levels.

- Timely, mandatory electronic reporting of AROs to public health and all other stakeholders.
• Horizontal vs. Vertical Infection Control
<table>
<thead>
<tr>
<th><strong>Goal</strong></th>
<th><strong>Reduce infections due to specific pathogen(s) (pathogen based)</strong></th>
<th><strong>Reduce all infections (population based)</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Application</strong></td>
<td>Selective or universal</td>
<td>Generally universal</td>
</tr>
<tr>
<td><strong>Interventions</strong></td>
<td>Unipotent</td>
<td>Multipotent</td>
</tr>
<tr>
<td><strong>Resource Utilization/Opportunity Cost</strong></td>
<td>Typically high</td>
<td>Lower</td>
</tr>
<tr>
<td><strong>Philosophy</strong></td>
<td>Exceptionalism</td>
<td>Utilitarianism</td>
</tr>
<tr>
<td><strong>Values Favored</strong></td>
<td>Hospital, infection prevention experts, advocates</td>
<td>Patient</td>
</tr>
<tr>
<td><strong>Temporal orientation</strong></td>
<td>Present</td>
<td>Present &amp; Future</td>
</tr>
<tr>
<td><strong>Examples</strong></td>
<td>ARO active detection &amp; isolation</td>
<td>Hand hygiene, BBTE Chlorhexidine bathing Care bundles Environmental hygiene</td>
</tr>
</tbody>
</table>
Vertical Infection Control

Horizontal Infection Control

Antimicrobial Stewardship, Primary Prevention
• Horizontal vs. Vertical Infection Control

Major infection prevention strategies

4. Do not conduct universal screening for AROs.
5. Pursue relentlessly and fully resource hand hygiene, environmental cleaning, antimicrobial stewardship and routine practices in hospitals.
6. Include a strong evaluation program with process and outcome measures.
7. Ensure consistent application of infection prevention and control practices province-wide.
8. Continue and/or implement targeted screening programs of high-risk populations at admission and at intervals during their hospital stay, based on local epidemiology.
9. Decolonize for AROs on a case by case basis only, after considering current evidence and with infectious disease/medical expert consultation.
Do contact precautions even work??
- YES!
- They decrease patient-to-patient transmission by 30%

‘Screen based on local epidemiology’ – what does that practically mean?
- Risk groups being screened should yield at least 2-3% positives
- UK:
  - >3% to be cost-effective
  - <0.5% +++ cost
- Netherlands:
  - >5% risk → pre-emptive isolation
  - 0.5-5% risk → screen
Organizational and environmental strategies

10. Incorporate evidence based design principles in all new build and significant renovations of hospitals. The majority of beds should be located in single rooms.

11. Optimize health systems by using human factor engineers.

12. Improve and integrate information technology systems that transfer information from point of admission through to the community care providers.

13. Create and embrace a culture of safety starting with senior leadership and governors.

14. Embed accountability for specific goals and targets at all levels of the organization.

15. Remove unnecessary barriers that prevent the local implementation of infection prevention and control practices.

- Engineering controls are far more important at changing human behaviour
- Environmental Factors >> Organizational Factors >> Individual Factors
• What factors can facilitate or hinder effective ARO control in practice? Organizational and cultural factors; Lab capacity.

Laboratory Capacity

16. Involve microbiology laboratory leaders in shaping and designing ARO control programs.
17. Ensure the optimum use of resources by harnessing new automated diagnostic and reporting microbiology laboratory platforms.
18. Enhance antibiotic stewardship by utilizing point of care diagnostics.

Miscellaneous factoid from discussion

• How big of a burden are ARO screens on the lab?
  ○ 15% of overall lab volume
  ○ 25% of acute care lab volume
  ○ 2nd largest volume test after urine cultures
Ethical and policy implications – What are the impacts of screening on patients and others? Can screening do harm? What is the economic cost/benefit of screening? What can patients, the public, and health care professionals do to help?

Ethics and patient engagement

19. Develop plain language materials about AROs and infection prevention and control practices in partnership with patients and families.
20. Minimize the potential adverse effects of patient isolation.

Unresolved: do isolation precautions have a negative impact on patients?

Do patients have the right to refuse screening?
The jury feels the most important area of research is “evaluating the effectiveness of ARO detection and control strategies”
That's all Folks!