Mechanisms of Resistance Made Simple and Fun

Beta-lactamases
Figure 1
Antibiotic Trapping by
Plasmid-Encoded CMY-2 β-Lactamase
Combined with Reduced Outer Membrane Permeability as a
Mechanism of Carbapenem Resistance in \textit{Escherichia coli}

Wil H. F. Goessens, Akke K. van der Bij, Ria van Boxtel, Johann D. D. Pitout, Peter van Ulsen, Damian C. Melles, Jan Tommassen
Overview

• Beta-lactamase Classification

• Carbapenemases

• Current status of beta-lactamases in Australia
Why beta-lactamases are so hard?

- Multiple classification schemes
- Three letter abbreviations with no consistency in nomenclature!
- Different descriptions of the same thing (eg, TOHO = CTX-M)
The Simplest Classification Scheme - Ambler

- Class A: TEM-1,2; SHV-1; ESBLs, KPC
- Class B: MBLs
- Class C: AmpC
- Class D: OXA
Class A

**Substrates:** Penicillins, cephalosporins (not cephapemycins), aztreonam  
**Inhibited by:** clavulanic acid

- **Narrow spectrum beta-lactamases**  
  - TEM-1, SHV-1
- **Extended-spectrum beta-lactamases**  
  - Mutated versions of parent TEM-1 and SHV-1  
  - Imported classes, eg, CTX-M
- **Carbapenemases**  
  - KPC
Class B

• Metallo-beta-lactamases (MBLs)
• **Substrate**: Penicillins, cephalosporins, carbapenems (not aztreonam)
• **Inhibited by**: EDTA (not inhibited by clavulanic acid)

• IMP, VIM, SPM, AIM, NDM.....
Class C

- **Substrate**: penicillins, cephalosporins (including cephamycins), aztreonam
- **Inhibitors**: boronic acid (not inhibited by clavulanic acid)
- **Chromosomal AmpC**: *Enterobacter, Serratia, Citrobacter freundii, Hafnia alvei, Acinetobacter baumannii, Providencia, Pseudomonas aeruginosa, Morganella morganii*
- **Plasmid-mediated**: CMY etc
Class D

- **OXA beta-lactamases**
- **Substrate:** Penicillins, cephalosporins, sometimes carbapenems
- **Inhibitor:** Usually not inhibited by clavulanic acid

- Notable examples: OXA-1, OXA-23, OXA-48, OXA-181
Some notable beta-lactamases
CTX-M-15

An ESBL which preferentially hydrolyses ceftriaxone compared to ceftazidime
ESBL+ *E. coli*

- 105 people with ESBL+ *E. coli* infections
  - 6: hospital-acquired infections
  - 9: healthcare-associated community infections
  - 90: community-acquired infections
- 77/105 positive for CTX-M genes
  - 55: CTX-M-15

*Pitout et al. AAC 2009;53:2539-2543*
Two hypotheses

1. Mobile genetic elements (eg, plasmids) harboring blaCTX-M-15 may be moving from strain to strain in *E. coli*

2. CTX-M-15 positive strains may be spreading in a clonal fashion
   - TMP/SMX resistant *E. coli* (“clonal group A” and *E. coli* O15:K52:H1)

*Manges et al. NEJM 2001;345:1007-1013*
*Prats et al JCM 2000;38:201-209*
Testing these hypotheses

- 13 French CTX-M-15+ *E. coli* isolates
  - Phylogenetic group B2; serotype O25:H4
- 23 isolates from
  - Europe (Spain, Portugal, Switzerland)
  - Lebanon
  - Canada
  - South Korea
- All shared B2 and O25:H4 and were ST131

*Nicolas-Chanoine et al JAC 2008 Feb;61:273-281*
Travel-related Infections

- **27** patients with symptomatic, community-onset CTX-M-15 *E. coli* UTI
- **14** had recent admission to hospital or nursing home
- **13** had recent overseas travel
  - 10 India/Bangladesh

Travel-related Infections (II)

• Isolation of CTX-M-15 positive ST131 was associated with travel to:
  – India and Pakistan
  – Africa
  – Middle East
  – Europe

• (In contrast, clonally related CTX-M-14 associated with travel elsewhere in Asia)

Pitout et al. AAC 2009;53:2539-2543
CTX-M-15+ *E. coli*

- ST131 worldwide epidemic clone
- Responsible for community-acquired infections
  - Ciprofloxacin resistant
  - ESBL producers
- Is likely present across Australia
- Consequences – inadequately treated UTI; sepsis following TRUS biopsy

*B. Rogers JAC 2011 Jan;66(1):1-14;*  
*H. Sidjabat JAC 2010 Jun;65(6):1301-3*
OXA-23

Carbapenemase found in
*Acinetobacter baumannii*
Carbapenem resistant Acinetobacter

![Graph showing the number of patients identified from clinical and surveillance specimens combined over time.](image_url)
Beta-lactamases in *Acinetobacter*

- All *A. baumannii* strains have a chromosomally encoded AmpC beta-lactamase (not inducible) and OXA-51 and related enzymes.
- OXA-23 is the most common acquired carbapenemase in *A. baumannii*.
- Typically associated with an insertion sequence (IS) which leads to overexpression of the carbapenemase.
Carbapenem resistance in *Enterobacteriaceae*

- IMP-4
  - East coast of Australia
- AIM
  - South Australia
- KPC
  - Imported
- OXA-48, OXA-181
  - Outbreaks
- NDM
  - Imported
**Recent carbapenem resistant isolates in QLD**

<table>
<thead>
<tr>
<th>Date</th>
<th>Organism</th>
<th>Site</th>
</tr>
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<tbody>
<tr>
<td>28/5/13</td>
<td><em>Enterobacter cloacae</em></td>
<td>Blood</td>
</tr>
<tr>
<td>24/5/13</td>
<td><em>Enterobacter cloacae</em></td>
<td>Urine</td>
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<tr>
<td>21/5/13</td>
<td><em>Enterobacter cloacae</em></td>
<td>Urine</td>
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<tr>
<td>14/5/13</td>
<td><em>Citrobacter freundii</em></td>
<td>Urine</td>
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<tr>
<td>21/4/13</td>
<td><em>Enterobacter cloacae</em></td>
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<tr>
<td>8/4/13</td>
<td><em>Enterobacter cloacae</em></td>
<td>Urine</td>
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</tbody>
</table>
Clonal analysis of *E. cloacae* with reduced susceptibility with meropenem
Global distribution of KPC
Identification of New Delhi Metallo-β-lactamase 1 in Acinetobacter lwofii of Food Animal Origin

Yang Wang¹, Congming Wu¹, Qijing Zhang², Jing Qi³, Hebing Liu¹, Yu Wang¹, Tao He¹, Licai Ma¹, Jing Lai¹, Zhangqi Shen², Yuqing Liu³, Jianzhong Shen¹*
OXA-48

The map shows the distribution of OXA-48-producing isolates across Europe and parts of North Africa and Asia. Different colors indicate different levels of infection:

- Yellow: Single OXA-48-producing isolates
- Orange: Outbreaks of OXA-48-producing isolates
- Red: Nationwide distribution of OXA-48-producing isolates

Countries highlighted in yellow include:
- The Netherlands
- United Kingdom
- Belgium
- France
- Switzerland
- Turkey
- Lebanon
- Israel
- Egypt

Countries in orange include:
- Spain
- Morocco
- Algeria
- Tunisia

Countries in red include:
- Senegal

India is marked with a specific notation (OXA-181).
Conclusions

• Beta-lactamases remain the most important mechanism of resistance for Gram negatives

• We must aggressively manage the introduction of carbapenem resistant Enterobacteriaceae and Acinetobacter into our hospitals