Carbapenemases from (not) detection to control

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Disclosure

- Achoagen Inc
- Allecra
- AstraZeneca
- Basilea Pharmaceutica LTD
- Biomerieux
- DaVolterra
- Durata
- Merck & Co. Inc.
- Rempex/The medicines company
- Synthezsa
- Valneva
The Carbapenems

- Introduced to clinical practice in the 1980’s
- Broad spectrum agents, highly active against GNR
- Stable to hydrolysis by almost all beta-lactamases including ESBL producers and AmpC producers
  - Until the 2000’s, resistance in enterobacteriaceae extremely rare
- In the 80’s and 90’s used primarily to treat severely ill patients in ICUs
- Wider use in the 2000’s due to increase in resistance to other beta-lactams (mainly due to ESBLs)
Spread of MDR among enterobacteriaceae: Carbapenems are often the only active agents.

Susceptibilities of 1,030 ESBL producing *E. coli* & *Klebsiella* spp., Israel.

**BSAC: ESBL E. coli**

Bacteraemia 2001-2008

Colodner R. DMID 2007
Carbapenem Usage Rise Dramatically


Carbapenem Days of Therapy (000s)

<table>
<thead>
<tr>
<th>Year</th>
<th>Days of Therapy</th>
</tr>
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<tbody>
<tr>
<td>2003</td>
<td>4869</td>
</tr>
<tr>
<td>2004</td>
<td></td>
</tr>
<tr>
<td>2005</td>
<td></td>
</tr>
<tr>
<td>2006</td>
<td></td>
</tr>
<tr>
<td>2007</td>
<td></td>
</tr>
<tr>
<td>2008</td>
<td>9079</td>
</tr>
</tbody>
</table>

86% increase
Carbapenemases

• Diverse beta-lactamases which hydrolyze carbapenems efficiently
  – 10-1000 more efficiently than other beta-lactams
• Acquired by Enterobacteriaceae (CPE), and spread within and between species by mobile genetic elements
• Transmission of carbapenamases genes between Enterobacteriaceae and non-fermenters is rare
• Belong to various classes and families
  – Serin
    • Class A: KPC, GES, SME
    • Class D: OXA 23, 40, 48
  – Zinc (metalo enzymes)
    • IMP, VIM, NDM
Carbapenemase producers are typically XDR organisms

- Carbapenemases often confer resistance to all beta-lactams
  - OXA enzymes do not hydrolyze cephalosporins efficiently
  - Metallo-enzymes do not hydrolyze monobactams efficiently
- Almost always are carried on plasmids and in clones that have multiple other mechanisms of resistance
CRE infections are associated with severe outcomes

<table>
<thead>
<tr>
<th>Variable</th>
<th>S-KP (n = 85)</th>
<th>ESBL-KP (n = 65)</th>
<th>CRKP (n = 42)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>In-hospital mortality (%)</td>
<td>20 (24)</td>
<td>25 (39)</td>
<td>29 (69)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Infection-related mortality (%)</td>
<td>14 (17)</td>
<td>14 (22)</td>
<td>20 (48)</td>
<td>0.001</td>
</tr>
<tr>
<td>LOS after infection, median days (IQR)</td>
<td>9 (16)</td>
<td>16 (34)</td>
<td>18 (22)</td>
<td>0.003</td>
</tr>
<tr>
<td>Total LOS, median days (IQR)</td>
<td>21 (36)</td>
<td>36 (70)</td>
<td>37 (31)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

CRKP, carbapenem-resistant *K. pneumoniae*; ESBL-KP, extended-spectrum beta lactamase-producing *K. pneumoniae*; IQR, interquartile range; LOS, length of stay; SKP, susceptible *K. pneumoniae*.
Explosive outbreaks reported upon admission of a colonized patient

- Admission of an unidentified carrier of KPC Klebsiella and 5 days delay until cohorting led to a difficult to control outbreak, involving 30 patients (6 clinical infections) in 4 wards\(^1\)
- Transfer overseas of a known carrier, but failure to isolate immediately, resulted in 9 additional clinical cases\(^2\)

1 Schechner V. ICAAC/IDSA 2008, paper 3806
2 Morris M. ICAAC/IDSA 2008, paper 1015
Single carrier transfer led to 18 cases; 11 deaths at NIH hospital
First-time CRE (carbapenem-resistant Enterobacteriaceae) isolations, clinical culture, Israeli general hospitals
Natural history of CPE spread

Proportion carbapenem resistant Klebsiella

Year of the outbreak

1st
2nd
3rd

Cyprus 2006-2008
Italy 2009-2011
Israel 2005-2007
Greece 2002-2004

EARSS DATA
Vatopoulus A. Eurosurveillance 2008
In patients admitted from and discharged to home: 50% clear carriage at 3 months. Others, especially in LTFCs, may remain carriers for prolonged periods.
Pivotal role of LTCFs as reservoirs and amplifiers of CPE

Prevalence of carriage in Chicago 10 fold higher in LTAC than in ICUs

Won SY. CID 2011
Lin MY. CID 2013
Measures to prevent the spread of CPE

• Should be tailored to the local epidemiology
  – The stage of the problem
  – Reservoir: who are the patients at risk
  – What is the mode of spread

• Interventions
  – Early detection of carriers
  – Containment
  – Decolonization?
  – Formulary interventions?

• Regional coordination
The local epidemiology

• Should be examined periodically by each hospital and by regional authorities
  – Surveillance of clinical specimens results
  – Screening of high risk patients data
  – Targeted periodic point prevalence studies
  – Investigation of each positive case
• Determine the stage of the outbreak
  – No cases or sporadic cases
  – Ongoing outbreak
  – Established endemicity in healthcare setting (regional/inter-regional spread)
  – Community as a major source of CPE
• Have a preparedness plan

Adapted from: Carmeli Y. CMI 2010, and Grundmann H. Eurosurveillance 2010
Case detection

• Clinical isolates:
  – All *Enterobactriaceae* isolated in a clinical laboratory should be tested for carbapenem susceptibility.
    • Non-susceptibility to ertapenem is a sensitive (but not specific) marker for suspected CPE
  – All suspected CPE should be confirmed in real time
    • At early stages of the outbreak by a reference center
    • If endemicity is established
      – by local lab using validated methodology
      – unusual isolates (phenotype or setting) should be sent to reference center
Case detections-carriers

• Only 1:8 CPE carriers become clinically apparent by clinical cultures, but all carriers may be source of spread

• Hospitalized, high risk populations need to be defined by the local infection control team based on general principal and local epidemiology
  – Patients who were in contact with CPE carrier
  – Patients from LTCFs/other hospital/out of region
  – Hospitalized in endemic/unknown regions
  – Visited recently countries with suspected community spread

• Measures to identify these patients ASAP
  – Screening
  – Pre-emptive isolation?
Risk Factors for Acquisition of CRE Following Close Contact with a Colonized Patient

- 22 CRE screen-positive contacts (cases)
- 43 screen-negative contacts (controls) compared:
  - Contact period of $\geq 7$ days (OR 6.9; $p=0.006$)
  - Debilitated functional status (OR 5.8; $p=0.027$)
  - Age $\geq 80$ years (OR 4.5; $p=0.038$)
  - Fluoroquinolones (OR 21.8; $p=0.004$)
  - Metronidazole (OR 9.0; $p=0.025$)
Screening

• Rectal swabs containing stool.
  – Perirectal swabs have lower yield
• Validated sensitive methodology
• Results should be reported in 24-48h at least as: negative, suspected, or confirmed CPE, in order to not delay infection control activities
• Mechanisms to ensure that all high risk patients were screened should be placed by the infection control team
Culture based and Molecular methods should complement each other

- **Culture based methods**
  - Easily available
  - Processing start soon after specimen receipt
  - Relatively cheap
  - Provides information on phenotype
  - Isolate available for further testing
  - Slow result
  - Requires further testing to confirm CPE

- **Molecular test**
  - Rapid result from start of processing
  - Often more sensitive in detection lower load
  - Provide information on genotype
  - Processing time may be delayed
  - May not detect all carbapenamases
  - Often expensive
Epidemiological investigation after case detection

• Determine the likely site and time of acquisition
  – Examine all likely sites in your institution

• Contact tracing and screening
  – For case detected within 2-3 days in hospital we typically screen 8-10 contacts
  – In high risk units (ICU, BMT): all patients in the unit at the “time at risk” are considered contacts
  – Contacts should be traced wherever they were transferred to, or if d/c on readmission

• In case of positive contact: wider circle of screening, and repeated screening of negative contacts (“incubation”)
Epidemiological investigation of the event

• Lessons to be learned to
  – facilitate early detection of future cases
    • Missed screen: improve identification and confirmation
    • Delayed result: discuss with lab
    • New regional “risk factor”
  – prevent future cases
    • Establish preemptive isolation
    • Failure of isolation

• Regional authorities should be updated to enable regional response
CPE spread in healthcare setting

• CPE are easily spreading from patient to patient in the healthcare environment
• Presumably the healthcare personnel serves as the vector
• Contaminated fomites may play an important role in transmission
• Single source outbreaks of CPE have been rarely reported
## Environmental Contamination by Carbapenem-Resistant Enterobacteriaceae

### Activity % contamination (gowns/gloves)

<table>
<thead>
<tr>
<th>Activity</th>
<th>% contamination</th>
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<tbody>
<tr>
<td>Wound care</td>
<td>36%</td>
</tr>
<tr>
<td>Touching catheter drain</td>
<td>37%</td>
</tr>
<tr>
<td>Touching infusion pump</td>
<td>20%</td>
</tr>
<tr>
<td>Touching bed rail</td>
<td>23%</td>
</tr>
</tbody>
</table>

### Recovery rates of positive samples collected at each of the sampling site (% positive samples)

<table>
<thead>
<tr>
<th>Location</th>
<th>% Positive Samples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pillow</td>
<td>33%</td>
</tr>
<tr>
<td>Crotch</td>
<td>31%</td>
</tr>
<tr>
<td>Legs</td>
<td>23%</td>
</tr>
<tr>
<td>Infusion pump</td>
<td>16%</td>
</tr>
<tr>
<td>Personal bed</td>
<td>14%</td>
</tr>
</tbody>
</table>

### HCW type

- Physician/nurse practitioner: 3.9 (3/78)
- Registered nurse: 16.3 (15/92)
- Other (physical, occupational, or respiratory therapist or patient care technician): 26 (13/50)

Lerner A. JCM 2013
Rock C. ICHE 2014
One hospital’s experience – moving from single room contact isolation to cohorting with dedicated staff

Incidence of KPC-producing *Klebsiella* spp.

Implementation of guidelines

*P*=0.01

Schechener V, ICAAC 2007
TABLE I. Interventions Undertaken to Curtail the Epidemic Spread of Carbapenem-Resistant *Klebsiella pneumoniae* (CRKP)

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Description</th>
<th>Date begun</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention 1</td>
<td>Single-room isolation and contact precautions</td>
<td>March 2006</td>
</tr>
<tr>
<td>Intervention 2</td>
<td>Cohorting of patients and nursing staff, screening of patients in the same room as newly identified carriers of CRKP (“snow ball” active surveillance), and local protocol for continued cohorting of returning patients</td>
<td>March 2007</td>
</tr>
<tr>
<td>Intervention 3</td>
<td>Weekly active surveillance in the intensive care unit</td>
<td>August 2008</td>
</tr>
<tr>
<td>Intervention 4</td>
<td>Active surveillance of patients on admission to the emergency department</td>
<td>March 2009</td>
</tr>
</tbody>
</table>

A

In Incidence:

<table>
<thead>
<tr>
<th>Intervention (period)</th>
<th>No. of cases per 1,000 hospital beds</th>
<th>Mean</th>
<th>Median</th>
<th>Slope</th>
<th>(P^*)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention 1 (Mar 2006–Mar 2007)</td>
<td>8.4</td>
<td>6.45</td>
<td>1.9</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td>Intervention 2 (Apr 2007–Aug 2008)</td>
<td>13.4</td>
<td>11.6</td>
<td>−0.7</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td>Intervention 3 (Sep 2008–Mar 2009)</td>
<td>8.3</td>
<td>7.7</td>
<td>−0.8</td>
<td>.76</td>
<td></td>
</tr>
<tr>
<td>Intervention 4 (Apr 2009–Aug 2010)</td>
<td>4.3</td>
<td>3.8</td>
<td>−0.008</td>
<td>.27</td>
<td></td>
</tr>
</tbody>
</table>
Containment of a Country-wide Outbreak of Carbapenem-Resistant *Klebsiella pneumoniae* in Israeli Hospitals via a Nationally Implemented Intervention

Mitchell J. Schwaber,1 Boaz Lev,2 Avi Israeli,2 Ester Solter,1 Gill Smolian,1 Bina Rubinovitch,3 Itamar Shalit,3 Yehuda Carmeli,1 and the Israel Carbapenem-Resistant Enterobacteriaceae Working Group*  

1National Center for Infection Control, Israel Ministry of Health, Tel Aviv, and 2Israel Ministry of Health, Jerusalem, Israel
Potential Role of Active Surveillance in the Control of a Hospital-Wide Outbreak of Carbapenem-Resistant *Klebsiella pneumoniae* Infection

Debby Ben-David, MD; Yasmin Maor, MD; Nathan Keller, MD; Gili Regev-Yochay, MD; Ilana Tal, MS; Dalit Shachar, RN; Amir Zlotkin, PhD; Gill Smollan, MD; Galia Rahav, MD
Targeted screening for CRE upon admission

2% positivity
Infection control “Bundle”: isolation, cleaning, HCG baths, education, culture on admission

Munoz-Price S. ICHE 2010
8376 (100%) CR-KP surveyed patients (*):

- CR-KP screening on admission to selected wards (n: 3215 patients) (65%)
- Patients screened in contact with CR-KP positive index case (n: 1402 patients) (16.7%)
- Emergency room Flagging System (HRG) (n: 3759 patients) (38.3%)

+ CR-KP 66 patients Colonization rate (2.05%)
+ CR-KP 118 patients Colonization rate (8.4%)
+ CR-KP 249 patients Colonization rate (6.64%)

- Isolation room
- Contact precautions
- Preemptive isolation rooms

Admitted to a cohort ward/pace
N: 433 (5.16%) patients

Nursing Homes, other health care facility

Community

A total of 433/8376 (5.16%) + CR-KP patients

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Borer A. ICHE 2011
## Interventions in 13 large LTCF (2913 beds)

<table>
<thead>
<tr>
<th></th>
<th>2008</th>
<th>2010</th>
<th>2011</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Infection control score</strong></td>
<td>6.7</td>
<td>10.9</td>
<td>14</td>
</tr>
<tr>
<td><strong>Strategies for prevention of</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CRKP</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>cohorting patients</td>
<td>10</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>dedicated medical equipment</td>
<td>12</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>single-use gown</td>
<td>6</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>admissions screening</td>
<td>2</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>contact screening</td>
<td>5</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td><strong>Point prevalence carriage</strong></td>
<td>12.5%</td>
<td>8.5%</td>
<td>7.9%</td>
</tr>
</tbody>
</table>
An Ongoing National Intervention to Contain the Spread of Carbapenem-Resistant Enterobacteriaceae
Communication is essential for successful control

- Within an institution:
  - Between infection control – wards – lab: to ensure that high risk population are screened ASAP, micro-lab is able to process the samples – receive preliminary reports and act upon them
  - Hospital administration
  - Across admissions “flags” of carrier status, or “exposed to be screened”

- Between institutions
  - Reports on outbreaks or endemic institutions
  - History of carriage regarding transferred patients
Community CPE

- Likely prevalent in the Indian subcontinent (NDM)
  - Believed to spread via contaminated water, the fecal-oral route due to poor sanitation and drainage
  - Much work is required to understand where and what can be done, however, without improvement of the infrastructure and sanitation spread will continue

- Situation unclear in the southern Mediterranean basin (OXA-48)
  - Likely spread in the community
  - Epidemiology not well described
Decolonization show temporary effect, risk of emergence of resistance should be further explored.

Saidel-Odes L. ICHE 2012
Formulary interventions/antibiotic stewardship?

**Figure 2. Trends in broad-spectrum antibacterial drug use (in days of therapy [DOTs] per 1000 patient days [PDs]) at 22 US academic health centers from 2002 to 2006.** There is a statistically significant increase in total broad-spectrum antibacterial use. Increases in carbapenem and piperacillin-tazobactam use were statistically significant, as was the decline in aminoglycoside use. There was no significant change in fluoroquinolone or cephalosporin use.

*Arch Intern Med. 2008;168(20):2254-2260*
In multivariate analyses CRE is:
- no correlated with carbapenemase use.
- Moderately correlated (OR 1.8-4.7) with cephalosporins
Summary

• CPE are here to stay
  – Once introduced have the potential for rapid spread within institutions and between institutions

• The pillars of successful prevention are understanding the concurrent epidemiology, and tailoring the local plan:
  – Early reliable detection of carriers
  – Containment
    • in most settings cohorting with dedicated staff
  – Communication
  – Regional coordination

• God is in the details: written protocols, education, ensuring compliance, root cause analysis of failures

• Open questions:
  – Control where spread in the community is common
  – The role of formulary interventions