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Extended Spectrum Beta-lactamases: Epidemiology and Infection Control Issues

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Objectives
1) What are Extended Spectrum Beta-Lactamases (ESBLs)?
2) Epidemiology - Europe, USA,
3) Canadian ESBL isolates
4) Rationale for controlling antibiotic resistance in these isolates
5) Infection Control measures and their effectiveness

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What are ESBLs?
- Plasmid-encoded enzymes which hydrolyze newer cephalosporins and aztreonam, but with little effect on the cephapmecins. Their action is blocked by clavulanic acid.
- Strains may appear to be susceptible in vitro to the third generation cephalosporins making them difficult to detect
- No one-size-fits-all screening test for ESBLs
Just to make it more confusing!

- Most commonly seen in E.coli and Klebsiella but can be found in other gram negative organisms
- Different types of ESBLs and bacteria may produce more than one
- Can be difficult to sort out when combined with other types of beta-lactamase resistance (e.g. AmpC beta-lactamases)

Laboratory capacity to detect resistance

Ability to detect ESBLs is limited:
- ESBLs may not exhibit third generation cephalosporin resistance
- Screening methods are not reliable:
  - Automated systems not reliable
  - Compliance varies widely
NCCLS Criteria

- Screening: reduced susceptibility to the recommended screening agents
- Confirmatory testing: based on tests with combinations of the screening agents and the beta-lactamase inhibitor, clavulanate.
  Done only after screening

Epidemiology

World-wide
- SENTRY Program (ICAAC 2001)
  - 18% of isolates had positive ESBL test
    - E.coli 0.2 - 8.5% to K.pneumoniae 0 to 34%.
- Rice (ICAAC 1999)
  - 455 consecutive cases of K.pneumoniae bacteremia from 6 continents
  - 19% had ESBL phenotype (2-67%)
  - 3.5% community, 43.5% ICU, 26% non-ICU

United States
  - 5% K.pneumoniae ESBLs
- Coudron (J Clin Microbiol 1997;35:2593-2597)
  - 9% of Enterobacteriaceae had ESBLs
- Jones (Diagn Microbiol Infect Dis 1998;20:215-228)
  - CAZ resistance E.coli 10.3% Klebsiella 24%
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**CHEC ESBL study**

Phase One: a one year study to:
- determine extent and nature of ESBL-producing *E. coli* and *Klebsiella*
- establish a national collection of these isolates
- characterize the isolates by plasmid profiling, DNA fingerprinting, isoelectric focusing and PCR genotyping
- determine the antibiotic susceptibilities of confirmed ESBL isolates
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### Number of Confirmed ESBLs

<table>
<thead>
<tr>
<th>NCCLS (%)</th>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td><strong>E. coli (n=389)</strong></td>
<td>81 (21)</td>
<td></td>
</tr>
<tr>
<td><strong>Kleb. (n=122)</strong></td>
<td>41 (34)</td>
<td></td>
</tr>
<tr>
<td><strong>Total (n=511)</strong></td>
<td>122 (24)</td>
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</tbody>
</table>

*511 isolates submitted out of 29,323 E.coli and 5,156 Klebsiella tested*

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### ESBL Canadian Distribution

<table>
<thead>
<tr>
<th>No. of Isolates</th>
<th>West (n=47)</th>
<th>Central (n=53)</th>
<th>East (n=73)</th>
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</thead>
<tbody>
<tr>
<td><strong>E. coli</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Klebsiella</strong></td>
<td></td>
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### Vitek Drug Resistance

<table>
<thead>
<tr>
<th>Drug</th>
<th>ESBL</th>
<th>Non-ESBL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>E</td>
<td>K</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>53</td>
<td>5</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>50</td>
<td>5</td>
</tr>
<tr>
<td>Nitrofurantoin</td>
<td>8</td>
<td>15</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>52</td>
<td>68</td>
</tr>
<tr>
<td>Amikacin</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>Tobramycin</td>
<td>42</td>
<td>46</td>
</tr>
<tr>
<td>Trimeth-Sulfa</td>
<td>72</td>
<td>56</td>
</tr>
</tbody>
</table>
IEF Analysis of ESBL Isolates

Summary of Laboratory Information
- ESBLs have been identified in West and Central regions
- ESBL generally more resistant to other classes of antimicrobials
- Numerous ESBL gene classes observed
- Fingerprints vary considerably and may not be useful in some cases
- Observed spread of plasmids across country in a few cases

Epidemiology
- 122 confirmed ESBLs
- 66.4% (81) E.coli and 33.6% (41) were K.pneumoniae
- ESBL E.coli: 57% Female, 43% male
- ESBL Kleb: 66% Female, 34% male
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ESBL E.coli

Mean Age = 59 yrs Rate of ESBL E.coli 0 - 1.79

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ESBL E.coli

Clinical Area

Mean Age = 61 yrs Rate of ESBL K.pneumoniae 0 - 3.25

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ESBL Klebsiella

Mean Age = 59 yrs Rate of ESBL E.coli 0 - 1.79
Should we use infection control precautions for ESBLs?

The jury is still out!

BUT outbreaks may be costly

- Meyer K (Ann Intern Med 1993;119;353-358)
  155 PTS with CAZ R Klebsiella: costs included personnel time, increased barrier precautions, increased laboratory screening, changes in antibiotic formulary

They may be associated with increased morbidity/mortality

- Schiappa (ID 1996;17:283-36)
  Case control analysis 31 pts with CAZ R K.pneumoniae or E.coli bacteremia. NSD in LOS after bacteremia, but higher risk of dying in case group if inappropriate tx received.

- Paterson et al (ICAAC 1999)
  K.pneumoniae bacteremia in 12 transplant units. 28% were ESBL. NSD in mortality, but more breakthrough bacteremias. Median LOS longer

- Qavi (IDSA 1999)
  NY case-control study ESBL + Klebsiella had greater likelihood of sepsis-related mortality
Do isolation/precautions make a difference?

- Paterson et al. 70% of units had cross-transmission. These units did not isolate pts.
- Rice. In 6/7 hospitals with evidence of genotypic spread - pts not isolated. 3/5 hospitals with no spread isolated pts after detection.

Isolation...

- Nordmann. Increased isolation and barriers decreased ESBL rate from 16 to 10%.
- Soulier (J Hosp Infect 95;31:85-97) ICU gut colonization ESBL: 70% pre-intervention, 40% post-intervention. Intervention = handwashing, single-use equipment, waste control, increased barriers. No change in antibiotic protocols.
- Paterson DL (CID 2001;33:126-128) interventions included emphasis on hand hygiene and gut decolonization with quinolones.

Role of Precautions....

- Miller et al. (ICAAC 2001) both infection control and abx control measures were used but time-line analysis showed that infection control most likely responsible for decreasing ESBLs which were polyclonal in origin?
Long-Term Care as a Reservoir?

  Over 2 yr pd, 31/55 ESBL + pts were from LTC; most harboured same beta-lactamase. Stool cultures from one LTC revealed 18/30 residents carried E.coli strain with same plasmid
- Rahal (JAMA 1998;280-1253-1257)
  27% of R Klebsiella arose in LTC
- Schiappa (JID 116;174:529-36)
  1/2 Of ESBL bacteremias arose in LTC

Summary

- Ability to detect ESBL in Canadian laboratories varies
- Many laboratories do not screen and/or confirm for ESBLs
- Prevalence remains largely unknown in many institutions but ESBLs not a large problem in Canada
- Evidence suggests increased morbidity from ESBLs due to inappropriate antibiotics
- Most hospitals have no formal infection control policies on ESBLs. Infection control useful in outbreak situations?