Preventing and Controlling ESBLs, The Future is Here
Prof. Hilary Humphreys, Royal College of Surgeons, Dublin
Broadcast live from the Infection Prevention Society Conference September 22, 2010

Aylliffe Lecture
Preventing and Controlling ESBLs, The Future is Here

Hilary Humphreys
The Royal College of Surgeons in Ireland & Beaumont Hospital, Dublin

Declaration Slide
The views expressed are in a personal capacity & do not necessarily reflect those of the RCSI or Beaumont Hospital.

I have recently being in receipt of research funding from Steris Corporation, 3M, Inov8 Science, Pfizer & Cepheid. I have recently received lecture or consulting fees from 3M, Novartis & Astellas.

Graham Ayliffe

Outline
What are extended-spectrum β-lactamases (ESBLs)?
Why are ESBLs important?
How can we treat ESBL infections?
How can we prevent ESBLs?

B-lactam Antibiotics
An antibiotic that has a B-lactam ring e.g.
- Penicillins
- Cephalosporins
- Monobactams
- Carbapenems

What Are ESBLs?

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Definition

- Enzymes produced by bacteria that hydrolyse & cause resistance to a wide variety of β-lactam antibiotics, including 3rd generation cephalosporins (e.g. cefotaxime), penicillins & monobactams (i.e. aztreonam).
- Produced by Enterobacteriaceae, e.g. E. coli & Klebsiella pneumoniae but also by Pseudomonas aeruginosa & Actinobacter baumannii.

Origin

Chromosomally-located in Klebsiella spp. in the environment & then spread via plasmids to pathogenic bacteria in the hospital & in the community.

Selective pressures, including antibiotic use/abuse, has facilitated their survival & subsequent dissemination.

Acquired Resistance

Horizontal gene transfer, i.e.
transformation, conjugation & transduction.

Selection for Resistance by Cephalosporins

Classification of ESBLs

1) According to molecular class, substrate, e.g. cephalosporin, & the enzyme
2) TEM, SHV & CTX-M account for most of these
3) Many enzymes are very similar & differ only by a few amino acids, e.g. > 50 CTX-Ms

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ESBL Varieties

- TEM: 160 TEM-type enzymes described
- SHV: >100 varieties known. Predominant ESBL type in the US
- CTX-M: greater activity against cefotaxime than other agents
  - Plasmid acquisition of beta-lactamase genes
  - >60 enzymes described
  - Most common ESBL type worldwide

Why Are ESBLs Important?

i. Treatment failure leading to death, morbidity & additional expense
ii. Local (e.g. outbreaks) & international spread
iii. Laboratory detection not straightforward
iv. Prevention & control a major challenge

Risk Factors for ESBLs

Previous antibiotics
Contact with healthcare
ICU Stay
Serious underlying disease, e.g. diabetes mellitus
Contact with other cases

.........not unlike MRSA, VRE & Clostridium difficile

ESBLs in Various Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Date</th>
<th>Samples</th>
<th>E. coli</th>
<th>K. pneumoniae</th>
</tr>
</thead>
<tbody>
<tr>
<td>SENTRY</td>
<td>1997-98</td>
<td>Blood, urine, RT, SSI</td>
<td>1.3%</td>
<td>18.4%</td>
</tr>
<tr>
<td>SMART</td>
<td>2004</td>
<td>Intra-abdominal</td>
<td>6.4%</td>
<td>8.8%</td>
</tr>
<tr>
<td>TEST</td>
<td>2004-06</td>
<td>Blood, urine, RT, SSI, sterile fluids</td>
<td>7.6%</td>
<td>13.3%</td>
</tr>
<tr>
<td>MYSTIC</td>
<td>2006</td>
<td>Blood, urine, RT, SSI, sterile fluids</td>
<td>8.2%</td>
<td>9.8%</td>
</tr>
</tbody>
</table>

3rd Gen. Cephalosporin Resistance in ICUs

Intensive Care Med 2009; 35: 91-96

Survey of 35 European ICUs on antibiotic consumption, microbial resistance, & infection control

Overall, 3.9% of E. coli & Klebsiella pneumoniae are ESBL positive

<table>
<thead>
<tr>
<th></th>
<th>Croatia</th>
<th>Hungary</th>
<th>Sweden</th>
</tr>
</thead>
<tbody>
<tr>
<td>E. coli</td>
<td>3.6%</td>
<td>18%</td>
<td>1.6%</td>
</tr>
<tr>
<td>Enterobacter cloacae</td>
<td></td>
<td>18.6%</td>
<td>20%</td>
</tr>
<tr>
<td>Klebsiella pneumoniae</td>
<td>17.8%</td>
<td>29%</td>
<td>0%</td>
</tr>
</tbody>
</table>

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ESBLs in London
- Controlled study of bloodstream infection (56) with controls (56)

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Cases</th>
<th>Controls</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CVC</td>
<td>57%</td>
<td>43%</td>
<td>0.06</td>
</tr>
<tr>
<td>Urinary catheter</td>
<td>60%</td>
<td>42%</td>
<td>0.07</td>
</tr>
<tr>
<td>Prior antibiotics</td>
<td>88%</td>
<td>12%</td>
<td>0.003</td>
</tr>
<tr>
<td>β-lactams</td>
<td>60%</td>
<td>41%</td>
<td>0.006</td>
</tr>
<tr>
<td>ICU admission, &gt;15d</td>
<td>80%</td>
<td>20%</td>
<td>0.01</td>
</tr>
</tbody>
</table>

*significant on multi-variate analysis
- A patient receiving β-lactams was almost 11 times more likely to have ESBL BSI

ESBLs in Beaumont Hospital
- Weekly review of all isolates
- 67.70% urine, 14% blood or line tips

Cases Controls p value
CVC 57% 43% 0.06
Urinary catheter 60% 42% 0.07
Prior antibiotics 88% 12% 0.003
β-lactams 60% 41% 0.006
ICU admission 80% 20% 0.01
Hospital stay, >15d 65% 35% 0.01

Community-Onset ESBL E. coli BSI
- 13 Spanish hospitals & assessed epidemiology
- 191 BSI due to ESBL E. coli; 50% community-acquired

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt; 65</td>
<td>2.3</td>
</tr>
<tr>
<td>Female</td>
<td>1.9</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>3.5</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>4.7</td>
</tr>
<tr>
<td>NH resident</td>
<td>8.6</td>
</tr>
<tr>
<td>Fluoroquinolones</td>
<td>2.8</td>
</tr>
</tbody>
</table>

ESBLs in Nursing Homes, Northern Ireland
- Screening of NH residents in Belfast via faeces
- 294 residents from 16 NHs; 40.5% +ve with 49% the one strain

Characteristic OR p value
Fluoroquinolone 2.79 0.09
History of UTI 3.73 0.003
Visits to ED 1.2 0.20
Admitted to hospital 1.69 0.36

MDR Gram Negative Bacteria in Long-Term Facilities
- Point prevalence study on 4 wards; residents, environment & HCWs
- 23% of residents +ve; 7.7% of HCWs & 3/175 (1.8%) of environmental sites
- VRE from 1 (0.6%) resident; MRSA from 11.2% of residents & 1.2% of environment

* ESBLs more common than MRSA/VRE but rare from the environment

Prevalence of BSI E. coli Resistance
- HPA (England, Wales & NI) data from 2004:
  Reporting is not mandatory
- E. coli BSI increased from 17,411 to 23,874
- West Midlands & NI had the highest rates

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BSI E. coli Resistance

Outcome from ESBL Infections

ESBLs in ICU

<table>
<thead>
<tr>
<th>ESBL Infection</th>
<th>OR</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls</td>
<td>1.00</td>
<td>0.00</td>
</tr>
<tr>
<td>Cases</td>
<td>3.53</td>
<td>0.002</td>
</tr>
</tbody>
</table>

Control for Rx:

| Controls       | 0.96| 0.003   |
| Cases          | 0.43| 0.009   |

Control for disease severity:

| Controls       | 0.04| 0.009   |
| Cases          | 1.44| 0.009   |

Community ESBL & Death

<table>
<thead>
<tr>
<th>Urinary tract</th>
<th>OR</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls</td>
<td>1.00</td>
<td>0.001</td>
</tr>
<tr>
<td>Cases</td>
<td>0.02</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>P E score</th>
<th>OR</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls</td>
<td>0.001</td>
<td>0.007</td>
</tr>
<tr>
<td>Cases</td>
<td>0.004</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Laboratory Detection of ESBLs

The Challenges
- More than one genus
- Different species, hospital & community
- ≥1 mechanism

The Approaches
- Phenotypic – detect enzymes, commonly used
- Genotypic – detect genes, research

Phenotypic

Screening – testing for resistance to cefotaxime, ceftriaxone, etc.
Confirmatory – synergy between cephalosporins & clavulanic acid, i.e.
double disk or E tests

* Do not detect Amp C or metaphenyl-β-lactamase
* Automated systems, e.g., VITEK can get it wrong
* Can take ≥ 72 h to give the result

Hodge Test

K. pneumoniae Positive Control
MicroBiologica® 01005 ATCC® BAA-1705™
MHT using MicroBiologica Quali-Control Microorganisms

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Genotypic
1. PCR to detect bla<sub>TEM</sub> & bla<sub>SHV</sub> with sequencing to determine various categories
2. Difficult to cover the whole range of mutations; not like mecA & MRSA
3. Largely a reference laboratory & research activity at present

How Can We Treat ESBL Infections?

Intriguing Case
• 32 year old policeman in Dublin presents with acute appendicitis
• No perforation at surgery; given co-amoxiclav prophylaxis
• ESBL +ve blood culture perioperatively but apyrexial & stable after surgery

Q. Does he need antibiotics? If so, which?

Treatment Options
• Many strains are resistant to other groups of antibiotics, e.g. aminoglycosides fluoroquinolones
• Delay in identification of ESBL in the laboratory
• Underlying disease/complicating conditions
  - elderly
  - ICU
• Few, if any, controlled trials

Treatment Options 1
Cephalosporins
Avoid use even of ceftriaxone & cefepime as results of studies are at best mixed

β-lactam-β-lactamase inhibitor
Some success with piperacillin-tazobactam but In-vitro activity may not be reflected In-vivo

Cephamycins
Cefoxitin in theory susceptible but other resistant mechanisms may be present, e.g. Amp C β-lactamase, porin loss

Carbapenems
Meropenem/imbipenem/imipenem, the drugs of choice. Early use favours good outcome

Treatment Options 2
Fluoroquinolones
If susceptible, can use, but may be inferior to carbapenems

Tigecycline
Good In-vitro activity but few trials & low levels in urine & blood

Colistin
Used for ESBLs & Acinetobacter spp. Can be administered IV, Intra-thecally & inhaled, potentially toxic

Fosfomycin
UTI & possibly for systemic infections

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Summary of Studies on ESBL Treatment

<table>
<thead>
<tr>
<th>Region</th>
<th>Treatment</th>
<th>Infection</th>
<th>Antibiotic Therapy</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Europe</td>
<td>Cefotaxim</td>
<td>Enterobacteria</td>
<td>Carbapenems</td>
<td>Small numbers of patients resistant to carbapenems</td>
</tr>
<tr>
<td>USA</td>
<td>Ciprofloxacin</td>
<td>Pseudomonas</td>
<td>Carbapenems</td>
<td>Increased resistance to carbapenems</td>
</tr>
</tbody>
</table>

Resistance to Carbapenems - 1

KPC Klebsiella pneumoniae carbapenemases found in USA, Israel, Greece & occasionally in UK

The gene bla KPC found on plasmid with resistance to other β-lactams
Problems in laboratory detection

Resistance to Carbapenems-2

NBM-1 New Delhi metallo-β-lactamases, found in 25 UK laboratories
Travel to India/Pakistan
67% susceptible to tigecycline, 100% to colistin
Diverse range of plasmid sizes, readily transferrable

How Can We Prevent & Control ESBLs?

The Answer

With difficulty, because
- different bacteria, different genes, different strains
- a human, animal & an environmental problem
- delays in recognition
- no consensus on screening
- few specific measures
- community reservoir

Principles of Prevention & Control

1) Education
2) Surveillance & early detection
3) Antibiotic stewardship
4) Isolation/cohorting as part of standard precautions

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HICPAC Overview of MDRO

<table>
<thead>
<tr>
<th>Focus of MDRO</th>
<th>MDR-GBS (no. of Studies)</th>
<th>MRSA (no. of Studies Using Control Measure)</th>
<th>VRE (no. of Studies)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Education of staff, patients or visitors</td>
<td>19 (63)</td>
<td>11 (51)</td>
<td>20 (50)</td>
</tr>
<tr>
<td>Emphasis on handwashing</td>
<td>16 (63)</td>
<td>24 (60)</td>
<td>11 (28)</td>
</tr>
<tr>
<td>Use of antiseptics for handwashing</td>
<td>12 (42)</td>
<td>12 (42)</td>
<td>10 (27)</td>
</tr>
<tr>
<td>Contact Precautions or isolation</td>
<td>12 (42)</td>
<td>12 (42)</td>
<td>10 (27)</td>
</tr>
<tr>
<td>Private Rooms</td>
<td>10 (34)</td>
<td>13 (32)</td>
<td>10 (27)</td>
</tr>
<tr>
<td>Segregation of cases</td>
<td>7 (25)</td>
<td>7 (25)</td>
<td>8 (21)</td>
</tr>
<tr>
<td>Cohorting of Patients</td>
<td>12 (42)</td>
<td>12 (42)</td>
<td>14 (36)</td>
</tr>
<tr>
<td>Cohorting of Staff</td>
<td>2 (7)</td>
<td>6 (17)</td>
<td>9 (25)</td>
</tr>
<tr>
<td>Change in Instrumental Use</td>
<td>4 (14)</td>
<td>1 (3)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Surveillance cultures of patients</td>
<td>19 (63)</td>
<td>34 (87)</td>
<td>26 (66)</td>
</tr>
<tr>
<td>Surveillance cultures of staff</td>
<td>9 (31)</td>
<td>8 (25)</td>
<td>7 (19)</td>
</tr>
<tr>
<td>Environmental cultures</td>
<td>15 (50)</td>
<td>14 (42)</td>
<td>10 (26)</td>
</tr>
<tr>
<td>Hand hygiene &amp; disinfection</td>
<td>11 (37)</td>
<td>8 (25)</td>
<td>12 (32)</td>
</tr>
<tr>
<td>Setting up &amp; managing isolation unit</td>
<td>3 (10)</td>
<td>2 (7)</td>
<td>4 (11)</td>
</tr>
<tr>
<td>Ward closure to new admission or to all patients</td>
<td>1 (3)</td>
<td>4 (12)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Other miscellaneous measures</td>
<td>2 (2)</td>
<td>3 (9)</td>
<td>17 (46)</td>
</tr>
</tbody>
</table>

Antibiotic Stewardship

1. Reduce the total use of antibiotics
   - In humans
   - In animals
2. Avoid the use of 3rd generation cephalosporins which also controls MRSA, VRE & C. difficile
3. Restrict the use of fluoroquinolones

Antibiotic Guidelines in European ICUs

- Based on local and national resistance patterns
- Based on local and national resistance patterns
- Revised at least once a year
- Revised less often than once a year
- No guidelines

Percentage of ICUs

Screening for ESBLs

Q. Should we actively screen for ESBLs?

Q. If yes, who should we screen, when should we screen & how?

Screening in Freiburg, Germany

- Screening on admission to 4 ICUs using chromogenic media (bio Merieux), using rectal samples. Also check clinical samples
- 755/1,674 (46%) screened, August-December 2007; 35 (5%) +ve
- Only 6/35 (17%) already known to be ESBL + ve; 9/35 (26%) developed an infection

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### Practical Measures

- Flag/alert charts & electronically
- Control access of individuals & equipment to +ve patients in isolation
- Improve cleaning & liaise with staff
- Consider changing empirical antibiotic use if ESBLs prevalent
- Provide +ve feedback

### Conclusions - 1

1. The problem of ESBLs is already with us & has been for some years
2. More difficult to prevent & control than MRSA, VRE & *Clostridium difficile*
3. Complex interplay between patients, the environment (hospital & external) & possibly staff

### Conclusions - 2

4. Laboratory detection is slow, laborious & compromises prevention
5. Unlike for MRSA, no new agents available or likely to emerge for treatment
6. Prevention & control is multi-faceted but non-specific, e.g. no decolonisation strategies
7. The value of active screening should be assessed; knowledge is power!

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**Enumeration and Characterization of Antimicrobial-Resistant *Escherichia coli* Bacteria in Effluent from Municipal, Hospital, and Secondary Treatment Facility Sources**

Sandra Gabriel,1,2 Enis Bojic,3 Paul Trickey,3 Norma,4,5 Mike O’Regan,2 Deirdre Shand,1 Maria Castaneda5

1School of Medicine, National University of Ireland, Galway, Ireland; 2Antrim, Sligo, and Rannafast Health Office, Health Service Executive, Northern Ireland, Ireland 3Department of Medical Microbiology, University Hospital Galway, Galway, Ireland 4Department of Medical Microbiology, IMH, UCD, St. James’s Hospital, Dublin, Ireland 5Department of Medical Microbiology, IMH, UCD, St. James’s Hospital, Dublin, Ireland

We describe a modification of the most probable number (MPN) method for rapid enumeration of antimicrobial-resistant bacteria in wastewater effluent samples. Bacterial 16S rDNA sequences were determined by PCR amplification of a defined 100 bp fragment of the 16S rDNA gene, followed by sequencing. 16S rDNA sequences were used to identify antimicrobial-resistant bacteria from wastewater effluent samples from a hospital in Ireland and municipal sewer systems in northern Ireland. DNA extracted from the mobile effluent samples from the hospital and municipal sewer systems was used to identify the predominant species of bacteria that are resistant to various antimicrobial agents. The bacteria were then cultured in the laboratory to determine the antimicrobial resistance patterns. The results were presented in this study.

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**Thank you**

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