Diagnosis of CPE: time to throw away those agar plates?

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Disclosures

- I am employed part-time by Bioquell
- I have research funding from the Guy’s and St. Thomas’ Charity
- I have given paid lectures for 3M and BD
THE END OF ANTIBIOTICS IS NIGH
What’s the problem?

“CRE 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-GNR

% 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*

What’s the problem? Resistance

<table>
<thead>
<tr>
<th>Date</th>
<th>Test Type</th>
<th>Result</th>
<th>Organism</th>
<th>Antibiotics</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 Jun 2014 00:00</td>
<td>BC - Blood culture</td>
<td>AICU - AICU</td>
<td>CNS - Coagulase Negative Staphylococcus</td>
<td>AK, AMP, AUG, CAZ, COL, CP, CPD, CXM, ERT, GEN, MER, TAZ, TGC, TRI</td>
</tr>
<tr>
<td>30 Jun 2014 00:00</td>
<td>ASC - Ascitic fluid</td>
<td>AICU - AICU</td>
<td>GPC - Unidentified Gram positive coccus</td>
<td>AK, AMP, AUG, CAZ, COL, CP, CPD, CXM, ERT, GEN, MER, TAZ, TGC, TRI</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>SE - Staphylococcus epidermidis</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>KP - Klebsiella pneumoniae</td>
<td>AK, AMP, AUG, CAZ, COL, CP, CPD, CXM, ERT, GEN, MER, TAZ, TGC, TRI</td>
</tr>
</tbody>
</table>
What’s the problem? Mortality

<table>
<thead>
<tr>
<th>Organism</th>
<th>Enterobacteriaceae</th>
<th>Non fermenters</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AmpC / ESBL</td>
<td>CPE</td>
</tr>
<tr>
<td>Attributable mortality</td>
<td>Moderate</td>
<td>Massive (&gt;50%)</td>
</tr>
<tr>
<td></td>
<td>A.baumannii</td>
<td>Minimal</td>
</tr>
</tbody>
</table>

What’s the problem? Rapid spread

- Clonal expansion
- Rapid spread
- Horizontal gene transfer
- GI carriage
DANGER MINES
Acronym minefield

- CPE
- MDR-GNR
- CPC
- ESBL
- MDR-GNB
- CRO
- CPE
- CRE
- CRC
- KPC
- CRAB
What are CRE?

*Carbapenem-resistant Enterobacteriaceae (CRE)* – 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 CRE is not CPE

Wild-type

Carbapenemase

ESBL / AmpC + porin loss or true carbapenemase?

Carbapenem MIC

Courtesy of Dr Katie Hopkins, PHE.
Understand the enemy

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>CRE(^1)</th>
<th>CRAB(^2)</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. Carbapenem-resistant Enterobacteriaceae.
2. Carbapenem-resistant *Acinetobacter baumannii*. 
CRE in the USA

CRE in the USA
25 community hospitals in Southwestern USA

CRE in LTACs, USA

Invasive multidrug-resistant *K. pneumoniae*

![Graph showing the percentage of invasive multidrug-resistant *K. pneumoniae* in Greece, Italy, Portugal, and the UK from 2005 to 2013.](image)

- **Greece**
- **Italy**
- **Portugal**
- **UK**

**EARS-Net**

CIDR Centre for Clinical Infection & Diagnostics Research
Emergence of CPE in the UK

PHE ARMRL, 24/01/14
Courtesy of Dr Neil Woodford
CRE in the UK and US
Who do I screen?

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.
You have positive case: now what?

‘Contact precautions’
Single room+glove/gown
Consider staff cohort

Contact tracing
Trigger for screening contacts or whole unit?

Flagging
Patient notes flagged
Receiving unit informed

Education
Staff
Patient / visitor

Cleaning / disinfection
Use bleach or H_2O_2 vapor at discharge

Decolonization?
‘Selective decontamination’ / chlorhexidine bathing?
How do I screen?

Rectal swab

Agar plate

AST

MADLDI-TOF MS

NAAT

WGS

NAAT

NAAT = nucleic acid amplification techniques
AST = antimicrobial susceptibility testing
MALDI-TOF = Matrix-assisted laser desorption/ionization – time of flight mass spectrometry
WGS = whole genome sequencing
Agar plates

**MacConkey**
Selective for all Gram-negative bacteria (including Enterobacteriaceae and non-fermenters)

**Chromogenic Media**
Selective for resistant Enterobacteriaceae only (ESBL or CRE options available); several options
Antimicrobial susceptibility testing (AST)

Quantitative (MIC or breakpoint)
Agar or broth dilution (manual or automated), E-tests

Qualitative (R/I/S)
Disc diffusion; supplemental tests for mechanisms (e.g. ESBL, CRE)
MALDI-TOF, WGS, NAAT (PCR and Array Chips)

**MALDI-TOF**
Rapid and accurate speciation of bacteria from a colony; potential to detect resistance genes

**WGS**
Whole genome sequence; gold standard typing method; costs coming down; can detect abx resistance genes

**PCR**
PCR can be used to detect a single or multiple genes of interest from a pure colony

**Array Chips**
>100 PCRs on a single chip for simultaneous detection of a range of genes and markers
How do I screen?

Rectal swab

Agar plate

AST

MADLDI-TOF MS

WGS

NAAT

NAAT = nucleic acid amplification techniques
AST = antimicrobial susceptibility testing
MALDI-TOF = Matrix-assisted laser desorption/ionization – time of flight mass spectrometry
WGS = whole genome sequencing
NAAT direct from clinical specimens

**PCR**
Rapid real-time PCR kits available to detect resistance genes direct from clinical specimens; point of care tests coming

**Rapid sequencing kits**
Kits available for rapid sequence-based simultaneous detection of common organisms and resistance genes
Before you throw away the agar plates…

Molecular diagnostics are great but:

- but do not deal with changing epidemiology; struggle with target variability;
- are expensive;
- rely on validation of carriage sites;
- do not tell you about phenotypic susceptibility;
- have a limit of detection often around a couple of logs;
- need to manage shared resistance genes between species, especially for MDR-GNR;
- and is PCR+ culture- (as) clinically significant?

See further details in talk by Dr Dan Diekema
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?
Summary

1. MDR-GNR are emerging worldwide and represent a unique threat.
2. CRE 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.