**Extended spectrum B-lactamase (ESBL) producing E.coli**

Dr. Graham Harvey, Shrewsbury & Telford Hospitals NHS Trust, Shropshire, UK

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**What are Beta-lactamases?**

- Enzymes produced by bacteria
- Break down the B-lactam ring
- Eg in Penicillin
- Some have an “extended spectrum” and break down more agents eg cephalosporins

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**ESBL Evolution**

- Mid 1980s
- Variants of TEM and SHV
- Breakdown 3rd generation cephalosporins
- Mainly in hospital Klebsiella
- Spread worldwide

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**Spread of CTX-M**

- Cefotaximases
- CTX-Modifying (CTX-M)
- Late 1990s – Many parts of the world
- 2000-1 – First UK isolates (Klebsiella)
- 2003 onwards – widespread across UK
- Especially CTX-M-15

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**CTX-M evolution**

- 40 enzymes since 1986 largely in last 3 years
- 5 subgroups:
  - CTX M (inc.15- India, Poland, Bulgaria, France, Japan) Far East
  - CTX M9 Korea
  - CTX MKluyvera georgiana homology)
  - CTX M2 Birmingham, UK
  - CTX M2K ascorbata) S America. Far East

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**The British national CTX M5 E.coli outbreak January 2003 - September 2004**

- Strain A 025, with IS26, usually gentamicin S:
  - 12 labs 33% referrals:
  - >300 cases in 3 centres >250 miles apart
- Strains B 025, no IS26, often gentamicin R:
  - >50 labs 33% referrals, (occasional CTX M3)
- Diverse strains:
  - >50 labs. 95% usually CTX M5, rarely CTX M9 group.

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Why are ESBL producers a problem?
- Confer resistance to cephalosporins, penicillins & penicillinase inhibitors
- Often have multiple resistance
- Spread to commonest species : E.coli
- Asymptomatic pre- & post- infection carriage
- Recognition/testing problems
  - Some apparently susceptible to 1st/2nd gen cephalosporins

ESBL producing E.coli in Shropshire England
- Emerging problem since 2003
- Hospital and community infections
- Several control measures introduced
- Describe our local experience

Maps of Europe and Shropshire, UK.

Shropshire geography:

Shropshire hospital setting
- 540,000 population.
- 2 general hospitals 300 & 520 beds 18 miles apart
- 7 intermediate care hospitals : 3 in Wales
  - specialist 230 bed spinal injury & orthopaedic hospital.
- 12% single rooms
- Minimal neutropenia / transplantation.

Start of the Shropshire 2003 outbreak
- Multi-resistant UTIs in community patients emerging problem early May 2003 - computer search shows emergence from Jan 2003
- Two E.coli strains both resistant to quinolones, cephalaxin and trimethoprim, one gentamicin resistant.
- Both sensitive to nitrofurantoin & carbapenems
- Cefpodoxime resistant but clavulanate enhanced (ESBL)
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Quinolone-resistant cefpodoxime-resistant but non-ESBL-producing E coli
- Not O25
- Cefoxitin resistant (unlike ESBL)
- Half trimethoprim susceptible
- 26 PFGE typed.
  - 18 unique
  - 4 pairs
  - No epidemiological association between pairs
- Same therapeutic implications
- Co-selected?

Quinolone R.Cephalexin S Urinary E coli
- Jan 2003 to Mar 2004
- 562 isolates, 370 patients
- 27/98 patients with TriR NitS strain, ESBL

Estimate of missed Lex S ESBL

Shropshire case definition
- ESBL cases defined as:
  New cases of infection with E. coli
  With ESBL and resistance to quinolones (and trimethoprim in urine)
  Diagnosed in the Shropshire laboratory since January 2002.

Insertion sequence (Is26) issues
- In Shropshire O25 cluster
- In Group A inserted between ISEcp1 and beta-lactamase-CTX-M-15
- Associated with 8-fold decreased MIC to ceftazidime, cefotaxime, cefpodoxime & cefalexin.
- Marked change in antibiotic disc zone sizes sufficient to cause error

Shropshire outbreak of ESBL producing E coli.
- 364 clinical cases (infections) 1 Jan 03 to 30 Sep 04
  - 68% female, mean age 74 years
  - 49% community samples/51% acute trust samples
  - 85% community previously hospitalised.

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E.S.B.L producing E.coli in Shropshire

- Mainly causes urinary tract infections but have also post-operative wound infections, pneumonia and septicemia.
- Malignancy, diabetes, dementia

Early Findings

- Gentamicin sensitive strain initially apparent as a community problem.
  - samples from GPs and few from psychiatric hospital.
  - Only 1 nursing home resident.
  - No apparent serious cases.

- Gentamicin resistant strain mainly in Telford Hospital.

The evolution of the outbreak – Clinical and epidemiology 1.

- In-patient cases initially in Telford area.
- Later spread across the county
- No obvious ward focus (21 wards)
- 90% Hospital contact in past 3 years
- But in 10% cases no local acute hospital contact.

E.S.B.L producing E.coli in Shropshire

- Where did it come from?
- Not alone – Southampton + Belfast have identical strain to our gentamicin sensitive isolates (“strain A”)
- 70 labs across UK
- ? Food source

New cases of ESBLs within the Telford and Wrekin PCT

New cases of ESBLs within the Shropshire County PCT

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**Response to the outbreak .1**
- Community/Hospital outbreak team (Aug 03)
- Letter to consultants/GPs Sept 03
- Restrictive antibiotic reporting
- Increased use of carbapenems
- Cases isolated in side rooms

**Less obvious serious infections**
- First 105 cases, mainly UTI – 28 deaths
- Only 5 had bacteraemia - 2 died
- Case note review by GH and REW
- 16/21 causal/associated with death
- Reported as a “Serious Untoward Incident” to StHA
- External review by Prof Gary French

**Antibiotic Policy changes**
- Nitrofurantoin substituted for quinolones in UTIs
- Imipenem substituted for quinolones in routine reporting serious sepsis
- Ertapenem introduced
- Gentamicin substituted for cephalosporins in surgical prophylaxis/serious sepsis
- Return to amoxycillin in respiratory tract infections

**Response to the outbreak .2**
- March 2004 new hospital antibiotic guidelines introduced and strongly promoted

**Response to the outbreak .3**
- Increased use of hand gel
  - Hand gel by each bedside
- Marking of patient’s electronic records
- Daily computer search for re-admissions
- “ESBL management unit”
  - Cohort ward
  - Opened May to June 04
  - Re-opened October 04

**Further review of deaths**
- 87 deaths out of the 326 cases to August 04
- Case note review and data collection of 50 deaths
- Major burden
  - One third discharged then died: GP records
  - 10 death certificates mention UTI + 2 septicaemia
- External review by Prof French
  - Direct mortality of 19%

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"Community" cases of ESBL producing E.coli – associated features

- Follow-up of 73 (62%) cases April-June 2004
  - 19% in residential/ nursing home
  - 59% had underlying medical conditions
  - 38%, only, of patients had classical UTI symptoms
  - 82% had been treated with antibiotics
  - Initial antibiotics used norfloxacin, trimethoprim and cephalaxin

Community acquired ??

Patients tested within 3 days of admission

The iceberg of faecal colonisation

<table>
<thead>
<tr>
<th>Opportunistic tests:</th>
<th>No. tested</th>
<th>Positive</th>
<th>% Positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 Local Hospitals</td>
<td>291</td>
<td>15</td>
<td>5.2%</td>
</tr>
<tr>
<td>3 Local communities</td>
<td>475</td>
<td>11</td>
<td>2.3%</td>
</tr>
<tr>
<td>7/11 not hosp assoc.*</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- * 4 unrelated types (1 Thailand, 1 RAF),
- 1 E.coli O25 Group B (Nepal)
- 2 E.coli O25 Group A (1 recent typhoid non UK)
- So IMPORTATION of non-clonal types?

Bacteraemias

- 24 patients, 27 bacteraemias throughout period
- 19 the isolates was the patient’s first isolate
  - Often associated with urinary infection
- 12 bacteraemic patients dead
  - (0,1,1,2,12,14,24,28,43,58,159,217 days post)
- 10 patients had gentamicin resistant strains
  - 5 deaths/10 vs 7/14 gentamicin susceptible strains
  - (0,2,14,43,159 days post)

Mortality after initial isolation: Non bacteraemias.

- Deaths/week
- Week post 1st isolation

?Relevance to attribution/underlying disease
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Royal Shrewsbury Hospital - Antibiotic Reduction

Royal Shrewsbury Hospital Increase

Shropshire ESBL outbreak by gent resistance
Aug02-Dec04

Health Protection Agency report September 2005

Local lessons learnt
• Shared community/hospital problem requiring treatment with carbapenems in acute & chronic healthcare settings
  - Empirical use in elderly - bacteraemia & occult severe infection
  - Recurrent urinary tract infection and re-infection very common
• Infection control very difficult.
  - Silent carriage offers opportunities for spread.

Antibiotic policy
Isolation ward

Recommendations
• Laboratory recognition of ESBL producers
• Guidance to GPs on sending urine samples
• Local updates on antibiotic resistance
• Informing CCDC
• Increased surveillance
• Extent of asymptomatic carriage
• Investigation of infection control measures
• Investigation of animal carriage

www.hpa.org.uk/hpa publications/esbl_report_05/default.htm

Investigations into multi-drug resistant ESBL-producing Escherichia coli strains causing infections in England
September 2005

www.hpa.org.uk/hpa publications/esbl_report_05/default.htm
Conclusion

- Ertapenem and Imipenem are likely to replace cephalosporins for empirical therapy in the face of a rise in CTX-M ESBLs & AmpC in E. coli.
- Trimethoprim/quinolone resistance of ESBLs limits therapeutic options
- Role of older agents such as aminoglycosides needs review—can they be used to spare carbapenems?
- Need for oral carbapenems/ & study of cephalosporin + β-lactamase inhibitors

Acknowledgements

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Presented by Dr. Robert Garcia
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December 8 – Bloodborne Pathogen Control in the Community
Presented by Dr. Jun Wu

December 15 – C. difficile: Environmental Survival
Presented by Dr. Michelle Allo
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