# Extended Spectrum Beta Lactamases (ESBL) and Infection Control

**Prof. David Patterson, University of Queensland**

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***Extended-spectrum beta-lactamases (ESBLs) and Infection Control***

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Broadcast live from the annual conference of the
New Zealand National Division of Infection Control Nurses
*www.infectioncontrol.co.nz*

NEW ZEALAND NURSES ORGANISATION


The Weather


**A Webber Training Teleclass**
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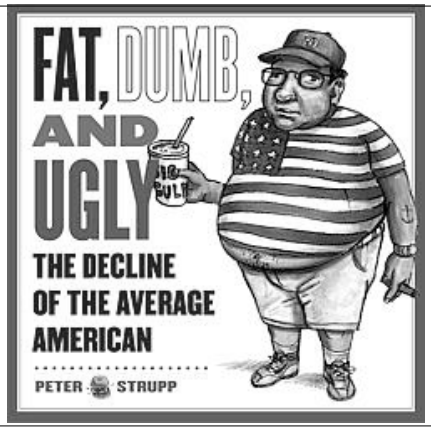
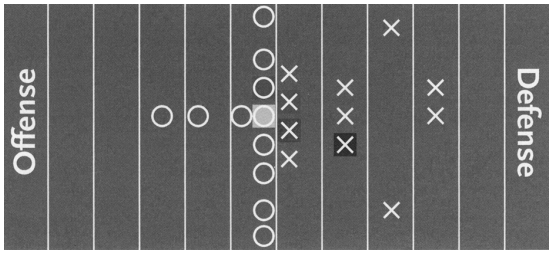
American Physical Fitness

And Sport







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## Rugby World Cup 2007

- Tonga 25 defeated USA 15

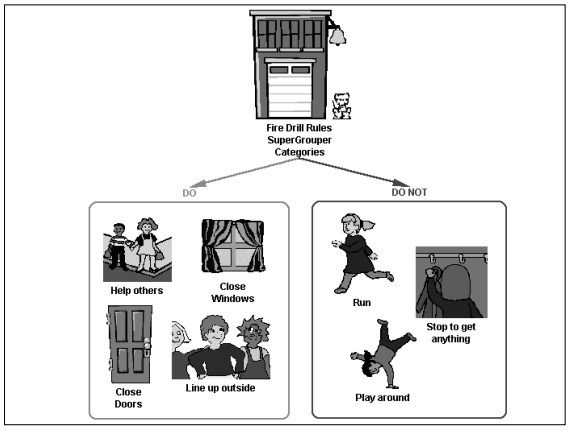
## Populations

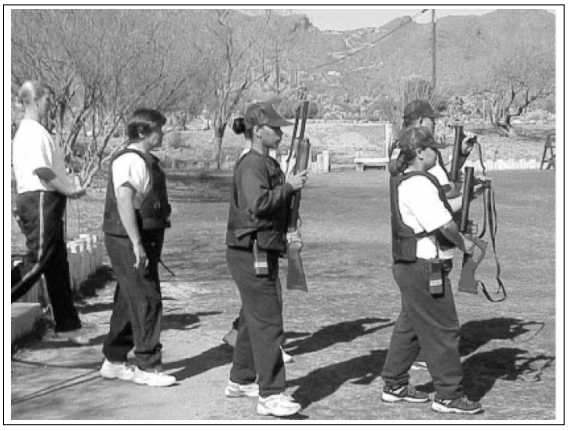
- Tonga 100,000
- USA 300 million

## Adjusted scores

- Tonga 75,000 def. United States 15

## 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

# Extended Spectrum Beta Lactamases (ESBL) and Infection Control

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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 cephamycins** (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

## XXX

This slide is censored!

## 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*

## 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*

## 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

## Some examples of agricultural antibiotic use

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

## 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

## Worldwide prevalence of ESBL producers

| | Kpn | *E.coli* |
|---|---|---|
| USA | 5.3% | 2.8% |
| Latin America | 27.6% | 12.0% |
| Northern Europe | 5.2% | 1.4% |
| Southern/East. Europe | 25.7% | 6.6% |
| China | 37.3% | 31.3% |
| Australasia | 4.6% | 1.6% |

## 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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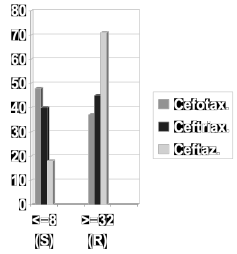
## ESBL producers frequently appear susceptible to cephalosporins




- *Enterobacteriaceae* are traditionally reported as susceptible to ceftazidime, cefotaxime, ceftriaxone, aztreonam, and cefepime when MIC <= 8 µg/mL

## Whose breakpoints should we be using?

| | CLSI | | EUCAST | |
|---|---|---|---|---|
| | S | R | S | R |
| | ≤ | > | ≤ | > |
| Cefotaxime | 8 | 32 | 1 | 2 |
| Ceftazidime | 8 | 16 | 1 | 8 |
| Ceftriaxone | 8 | 32 | 1 | 2 |

## 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 ≤ 1 µg/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

## 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

## Carbapenems - treatment of choice for serious infections with ESBL producers

- Carbapenems are not hydrolyzed by ESBLs to any great extent
- Minimal inoculum effect
- 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]*

## Which carbapenem?

- Most data has been with imipenem/meropenem
- Ertapenem and ESBL producers
  - 91% (10/11) patients with bacteremia were successfully treated
  - 83% (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

| | $MIC_{50}$ | $MIC_{90}$ |
|---|---|---|
| *E. coli* | ≤ 0.06 | ≤ 0.06 |
| *K. pneumoniae* | ≤ 0.06 | 0.12 |
| *P. mirabilis* | 0.12 | 0.25 |

*[Fritsche ICAAC 2006 – E219]*

## 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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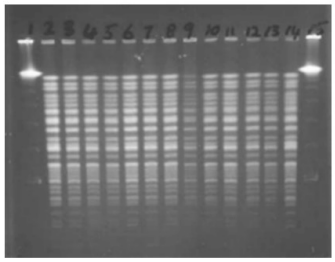
## What should we do in the hospital for ESBL producers?

- > 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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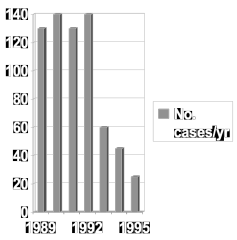
## Rectal swabs and ESBL producers

- 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

- Tixador R et al. Acta Astronaut 1985;12:131-134
- Cytos 2 experiment (French-Soviet manned flight July 1982)
- Bacteria became less resistant when taken into outer space

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## 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