ESBL INFECTIONS

Presenter: Dr. CP Yam
Chairman: Dr. Helen Wu

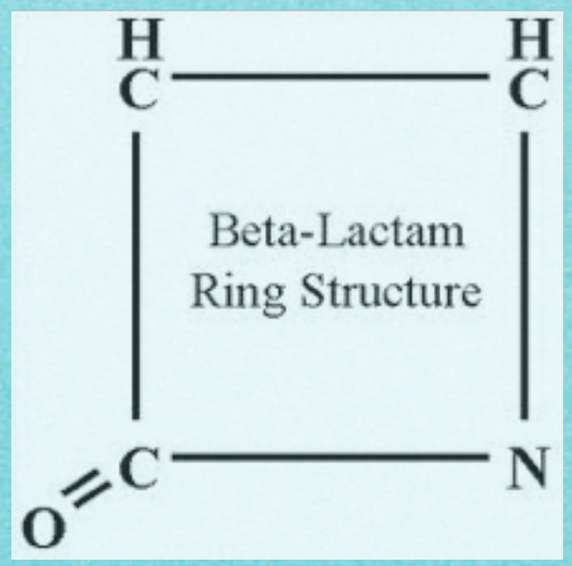
15 July 2011 PYNEH ICU Friday Lecture

Terminology

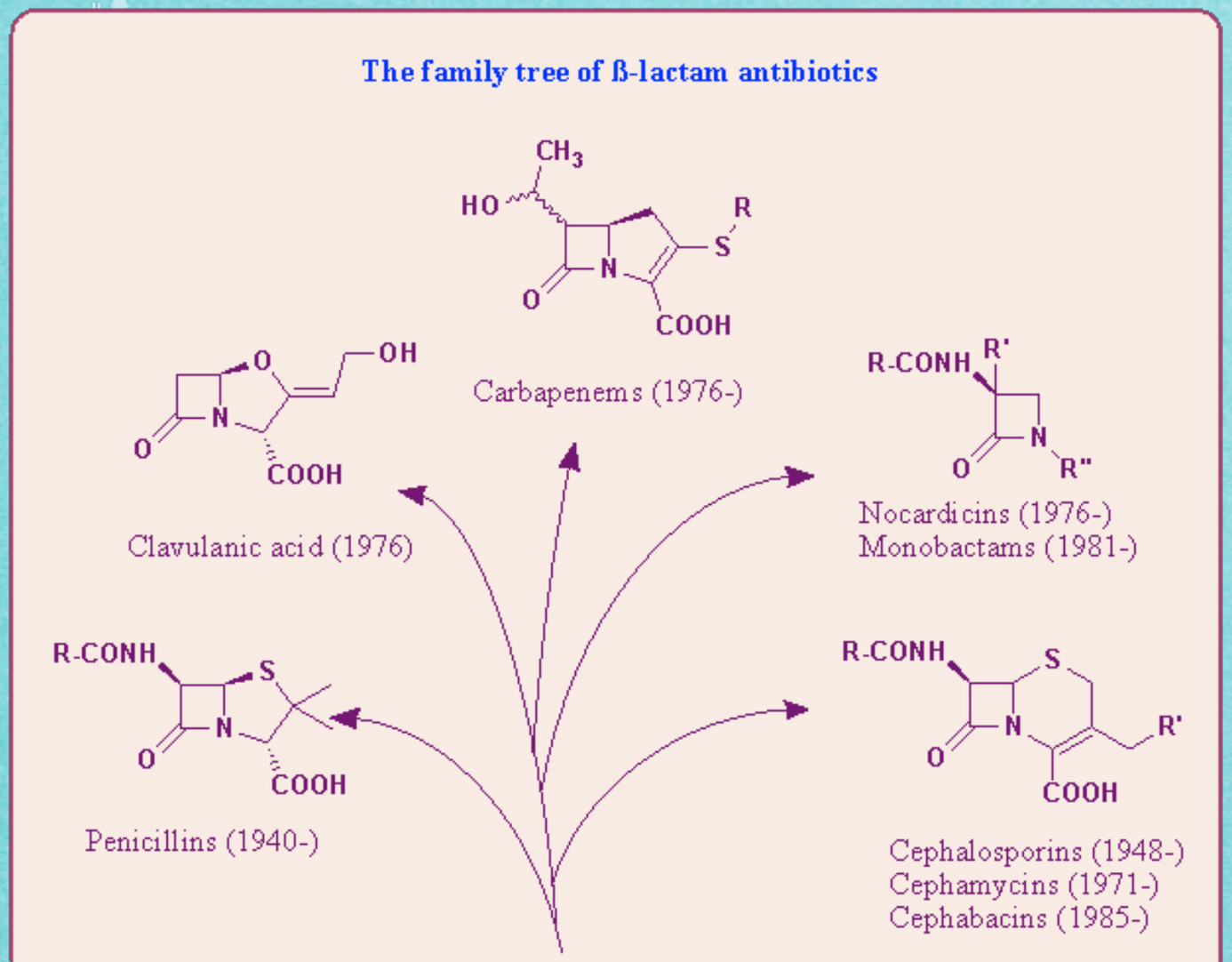
- **ESBL**: Extended-spectrum beta-lactamases
- **Beta-lactamase**: enzymes that open the beta-lactam ring of beta-lactam antibiotics
- **ESBL infections**: infections caused by bacteria that produce ESBL

Beta-lactam

- A beta-lactam ring is a lactam with a ring structure, consisting of three carbon atoms and one nitrogen atom



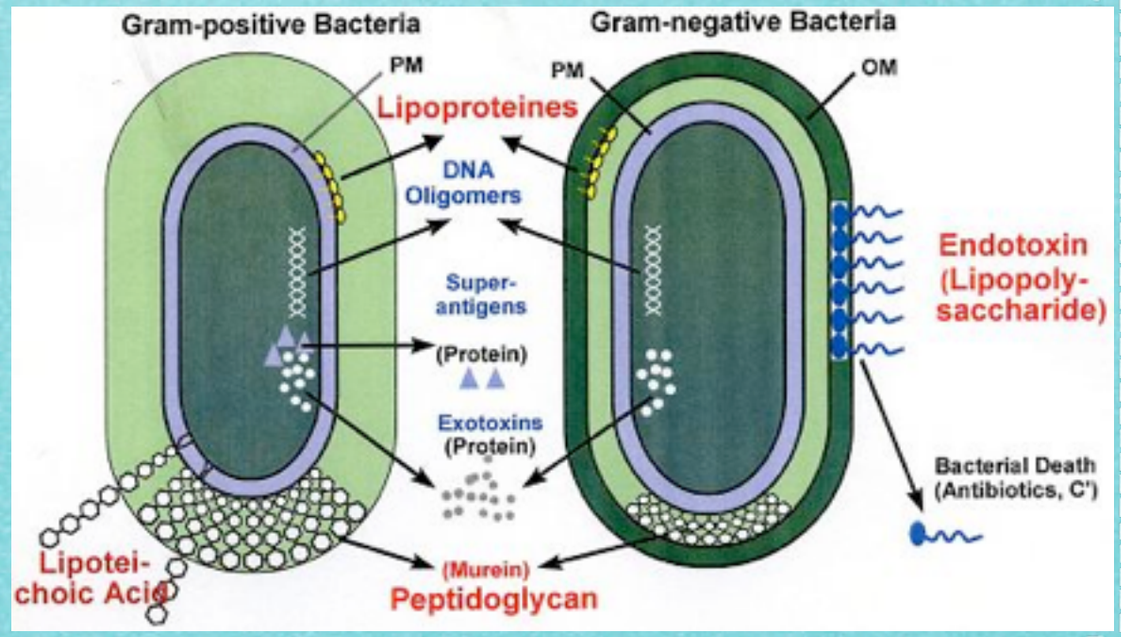
Beta-lactam Family



- Includes
  - • Penicillins
  - • Cephalosporins
  - • Cephamycins
  - • Carbapenems
  - • Monobactams
  - • Beta-lactamase inhibitors (e.g. clavulanic acid)
- The **beta-lactam ring structure** is common to all beta-lactams and must be intact for anti-bacterial action

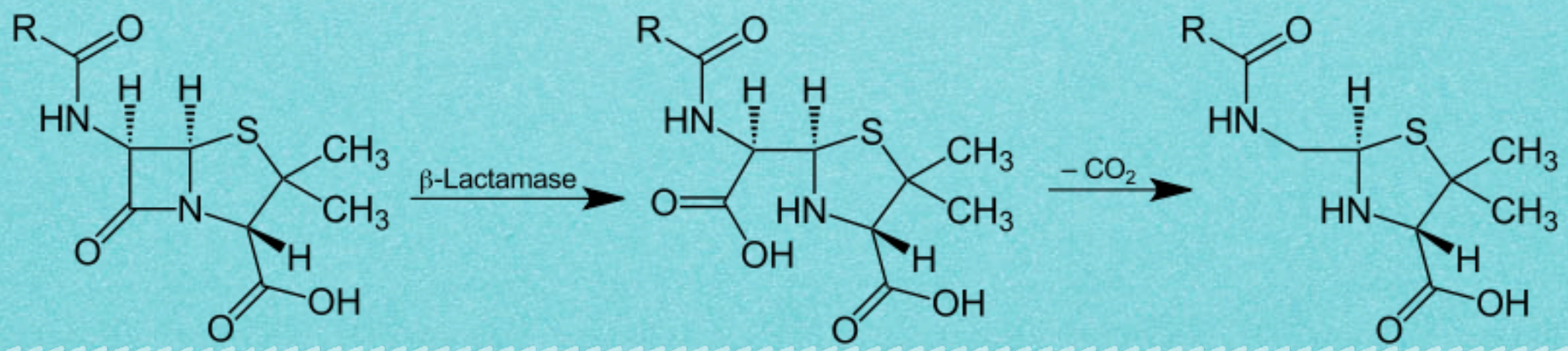
Action of beta-lactams

- **bactericidal**
- inhibit the growth of sensitive bacteria by inactivating enzymes located in the bacterial cell membrane, which are involved in the third stage of cell wall synthesis
  - activation of the autolytic system
    - initiates a cell death program
      - cell lysis



Beta-lactamases

- **Enzymes** produced by bacteria
  - binds convalently to the beta-lactam ring
    - hydrolysis
      - open the beta-lactam ring
        - inactivating the beta-lactam antibiotic



Beta-lactamases (2) AmpC

- Most Gram -ve bacilli process naturally chromosomally coded beta-lactamase (**AmpC**)
  - found in ESCAPPM Group of organisms (Enterobacter, Serratia, Citrobacter, Acinetobacer, Proteus, Providencia, Morganella)
  - resistant to penicillins and **third generation cephalosporin**
  - also resistant to clavulanic acid
  - not resistant to carbapenems
  - traditionally not classified as ESBLs since it is resistant to clavulanate
- Beta-lactamase in other bacteria are usually coded/transmitted by plasmids

Beta-lactamase (3)

- **Penicillinase** was the first β-lactamase identified
  - first isolated by Abraham and Chain in 1940 from E. coli before penicillin entered into clinical use
- The first *plasmid-mediated* beta lactamase in Gram-negative bacteria was discovered in Greece in the 1964, soon after ampicillin was released for medical use
  - isolated from the urine of Mrs. Temonerira
  - TEM, the name of this type of beta-lactamase was named after her
  - Subsequently, a closely related enzyme was discovered and named TEM-2
    - Up to 90% of ampicillin resistance in E. coli is due to the production of TEM-1

Beta-lactamase (4)

- **TEM-1** and **TEM-2** are the most common plasmid-mediated beta-lactamases in Gram-negative bacteria

- Hydrolyse penicillins and narrow spectrum (first generation) cephalosporins, such as cephalothin or cefazolin

- **Not effective against higher generation cephalosporins with an oxyimino side chain**, such as cefotaxime, ceftazidime, ceftriaxone, cefepime

Beta-lactamase (5)

- Various subtypes of beta-lactamases identified
- There are more than 200 beta-lactamase types in Gram negative bacilli
- 2 major classifications:
  - molecular classification: Ambler classification
  - functional classification: Bush-Jacoby-Medeiros classification

Ambler Classification

- Class A: TEM-1,2; SHV-1; CTX-M, KPC
- Class B: MBLs (metallo-beta-lactamase, zinc-dependent enzymes)
- Class C: AmpC
- Class D: OXA

Beta-lactamase (6)

TABLE 1. Classification schemes for bacterial β-lactamases

Bush-Jacoby-Medeiros group	1989 Bush group (44)	Richmond-Sykes class (253)	Mitsuhashi-Inoue type (194)[a]	Molecular class (2, 121, 132)	Preferred substrates	Inhibited by:		Representative enzymes
						CA[b]	EDTA	
1	1	Ia, Ib, Id	CSase	C	Cephalosporins	−	−	AmpC enzymes from gram-negative bacteria; MIR-1
2a	2a	Not included	PCase V	A	Penicillins	+	−	Penicillinases from gram-positive bacteria
2b	2b	III	PCase I	A	Penicillins, cephalosporins	+	−	TEM-1, TEM-2, SHV-1
2be	2b′	Not included except K1 in class IV	CXase	A	Penicillins, narrow-spectrum and extended-spectrum cephalosporins, monobactams	+	−	TEM-3 to TEM-26, SHV-2 to SHV-6, *Klebsiella oxytoca* K1
2br	Not included	Not included	Not included	A	Penicillins	±	−	TEM-30 to TEM-36, TRC-1
2c	2c	II, V	PCase IV	A	Penicillins, carbenicillin	+	−	PSE-1, PSE-3, PSE-4
2d	2d	V	PCase II, PCase III	D	Penicillins, cloxacillin	±	−	OXA-1 to OXA-11, PSE-2 (OXA-10)
2e	2e	Ic	CXase	A	Cephalosporins	+	−	Inducible cephalosporinases from *Proteus vulgaris*
2f	Not included	Not included	Not included	A	Penicillins, cephalosporins, carbapenems	+	−	NMC-A from *Enterobacter cloacae*, Sme-1 from *Serratia marcescens*
3	3	Not included	Not included	B	Most β-lactams, including carbapenems	−	+	L1 from *Xanthomonas maltophilia*, CcrA from *Bacteroides fragilis*
4	4	Not included	Not included	ND[c]	Penicillins	−	?	Penicillinase from *Pseudomonas cepacia*

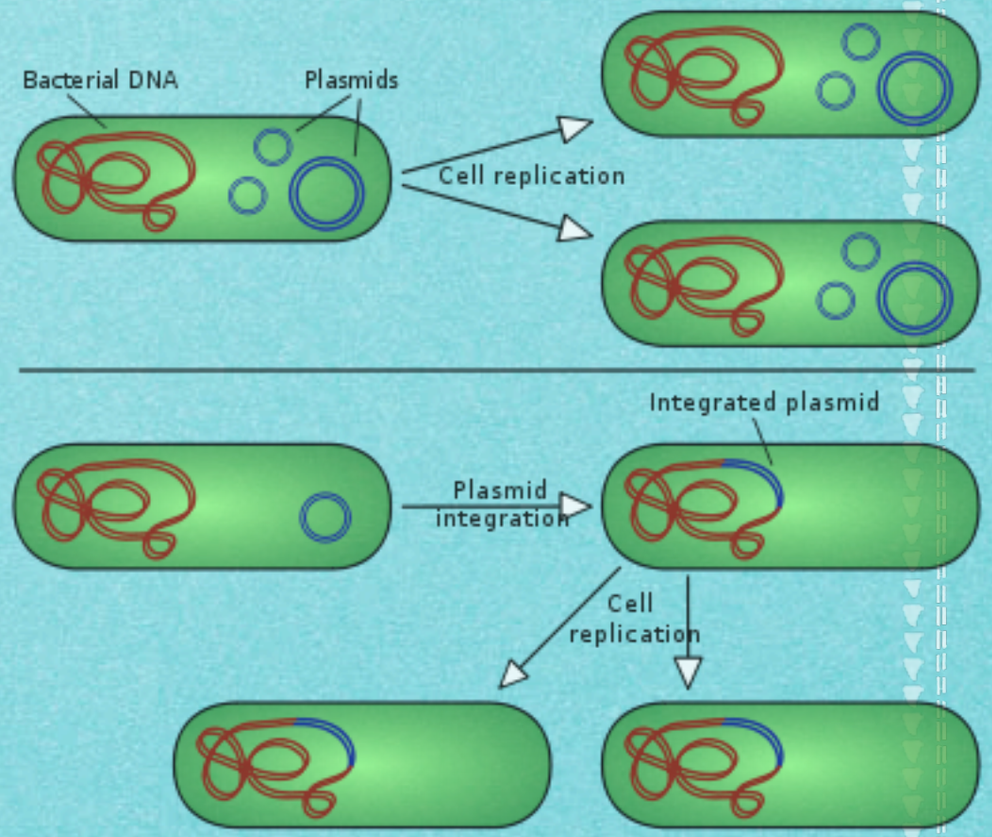
[a] Csase, cephalosporinase; PCase, penicillinase; CXase, cefuroxime-hydrolyzing β-lactamase.
[b] CA, clavulanic acid.
[c] ND, not determined.

Extended-spectrum beta-lactamases (ESBLs)

- A specific group of beta-lactamases
  - First discovered in Germany in 1980's
  - The amino acid substitutions responsible for the ESBL phenotype cluster around the active site of the ESBL enzyme
    - **1.** Act by hydrolysis of the antibiotics: penicillins, first to **third generation** of cephalosporins (**extended spectrum** of cephalosporin with an oxyimino side chain), aztreonam
    - **2.** Do not hydrolyse cephamycins (some of the second generation cephalosporins, e.g cefoxitin, cefotetan, cefmetazole) or carbapenems (e.g imipenem, meropenem, ertapenem)
    - **3.** Inhibited by beta-lactamase inhibitors (e.g clavulanate, sulbactam, tazobactam)

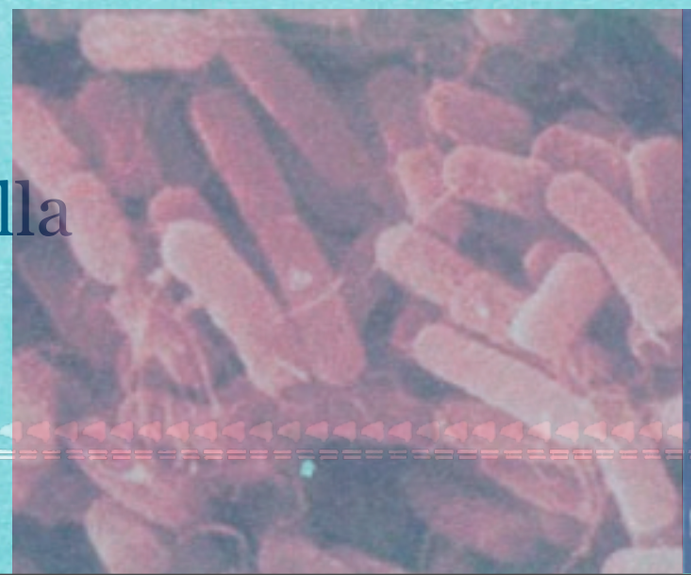
ESBLs (2)

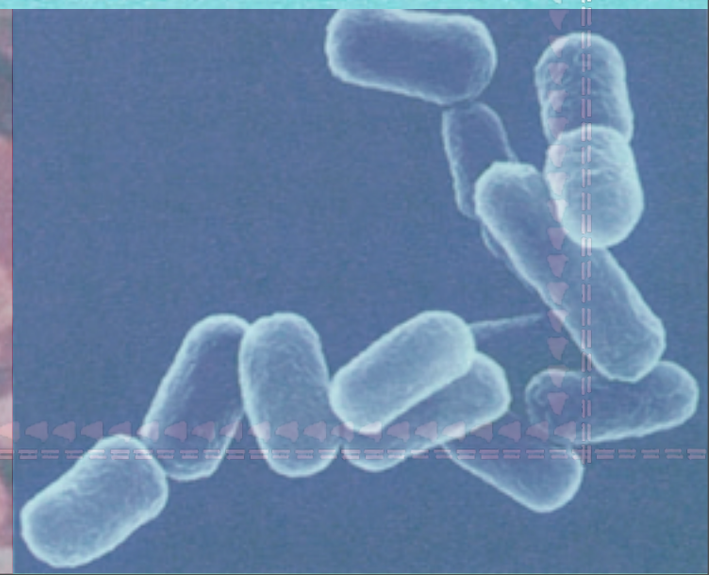
- Commonly derived from genes for TEM-1, TEM-2, or SHV-1 by mutations
  - alter the configuration around the active site of these β-lactamases by amino acid substitution to allow access to 3rd generation cephalosporins
- Frequently plasmid encoded
- Plasmids responsible for ESBL production frequently carry genes encoding resistance to other drug classes (for example, aminoglycosides)



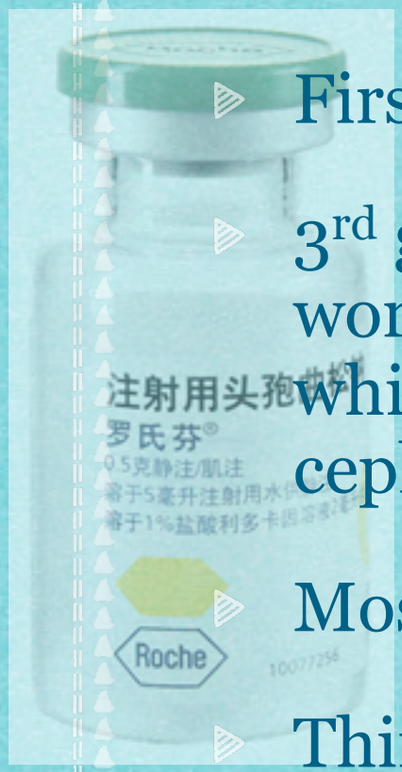
ESBLs (3)

- Commonly found in the following Gram -ve bacteria:
  - **Klebsiella pneumoniae**
  - **Escherichia coli**
  - Proteus mirabilis
  - Enterobacter cloacae
  - Non-typhoidal Salmonella (in some countries)
- Rarely found in:
  - Pseudomonas aeruginosa
  - Acinetobacter baumannii





Cephalosporins



- First discovered in Italy
- 3rd generation cephalosporins were developed to tackle the worldwide proliferation of beta-lactamases in Gram -ve bacteria which are active against ampicillin and first generation cephalosporins
- Most of them have oxyimino-side-chains
- 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

Different varieties of ESBLs (1) TEM, (Class A beta-lactamase)

- TEM 3 was reported in 1989
- Single amino acid substitutions at positions 104, 164, 238, and 240 produce the ESBL phenotype
- Over 160 types of TEM identified
- TEM-10, TEM-12, and TEM-26 are most common

Different varieties of ESBLs (2) SHV (Class A beta-lactamase)

- Predominant ESBL type in Europe and the United States
- Share 68 percent of its amino acids with TEM-1 and similar overall structure
- amino acid changes most commonly at positions 238 or 238 and 240
- More than 60 varieties are known
- SHV-5 and SHV-12 are among the most common

Different varieties of ESBLs (3) CTX-M (Class A beta-lactamase)

- Found in some Enterobacteriaceae, including E. coli and Salmonella
- Named for their greater activity against cefotaxime than other oxyimino-beta-lactam substrates (e.g. ceftazidime, ceftriazone, or cefepime)
- Acquisition of beta-lactamase genes which are normally found on the chromosome of **Kluyvera species** (a Enterobacteriaceae, a group of rarely pathogenic commensal organisms,facultatively anaerobic, rod-shaped bacteria) by plasmid action
- More than 80 CTX-M enzymes are currently known
- CTX-M-14, CTX-M-3, and CTX-M-2 are the most common

Different varieties of ESBLs (4) OXA (Class D beta-lactam)

- less common
- plasmid-mediated beta-lactamase variety
- could hydrolyse oxacillin and related anti-staphylococcal penicillins
- found mainly in Pseudomonas aeruginosa isolates from Turkey and France
- some also have carbapenemase activity

Different varieties of ESBLs (5) Others

- PER, VEB, GES, and IBC beta-lactamases
  - found mainly in Pseudomonas aeroginosa
    - PER-1 in isolates in Turkey, France, and Italy;
    - VEB-1 and VEB-2 in strains from Southeast Asia;
    - GES-1, GES-2, and IBC-2 in isolates from South Africa, France, and Greece.
    - PER-1 is also common in multi-resistant acinetobacter species in Korea and Turkey
- Other uncommon ESBLs: BES-1, IBC-1, SFO-1, and TLA-1

METHODS OF IDENTIFICATION

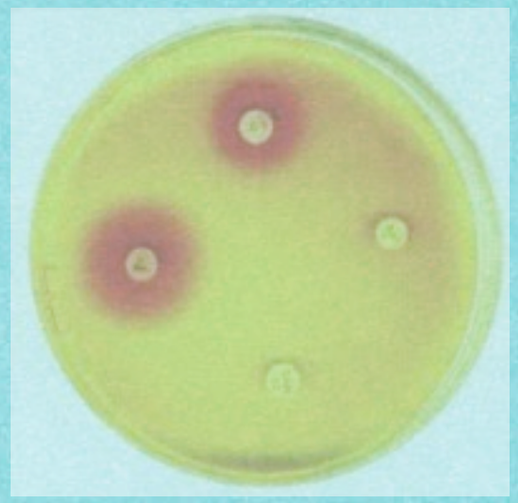
- Detection of ESBLs is based upon
  - 1. the resistance they confer to oxyimino-beta-lactam substrates (eg, cefotaxime, ceftazidime, ceftriaxone, or cefepime)
  - 2. the ability of a beta-lactamase inhibitor, usually clavulanate, to block this resistance
- Other enzymes have different features that can be misleading in the laboratory

METHODS OF IDENTIFICATION (2)

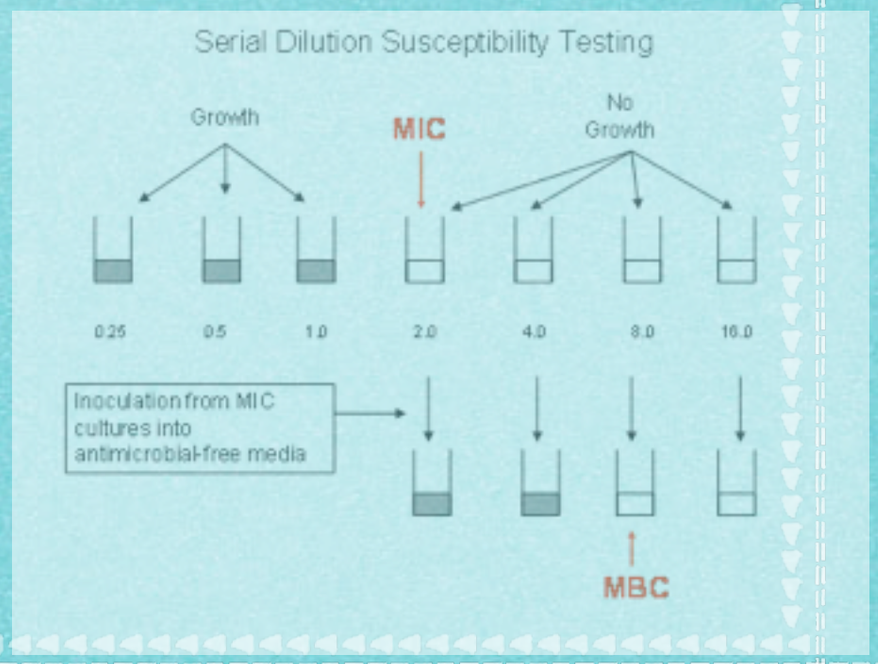
- Criteria for ESBL detection have changed over time; and clinical laboratories vary in their success in diagnosis
- Problems in identification arise because ESBLs are heterogeneous
- OXA-type ESBLs, for example, are poorly inhibited by clavulanate
- AmpC is not classified as ESBL due to its intrinsic resistance to clavulanate and other betalactamse inhibitors

METHODS OF IDENTIFICATION (3)

- **The Clinical and Laboratory Standards Institute (CLSI)** recommends screening isolates of E. coli, K. pneumoniae, K. oxytoca, P. aeruginosa or Proteus spp. by



- disk diffusion or broth dilution for resistance,
  - followed by a confirmatory test for increased susceptibility in the presence of clavulanate



EPIDEMIOLOGY

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%

Paterson et al

Hong Kong

RESEARCH FUND FOR THE CONTROL OF INFECTIOUS DISEASES

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Antimicrobial resistance among uropathogens causing cystitis in women

Key Messages

1. Among *Escherichia coli* from adult women with acute cystitis, the rates of antimicrobial resistance were 52.8% for

Introduction

Hong Kong Med J 2011;17(Suppl 2):S21-3

Key Messages

1. Among *Escherichia coli* from adult women with acute cystitis, the rates of antimicrobial resistance were 52.8% for ampicillin, 29.5% for co-trimoxazole, and 12.9% for ciprofloxacin. Nitrofurantoin and fosfomycin remain active against >90% of the isolates.
2. The respective age-stratified rates for co-trimoxazole and ciprofloxacin resistance were 26.4% and 9.6% for women aged 18-50 years, and 35.5% and 19.4% for women aged ≥51 years. Being aged ≥51 years (Odds ratio [OR]=2.3, 95% confidence interval [CI]=1.1-4.8, P=0.02) and receipt of recent antibiotic treatment (OR=2.5, 95% CI=1.1-5.8, P=0.03) were significantly associated with fluoroquinolone resistance.
3. Ampicillin and co-trimoxazole should not be used as first-line agents for empirical treatment of acute cystitis. As fluoroquinolone resistance was less than 10% among isolates obtained from younger women, these agents are still useful for empirical treatment. Nonetheless, the high rates of fluoroquinolone resistance among women who were older or who had received antibiotic treatment recently indicates the need to consider alternatives such as nitrofurantoin, fosfomycin and amoxicillin-clavulanate as initial therapy.
4. Molecular analysis of the multidrug resistant strains showed that they were genetically diverse, with no evidence of epidemic strains. Nonetheless, resistant strains possess virulence traits distinct from susceptible isolates, suggesting that they may evolve from other sources and not by acquisition of resistance mutations in susceptible isolates from humans.

In the conjugation experiments, the ESBL phenotype could be transferred from five of the 14 isolates. The frequency of transfer was 10^{-3} to 10^{-2} per donor cells. Polymerase chain reaction and sequencing showed that the presence of CTX-M-14 in 11 isolates, CTX-M-24 in two isolates, and CTX-M-9 in one isolate.

In accordance with current guidelines,[5] the empirical use of co-trimoxazole as first-line therapy for women with community-acquired UTIs should be avoided. For younger women with cystitis, fluoroquinolones remain valuable as first-line agents. As ciprofloxacin-resistant isolates usually prevail in post-menopausal women, drugs other than fluoroquinolones may need to be re-considered for this patient population, especially those with a history of recent antibiotic treatment. Nitrofurantoin and fosfomycin remain active against most *E coli* isolates. In using nitrofurantoin, the duration of treatment should be extended to 5 to 7 days as there is insufficient data to support the efficacy of 3-day therapy. In selection of alternative agents, *in vitro* activity, clinical efficacy and side effects are important considerations. In future revision of management guidelines, we suggest inclusion of age as a variable in the approach to empirical therapy.

Hong Kong (2)

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Detection and characterisation of extended-spectrum beta-lactamases among blood stream isolates of *Enterobacter* species in Hong Kong

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Aims and objectives

To study the production of AmpC and extended-spectrum beta-lactamases in *Enterobacter* spp, with a view to improve surveillance of this type of emerging antibiotic resistance mechanisms.

Key Messages

1. Extended-spectrum beta-lactamase (ESBL) resistance in *Enterobacter* spp may be under-recognised.
2. Detection methods for ESBL resistance in *Enterobacter* spp may need to be modified.

Results

The ESBLs were identified in nine isolates (7%), including seven of 39 (18%) *E hormaechei*, one of 27 (4%) *E aerogenes* and the only *E intermedius* strain. The *E intermedius* strain was positive only in the three-dimensional extract test but not in the other two tests. The other eight strains were positive in all three tests. No ESBL was detected in other species, including non-hormaechei members of the *E cloacae* complex (n=61), *E agglomerans* (n=7), *E gergoviae* (n=4) and *E sakazakii* (n=1). For the detection of ESBL, the NCCLS screen method lacked specificity (63-72%). Discrimination could be improved using cefepime at a cut-off of ≤25 mm (sensitivity 90%, specificity 94%). The ESBL content included five different CTX-M enzymes (CTX-M-9, CTX-M-13, CTX-M-14, CTX-M-24 and a novel CTX-M-2-like ß-lactamase), SHV-12 (n=2) and unidentifiable ESBLs with a pI of 7.7 or 7.9 in two strains. The seven ESBL-producing *E hormaechei* were genotyped by pulsed-field gel electrophoresis and were found to be unrelated to each other. In three of the CTX-M-producing strains, ISEcp1-like elements, including promoters for the ß-lactamase gene, were found.

Conclusions

The prevalence of ESBL among *Enterobacter* spp in Hong Kong is high and that their ß-lactamase content is diverse. Our finding adds to the increasing recognition of CTX-M enzymes in the Far East and further emphasises the need for screening ESBL in clinical isolates of *Enterobacter* spp.

The detection of ESBL in *Enterobacter* spp could be enhanced by: (1) inclusion of the glucose oxidation test for more accurate speciation of *E hormaechei*, and (2) inclusion of cefepime as an indicator in the ESBL screen.

Hong Kong (4)

- Other published studies:

Pai H, Hong JY, Byeon JH, Kim YK, Lee HJ. High prevalence of extended-spectrum beta-lactamase-producing strains among blood isolates of *Enterobacter* spp. collected in a tertiary hospital during an 8-year period and their antimicrobial susceptibility patterns. Antimicrob Agents Chemother 2004;48:3159-61.

Ho PL, Shek RH, Chow KH, et al. Detection and characterization of extended-spectrum beta-lactamases among bloodstream isolates of *Enterobacter* spp. in Hong Kong, 2000-2002. J Antimicrob Chemother 2005;55:326-32.

Ho PL, Tsang DN, Que TL, Ho M, Yuen KY. Comparison of screening methods for detection of extended-spectrum beta-lactamases and their prevalence among *Escherichia coli* and *Klebsiella* species in Hong Kong. APMIS 2000;108:237-40.

CHINA

- CTX-M types are more diverse
- most common: CTX-M-14
- 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]

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 also ciprofloxacin and aminoglycoside resistant
  - No dominant clone but almost always associated with a large (>100kb) plasmid

[*Ensor JAC 2006; Walsh JAC 2007*]

Thailand

- The faecal carriage of ESBL-producing Enterobacteriaceae (predominantly E. coli, CTX-M) is very high in asymtomatic individuals in Thailand, with some variations among the provinces, this high prevalence may be linked to antibiotic abuse

- [Analysis of risk factors for a high prevalence of ESBL Enterobacteriaceae in asymtomatic individuals in rural Thailand, Journal of Medical Microbiology 2011, 60, Ulzii-Orshikh et al]

Western Countries (1)

- In a sample of more than 4600 **K. pneumoniae** isolates from 1997 to 1999, the percentage expressing an ESBL phenotype was highest in isolates from Latin America (45 percent), the Western Pacific (25 percent), and Europe (23 percent) and lowest in strains from the United States and Canada (7.6 and 4.9 percent, respectively)
  - Comparable percentages for the ESBL phenotype in more than 12,800 **E. coli strains** were: Latin America (8.5 percent), Western Pacific (7.9 percent), Europe (5.3 percent), Canada (4.2 percent), and the United States (3.3 percent)
    - [Winokur, PL, Canton, R, Casellas, JM, Legakis, N. Clin Infect Dis 2001]

Western Countries (2)

- In a prospective study of 455 consecutive episodes of **K. pneumoniae bacteremia** in 12 hospitals in seven countries in 1996 and 1997, 85 (19 percent) were due to an ESBL-producing organism
  - The rate was higher in the 253 nosocomial infections (31 percent), particularly those acquired in the intensive care unit (43 percent) [Paterson et al 2004 Ann Int Med]
- A resistant strain or plasmid may cause problems in several hospitals locally or involve a large geographic area. Community clinics and nursing homes have also been identified as potential reservoirs for ESBL-producing K. pneumoniae and E. coli [Wiener et al 1999 JAMA]

ESBLs from food?

- Cephalosporin resistant *E. coli* from retail meat in the United States and Spain. [Y. Doi et al. 2007]
  - CTX-M producing *E. coli* grown from chicken purchased at supermarkets
  - Most of them at AmpC beta-lactamase, not ESBLs
- Agriculture products
  - source of antibiotic resistance
    - low dose antibiotics are use for disease prevention and weight gain of poultries especially pigs and chickens

RISK FACTORS for ESBLs

- Length of hospital stay
- Length of ICU stay
- Presence of central venous or arterial catheters
- Emergency abdominal surgery
- Presence of a gastrostomy or jejunostomy tube
- Gut colonization
- Low birth weight
- Prior administration of any antibiotic
- Prior residence in a long-term care facility (e.g nursing home)
- Severity of illness
- Presence of a urinary catheter
- Ventilatory assistance
- Undergoing hemodialysis

Community-acquired ESBL producers

- First reported as major health problem in Canada, Spain and the United Kingdom
- Many “community-acquired” cases were actually from residential care homes or recently hospitalized patients
- some were truly from the community

Hong Kong (3)

Journal of Antimicrobial Chemotherapy (2007) **60**, 140–144
doi:10.1093/jac/dkm144
Advance Access publication 12 May 2007

JAC

Community emergence of CTX-M type extended-spectrum β-lactamases among urinary *Escherichia coli* from women

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In conclusion, this study found significant rates of ESBL among urinary *E. coli* from adult women of all ages in the Hong Kong community, largely due to the spread of CTX-M-14 β-lactamase. The emergence of CTX-M-14 among community strains from young women is concerning and deserves close monitoring.

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

Implications

- Diminished susceptibility to cephalosporins, penicillins and aztreonam
- Increased risk of inadequate empiric therapy if these antibiotics are used
- Increased risks of increased use of other antibiotic classes
  - More carbapenem use
  - May lead to development of more **carbapenem resistant organisms**
    - KPC producers (Klebsiella pneumoniae carbaoenenmase)
    - CRAB (Carbapenem-Resistant Acinetobacter baumannii)
    - Carbapenem resistant Pseudomonas
- Increased cost in treatment in some of the usual disease such as UTI

Short summary

- Community ESBLs are mainly of CTX-M type, most commonly in E. coli
- Hospital ESBLs are mainly of TEM or SHV types
- But due to community emergence of ESBLs, more CTX-M type infection in hospitals

Treatments

- There are no major randomized controlled trials of therapy for ESBL infections
- Most of the reports are a compilation of a small number of cases involving different classes of ESBLs,treated with different antibiotics, and mainly in outbreak settings
- Whether results can be generalized to infections with other ESBL types is generally not known

Treatments (2)

- The only current proven therapeutic option for severe infections caused by ESBL-producing organisms is the **carbapenem family** (e.g imipenem, meropenem, and ertapenem)
- Carbapenems are not hydrolyzed by ESBLs
- Success rates with carbapenems for ESBL producers consistently **exceed 80%**
  - [Paterson CID 2004; Bhavnani DMID 2006; Zanetti AAC 2003]

Carbapenems

- Treatment with **imipenem** or **meropenem** has produced the best outcomes in terms of survival and bacteriologic clearance

- **Ertapenem** has good in vitro activity [Jacoby 1997], but there are limited clinical data regarding its use

  - In a series of 20 ICU patients with ventilator-associated pneumonia due to ESBL producing organisms, for example, ertapenem was effective treatment in 16 patients [Munoz 2004]

  - Ertapenem resistance may develop on therapy [Lartigue 2007]

Doripenem

- FDA approved
- Appears highly active to 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]

Treatments (2)

- ESBL-producing organisms vary in their susceptibility to different oxyimino-beta-lactams; despite resistance to some, they may appear sensitive to others.
- Strains making **TEM and SHV-type ESBLs** usually appear susceptible to cefepime and to piperacillin-tazobactam, but both drugs show an **inoculum effect with diminished susceptibility** as the inoculum is raised from 10(5) to 10(7) organisms
- Some **CTX-M- and OXA-type** ESBLs test resistant to cefepime despite use of a low inoculum
- [Thomson et al Antimicrob Agents Chemother 2001 Dec]

Cephalosporins

- In a review of 28 patients with ESBL-producing Klebsiella pneumoniae with reported susceptibility to cephalosporins, 15 failed to respond to cephalosporin therapy [Paterson 2001]

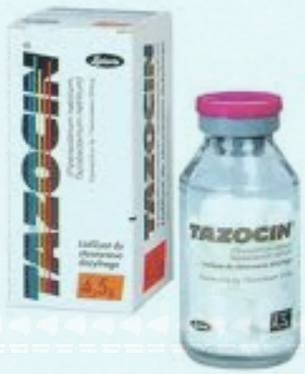
- **Cefepime** may be effective against ESBL-producing organisms if it is administered in high doses [Zanetti 2003;Goethaert 2006] but not in standard doses (1 g every 12 hours) [Kotapati 2005]

- In a European study of nosocomial pneumonia due to ESBL-producing pathogens, nine of thirteen patients treated with high-dose cefepime (2 g every eight hours) responded clinically [Zanetti 2003]

- However, most available data do not encourage cefepime use for ESBL-producing pathogens

Piperacillin-tazobactam (Tazocin)

- Many failures have been described with piperacillin-tazobactam for treatment of ESBL isolates
- In addition, resistance may develop during therapy
- Piperacillin-tazobactam may be effective for ESBL isolates with piperacillin-tazobactam MIC ≤16/4 mcg/mL and **for urinary tract infections**, regardless of susceptibility [Gavin 2006].
  - The latter observation is a presumed reflection of the much higher drug concentrations seen in urine compared to plasma
- Ticarcillin is intrinsically inferior to piperacillin versus Klebsiella



Other antibiotics

- Data regarding the use of quinolones and/or aminoglycosides are also sparse
  - One study evaluated bacteremia caused by ESBL-producing K. pneumoniae that were susceptible to ciprofloxacin [Endimiani 2004]
    - Among seven patients treated with ciprofloxacin, five failed treatment and two had a partial response; patients treated with imipenem did much better (complete response in eight of ten).
- ESBL-producing isolates typically show greater than average resistance to other agents including aminoglycosides and fluoroquinolones. [Paterson el at Clin Infect Dis 2004 Jul]
  - could be related to plasmid transmitted resistance
- There are no clinical data supporting the use of double antibiotic coverage for treatment of ESBL producing organisms

Tigecycline

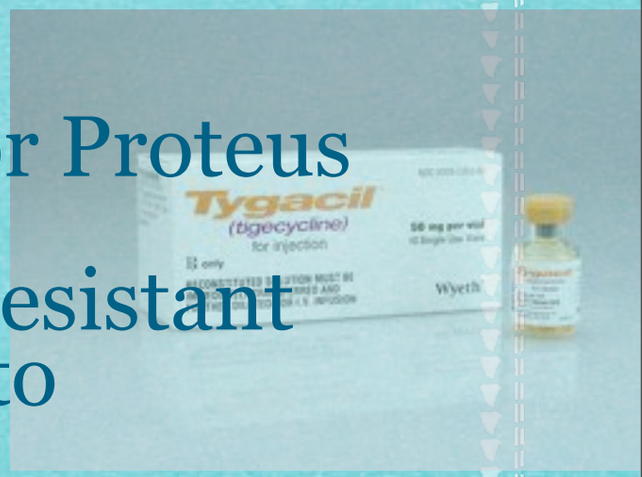
- Active against 93.7% of ESBL producers using EUCAST breakpoint of 1 µg/mL *[Morosini AAC Aug 2006]*

- Increased mortality in VAP patients compared to Imipenem

- Active against MRSA, Stenotrophomonas maltophilia, Haemophilus influenzae, and Neisseria gonorrhoeae and multi-drug resistant strains of Acinetobacter baumanii

- It has no activity against pseudomonas spp. or Proteus

- New Delhi metallo beta lactamse multidrug-resistant Enterobacteriaceae has shown susceptibility to tigecycline [Kumarasamy et. al 2010 Lancet ID]



CLINICAL OUTCOMES

- Studies evaluating clinical outcomes in patients with ESBL infections have shown a trend toward
  - **higher mortality**
  - **longer hospital stay**
  - **greater hospital expenses**
  - **reduced rates of clinical and microbiologic response** [Lautenbach 2001; Meyer 1999; Paterson 2004]

CLINICAL OUTCOMES (2)

- 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 (treatment not started within 24-48 hours after admission or positive C/ST results notified)

[Schwaber JAC Nov 2007; Goff ICAAC 2006]

OUTBREAK CONTROL

- Two main strategies to control outbreaks due to ESBL-producing bacteria have been reported:
  - 1. **class restriction of oxyimino-beta-lactams**
  - 2. **barrier protection of colonized and/or infected patients**
- A study performed in Spain showed that there was a marked decrease in the number of infections caused by ESBL-producing K. pneumoniae (from 4.9 episodes to 0.6 episodes per 1000 patient-days) after institution of barrier protections (**gloves and gowns**) and restriction of oxyimino cephalosporins [Pena 1998]
- A similar result was observed in New York where the number of cases with ESBL-producing K. pneumoniae declined significantly after the institution of barrier precautions and restriction of ceftazidime use at one hospital [Meyer 1993]

HA INFECTION CONTROL

- Infection Control Consideration
- Barrier methods are effective for preventing spread of ESBL producing organisms.
- Patients with these organisms should be nursed with Contact Precautions which
- involves;
  - a) Wear gloves for contact with patient's excretions and secretions. After removing gloves, decontaminate hands with alcohol handrub or aqueous antiseptic handwash.
  - b) Wear gown if you expect that clothing will be extensively exposed to the patient, the patient's environment, or the patient is incontinent.
  - c) When possible, dedicate patient care equipment to a single patient. If sharing is required, adequate cleaning and disinfection is required.
  - d) Decontaminate patient's immediate environment with chlorine solution (1000ppm) e.g. bedrails, table, drip stand etc.
  - e) Placement in a single room is optimal, but not essential.

Summary

- ESBL infections are common nowadays worldwide
- Could cause severe infections with high mortality
- Best treatment option: Imipenem; Meropenem
- Outbreak control is important, barrier precaution is effective
- Judicious use of antibiotics to prevent emerging antibiotic resistances and for effective treatment
- Newer antibiotics may be needed in future

THE END

Thank you!