AmpC EXTENDED SPECTRUM 

BETA-LACTAMASES (ESBL) AND INFECTION CONTROL
Overview

- Classifications of β-lactamases
- What is an ESBL?
- Spread and prevalence of ESBL
- Impact of ESBL production on outcome
- Detection of ESBL
- AmpC description and prevalence
Classification of β-lactamases

- **β-lactamases**
  - Serine enzymes
    - Class A enzymes
      - (Plasmid)
    - Class C enzymes
      - (Chromosomal)
  - Class D enzymes
    - (Plasmid)
  - Metallo-enzymes
    - Class B enzymes
      - (Chromosomal)

- ESBL
  - Pen-Cephs-Inh-S
- AmpC
  - Cephs-Inh-R
- OXA
  - Pens, esp Oxa Inhib-R/S
- MbL (IMP/VIM)
  - Carbapenems Inh-R

References:
### Broad Spectrum β-lactamases:

<table>
<thead>
<tr>
<th>β-Lactamase</th>
<th>Examples</th>
<th>Substrates</th>
<th>Inhibition by Clavulanic Acid*</th>
<th>Molecular Class</th>
</tr>
</thead>
<tbody>
<tr>
<td>Broad-spectrum</td>
<td>TEM-1, TEM-2, SHV-1</td>
<td>Benzylpenicillin (penicillin G), amoxicillin and ampicillin, carboxypenicillins (carbenicillin and ticarcillin), ureidopenicillin (piperacillin), narrow-spectrum cephalosporins (cefazolin, cephalothin, cefamandole, cefuroxime, and others)</td>
<td>+++</td>
<td>A</td>
</tr>
<tr>
<td>OXA family</td>
<td>Substrates of the broad-spectrum group plus cloxacillin, methicillin, and oxacillin</td>
<td>+</td>
<td>D</td>
<td></td>
</tr>
</tbody>
</table>

- E. coli (90%), H. influenzae N. gonorrhoeae and K. pneumoniae
- Treatment:
  - Third generation cephalosporins,
  - β-lactamases inhibitors
## Extended Broad Spectrum β-lactamases:

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<th>Molecular Class</th>
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</thead>
<tbody>
<tr>
<td>Expanded-spectrum</td>
<td>TEM family and SHV family</td>
<td>Substrates of the broad-spectrum group plus oxyimino-cephalosporins (cefotaxime, cefpodoxime, ceftazidime, and ceftriaxone) and monobactam (aztreonam)</td>
<td>++++</td>
<td>A</td>
</tr>
<tr>
<td>Others (BES-1, GES/IBC family, PER-1, PER-2, SFO-1, TLA-1, VEB-1, and VEB-2)</td>
<td>Same as for TEM family and SHV family</td>
<td></td>
<td>++++</td>
<td>A</td>
</tr>
<tr>
<td>CTX-M family</td>
<td>Substrates of the expanded-spectrum group plus, for some enzymes, cefepime</td>
<td></td>
<td>++++</td>
<td>A</td>
</tr>
<tr>
<td>OXA family</td>
<td>Same as for CTX-M family</td>
<td></td>
<td>+</td>
<td>D</td>
</tr>
</tbody>
</table>
Extended-Spectrum $\beta$-Lactamases

- $\beta$-lactamases capable of conferring bacterial resistance to
  - Penicillins
  - First-, second-, and third-generation cephalosporins
  - Aztreonam
- **Do not appreciably hydrolyse cephamycins (cefoxitin or cefotetan)** or carbapenems
- Inhibited by $\beta$-lactamase inhibitor: clavulanic acid
Extended-spectrum β-lactamases (ESBL)

- Derived from Class A β-lactamases (exceptions are Class D, OXA): TEM, SHV, CTX-M, OXA, VEB, PER,...

- Therapeutic options:
  - Carbapenems
  - Tigecycline
Extended-Spectrum β-Lactamase-Producing Gram-Negative Bacilli

More Likely:
- Klebsiella sp
- E. coli
- Proteus mirabilis

Less Common:
- Enterobacter sp
- P. aeruginosa
- Citrobacter freundii
- Morganella morganii
- Serratia marcescens
Increase in numbers of Group 1, 2 and 3 β-lactamases from 1970 to 2009

- Group 1/class C cephalosporinases
- Group 2/class A and class D β-lactamases
- Group 3/class B metallo-β-lactamases
Rise in the proportions of *E. coli* from bacteraemias in England, Wales and Northern Ireland resistant to fluoroquinolones (white), oxyimino-cephalosporins (grey) and both (black)

The ESBL-producing E. coli ‘Epidemic’

Prevalence of extended spectrum $\beta$-lactamases (ESBLs) in Enterobacteriaceae

2. Edelstein et al. ICAAC, Washington, USA 2004 Poster: C2-1331

**MYSTIC data on file, October 2007**

**Middle East Critical Care Assembly**
Impact of ESBLs

Increased healthcare costs

Longer hospital stays

Higher mortality rates

Emerging in the community

ESBLs

### Outcomes of ESBL production in multivariate analysis

<table>
<thead>
<tr>
<th>Outcome</th>
<th>OR (95% CI) or ME</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>3.6 (1.4–9.5)</td>
<td>0.008</td>
</tr>
<tr>
<td>Length of stay</td>
<td>1.56</td>
<td>0.001</td>
</tr>
<tr>
<td>Delay in appropriate therapy</td>
<td>25.1 (10.5–60.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cost of hospitalisation</td>
<td>1.57</td>
<td>0.003</td>
</tr>
</tbody>
</table>

CI, confidence interval; ME, multiplicative effect

Predictors of mortality in patients with BSI caused by ESBL-producing Enterobacteriaceae: Effect of initial antibiotic therapy on mortality


n=186
Seemingly adequate initial therapy
21-day mortality rates

- Aminoglycosides (n=20)
  - Non-survivors: 27.8%
  - Survivors: 14%
  - p=0.40

- β-lactam/β-lactamase inhibitors (n=33)
  - Non-survivors: 22.2%
  - Survivors: 36.7%
  - p=0.24

- Carbapenems (n=28)
  - Non-survivors: 5.5%
  - Survivors: 34.2%
  - p=0.01

- Ciprofloxacin (n=16)
  - Non-survivors: 44.4%
  - Survivors: 10.1%
  - p<0.001


n=97
Routes of infection

- ESBL producers act like VRE
- Faecal colonization
- Skin colonization
- Transient contamination of the hands of staff

Coulter et al: 13% of “ambushed” ICU nurses had positive hand cultures
Detection

- Difficult
- Susceptible at standard inoculum
- Screen for ESBL in *Klebsiella pneumoniae* & *E. coli* that demonstrate reduced susceptibility to ceftazidime, cefotaxime or aztreonam

Photo courtesy of Dr D Lyon
Dept of Microbiology, Prince of Wales Hospital
Double Disc Tests
Figure 1. Detection of ESBL carriage with an E-test ESBL strips. Ceftazidime MIC against *E. coli* isolate in A is > 32µg/mL in the absence of clavulanate and 0.125µg/mL in the presence of clavulanate. Ceftazidime MIC against *K. pneumoniae* isolate in B is > 32 µg/mL in the absence of clavulanate and 0.125µg/mL in the presence of clavulanate. Observe the phantom zone production in B. As the ratio of ceftazidime with and without clavulanate is ≥8, the isolates were phenotypically determined as ESBL producers.
<table>
<thead>
<tr>
<th>Agent</th>
<th>CLSI 2009</th>
<th>CLSI 2010</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>S</td>
<td>I</td>
</tr>
<tr>
<td>Cefazolin</td>
<td>≤8</td>
<td>16</td>
</tr>
<tr>
<td>Cefotaxime</td>
<td>≤8</td>
<td>16-32</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>≤8</td>
<td>16-32</td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>≤8</td>
<td>16</td>
</tr>
<tr>
<td>Aztreonam</td>
<td>≤8</td>
<td>16</td>
</tr>
<tr>
<td>Cefipime</td>
<td>≤8</td>
<td>16</td>
</tr>
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CLSI: Clinical And Laboratory Standards Institute
AmpC β-lactamases:

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<tbody>
<tr>
<td>AmpC</td>
<td>ACC-1, ACT-1, CFE-1, CMY family, DHA-1, DHA-2, FOX family, LAT family, MIR-1, MOX-1, and MOX-2</td>
<td>Substrates of expanded-spectrum group plus cephemycins (cefotetan, cefoxitin, and others)</td>
<td>0</td>
<td>C</td>
</tr>
</tbody>
</table>
AmpC β-Lactamases

- Chromosomal AmpC β-lactamases
  - Several Enterobacteriaceae, including *Enterobacter*, *Citrobacter*, and *Serratia* contain an inducible, chromosomal gene coding for a β-lactamase
  - Resistant to penicillins, cephalosporins (weakly to cefepime) and monobactams; not inhibited by clavulanate; Class C β-lactamases

- Plasmid-mediated AmpC β-lactamases
  - Arose through transfer of AmpC chromosomal genes into plasmids
  - Highly prevalent in the naturally AmpC-deficient *K. pneumoniae*
  - Emergence predominantly in community-acquired infections (*Salmonella* spp., *E. coli*)
  - Co-resistance to aminoglycosides, SXT, quinolones

- Therapeutic options:
  - 4th generation cephalosporins (but resistance may occur with minor AA changes)
  - Carbapenems
Prevalence of AmpC-producing Enterobacter spp. over time in Europe and USA

- **AmpC (%)**
  - Europe
  - USA

Population-based Laboratory Surveillance for AmpC β-Lactamase–producing Escherichia coli, Calgary

Johann D.D. Pitout,* Daniel B. Gregson,* Deirdre L. Church,* and Kevin B. Laupland*
*University of Calgary, Calgary, Alberta, Canada
Vol. 13, No. 3 • March 2007
Traditional view of “who gets ESBL producers”

- Hospitalised patients or Nursing home patients
  - ICU
  - Previous use of antibiotics
  - Long length of stay
  - Lots of procedures and tubes
  - Higher APACHE score
Community-acquired ESBL producers

- First became a problem in Canada, Spain and the United Kingdom

- While many “community-acquired” cases were actually from residential care homes or recently hospitalised patients, some were truly from the community
Importance of community-acquired ESBL producers

• All of the first line options for community-acquired UTI are lost
  – Trimethoprim
  – Trimethoprim/sulfamethoxazole
  – Gentamicin
  – Ceftriaxone
  – Ticarcillin/clavulanate
  – Piperacillin/tazobactam
  – Ciprofloxacin
ESBL types

- Hospital ESBLs are of TEM or SHV type

- Community ESBLs are of CTX-M type
  - Very closely related to chromosomal beta-lactamases of *Kluyvera* spp.
  - Most commonly occur in *E. coli*
Another implication of ESBL producers

- More carbapenem use

- This translates to more carbapenem resistant organisms
  - KPC producers
  - CRAB
  - Carbapenem resistant *Pseudomonas*
### β-lactamases: Summary

<table>
<thead>
<tr>
<th>Class</th>
<th>Broad Spectrum</th>
<th>Expanded Spectrum</th>
<th>AmpC</th>
<th>Carbapenemase</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TEM/SHV</td>
<td>TEM/SHV</td>
<td>KPC</td>
<td>MBL</td>
</tr>
<tr>
<td>Inhibition by Clavulanic Acid</td>
<td>A</td>
<td>A</td>
<td>C</td>
<td>A</td>
</tr>
<tr>
<td>Penicillins</td>
<td>D</td>
<td>A</td>
<td>A</td>
<td>B</td>
</tr>
<tr>
<td>Oxacilin</td>
<td>D</td>
<td>A</td>
<td>D</td>
<td>D</td>
</tr>
<tr>
<td>Narrow Spectrum Cephalosporins</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Cephamycins</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Oxyiminocephalosporins</td>
<td></td>
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<td></td>
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<tr>
<td>Cefepime</td>
<td></td>
<td></td>
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<tr>
<td>Monobactam</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Carbapenems</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Polymyxin E</td>
<td></td>
<td></td>
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</tbody>
</table>

**Notes:**
- **Green** indicates no inhibition.
- **Yellow** indicates partial inhibition.
- **Red** indicates full inhibition.

**Classes:**
- **A**:
  - Narrow Spectrum Cephalosporins
  - Cephamycins
  - Oxyiminocephalosporins
  - Cefepime
  - Monobactam
  - Carbapenems
  - Polymyxin E

**Inhibition by Clavulanic Acid:**
- TEM/SHV: A
- OXA: D

**Expanded Spectrum:**
- TEM/SHV: A
- CTX-M: A
- OXA: D

**AmpC:**
- KPC: C
- MBL: A
- OXA: B

**Carbapenemase:**
- KPC: A
- MBL: B
- OXA: D
Take home

• ESBL are common
• ESBL is widely spread
• Hospital and community
• Impact on outcome
• Detection in lab is based on decreased susceptibility to cephalosporin
• Limited treatment options: Carbapenems or Tigecycline