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

Ayliffe Lecture

Preventing and Controlling ESBLs, The Future is Here

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

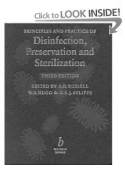
Broadcast live from the 2010 conference of the Infection Prevention Society
www.ips.uk.net

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



WORKING PARTY REPORT

Decontamination of minimally invasive surgical endoscopes and accessories

Chaired by G Ayliffe for the Minimal Access Therapy Decontamination Working Group*

Risk of airborne transmission in an operating theatre containing four ultraclean air units

J. B. Babb, P. Lynam and G. A. J. Ayliffe

Hospital Infection Research Laboratory, City Hospital NHS Trust, Dudley Road, Birmingham B18 7QH, UK.

Accepted for publication 1 June 1995

Aldehyde disinfectants and health in endoscopy units

The report of a working party of the British Society of Gastroenterology Endoscopy Committee

R E Cowan, A P Manning, G A J Ayliffe, A T R Axon, J S Causton, N F Cripps, R Hall, P J V Hanson, J Harrison, R J Leicester, C Neumann, J Wicks

Outline

What are extended-spectrum β-lactamases (ESBLs)?

Why are ESBLs important?

How can we treat ESBL infections?

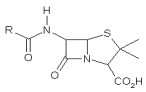
How can we prevent ESBLs?

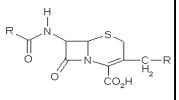
What Are ESBLs?

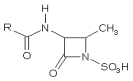
B-lactam Antibiotics

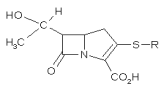
An antibiotic that has a B-lactam ring e.g.

- Penicillins
- Cephalosporins
- Monobactams
- Carbapenems


Penicillin nucleus


Cephalosporin nucleus


Monobactam nucleus


Carbapenem nucleus

Jerome Fennell, Dublin

A Webber Training Teleclass
www.webbertraining.com

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* & *Actinetobacter baumannii*

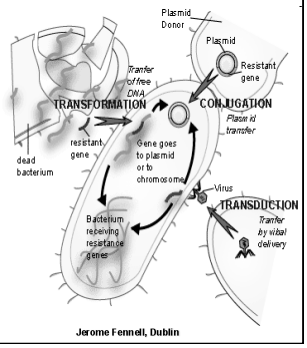
Origin

Chromosomally-located in *Kluyvera* 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



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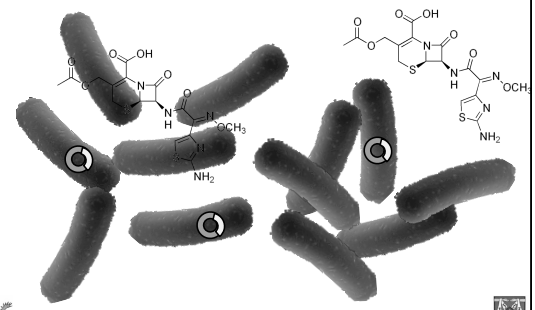
Selection for Resistance by Cephalosporins



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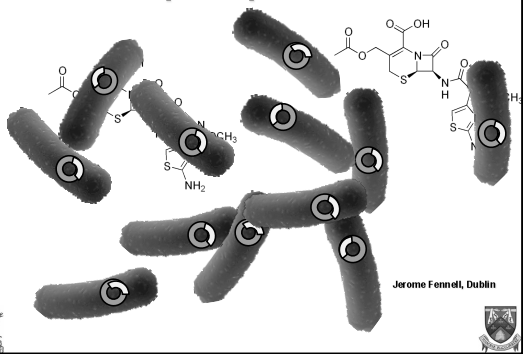
Selection for Resistance by Cephalosporins



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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

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

Jerome Fennell, Dublin

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

Study	Date	Samples	*E. coli*	*K. pneumoniae*
SENTRY	1997-98	Blood, urine, RT, SSI	1.3%	18.4%
SMART	2004	Intra-abdominal	6.4%	8.8%
TEST	2004-06	Blood, urine, RT, SSI, sterile fluids	7.6%	13.3%
MYSTIC	2006	Blood, urine, RT, SSI, sterile fluids	8.2%	9.8%

Eurosurveillance 2008; 13 (47)

3rd Gen. Cephalosporin Resistance in ICUs

Intensive Care Med 2009; 35: 91-100

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

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

	Croatia	Hungary	Sweden
E. coli	3.6%	18%	1.6%
Enterobacter cloacae	-	18.2%	20%
Klebsiella pneumoniae	17.8%	29%	0%

ESBLs in London

- Controlled study of bloodstream infections (50) with controls (50)

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

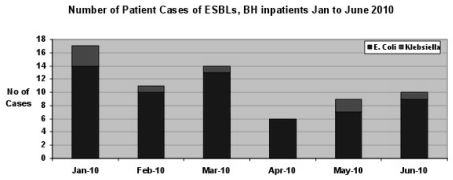
*significant on multi-variate analysis

- A patient receiving β-lactams was almost 11 times more likely to have ESBL BSI

J Hosp Infect 2006; 64: 115-123

ESBLs in Beaumont Hospital

- Weekly review of all isolates
- 67;70% urine, 14% blood or line tips



Community-Onset ESBL *E. coli* BSI

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

Risk Factor	OR
Age > 65	2.3
Female	1.9
Urinary tract infection	3.5
Cirrhosis	4.7
NH resident	8.6
Fluoroquinolones	2.8

Clin Infect Dis 2010; 50: 40-8

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
Fluorquinolone	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

J Antimicrobial Chemother 2009; 64: 635-641

MDR Gram Negative Bacteria in Long-Term Facilities

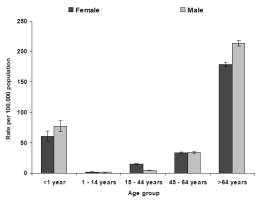
- Point prevalence study on 4 wards; residents, environment & HCWs
- 23% of residents +ve; 7.7% of HCWs & 3/175 (1.8%) of environmental sites
- VRE from 1 (0.6%) resident ; MRSA from 11.2% of residents & 1.2% of environment

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

Infect Control Hosp Epidemiol 2009; 30: 1172-1179

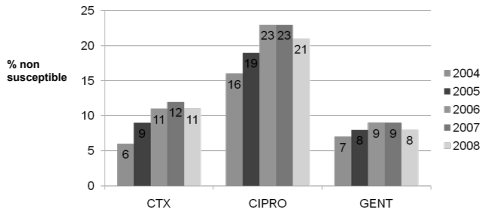
Prevalence of BSI *E. coli* Resistance

- HPA (England, Wales & NI) data from 2004: Reporting is not mandatory
- *E. coli* BSI increased from 17,411 to 23,974
- West Midlands & NI had the highest rates



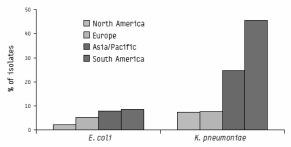
HPA, 21/8/2009

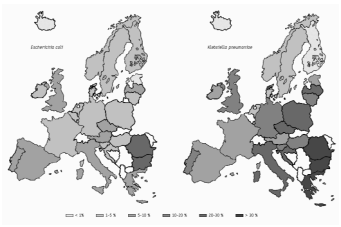
BSI *E. coli* Resistance



HPA, 21/8/2009

Invasive *E. coli* & *K. pneumoniae* in Europe & Beyond





Eurosurveillance Nov 2008

Outcome from ESBL Infections

ESBLs in ICU

	OR	p value
ESBL Infection		
Controls	1	
Cases	3.93	0.03
Control for Rx.		
Controls	1	
Cases	6.84	0.03
Control for disease severity		
Controls	1	
Cases	8.4	0.009

J Hosp Infect 2008; 68: 108-115

Community ESBL & Death

Urinary tract	0.001
Pitt score	<0.001
Inappropriate Rx.	0.007
14-Day mortality	0.02

Clin Infect Dis 2010; 50: 40-8

Laboratory Detection of ESBLs

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

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

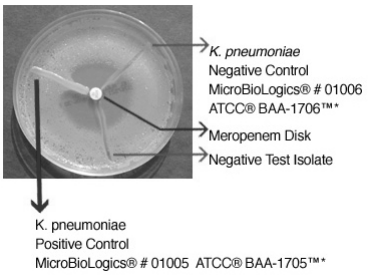
Phenotypic

Screening – testing for resistance to cefotaxime, ceftazidime, etc.

Confirmatory – synergy between cephalosporins & clavulanic acid, i.e. double disk or E tests

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

Hodge Test



MHT Using MicroBioLogics Quality Control Microorganisms

Genotypic

1. PCR to detect *bla*$_{TEM}$ & *bla*$_{SHV}$ 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-amoxyclav 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 fluorquinolones
- 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 ceftazidime & 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/etrapenem/imipenem, the drugs of choice. Early use favours good outcome

J Hosp Infect 2009; 73: 345-354

Treatment Options 2

Fluorquinolones	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

J Hosp Infect 2009; 73: 345-354

Summary of Studies on ESBL Treatment

	Type of study	Organisms	Infection	Antimicrobial therapy	Conclusions	Limitations
Burgess et al[28]	Retrospective	E coli, Klebsiella spp	Various	Carbapenems, piperacillin-tazobactam, fluroquinolones	Limited	Small number of patients; multiple assessments per patient; investigators not blinded
Endimiani et al[27]	Retrospective	K pneumoniae	Bacteraemia	Imipenem, ciprofloxacin	Good response with imipenem; poor response with ciprofloxacin	Small number of patients; potential for biases
Ho et al[29]	Case-control	E coli	Bacteraemia	Different empirical regimens	Higher crude mortality among ESBLs; poor response with ceftazidime	Specific data were not reported on treatment and outcome of patient subgroups
Kim et al[30]	Retrospective	K pneumoniae	Bacteraemia	Carbapenems, ciprofloxacin, aminoglycosides	Good outcome with carbapenems; limited numbers for ciprofloxacin and aminoglycosides	Small number of patients
Kim et al[31]	Observational	E coli, K pneumoniae	Bacteraemia	Empirical regimens with cephalosporins and aminoglycosides	Poor outcome with cephalosporins and aminoglycosides	Small number of patients; investigators not blinded
Kang et al[32]	Observational	E coli, K pneumoniae	Bacteraemia	Various regimens (empirical and definitive)	Poor outcome with empirical cephalosporins; good outcome with ciprofloxacin and carbapenems	Observational study with conflicting results
Paterson et al[33,51]	Observational, multicentre	K pneumoniae	Bacteraemia	Various	Good outcome with carbapenems compared with non-carbapenem regimens	Small number of patients; effect of empirical therapy not reported
Zanetti et al[34]	Randomised controlled trial	Various	Nosocomial pneumonia	Imipenem vs cefepime	Superior outcome with imipenem	Small number of patients
Lee et al[35]	Retrospective	K pneumoniae	Various	Carbapenems, flomoxef	Flomoxef as effective as carbapenems	Small number of patients
Bin et al[36]	Observational	CTX-M-producing E coli	Bacteraemia	Imipenem, ceftazidime, cefoperazone-sulbactam	Outcomes were similar in the three groups	Small number of patients; observational study

Lancet Infect Dis 2008; 8: 159-66

Resistance to Carbapenems - 1

KPC ***Klebsiella penumoniae*** **carbapenamases found in USA, Israel, Greece & occasionally in UK**

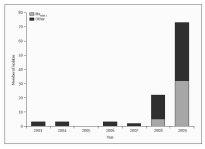
The gene *bla* $_{KPC1}$ found on plasmid with resistance to other β-lactams

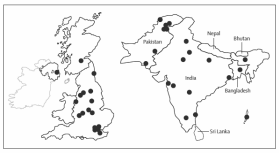
Problems in laboratory detection

J Antimicrobial Chemother 2010; 65: 1119-25

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





Lancet Infect Dis 2010; 10: 597-602

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

HICPAC Overview of MDRO

Focus of MDRO (No. of Studies)	MDR-GNB (n=30)	MRSA (n=35)	VRE (n=39)
	No. (%) of Studies Using Control Measure		
Education of staff, patients or visitors	19 (63)	11 (31)	20 (53)
Emphasis on handwashing	16 (53)	21 (60)	9 (23)
Use of antiseptics for handwashing	8 (30)	12 (36)	16 (41)
Contact Precautions or glove use[α]	20 (67)	27 (77)	34 (87)
→ Private Rooms	4 (15)	10 (28)	10 (27)
Segregation of cases	4 (15)	3 (9)	5 (14)
Cohorting of Patients	11 (37)	12 (34)	14 (36)
→ Cohorting of Staff	2 (7)	6 (17)	9 (23)
Change in Antimicrobial Use	12 (41)	1 (3)	17 (44)
→ Surveillance cultures of patients	19 (63)	34 (97)	36 (92)
Surveillance cultures of staff	9 (31)	8 (23)	7 (19)
Environmental cultures	15 (50)	14 (42)	15 (38)
Extra cleaning & disinfection	11 (37)	7 (21)	20 (51)
Dedicated Equipment	5 (17)	0	12 (32)
Decolonization	3 (10)	25 (71)	4 (11)
Ward closure to new admission or to all patients	6 (21)	4 (12)	5 (14)
Other miscellaneous measures	6 (22)[β]	9 (27)[χ]	17 (44)[δ]

ecdc
EUROPEAN CENTRE FOR DISEASE PREVENTION AND CONTROL

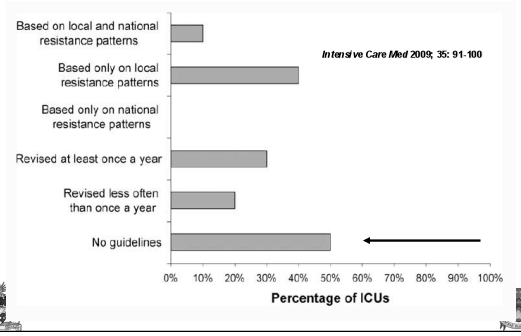
ECDC Threat Assessment

New Delhi metallo-beta-lactamase (NDM-1) carbapenemase-producing *Enterobacteriaceae* from the Indian subcontinent, August 25, 2010.

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 fluorquinolones

Antibiotic Guidelines in European ICUs



Intensive Care Med 2009; 35: 91-100

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 Mérieux), using rectal samples. Also check clinical samples
- 755/1,674 (45%) screened, August-December 2007; 35 (5%) +ve
- Only 6/35 (17%) already known to be ESBL + ve; 9/35 (26%) developed an infection

Infect Control Hosp Epidemiol 2009; 30: 103-5

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!

"*The emergence of ESBLs may be an inevitable evolutionary consequence*"

"Effective prevention & control may be outside the capacity of the healthcare community"

"Industry/agriculture, & politicians essential to solve the problem of prevention and treatment"

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0099-2240/10/$12.00 doi:10.1128/AEM.02898-09

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

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Received 1 December 2009/Accepted 18 May 2010

We describe a modification of the most probable number (MPN) method for rapid enumeration of antimicrobial-resistant *Escherichia coli* bacteria in aqueous environmental samples. *E. coli* (total and antimicrobial-resistant) bacteria were enumerated in effluent samples from a hospital (n = 17) and municipal sewers upstream (n = 5) and downstream (n = 5) from the hospital, effluent samples from throughout the treatment process (n = 4), and treated effluent samples (n = 13). Effluent downstream from the hospital contained a higher proportion of antimicrobial-resistant *E. coli* than that upstream from the hospital. Wastewater treatment reduced the numbers of *E. coli* bacteria (total and antimicrobial resistant); however, antimicrobial-resistant *E. coli* was not eliminated, and *E. coli* resistant to cefotaxime (including extended-spectrum beta-lactamase [ESBL] producers), ciprofloxacin, and cefoxitin was present in treated effluent samples.