ESBLs - Where Are We Now?
Dr. Fong Chiew
A Webber Training Teleclass

Perspectives from a Clinical/Medical Microbiologist Working in a Routine Laboratory

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American Society for Microbiology
Singapore Society of Pathology

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New Zealand

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Literature Search on PubMed
Paterson DL & Bonomo RA *Clin Micro Rev* 2005:
Explosion of knowledge on ESBL (upto October 2005)

The Woes of a Medical/Clinical Microbiologist

- Last 2 years: > 400 articles on ESBL
- For the more enthusiastic – search ‘pathogens’ yield > 48480 articles from:

Outline of Lecture

I. Historical perspectives
II. Update of most recent ESBLs
III. Epidemiology of spread of ESBL
IV. High index of suspicion – when to apply it
V. Laboratory detection
VI. Multi-faceted approach to manage ESBL

Historical Perspectives (I-1)
The Evolution of β-lactamases:
‘Lamentations’ of Sanders CC & Sanders WE in *Clin Infect Dis* 1992

- >50% ampicillin resistance in *E. coli*
- One of the early reports of resistance to third generation cephalosporins

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Classification of β-Lactamases (I-2)

Ambler – Structure Group

Bush – Functional Group

Definition of ESBL (I-4)

• ESBL is acronym for Extended-Spectrum β-Lactamases
• First reported in 1983 (Knothe H et al, Infect 1983)
• Characteristics of ESBL:
  • Class A by Ambler or Group 2be by Bush classifications
  • Typically, enzymes are plasmid-mediated derived from older β-lactamases of TEM and SHV
  • In early 2000s, CTX-M derived β-lactamases are included

What is it in 2007? (I-5)

• Plasmid-mediated AmpC β-lactamases, PER, Toho, etc?
• Chromosomal AmpC in K. pneumoniae & E. coli?
• Integron-mediated β-lactamases with multidrug resistances?:
  Machado E et al; AAC 2007
  Poirel L et al; AAC 2006

Renaming ESBL? (I-6)

• Use clinical approach to depict multiplicity of enzymes in the same isolate?
• Change to Expanded Spectrum β-Lactamases or X-Spectrum β-Lactamases?
• Useful read on controversies about ESBL and AmpC β-lactamases – see Thomson KS, EID 2001

Update of Most Recent ESBLs (II-1)

Reference
http://www.lahey.org/studies/

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Update of Most Recent ESBLs (II-2)

- Important not to restrict singular enzyme per pathogen
- Rather, multiple enzymes can be found within the same pathogen
- Co-resistances to other antimicrobial groups compound the complexity (e.g. fluoroquinolones, trimethoprim, gentamicin, carbapenem)

The pathogens conduct their own conjugation and transformation experiments (without human funding)

Epidemiology of ESBL (III-1)

Paterson DL and Bonomo RA *Clin Microbiol Rev* 2005
- Europe
- North America
- South and Central America
- Africa
- Asia

Epidemiology of ESBL (III-2)

Europe
- France – early 1990s 25-35% nosocomial *K. pneumoniae*
  - Year 2000, 30.2% *Enterobacter aerogenes*
- SENTRY 1997 and 1998 - 25 European hospitals (ICU and non-ICU) 21% *K. pneumoniae*

North America
- NNIS 1998-2002 - 6.1% *K. pneumoniae* from 110 ICUs
  - 10% of ICU >25%
  - Non-ICU 5.7% *K. pneumoniae*
  - Outpatients 1.8% and 0.4%
- Between 2003-2004 – emergence of CTX-M

Epidemiology of ESBL (III-3)

South & Central America
- 1989 - CTX-M linked to *Salmonella enterica* spread to many parts of the continent. Did the method for detection included CTX in addition to CAZ?
  - ICUs (Brazil, Colombia, Venezuela) - 30-60% of *klesbiella*

Africa
- 36.1% of *K. pneumoniae* from a single South African hospital
- CTX-M found in Kenya reported in 2001

Australia
- SENTRY 1998-1999 Overall 5% in hospitals

Epidemiology of ESBL (III-4)

Asia
- SENTRY 1989-1999
  - 30.7% *K. pneumoniae* and 24.5% *E. coli*
  - Teaching hospital in Beijing reported in 2002 27%
    (both *K. pneumoniae* and *E. coli*) from blood cultures
  - Zhejiang Province (China)
    - 34% *E. coli* and 38.3% *K. pneumoniae*
  - Reports of CTX-M from 2001:
    - India, China, Japan, Korea, Taiwan and spreading

Epidemiology of ESBL (III-5)

Subsequent to 2005:
- Increasing reports of plasmid-mediated AmpC in *E. coli* and *K. pneumoniae*
- Co-existence of ESBL, AmpCs and other β-lactamases in the same isolate

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<tr>
<th>High Index of Suspicion in Healthcare Settings – when to apply it (IV-1)</th>
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<tbody>
<tr>
<td>• A) Endogenous – enemies from within</td>
</tr>
<tr>
<td>• B) Exogenous – enemies from without</td>
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<tr>
<td>• C) Level of infection control</td>
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<td>• D) Level of antimicrobial utilisation</td>
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<td>Others, e.g., antimicrobials &amp; food production</td>
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<tr>
<th>Endogenous: The Gastrointestinal Tract (IV-2)</th>
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<tr>
<td>• Within the 7 feet or so of intestinal tract in humans, genetic exchange can occur between pathogens and/or microbes?</td>
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<tr>
<td>• For e.g. AmpCs from Enterobacter spp (&amp; others) can pass onto E. coli and K. pneumoniae and vice versa?</td>
</tr>
<tr>
<td>[The same events occur in food animals?]</td>
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<th>Exacerbation of Genetic Exchange (IV-3)</th>
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<tr>
<td>• Multiple courses of antimicrobials</td>
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<tr>
<td>• Indwelling catheters</td>
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<td>• Multiple premorbid conditions</td>
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<tr>
<th>B. Exogenous – Enemies from Without (ie in the vicinity) (IV-4)</th>
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<tr>
<td>• Long hospital stay</td>
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<td>• Residing in long term care facilities</td>
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<td>• Patient in the next cubicle or someone transferred from elsewhere who harbours ESBL (hospital, centre, country)</td>
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<th>C. Level of infection control (IV-5)</th>
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<td>Is this a recent implementation?</td>
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<td>For a long time, MRSA was the only pathogen deserving strict hand hygiene &amp; not GNR</td>
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<th>D. Level of Antimicrobial Utilisation (IV-6)</th>
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<td>What are the significance and relevance of selective pressure?</td>
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Is There an Association Between Cephalosporins Usage and Their Corresponding Resistances? (IV-8)

- How much cephalosporins are used and what are these?
- If cefotaxime (and or ceftriaxone) are used in far greater excess over ceftazidime, then CTX (and or ‘CEF’) predominates?

Monnet D ‘How Antimicrobials Drive Resistance’
ASA 2007 see http://www.aasri.net.au/ross/ (IV-9)

V. Laboratory Detection (V-1)
Historical perspectives
1988
Jarlier effect – CTX with Augmentin (Jarlier V et al Rev Infect Dis 1988)
1990
NCCLS– ceftazidime zone <15mm Kirby Bauer Method for screening
1994
Synergy testing with ceftazidime (Sader HS et al Diagn Microbiol Infect Dis 1994)

Laboratory Detection (V-2)
1996
Etest with ceftazidime and clavulanate was recommended (Cornican MG et al JCM)
1996
>50% ESBL E. coli and 29% of ESBL K. pneumoniac were resistant to cefotixin and 10% of non-ESBL E.coli and K. pneumoniac also resistant to cefotixin
(Jacoby GA & Han P JCM )
2001
Cefpodoxime recommended for screening Clin Microbiol Rev
2001

Current Modern Methods (V-3)

- CLSI – Clinical Laboratory and Standards Institute
- ARMRL - Antibiotic Resistance Monitoring and Reference Laboratory, Health Protection Agency Centre for Infections, London
- EUCAST- European Society of Clinical Microbiology & Infectious Diseases
- Commercial methods – Etest, BD Phoenix, Vitek, Neo-tabs & others

Law of Serendipity (V-4)
in association with:
Otago Diagnostic Laboratories (ODL)
Method for the detection of β-lactamases in Enterobacteriaceae

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Observations and Questions from Staff of ODL in Dunedin Hospital, NZ (V-5)

- Routine laboratory struggles with ESBL detection: clinical isolates do not conform to behaviour of research isolates
- Jarlier effect appears obsolete for the detection of ESBL
- Reference laboratories e.g. ESR Wellington (NZ) uses it (Jarlier effect)
- Double Disk Test for ESBL from Mount Sinai Hospital, Toronto, Canada looks plausible

TRICKS OR TREATS
Presented at 2004 NZ National AIDS Meeting
Refer Pathology Oct 2005;37(7):37-1-7

Improved Template for Placement of Antimicrobial Discs (V-6)

Reference Strain E. cloacae ARL04/111 Demonstrates derepressed AmpC and ESBL (V-7)

Reference Strain E. cloacae ARL04/173 Demonstrates Inducible AmpC and ESBL (V-8)

Clinical Isolate E. cloacae Demonstrates Inducible AmpC and CTX-M (V-9)

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Clinical Isolate E. coli Demonstrates AmpC-like β-Lactamase (note resistance to cefoxitin) (V-10)

ATCC K. pneumoniae 700603 Reference Strain for ESBL: note cefoxitin resistance (V-11)

NB: Older version of ODL Method was used

Real vs Apparent (V-12)

Is Epidemiology of ESBL directed by laboratory methods?

VI. Multi-faceted Approach to Manage ESBL / XSBL (VI-1)
A) Ascertain clinical significance of isolate obtained
B) Reduce unnecessary antibiotic utilisation (& reduce unnecessary adverse effects too)
C) Determine third generation cephalosporins usage
D) Pharmacokinetics and Pharmacodynamics
E) Infection control
F) Funding
G) Closer collaboration between research and clinical laboratories
H) Investments by manufacturer on education
I) Manage antimicrobials in food production

A. Ascertain Clinical Significance of Isolate Obtained (VI-2)

Is it a contaminant, colonizer or true invasive pathogen?

Overdiagnosis of Infections (VI-3)
The quality of measurement of surgical wound infection as the basis for monitoring: a systematic review

Ehrenkranz NJ et al; Infect Control Hosp Epidemiol 1995 Dec;16(12):712-6
An apparent excess of operative site infections: analyses to evaluate false-positive diagnoses

Effect of surgeon's diagnosis on surgical wound infections

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Interpretation of Laboratory Results (VI-5)
Close clinician-laboratory interaction to minimise over-diagnosis and miss-diagnosis of infections

Metaphorically Speaking…….(VI-6)
Prof Ben de Pauw’s presentation at ISAAR 2007

B. Reduce Unnecessary Antibiotic Utilisation
To Decrease Selective Pressure & Reduce Unnecessary Adverse Effects Too (VI-7)

  Hospital-based intensive monitoring of antibiotic-induced adverse events in a university hospital.
- Sanford Guide to Antimicrobial Therapy: http://www.sanfordguide.com/

C. Determine Third Cephalosporins Usage and Frequency of ESBLs (VI-8)
K Urbanek, M Kolar, Y Lovecova, J Strojil, and L Santava
Influence of third-generation cephalosporin utilization on the occurrence of ESBL-positive *Klebsiella pneumoniae* strains
http://highwire.stanford.edu/cgi/medline/pmid:17635342

D. Choice of Antimicrobials for Treatment (VI-9)
A Carbapenem?
What are the Pharmacokinetics and Pharmacodynamics?

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D. Pharmacokinetics and Pharmacodynamics (VI-10)

Lessons learnt and Questions arising from
46th ICAAC Workshops
San Francisco, USA

Questions/Problems about PK/PD approach to prevent emergence of resistance (VI-11)

- Polymicrobial infection
- Subtherapeutic dosing in the presence of biofilm formation arising from indwelling catheters
- Choice of parameters? – for e.g. [C]/MIC, AUC/MIC, T>MIC
- MIC is not sufficient to evaluate the PK/PD relationships of antimicrobial agents.
- PK/PD analysis based on MIC alone can be misleading.
- Protein binding and tissue distribution are important pharmacokinetic parameters that need to be considered
- Variance of PK in population?
- What is the correct PD index target (static, -1 log, -2 log drop@24h?, 48h? 5d end point?)

Questions/Problems about PK/PD approach to prevent emergence of resistance (VI-12)

- Variability in the PD target size ie inoculum.
- Variance of PD for different micro-organisms groups?
- What is the prediction in chronic infection (bone; abscess formation)
- There are variations in methods and definitions of indices as well as uncertainty about errors.
- What about combination antimicrobial therapies – synergy, antagonism, additional effects?
- What about drug interactions with non-antimicrobial agents?
- MICs may be lower or higher for different regions?
- Is PK/PD different for neutropenics and non-neutropenics?

Nevertheless……(VI-13)

PK/PD is vital to prevent:

- Subtherapeutic dosing which leads to emergence of resistance
- Overdosing which leads to toxicity

E. Infection Control (VI-14)

Plays a vital role in centres where ESBL rates are low but becomes desperate when rates >50%

ESBL and Infection Control (VI-15)

  "Gramian outbreak"
- Contantino LO et al J Hosp Infect 2007
  Impact and cost of infection control measures to reduce nosocomial transmission of extended-spectrum beta-lactamase-producing organisms in a non-outbreak setting
  Surveillance of multidrug-resistant gram-negative bacilli in a neonatal intensive care unit: prominent role of cross transmission
  Emergence and prevalence of beta-lactamase-producing Klebsiella pneumoniae resistant to cefepime in Japan
  Influx of extended-spectrum beta-lactamase-producing enterobacteriaceae into the hospital.

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F. Funding – for what? (VI-16)
- For e.g. inadequate staffing and inadequate training?
- And for all of the mentioned VI (A-I)

G. Closer Collaboration Between Research and Clinical Laboratories (VI-17)
Clinical isolates are more complex than the research ones and they evolve faster too in clinical settings

H. Contributions by Manufacturer Towards Combating Antimicrobial Resistance e.g. ESBL (VI-18)
Priority (amongst others) given to education concerning:
- antimicrobial resistance
- how to sustain shelf-lives of antimicrobials
- benefits to individual patient care
- consequential profit gains

I. Antimicrobial Usage in Food Production (VI-19)
Direct effects of selective pressure are more urgent/important on human pathogens?
- For e.g. Rapid spread of Staphylococcus aureus with reduced susceptibilities to vancomycin widely reported in Europe due to prescriptions in healthcare - despite withdrawal of avoparcin in food production?

Nevertheless, Indirect Selective Pressure Is Eminent & Imminent (VI-20)
- Mayrhofer et al Microb Drug Resist 2006
- Bengtsson B & Wierup M al Anim Biotechnol 2006
- Slorach SA Rev Sci Tech 2006
- Fluckey WM et al J Food Prot 2007
- Many others

What Approach Should We Adopt to Address Antimicrobial Resistance? (VI-21)
- Gentle approach
- Forceful approach

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Gentle Historical Approach (VI-22)
French Philosopher Blaise Pascal said:
“No one is strong unless he or she bears within their character antithesis strongly marked”
In the arena where we watch humans pit their wits against the ingenuity of microbes, some resemblance to this philosophy may be observed. The brilliance and tenacity of the human mind that I shall summarily call “Thesis” are in constant battle with the counterattacks from microbes. “Anti-thesis” in the form of Human Arrogance or Despair may well tip the balance in favor of the counterraids. Our “Thesis” must be held in tension with other virtues like Humility or Hope accordingly – where strength is to be found. And by balancing these virtues, we then become more fully developed and stronger people.
Taken from MD Thesis “The Epidemiology and Laboratory Detection of Resistant Enterococci” carried out by Dr Yeko-Fong Chiew at the National University of Singapore

Modern More Forceful Approach
At The ISAAR 2007 (VI-23)
Dr Keryn Christiansen (Royal Perth Hospital, Australia) on ‘Managing Antibiotic Policies’
Dr Wing Hong Seto (Queen Mary Hospital, HK) on ‘Immediate Concurrent Feedback’
Dr Walter R Wilson on ‘Pathogens vs Humans’, some e.g.s: Similarities: Both are diversified competities
Differences: United (Pathogens) vs Divided (Humans)

Nobel Prizes and Antimicrobials
• Nobel prize awarded to discovery of penicillin
• Nobel prize to be awarded for capping antimicrobial resistances or miraculously reversing the trends for some of them?
What are involved?
Processes and team efforts?

Process and Team Efforts Outlined By CDC Campaign on Combating Antimicrobial Resistances in Healthcare Settings

Solution VI (A-I) to Enigma of ESBL
PERSEVERE!
Don’t Give Up
Have a Good Day

Contact: yfchiew@hotmail.com
For more beautiful jpegw images
by Mr Stephen Linkert, refer -
http://www.stephan.com/eng/engi
igma.html

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