Rising to the challenge of multidrug-resistant Gram-negative bacteria

Jon Otter, PhD FRCPath
Imperial College Hospitals NHS Trust

Hosted by Prof. Jean-Yves Maillard
Cardiff University, Wales

THE END OF ANTIBIOTICS IS NIGH

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What's the problem?

"CPE are nightmare bacteria."
Dr Tom Frieden, CDC Director

“If we don’t take action, then we may all be back in an almost 19th Century environment where infections kill us as a result of routine operations.”
Dame Sally Davies, Chief Medical Officer

“If we fail to act, we are looking at an almost unthinkable scenario where antibiotics no longer work and we are cast back into the dark ages of medicine where treatable infections and injuries will kill once again.”
David Cameron, Prime Minister, UK

“The rise of antibiotic-resistant bacteria, however, represents a serious threat to public health and the economy.”
Barack Obama, President USA

Rising threat from MDR-GNB

% of all HAI caused by GNRs. % of ICU HAI caused by GNRs.

Non-fermenters
- Acinetobacter baumannii
- Pseudomonas aeruginosa
- Stenotrophomonas maltophilia

Enterobacteriaceae
- Klebsiella pneumoniae
- Escherichia coli
- Enterobacter cloacae

CPE

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**Enterobacteriaceae vs. non-fermenters**

<table>
<thead>
<tr>
<th>Share</th>
<th>Differ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gram stain reaction</td>
<td>Risk factors &amp; at-risk population</td>
</tr>
<tr>
<td>Concerning AMR</td>
<td>Potential for epidemic spread</td>
</tr>
<tr>
<td></td>
<td>Infection profile &amp; mortality</td>
</tr>
<tr>
<td></td>
<td>Prevalence</td>
</tr>
<tr>
<td></td>
<td>Colonisation site &amp; duration</td>
</tr>
<tr>
<td></td>
<td>Transmission routes</td>
</tr>
<tr>
<td></td>
<td>Resistance profile &amp; mechanisms</td>
</tr>
</tbody>
</table>

---

**What’s the problem? Resistance**

![Image of bacteria and antibiotic resistance pattern]

*Courtesy of Pat Cattini*

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**What’s the problem? Mortality**

<table>
<thead>
<tr>
<th>Enterobacteriaceae</th>
<th>Non fermenters</th>
</tr>
</thead>
<tbody>
<tr>
<td>Organism</td>
<td>AmpC / ESBL</td>
</tr>
<tr>
<td>Attributable</td>
<td>Moderate</td>
</tr>
<tr>
<td>mortality</td>
<td></td>
</tr>
</tbody>
</table>


**What’s the problem? Rapid spread**

- Clonal expansion
- Horizontal gene transfer
- GI carriage

Rapid spread

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Acronym minefield

CPE  MDR-GNB  CPC
ESBL  MDR-GNB  CRO
CPE  CPE  CRC
KPC  CRAB

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What are CPE?

Carbapenem-resistant Enterobacteriaceae (CPE) – Enterobacteriaceae that are resistant to carbapenems by any mechanism.

Carbapenemase-producing Enterobacteriaceae (CPE) – Enterobacteriaceae that are resistant to carbapenems by means of an acquired carbapenemase.

When CPE is not CPE

Wild-type

Carbapenemase

ESBL / AmpC + porin loss or true carbapenemase?

Carbapenem MIC

0.5 16

Courtesy of Dr Katie Hopkins, PHE.
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Understanding the enemy

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>CPE¹</th>
<th>CPAB²</th>
<th>MRSA</th>
<th>VRE</th>
<th>C. difficile</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resistance</td>
<td>+++</td>
<td>+++</td>
<td>+</td>
<td>+</td>
<td>+/-</td>
</tr>
<tr>
<td>Resistance genes</td>
<td>Multiple</td>
<td>Multiple</td>
<td>Single</td>
<td>Single</td>
<td>n/a</td>
</tr>
<tr>
<td>Species</td>
<td>Multiple</td>
<td>Single</td>
<td>Single</td>
<td>Single</td>
<td>Single</td>
</tr>
<tr>
<td>HA vs CA</td>
<td>HA &amp; CA</td>
<td>HA (ICU)</td>
<td>HA</td>
<td>HA</td>
<td>HA</td>
</tr>
<tr>
<td>At-risk pts</td>
<td>All</td>
<td>ICU</td>
<td>Unwell</td>
<td>Unwell</td>
<td>Old</td>
</tr>
<tr>
<td>Virulence</td>
<td>+++</td>
<td>+/-</td>
<td>++</td>
<td>+/-</td>
<td>+</td>
</tr>
<tr>
<td>Environment</td>
<td>+/-</td>
<td>+++</td>
<td>+</td>
<td>++</td>
<td>+++</td>
</tr>
</tbody>
</table>

1. Carbapenemase-producing Enterobacteriaceae.
2. Carbapenemase-producing Acinetobacter baumannii.

CPE in the USA

K. pneumoniae / oxytoca
All Enterobacteriaceae

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CPE in the USA
25 community hospitals in Southwestern USA

CPE rate per 100,000 patient days

2008 2012


CPE in LTACs, USA

% CPE carriers

ICU LTAC


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Who’s carrying CPE?

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Location</th>
<th>Setting</th>
<th>n patients</th>
<th>n carriers</th>
<th>% carriers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adler*†</td>
<td>2015</td>
<td>Israel</td>
<td>CPE carriage in post-acute hospitals, 2008</td>
<td>1147</td>
<td>184</td>
<td>16.0</td>
</tr>
<tr>
<td>Mack</td>
<td>2014</td>
<td>London</td>
<td>High-risk inpatients and admissions</td>
<td>2077</td>
<td>7</td>
<td>0.3</td>
</tr>
<tr>
<td>Ra†</td>
<td>2014</td>
<td>East Delhi, India</td>
<td>Outpatients</td>
<td>242</td>
<td>24</td>
<td>9.9</td>
</tr>
<tr>
<td>Zhao*‡</td>
<td>2014</td>
<td>Fujian, China</td>
<td>Stool samples from hospitalized patients</td>
<td>303</td>
<td>20</td>
<td>6.6</td>
</tr>
<tr>
<td>Birgand*‡</td>
<td>2014</td>
<td>Paris, France</td>
<td>Patients repatriated or recently hospitalized in a foreign country</td>
<td>132</td>
<td>9</td>
<td>6.8</td>
</tr>
<tr>
<td>Kim*</td>
<td>2014</td>
<td>Seoul, Korea</td>
<td>ICU admissions</td>
<td>347</td>
<td>1</td>
<td>0.3</td>
</tr>
<tr>
<td>Girlich*‡</td>
<td>2014</td>
<td>Morocco</td>
<td>Hospitalized patients</td>
<td>77</td>
<td>10</td>
<td>13.0</td>
</tr>
<tr>
<td>Lin*‡</td>
<td>2013</td>
<td>Chicago, USA</td>
<td>Long term acute care hospitals</td>
<td>391</td>
<td>119</td>
<td>30.4</td>
</tr>
<tr>
<td>-</td>
<td>2013</td>
<td>–</td>
<td>Short stay hospital ICU</td>
<td>910</td>
<td>30</td>
<td>3.3</td>
</tr>
<tr>
<td>Villar*‡</td>
<td>2013</td>
<td>Buenos Aires, Argentina</td>
<td>Non-hospitalized individuals</td>
<td>164</td>
<td>8</td>
<td>4.9</td>
</tr>
<tr>
<td>Kothari*‡</td>
<td>2013</td>
<td>New Delhi, India</td>
<td>Healthy neonates</td>
<td>75</td>
<td>1</td>
<td>1.3</td>
</tr>
<tr>
<td>Day*</td>
<td>2013</td>
<td>Pakistan</td>
<td>Patients attending a military hospital</td>
<td>175</td>
<td>32</td>
<td>18.3</td>
</tr>
<tr>
<td>Swaminathan*†</td>
<td>2013</td>
<td>New York</td>
<td>All admissions to 7 units, including ICU, of 2 hospitals</td>
<td>5676</td>
<td>306</td>
<td>5.4</td>
</tr>
<tr>
<td>Nüesch-Inderbinen*‡</td>
<td>2013</td>
<td>Zurich, Switzerland</td>
<td>Healthy community residents and outpatients</td>
<td>605</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>Armand-Lefèvre*‡</td>
<td>2013</td>
<td>Paris, France</td>
<td>ICU patients</td>
<td>50</td>
<td>6</td>
<td>12.0</td>
</tr>
<tr>
<td>Wiener-Well*‡</td>
<td>2010</td>
<td>Jerusalem, Israel</td>
<td>Hospitalized patients</td>
<td>298</td>
<td>16</td>
<td>5.4</td>
</tr>
</tbody>
</table>

For refs see: [http://reflectionsipc.com/2014/12/22/whos-harbouring-cpe](http://reflectionsipc.com/2014/12/22/whos-harbouring-cpe)
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Colistin resistance in Italy

Survey of 191 CPE from 21 labs across Italy.

43%

Colistin resistant *K. pneumoniae*.
Range = 10-80% for the 21 labs.

Monaco et al. 2014; Euro Surveill 2014;19 pii=20939.

Emergence of CPE in the UK

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CPE in the UK and US

Evidence-free zone
Guidelines ≠ Policy

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Who do I screen?

**UK PHE CPE Toolkit** screening triggers:

a) an inpatient in a hospital abroad, or
b) an inpatient in a UK hospital which has problems with spread of CPE (if known), or
c) a‘previously’positive case.

Also consider screening admissions to high-risk units such as ICU, and patients who live overseas.

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How do I screen?

- Rectal swab is the best sample
  - Insert no more than 2cm into rectum
  - Twist gently and withdraw
  - Ideally want to see faeces on swab.
- Patient and staff education as to why this is needed in order to overcome taboos
- Alternate specimen is stool sample, but have to wait for the patient to ‘go’

NAAT = nucleic acid amplification techniques
AST = antimicrobial susceptibility testing
MALDI-TOF MS = Matrix-assisted laser desorption /ionization – time of flight mass spectrometry
WGS = whole genome sequencing
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Does screening and isolation work?

<table>
<thead>
<tr>
<th></th>
<th>All MDROs</th>
<th>MRSA</th>
<th>VRE</th>
<th>ESBLs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline trend</td>
<td></td>
<td>↑</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hygiene intervention</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>step-change</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hygiene intervention</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>trend change</td>
<td>↓</td>
<td>↓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Screening step-change</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Screening trend change</td>
<td></td>
<td>↑</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rapid vs. conventional</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>step-change</td>
<td></td>
<td></td>
<td></td>
<td>↑</td>
</tr>
<tr>
<td>Rapid vs. conventional</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>trend-change</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


Hand hygiene

MDR-GNB Toolbox

- Antibiotic stewardship
- Active screening
- Contact precautions
- Cleaning / disinfection
- HCW screening
- Env. screening
- Education
- Note flagging
- Cohorting staff / patients
- Decol.


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Hand hygiene

40%
Median hand hygiene compliance from 95 studies.


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Surface survival

![Graph showing the survival of different bacteria over time.]


Surface survival – strain variation

![Graph showing the survival of different strains of Klebsiella pneumoniae over time.]

K. pneumoniae vs. E. coli

- *K. pneumoniae* seems to be more environmental than *E. coli.*\(^1,2\)
- Surface contamination on five standardized sites surrounding patients with ESBL-producing *Klebsiella* spp. (n=48) or ESBL-producing *E. coli* (n=46).\(^1\)


**Persistent contamination**

- % sites contaminated with *A. baumannii*
- % sites contaminated with MRSA

- 140 samples from 9 rooms after 2xbleach
- 5705 samples from 312 rooms after 4xbleach
- 2680 sites from 134 rooms after HP vapor decon

26.6% of rooms remained contaminated with either MRSA or *A. baumannii* following 4 rounds of bleach disinfection

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Enterobacteriaceae “less environmental”

- Nseir A.baumannii
- Nseir P.aeruginosa
- Nseir ESBL
- Ajao ESBL

Odds ratio


MDR-GNB cleaning & disinfection checklist

- Clean / declutter
- Monitor cleaning process (e.g. fluorescent markers)
- All equipment disinfected before leaving room
- Enhanced daily disinfection using bleach
- Terminal disinfection using bleach or, ideally, H₂O₂ vapor

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Carbapenem use, Europe

ECDC point prevalence survey 2013.
Can we forecast a CPE storm?

- Could we find and implement an "alert" level of carbapenem use?
- The authors claim a stewardship intervention brought the CPE outbreak under control – but also implemented 'case isolation, screening of contacts, barrier nursing and other infection control interventions'.
- Study focussed only on OXA-48 \textit{K. pneumoniae}; what about other Enterobacteriaceae and non-fermenters.


Antimicrobial stewardship – impact

Evaluating impact of 6 month antimicrobial stewardship intervention on an ICU by comparing bacterial resistance for matched 6 month periods either side of intervention.

Hou \textit{et al.} \textit{PLoS ONE} 2014;9:e101447; * = significant difference before vs. after.
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Deisolation?

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Setting</th>
<th>N pts</th>
<th>Organism</th>
<th>Duration of colonization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bird¹</td>
<td>1998</td>
<td>Elderly care facilities, Scotland</td>
<td>38</td>
<td>ESBL K. pneumoniae</td>
<td>Mean 160 days (range 7-548)</td>
</tr>
<tr>
<td>Pacio²</td>
<td>2003</td>
<td>Long term care facility, USA</td>
<td>8</td>
<td>Resistant Gram-negative rods</td>
<td>Median 77 days (range 47-189)</td>
</tr>
<tr>
<td>Zahar³</td>
<td>2010</td>
<td>Paediatric hospital, France</td>
<td>62</td>
<td>ESBL Enterobacteriaceae</td>
<td>Median 132 days (range 65-228)</td>
</tr>
<tr>
<td>O’Fallon⁴</td>
<td>2009</td>
<td>Long term care facility, USA</td>
<td>33</td>
<td>Resistant Gram-negative rods</td>
<td>Median 144 days (range 41–349)</td>
</tr>
<tr>
<td>Zimmerman⁵</td>
<td>2013</td>
<td>Patients discharged from hospital, Israel</td>
<td>97</td>
<td>CRE</td>
<td>Mean 387 days</td>
</tr>
</tbody>
</table>

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‘Selective’ digestive decontamination

20 CRE colonized patients in each arm given gentamicin + polymyxin (SDD arm) or placebo (Control arm)


ANTIBIOTICS = ‘A’ BOMBS

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Decolonisation using faecal microbiota transplantation (FMT)

- 82 year old colonised with CPE.
- Carriage was delaying her admission to a nursing home.
- Single dose of FMT decolonised her at 7 and 14 days.


Chlorhexidine – efficacy

Impact of chlorhexidine gluconate (CHG) daily bathing on skin colonization with KPC-producing K. pneumoniae in 64 long-term acute care patients.

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Chlorhexidine – reduced susceptibility
Proportion of BSI isolates with reduced susceptibility to chlorhexidine on units using chlorhexidine gluconate (CHG) daily bathing (n=28) or not (n=94).


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Which do you consider to be the most important measure to prevent transmission?

Data from around 150 webinar participants, mainly in the US, 2014.

<table>
<thead>
<tr>
<th>Type</th>
<th>n studies</th>
<th>Failure rate</th>
<th>Odds ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bundled intervention</td>
<td>75</td>
<td>28%</td>
<td>1.9</td>
</tr>
<tr>
<td>Single intervention</td>
<td>11</td>
<td>45%</td>
<td></td>
</tr>
</tbody>
</table>

Cataldo et al. ECCMID 2014. 0125.
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What works? Israel


Key questions

- Which interventions work?
- Are they different for Enterobacteriaceae and non-fermenters? (Probably, given their epidemiology.)
- What is the prevalence of CPE?
- How much do we believe a single negative screen? What is the duration of colonisation?
- Do we need rapid molecular diagnostics?
- Are there decolonisation strategies other than (virtually non) 'selective decontamination' using abx?
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Summary

1. MDR-GNB are emerging worldwide and represent a unique threat.
2. CPE in particular combine resistance, virulence and the potential for rapid spread.
3. Prevalence in the US appears to be patchy, but increasing.
4. We do not yet know what is effective in terms of prevention and control, but screening and isolation of carriers seems prudent.
5. Diagnosis can be challenging, and relies on close liaison with the microbiology laboratory.

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Rose George, Author & Journalist

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