Extended Spectrum Beta Lactamases (ESBL) and Infection Control
Prof. David Patterson, University of Queensland
Sponsored by Intronics  www.intronics.co.uk

The Weather

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Rugby World Cup 2007

• Tonga 25 defeated USA 15

Adjusted scores

• Tonga 75,000 def. United States 15

Populations

• Tonga 100,000

• USA 300 million

Schools

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Explosion of interest in ESBLs

• 1386 articles published with the key-word “beta-lactamase” in the last 2 years
  – 338 articles on ESBLs

• 259 abstracts with the key-word “beta-lactamase” at ICAAC 2007
  – 118 abstracts on ESBLs

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Overview

- What is an ESBL?
- Impact of ESBL production on outcome
- Special issues in *Enterobacter*, *Salmonella* and *Proteus*
- Infection Control Implications

Something controversial...

New drugs against MRSA/VRE

- Quinupristin-dalfopristin
- Linezolid
- Tigecycline
- Daptomycin
- Dalbavancin
- Telavancin
- Ceftobiprole
- Ceftaroline

New drug classes active against Gram negatives

There are more than 200 beta-lactamase types in *Gram negative bacilli*

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

- Hydrolyse third generation cephalosporins (and aztreonam, penicillins and many other cephalosporins)
- Do not appreciably hydrolyse cephemycins (cefoxitin or cefotetan) or carbapenems
- Are inhibited by beta-lactamase inhibitors such as clavulanic acid

How did ESBLs get here?

Why is *E. coli* frequently resistant to ampicillin?

- June 1964 – ampicillin released in Europe
- December 1964 – the first case of ampicillin resistant *E. coli* detected
- Mrs Temoneira (Athens, Greece)
  - Urinary isolate of *E. coli*
  - Produced beta-lactamase (TEM-1)
  - Genes encoding the beta-lactamase were on a plasmid

The cephalosporins

- Discovery in Italy
- 3rd generation cephalosporins developed in part in response to the worldwide proliferation of beta-lactamases active against ampicillin and first generation cephalosporins

Bacteria vs. the drug industry

- Third generation cephalosporins (cefotaxime) marketed in Germany in September 1981
- In March 1982 in Frankfurt, *Klebsiella* isolates were discovered which were resistant to cefotaxime! This was the first known ESBL producer

What is the IQ of a bacteria?
ESBLs- What are They?
- Extended
- Spectrum
- Beta-
- Lactamases

Common ESBL producers
- Klebsiella pneumoniae
- Escherichia coli
- Proteus mirabilis
- Enterobacter cloacae
- Non-typhoidal Salmonella (in some countries)

ESBLs are rare in:
- Pseudomonas aeruginosa
- Acinetobacter baumannii
- While these organisms can become very resistant, this is not actually due to ESBLs

Case study
- 63 year old man presents with acute onset of abdominal pain
- Mass found on physical examination
- Goes to laparotomy
- Found to have colonic tear and faecal peritonitis
- Long and stormy course with subsequent intra-abdominal abscess with ESBL producing Klebsiella pneumoniae

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Traditional view of “who gets ESBL producers”
• Hospitalised patients
  – ICU
  – Long length of stay
  – Lots of procedures and tubes
• Nursing home patients

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*

Why are they becoming more frequent?
• J. Pitout et al. Emergence of *E. coli* clone ST131 producing CTX-M-15 in the Calgary Health Region. ICAAC 2007
• Canadian strains identical to those in Europe, India and Asia

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ESBL producing *E. coli* - *INDIA*

- CTX-M-15 is the overwhelmingly dominant ESBL
  - Evaluation of isolates collected in the late 1990s suggest it was well-established in the "*E. coli* gene pool" almost a decade ago
  - Often ciprofloxacin and aminoglycoside resistant
  - No dominant clone but almost always associated with a large (>100kb) plasmid

*Ensor JAC 2006; Walsh JAC 2007*

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ESBL-producing *E. coli* - *CHINA*

- CTX-M types more diverse, but especially CTX-M-14
  - Emergence of community-acquired ESBL producing *E. coli* in Hong Kong
  - ESBL producing *E. coli* in farm animals (chicken, ducks, pigs, cattle) in Guangdong Province and Hong Kong

*Liu Int J Antimicrob Agents 2007; Duan Microb Drug Resist 2006; Ho JAC 2007*

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From food?

- Y. Doi et al. Cephalosporin resistant *E. coli* from retail meat in the United States and Spain. *ICAAC 2007*
- CTX-M producing *E. coli* grown from chicken purchased at supermarkets

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Some examples of agricultural antibiotic use

- Quinolones in animal feed
- Ceftiofur injected into eggs
- Fluconazole sprayed onto citrus fruit

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Food sampling

- Doi et al. *Emerging Infectious Diseases 2007*
- Chicken, beef, pork, turkey purchased in supermarkets
- *E. coli* cultured from meat
- 85% samples harboured *E. coli* resistant to third generation cephalosporins – the majority of these produced AmpC beta-lactamases not ESBLs

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Worldwide prevalence of ESBL producers

<table>
<thead>
<tr>
<th>Region</th>
<th>Kpn</th>
<th><em>E. coli</em></th>
</tr>
</thead>
<tbody>
<tr>
<td>USA</td>
<td>5.3%</td>
<td>2.8%</td>
</tr>
<tr>
<td>Latin America</td>
<td>27.6%</td>
<td>12.0%</td>
</tr>
<tr>
<td>Northern Europe</td>
<td>5.2%</td>
<td>1.4%</td>
</tr>
<tr>
<td>Southern/East. Europe</td>
<td>25.7%</td>
<td>6.6%</td>
</tr>
<tr>
<td>China</td>
<td>37.3%</td>
<td>31.3%</td>
</tr>
<tr>
<td>Australasia</td>
<td>4.6%</td>
<td>1.6%</td>
</tr>
</tbody>
</table>

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Asia, Latin America and E. Europe – over the counter dispensing of antibiotics

• “Ten well-trained medical students (simulated patients) presented to 40 drug stores with common complaints such as urethral discharge, acute watery diarrhoea ….”

• “Most antibiotics were dispensed inappropriately with respect to choice of drug and duration of treatment”

Thamlikitkul JAC 1988

Non-judicious dispensing of antibiotics by drug stores

• Six internists were trained as mock patients who pretended to have a friend with a common syndromic illness

• Acute fever, tender maxillary sinus with nonpurulent discharge
  – 23 received norfloxacin
  – 20 received ofloxacin

Anucha Apisarnthanarak ICHE June 2008

Implication of ESBL production

• Diminished susceptibility to cephalosporins, penicillins and aztreonam

• Therefore:
  – risk of inadequate empiric therapy if these antibiotics are used
  – risk of increased use of other antibiotic classes

Are ESBL producers associated with higher mortality?

• Meta-analysis of mortality from bacteremia with ESBL producers [Schwaber JAC Nov 2007]
  – 16 studies from 2000-2006
  – Crude mortality 34% (199/591) for ESBL producers vs. 20% (216/1091) for non-ESBL
  – Pooled RR 1.85; 95% CIs 1.39-2.47

• Delay in effective therapy in up to 44% patients with ESBL producers [Schwaber JAC Nov 2007; Goff ICAAC 2006]

Carbapenems - treatment of choice for serious infections with ESBL producers

• Carbapenems are not hydrolyzed by ESBLs to any great extent

• Success rates with carbapenems for ESBL producers consistently exceed 80%, and in no study has the outcome with carbapenems been surpassed [Paterson CID 2004; Bhavnani DMID 2006; Zanetti AAC 2003]

Another implication of ESBL producers

• More carbapenem use

• This translates to more carbapenem resistant organisms
  – KPC producers
  – CRAB
  – Carbapenem resistant Pseudomonas

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ESBL producers frequently appear susceptible to cephalosporins

- Enterobacteriaceae are traditionally reported as susceptible to ceftazidime, cefotaxime, ceftriaxone, aztreonam, and cefepime when MIC \( \leq 8 \mu g/mL \)

<table>
<thead>
<tr>
<th></th>
<th>CLSI</th>
<th>EUCAST</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>S</td>
<td>R</td>
</tr>
<tr>
<td>Cefotaxime</td>
<td>8</td>
<td>32</td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>8</td>
<td>16</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>8</td>
<td>32</td>
</tr>
</tbody>
</table>

Whose breakpoints should we be using?

Summary of problem

- Micro labs need to be “switched on” to detect ESBLs

Newer cephalosporins

- Cephalosporins plus beta-lactamase inhibitors
  - Cefepime
  - Cephamycins
  - Ceftobiprole

Cefepime and ESBL producers

- In general, I would avoid using cefepime as treatment of ESBL producers
- High doses (eg, 2 grams q 8hrs) may have satisfactory success with low MIC organisms (MIC \( \leq 1 \mu g/mL \))

Should breakpoints be changed and ESBL detection abandoned?

- NO – infection control implications are minimized without this information
- Therapeutic implications
  - Inoculum effect, while debatable, may be clinically important

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#### Ticarcillin/clavulanate
- Very little clinical data on Tic/clav versus ESBL producers
- Ticarcillin is intrinsically inferior to piperacillin versus Klebsiella
- Would not recommend its use for ESBL producers

#### Tigecycline
- Active against 93.7% of ESBL producers using EUCAST breakpoint of 1 µg/mL [Morosini AAC Aug 2006]
- Peak serum concentrations are only 0.67 µg/mL so would urge caution for treating bloodstream infections
- Poorly excreted in urine
- Pneumonia study – inferior to imipenem in VAP
- No published clinical experience thus far

#### Carabapenems - treatment of choice for serious infections with ESBL producers
- Carabapenems are not hydrolyzed by ESBLs to any great extent
- Minimal inoculum effect
- Success rates with carabapenems for ESBL producers consistently exceed 80%, and in no study has the outcome with carabapenems been surpassed [Paterson CID 2004; Bhavnani DMID 2006; Zanetti AAC 2003]

#### Which carabapenem?
- Most data has been with imipenem/meropenem
- Ertapenem and ESBL producers
  - 91% (10/11) patients with bacteremia were successfully treated
  - 63% (19/23) patients with complicated UTI were cured
  - 3 patients had development of ertapenem resistance during prolonged therapy [Munoz ICAAC 2004]
  - Combinations of beta-lactamase production plus impermeability/efflux appear responsible [Szabo AAC 2006; Woodford ICAAC 2006 – C1-34]

#### Doripenem
- Now FDA approved
- Appears highly active vs. ESBL producers
- $\text{MIC}_{90}$ $\leq 0.06$
- $\text{MIC}_{90}$ $\leq 0.06$
- $\text{E. coli}$
- $\text{K. pneumoniae}$
- $\text{P. mirabilis}$

#### Salmonella and ESBLs
- No ESBLs in S. Typhi
- Implication is for non-typhoidal salmonella - invasive infections in children where cefotaxime/ceftriaxone is widely used empirically

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What should we do in the hospital for ESBL producers?

• > 50 outbreaks of infection with ESBL producers (affecting >5000 patients) have been reported worldwide in which methods were used to ascertain the genotypic relatedness of strains
• IN EVERY REPORTED OUTBREAK, COMMON STRAINS WERE ISOLATED FROM > 2 PATIENTS

PFGE

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

Removable environmental foci are rare

• Ultrasound gel
  - Gaillot J Clin Micro 1998
• Glass thermometers used per axilla
  - Rogues J Hosp Infect 2000
• Contaminated bronchoscope
• Nurse with chronic hand carriage
  - AM Allworth (personal communication)

Arresting outbreaks

• Traditional Infection Control
  - Perform rectal swabs on patients in the same ward as infected patients
  - “Contact isolation” for patients infected OR colonized
  - Add alerts to medical charts to inform staff of ESBL + positive status on readmission, transfer etc

Importance of ESBL detection

• Numerous examples exist in which small outbreaks of infection with ESBL producers have been completely halted by use of “traditional” infection control procedures
  For example,
  – screening for asymptomatic carriers
  – “contact isolation”
  – attention to handwashing

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Rectal swabs and ESBL producers

- Not recommended hospital wide unless there is a massive outbreak
- Would target high-risk areas
  - ICUs
  - Transfer from residential care facility
  - Areas with outbreaks

“Clearing” an ESBL Positive Patient

- Most likely there will be some ongoing gut colonisation
- ESBL “positivity” will be enhanced by recent receipt of antibiotics
- Some institutions say positive for life
- Others say (1) wait 6 months, (2) if 3 negative rectal swabs then clear

Highly endemic situations - does infection control work?

- At end of 1991, contact isolation commenced
- At end of 1992, multiple other measures introduced based on discussions with ICU nurses
- Lucet CID 1999

Antibiotic utilization measures

- Numerous studies have linked usage of third generation cephalosporins with advent of ESBL producing Klebsiella
- Replacement of cephalosporins with other classes has resulted in reduction in isolation of ESBL producers
- cefepime (Mebis Leukemia 1998)
- pip/tazo (Rice CID 1996)
- tic/clav (Coulter 1995)

Why will we have an escalation in these problems in the future?

- Bacterial genetics
  - Selection of resistant mutants
  - Acquisition of genetic material from other bacteria
- Human factors
  - Antibiotic regimens for increasingly difficult patients
  - Use of antibiotics in agriculture
  - Hand hygiene
  - Pharmaceutical industry

The effects of space travel on antibiotic resistance

- Cytos 2 experiment (French-Soviet manned flight July 1982)
- Bacteria became less resistant when taken into outer space
It is not rocket science….

- Clean your hands between patients
  – Beware taking herpes simplex, ESBLs, C. difficile and MRSA home with you!
- Antibiotics are not the answer for every culture or every fever
- Clinicians hold the key to solving these emerging resistance problems

Don’t forget

- Don’t be dismayed – outbreaks of ESBL producers can be controlled
- Carbapenem resistance in Klebsiella, E.coli or Enterobacter is an infection control emergency
- Think of the environment as well as hands