Reporting β-lactam Susceptibility in Enterobacteriaceae

The Pro Case
Report in Accordance with Results

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In other words...

• **Phenotype?**

  » or

• **Genotype?**
β-Lactamases in Laboratory and Clinical Resistance

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beta-Lactamases - the Threat Renews.

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Has the era of untreatable infections arrived?

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β-lactam resistance mechanisms

- β-lactamases
- Porin mutations
- ??Altered PBPs
# Enterobactericeae β-lactamases

**Acquired**
- TEM-1/2
- OXAs
- ESBL TEMs
- ESBL SHVs
- CTX-Ms
- AmpC
- IMPs
- VIMs
- KPCs
- etc, etc etc

**Intrinsic**
- **Class C**
  - AmpC and similar
- **Class A**
  - SHV-1 (+OKP, LEN)
  - OXYs
  - CTX-M progenitors
  - *P. vulgaris & penneri* enzymes
  - *C. koseri* enzyme
Breakpoints and expert rules for 3rd and 4th generation cephalosporins and aztreonam for Enterobacteriaceae with and without acquired beta-lactam resistance mechanisms.

The following revised proposals are for breakpoints and expert rules in relation to 3rd and 4th generation cephalosporins and aztreonam for Enterobacteriaceae with and without acquired beta-lactam resistance mechanisms.
The current proposal made by the EUCAST Steering Committee (8-9 February, 2010) is as follows:

1. To retain current susceptible and resistant breakpoints for cefotaxime and ceftriaxone as follows.
   Cefotaxime \[ S \leq 1 \text{ / } R > 2 \text{ mg/L} \]
   Ceftriaxone \[ S \leq 1 \text{ / } R > 2 \text{ mg/L} \]

2. To reduce the I/R breakpoints for ceftazidime, cefepime and aztreonam from 8 mg/L to 4 mg/L.
   Cefepime \[ S \leq 1 \text{ / } R > 4 \text{ mg/L} \]
   Ceftazidime \[ S \leq 1 \text{ / } R > 4 \text{ mg/L} \]
   Aztreonam \[ S \leq 1 \text{ / } R > 4 \text{ mg/L} \]

As the pharmacokinetics and pharmacodynamics of these agents are similar it is appropriate to reduce the I/R breakpoints similarly.

3. To retain the non-species-related breakpoints for extended-spectrum cephalosporins (cefotaxime, ceftriaxone, ceftazidime and cefepime) and aztreonam.

4. To report all 3\textsuperscript{rd} and 4\textsuperscript{th} generation cephalosporin and aztreonam results "as found".

5. To modify expert rules in accordance with Pk/Pd criteria and current clinical evidence (distributed previously).

6. To avoid recommendations on how to detect specific beta-lactamases in the expert rules as this is not needed for expert rules. Recommendations will be provided in the future as a separate document.
The Case for the Phenotype

• Or what you see is what you get
No disagreement

• β-lactams are useful drugs for treating gram-negative infections
• β-lactamases are important in reducing response to treatment in many cases
• β-lactamases are becoming more common and diverse
• β-lactamases have infection control implications
• β-lactamases are fun!
Reporting “as tested”

- **Does not mean:**
  - Emerging β-lactamases
    - Are not important or
    - Should not be tracked
  - FAR FROM IT!

- **Does mean**
  - That patients will respond to therapy regardless of the presence of the β-lactamase (and its gene),
  - PROVIDED THAT THE MIC OF THE STRAIN IS BELOW THE CLINICAL BREAKPOINT
Clinical Breakpoint Data Components

- **MIC distributions and wild-type cut-offs (ECVs)**
  - Maybe supplemented by genotype
- **Pharmacokinetics and Pharmacodynamics**
  - Animal model data (PK/PD to define targets)
  - Human PK and PD
- **Validation in prospective studies**
In vitro
Cefepime / Escherichia coli
EUCAST MIC Distribution - Reference Database

MIC distributions include collated data from multiple sources, geographical areas and time periods and can never be used to infer rates of resistance.

MIC
Epidemiological cut-off: WT ≤ 0.125 mg/L
Clinical breakpoints: S ≤ 1 mg/L, R > 8 mg/L

4018 observations (47 data sources)
Cefepime / Klebsiella pneumoniae
EUCAST MIC Distribution - Reference Database

MIC distributions include collated data from multiple sources, geographical areas and time periods and can never be used to infer rates of resistance.

MIC (mg/L)

% microorganisms

Epidemiological cut-off: WT ≤ 0.125 mg/L
Clinical breakpoints: S ≤ 1 mg/L, R > 8 mg/L

1235 observations (2 data sources)
Ceftazidime / Escherichia coli

EUCAST MIC Distribution - Reference Database

MIC distributions include collated data from multiple sources, geographical areas and time periods and can never be used to infer rates of resistance.

MIC (mg/L)

% microorganisms

Epidemiological cut-off: WT ≤ 0.5 mg/L

Clinical breakpoints: S ≤ 1 mg/L, R > 8 mg/L
Ceftazidime / Klebsiella pneumoniae
EUCAST MIC Distribution - Reference Database

MIC distributions include collated data from multiple sources, geographical areas and time periods and can never be used to infer rates of resistance.

Epidemiological cut-off: WT ≤ 0.5 mg/L
Clinical breakpoints: S ≤ 1 mg/L, R > 3 mg/L

5319 observations (67 data sources)
In muride
Multiple ESBL-negative and ESBL-positive strains of *E. coli*, *Klebsiella* spp., *Enterobacter* spp. and *Serratia* spp.

ESBLs: TEM-3, TEM-7, TEM-12, TEM-26, SHV-2, SHV-4, SHV-5, SHV-7, CTX-M2, CTX-M3
Justifiable Conclusions

• %T above MIC is predictive of bacterial kill *in vivo*
  » Independent of presence of an ESBL
  » Independent of type of ESBL

• **It is the MIC that is predictive of kill, not the gene per se**

• **The MIC is related to level of gene expression**

• **If the ESBL is present, but expressed at a level such that MIC exceeds wild-type but is below the clinical breakpoint, the strain will respond normally to treatment using standard dosing regimens**
In homine
The problem of ‘proof’

- Natural resolution rates for many infections are high
- Prospective controlled clinical studies (registration trials) usually have pre-determined breakpoints, and tend to either
  - exclude patients whose isolates have higher MICs
  - or
  - recruit insufficient patients whose isolates have MICs around the near the breakpoint

- Real-world observational studies encounter problems too, e.g.:
  - Multiple agents used during treatment
  - Formal recording of MICs not done
The Wrong Breakpoints “Experiment”

- The CLSI breakpoints for cephalosporins prior to January 2010 allowed us to conduct a natural experiment:
  - Treatment of ESBL-producing Enterobacteriaceae with extended-spectrum generation cephalosporins whose MICs were at or below breakpoint (≤ 8 mg/L)
Outcome versus 3GC MIC

Septicaemia from *Klebsiella* spp and *E. coli* with ESBLs


Andes & Craig, CMI 2005; 11 (Suppl 6):10-17
Outcome versus CAZ MIC

Septicaemia from *E. coli* with CTX-M ESBLs
Treated with Ceftazidime alone 2g 8-hrly

Bin et al, DMID 2006; 56:351-7
Outcome versus Cefepime MIC

Gram-negative Septicaemia treated with Cefepime 1-2g 12-hrly

Bhat et al, AAC 2007; 51:4390-5
What about Isolates Harbouring Carbapenemases?

- Similar situation applies to that of extended-spectrum cephalosporins
- Emergence of IMP, VIM and KPC enzymes in particular but MICs sometimes below clinical breakpoint
Meropenem / Escherichia coli
EUCAST MIC Distribution - Reference Database

MIC distributions include collated data from multiple sources, geographical areas and time periods and can never be used to infer rates of resistance.

MIC Epidemiological cut-off. WT ≤ 0.125 mg/L
Clinical breakpoints: S ≤ 2 mg/L, R > 8 mg/L

9005 observations (68 data sources)
Meropenem / Klebsiella pneumoniae
EUCAST MIC Distribution - Reference Database

MIC distributions include collated data from multiple sources, geographical areas and time periods and can never be used to infer rates of resistance.

MIC
Epidemiological cut-off: WT ≤ 0.125 mg/L
Clinical breakpoints: S ≤ 2 mg/L, R > 8 mg/L

13171 observations (67 data sources)
Doripenem / Escherichia coli
EUCAST MIC Distribution - Reference Database

MIC distributions include collated data from multiple sources, geographical areas and time periods and can never be used to infer rates of resistance.

MIC (mg/L)

% microorganisms

Epidemiological cut-off: WT ≤ 0.125 mg/L
Clinical breakpoints: S ≤ 1 mg/L, R > 4 mg/L

5602 observations (7 data sources)
Doripenem / Klebsiella pneumoniae
EUCAST MIC Distribution - Reference Database

MIC distributions include collated data from multiple sources, geographical areas and time periods and can never be used to infer rates of resistance.

Epidemiological cut-off: WT ≤ 0.125 mg/L
Clinical breakpoints: S ≤ 1 mg/L, R > 4 mg/L
2626 observations (5 data sources)
• 162 patients with bacteraemia
• Treatments were frequently combinations
• Data on single agent carbapenem treatment not given
• > 4 µg/ml used in analysis to both imipenem and meropenem despite different activities of the two drugs

MIC not significant in Cox multivariate regression (>0.1)

FIG. 1. Kaplan-Meier curves of survival probability of patients with *K. pneumoniae* bloodstream infections according to susceptibility of the infecting organism to carbapenems. Patients infected with a VIM-positive organism for which the MICs of both imipenem and meropenem were >4 µg/ml were more likely to die than those infected with a VIM-positive carbapenem-susceptible or VIM-negative organism (log rank = 6.27, *P* = 0.044).
<table>
<thead>
<tr>
<th>Age (year)/sex</th>
<th>Underlying condition</th>
<th>Acute illness (tested isolate site)</th>
<th>Apache II</th>
<th>MIC (Vitek/Etest)</th>
<th>Treatment (days)</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>46/F</td>
<td>Skin graft</td>
<td>Bacteremia (blood)</td>
<td>6</td>
<td>4/8</td>
<td>Imipenem (7), port removal</td>
<td>Microbiologic and clinical success</td>
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<tr>
<td>61/F</td>
<td>CHF</td>
<td>Pycelonephritis (urine)</td>
<td>21</td>
<td>2/≥32</td>
<td>Imipenem (7)</td>
<td>Microbiologic and clinical success</td>
</tr>
<tr>
<td>82/M</td>
<td>None</td>
<td>Urosepsis (blood)</td>
<td>25</td>
<td>4/2</td>
<td>Imipenem (14)</td>
<td>Microbiologic and clinical success</td>
</tr>
<tr>
<td>92/M</td>
<td>Dementia</td>
<td>Pneumonia (resp)</td>
<td>12</td>
<td>4/2</td>
<td>Imipenem (3)</td>
<td>Clinical success</td>
</tr>
<tr>
<td>64/F</td>
<td>Esophageal cancer</td>
<td>Tracheobronchitis (resp)</td>
<td>15</td>
<td>4/2</td>
<td>Imipenem (12)</td>
<td>Microbiologic failure</td>
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<tr>
<td>76/M</td>
<td>Cerebral hemorrhage</td>
<td>Tracheobronchitis (resp)</td>
<td>21</td>
<td>2/0.25</td>
<td>Meropenem (7)</td>
<td>Clinical and microbiologic failure</td>
</tr>
<tr>
<td>69/F</td>
<td>Metastatic cancer</td>
<td>Pneumonia (resp)</td>
<td>36</td>
<td>4/8</td>
<td>Imipenem (6)</td>
<td>Clinical failure/death</td>
</tr>
<tr>
<td>77/M</td>
<td>MRSA abscess</td>
<td>Tracheobronchitis (resp)</td>
<td>23</td>
<td>4/≥32</td>
<td>Imipenem (7)</td>
<td>Microbiologic failure</td>
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<tr>
<td>52/M</td>
<td>Melanoma</td>
<td>UT1 (urine)</td>
<td>37</td>
<td>4/12</td>
<td>Imipenem (14)</td>
<td>Microbiologic failure</td>
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<tr>
<td>67/M</td>
<td>Polyneuropathy</td>
<td>Urosepsis (blood)</td>
<td>21</td>
<td>4/≥32</td>
<td>Tigecycline (7)</td>
<td>Clinical and microbiologic failure</td>
</tr>
<tr>
<td>65/M</td>
<td>Lung mass</td>
<td>Tracheobronchitis (resp)</td>
<td>15</td>
<td>4/1</td>
<td>Tigecycline (7)</td>
<td>Clinical and microbiologic success</td>
</tr>
<tr>
<td>83/F</td>
<td>Laryngeal cancer</td>
<td>Pneumonia (blood)</td>
<td>14</td>
<td>≥16/≥32</td>
<td>Tigecycline (7)</td>
<td>Clinical success</td>
</tr>
<tr>
<td>39/F</td>
<td>Stem cell transplant</td>
<td>Urosepsis (urine)</td>
<td>12</td>
<td>8/8</td>
<td>Tigecycline (14)</td>
<td>Clinical success</td>
</tr>
<tr>
<td>79/M</td>
<td>None</td>
<td>Pneumonia (resp)</td>
<td>27</td>
<td>8/32</td>
<td>Tigecycline (14)</td>
<td>Clinical success</td>
</tr>
<tr>
<td>19/M</td>
<td>Trauma, craniotomy</td>
<td>Shunt associated meningitis (CSF)</td>
<td>28</td>
<td>N/A</td>
<td>Tigecycline/gentamicin\a</td>
<td>Clinical and microbiologic success</td>
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<tr>
<td>79/F</td>
<td>s/p CABG</td>
<td>Bacteremia (blood)</td>
<td>29</td>
<td>8/2</td>
<td>Tigecycline/imipenem</td>
<td>Clinical failure/death</td>
</tr>
<tr>
<td>0/M</td>
<td>Seizures</td>
<td>Pneumonia (resp)</td>
<td>n/a</td>
<td>≥16/≥32</td>
<td>Gentamicin (7)</td>
<td>Clinical success</td>
</tr>
<tr>
<td>60/F</td>
<td>Metastatic cancer</td>
<td>Wound (wound)</td>
<td>25</td>
<td>8/≥32</td>
<td>Amikacin (7)</td>
<td>Clinical success</td>
</tr>
<tr>
<td>59/F</td>
<td>ESRD</td>
<td>Line infection (blood)</td>
<td>22</td>
<td>≥16/≥32</td>
<td>Gentamicin (10)</td>
<td>Clinical and microbiologic success</td>
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<td>Pelvic infection</td>
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<td>≥16/8</td>
<td>Meropenem (10)</td>
<td>Clinical and microbiologic failure</td>
</tr>
<tr>
<td>50/M</td>
<td>Liver transplant</td>
<td>Bacteremia</td>
<td>9</td>
<td>≥16/8</td>
<td>Meropenem (7)</td>
<td>Clinical and microbiologic success</td>
</tr>
</tbody>
</table>
In the end...

- An MIC is an MIC is an MIC
  (Apologies to Gertrude Stein, 1913)

- “It’s the MIC, stupid” (Kahlmeter, 2007)