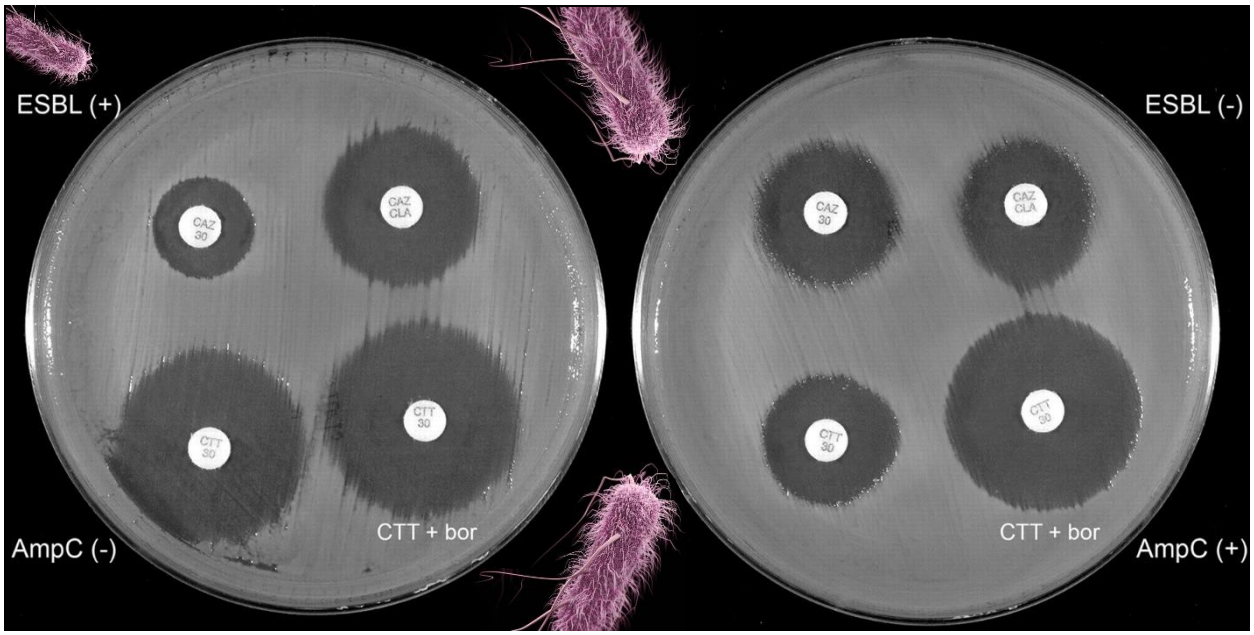
β-lactam/β-lactamase Inhibitors for the Treatment of Infections Caused by Extended-Spectrum β-Lactamase (ESBL)-producing Enterobacteriaceae



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Learning Objectives

At the completion of this activity, the participant will be able to:

1. Describe different classes of β-lactamases produced by gram-negative bacteria.
2. Identify β-lactamase inhibitors and their spectrum of inhibition of β-lactamases.
3. Evaluate the evidence for use of β-lactam/β-lactamase inhibitors compared to carbapenems for treatment of ESBL infections.

1. A Brief History of the Universe

A. Timeline: 1940s
   a. β-lactams and β-lactamases
      i. Sir Alexander Fleming discovered penicillin from *Penicillium notatum* (now *Penicillium chrysogenum*) in 1928.[1,2]
      ii. Chain, Florey, et al isolated penicillin in 1940, leading to its commercial production.[3]
      iii. First β-lactamase was described as a penicillinase in *Escherichia coli* in 1940.[4]
      iv. Giuseppe Brotzu discovered cephalosporin C from the mold *Cephalosporin acremonium* (now *Acremonium chrysogenum*) in 1945, but cephalosporins were not clinically used for another 2 decades.[2,5]
   b. What are β-lactamases?
      i. β-lactamases are enzymes that hydrolyze the amide bond of the β-lactam ring, thereby inactivating them.[6]

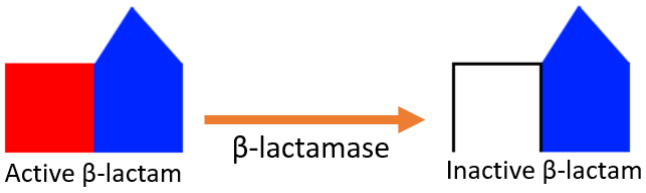

Figure 1: Mechanism of action of β-lactamases

      ii. β-lactamase production is the principal mechanism by which gram-negative bacteria resist β-lactam antibiotics.[6]
      iii. β-lactamases are encoded by:
         1. Chromosomal genes
         2. Transferable genes such as plasmids and transposons

B. Timeline: 1960s
   a. β-lactams and β-lactamases
      i. Ampicillin was introduced in 1961.[7]
      ii. The first cephalosporin, cephalothin, was introduced for clinical use in 1964.[8,9]
      iii. The first plasmid-mediated β-lactamase, TEM-1 (named after a Greek patient, Temoniera) emerged in 1963, causing ampicillin resistance in the 1960s.[10,11]
      iv. TEM-1 confers resistance to penicillins and early cephalosporins.[10]
   b. The Ambler molecular classification of β-lactamases was introduced in 1969.[12]
      i. This classification is based on amino-acid structure homology.[13]
      ii. Class A, C, and D β-lactamases hydrolyze the β-lactam ring through a serine residue at the active site.
      iii. Class B metallo-β-lactamases use zinc to break the amide bond.
   c. What are β-lactamase inhibitors?[14]
      i. Research on compounds that could inhibit β-lactamases began in mid-1960s.
      ii. Most are structurally similar to penicillin.
      iii. They bind β-lactamases and protect the active antibiotic from inactivation.
      iv. β-lactamase inhibitors alone generally have weak activity against bacteria.

C. Timeline: 1970s
    a. β-lactams and β-lactamases
        i. Cefazolin was introduced in 1973.[9,15]
        ii. Natural carbapenems, car from *Erwinia carotovora* and thienamycin (1976) from *Streptomyces cattleya*, were discovered but not clinically used at this time.[2,16]
        iii. Monobactam, nocardicin A, was discovered from *Nocardia uniformis* in 1977.[2,17]
        iv. Second-generation cephalosporins, cefamandole and cefuroxime, were introduced in 1978.[9]
        v. The first cephamycin, cefoxitin, was introduced in 1979.[9]
    b. β-lactamases inhibitors
        i. Clavulanate (clavulanic acid)
            1. Clavulanate was identified from *Streptomyces clavuligerus* in 1972.[13]
            2. It can induce AmpC in some bacteria.[18]
        ii. Sulbactam
            1. Sulbactam is semisynthetic and was identified in 1978.
            2. It has poor activity against TEM and SHV enzymes and weakly inhibits CTX-M enzymes.[13,19]

D. Timeline: 1980s
    a. β-lactams and β-lactamases
        i. In early 1980s, many new antibiotics including third-generation cephalosporins, cefotaxime, ceftazidime, and ceftriaxone, were introduced in an effort to cope with the growing problems of β-lactamase-producing bacteria.[9,10]
        ii. Imipinem-cilastatin (N -formimidoyl thienamycin) was the first carbapenem approved for clinical use in the U.S. in 1985.[16]
        iii. Aztreonam was approved in the U.S. in 1986.[20]
        iv. In 1985, the first ESBL was described in a *Klebsiella* spp isolate producing sulfhydryl variable (SHV) β-lactamase that hydrolyzed third generation cephalosporins and monobactams.[21]
    b. What are extended-spectrum β-lactamases (ESBLs)?
        i. ESBLs are defined by the capability to hydrolyze extended-spectrum cephalosporins and monobactams, and their susceptibility to β-lactamase inhibitors, but yet not hydrolyzing cephamycins and carbapenems.[22]

Table 1: The Ambler Molecular Classification of β-lactamases[13]

Class	Enzyme type	Substrates	Example
A	Penicillinases	Penicillins and narrow-spectrum cephalosporins	PC1 (*S. aureus*)
			TEM-1 (Enterobacteriaceae)
			SHV-1 (Enterobacteriaceae)
	Extended Spectrum β-Lactamases (ESBLs)	As above plus oxyimino-β-lactams and aztreonam	TEM type (Enterobacteriaceae)
			SHV type (Enterobacteriaceae)
			CTX-M type (Enterobacteriaceae)
			PER-1, VEB-1, VEB-2, GES-1, GES-2, IBC-2 (*P. aeruginosa*)
	Carbapenemases	Carbapenems	KPC-1, KPC-2, KPC-2
			NMC/IMI
			SME family

Table 1 continued			
Class	**Enzyme type**	**Substrates**	**Example**
B	Carbapenemases	All β-lactams except monobactam	NDM-1 (Enterobacteriaceae)
			IMP, VIM, GIM, SPM, SIM (*P. aeruginosa* & *Acinetobacter* spp.)
C	Cephalosporinases	Substrates of ESBLs plus cephamycins	AmpC-type (Enterobacteriaceae & *Acinetobacter* spp.)
D	Oxacillinases	Penicillins	OXA-family (*P. aeruginosa*)
	ESBLs	Extended-spectrum cephalosporins	OXA-family (*P. aeruginosa*)
	Carbapenemases	Carbapenems	OXA-family (*Acinetobacter* spp.)

ii. ESBLs are generally divided into 4 groups:[23]

1. TEM-derived
    a. There are more than 200 TEM-derived ESBLs.
    b. TEM-3, reported in 1988, was the first TEM-derived ESBL.[24]
    c. Majority of these enzymes remain susceptible to inhibition by clavulanic acid and tazobactam.
    d. Inhibitor-resistant enzymes have been described (e.g., TEM-30).[25]
2. SHV-derived
    a. They have similar structure to TEM (68% of amino acids are shared).[6]
    b. They are primarily found in *K. pneumoniae*.
    c. Inhibitor-resistant enzymes have been described (e.g., SHV-10).[25]
3. CTX-M-derived[26]
    a. CTX-M enzymes are the most prevalent type of ESBL enzymes in the U.S. and Europe, exceeding 50 different types.[27-29]
    b. They originated from the *Kluyvera* spp of environmental bacteria.
    c. They are not related to TEM or SHV.
    d. They have nearly displaced other ESBL enzymes in Enterobacteriaceae.[30]
    e. They usually have greater activity against cefotaxime than ceftazidime.
    f. They are inhibited more by tazobactam than by clavulanic acid and sulbactam.[31]
    g. CTX-M-15 is often concurrently expressed with OXA-1.[32]
4. OXA-derived[31]
    a. They are poorly inhibited by clavulanate or tazobactam.
    b. They are mainly described in *P. aeruginosa*.
    c. OXA-1 is often concurrently expressed with CTX-M-15.[32]

c. β-lactamases inhibitors
    i. Tazobactam[13]
        1. Tazobactam was identified in 1984.[33]
        2. It has a similar structure to sulbactam.
        3. Tazobactam has remained 10- to 25-fold more active than clavulanic acid against specific inhibitor-resistant mutants of TEM.[34]
        4. Tazobactam is a potent inhibitor of most CTX-M ESBLs, however CTX-M-15 is often resistant due to the concurrent expression of OXA-1.[28,29]

E. Timeline: 1990s
    a. β-lactams and β-lactamases
        i. Meropenem was approved for use in the U.S. in 1996.[16]
        ii. Piperacillin-tazobactam was approved.[35]
        iii. There was an outbreak of ESBL-producing *Klebsiella* spp. in a community hospital in Queens, NY.[36]
        iv. Decreasing the use of third-generation cephalosporins and increasing the use of imipenem-cilastatin or piperacillin-tazobactam has been associated with a significant decrease in the isolation of ESBL-producing bacteria.[36,37]
    b. Bush-Jacoby-Medeiros classification of β-lactamases was introduced in 1995.[38]
        i. This classification is according to substrate profile and susceptibility to β-lactamase inhibitors.

F. Timeline: 2000s
    a. β-lactams and β-lactamases
        i. Ertapenem was approved for use in the U.S. in 2001.[16]
        ii. Doripenem was approved for use in the U.S. in 2007.[39]
        iii. ESBLs
            1. Since 2000, there has been a global increase in CTX-M type ESBLs in both community-acquired *E. coli* and nosocomial *Klebsiella* spp.[40,41]
            2. Large surveillance studies of intra-abdominal infections (SMART 2007-2009)[42,43]
                a. ESBLs were present in 67-79% of isolates in India.
                b. ESBLs were present in 55-65% in China.
            3. Isolates from patients with appendicitis in 39 countries (SMART 2008-2010)[44]
                a. ESBL rate was highest in the Asia-Pacific region (28%), excluding India.
                b. ESBL rate was lowest in Europe (4.4%).
                c. ESBL rate was less than 10% in North America.
                d. Global mean was 16.3%.

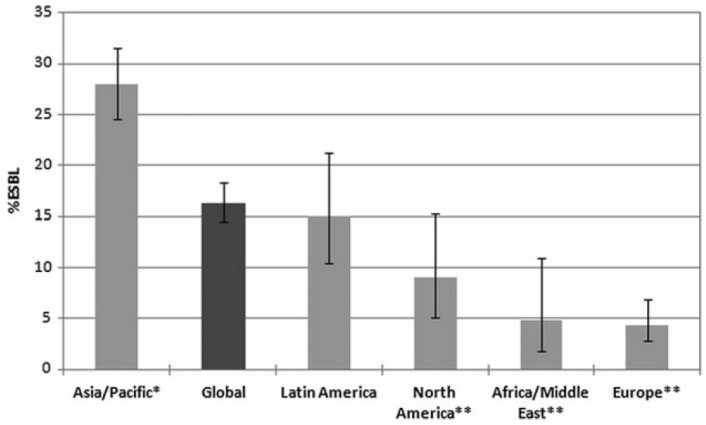

Figure 2. Proportion of ESBL-positive isolates with 95% confidence intervals among *E. coli*, *K. pneumoniae*, *K. oxytoca*, and *P. mirabilis* combined, by global region.[44] *%ESBL-positive significantly higher than average of the other regions combined. **%ESBL-positive significantly lower than the average of the other regions combined. Note: 2010 data for Asia/Pacific exclude India, from which isolates were not available.

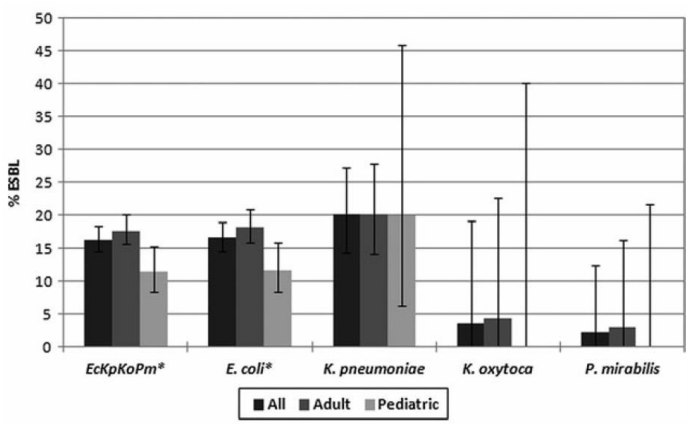

Figure 3. Proportion of ESBL-positive isolates by bacterial species with 95% confidence intervals.[44] *%ESBL-positive isolates significantly higher in adult than in pediatric patients.

iv. How are ESBL infections treated?

1. Carbapenems are usually recommended as first-line therapy for serious infections caused by ESBL producers.[45]
2. No randomized controlled trials have ever been performed to guide optimal treatment.[23,46]
3. *In vitro* studies and observational studies suggest that carbapenems (imipenem or meropenem) should be regarded as drugs of choice for serious infections due to ESBL-producing organisms.[44,46-53]
    a. ESBL-producing *E. coli* isolates were 97-100% susceptible to carbapenems.
    b. ESBL-producing *K. pneumoniae* isolates were 61-100% susceptible to carbapenems.
4. Based on observational studies, prognosis for patients treated with carbapenems is better than those treated with cephalosporins and fluoroquinolones.[23]
5. Burgess et al (2003) conducted a 2-year observational study at University Hospital in San Antonio, TX, consisting of 18 patients with ESBL-positive isolates.[54]
    a. 3/18 (**17%**) died and 6/18 (33%) failed treatment.
    b. All 3 patients treated with a carbapenem had clinical cure.
    c. Only 6/11 (55%) treated with piperacillin-tazobactam had successful outcome.
    d. This was a small uncontrolled study, with isolates from a range of clinical samples, and no adjustment for comorbidities.

6. Paterson et al (2004)[55,56]

Table 2: Antibiotic Therapy for *Klebsiella pneumoniae* Bacteremia: Implications of Production of Extended-Spectrum β-Lactamases.[55,56]

Objective	• To describe experience with various agents in the treatment of serious infections due to ESBL-producing organisms
Design	• Prospective observational international study in 7 countries
Population	• 440 patients older than 16 years with positive blood cultures for *K. pneumoniae* between January 1, 1996 and December 31, 1997
Endpoints	• All-cause mortality within 14 days
Methods	• The χ^2-test or Fisher's exact test were used to compare categorical variables • Student's t-test or the Mann-Whitney *U* test was used for continuous variables • A logistic regression model was used to estimate the effects of multiple factors associated with mortality
Baseline Characteristics	• Production of ESBLs by *Klebsiella pneumoniae* is widespread nosocomial problem

Variable	Carbapenem ($n = 42$)	No-ncarbapenem ($n = 29$)	*P*
Male sex	28 (66.7)	14/29 (48.3)	.15
Underlying disease			
Neutropenia	3 (7.1)	0 (0)	.27
Any immunocompromise	24 (57.1)	7/29 (24.1)	.006
Renal failure	11 (27.5)	10 (35.7)	.47
Any significant underlying disease	33 (78.6)	21 (72.4)	.55
Underlying source of infection			
Pneumonia	9 (21.4)	7 (24.1)	.79
Intra-abdominal infection	6 (14.3)	10 (34.5)	.08
Urinary tract infection	8 (19.0)	2 (6.9)	.18
Wound infection	4 (9.5)	1 (3.4)	.64
Other source	7 (16.7)	2 (6.9)	.29
Severity-of-illness marker			
Admission to ICU	15 (35.7)	13 (44.8)	.47
APACHE III score, mean ± SD	71.7 ± 16	59.2 ± 23	.16
Previous LOS, median days	11.5	15.0	.16

Results	• 455 episodes of *K. pneumoniae* bacteremia (253 [55.6%] nosocomial episodes) ○ 18.7% (85/455) episodes due to ESBL-producing organisms ○ 30.8% (78/253) episodes of nosocomial bacteremia due to ESBL-producing organisms ○ 43.5% (30/69) episodes acquired in ICU due to ESBL ○ 49 episodes treated with monotherapy • Overall mortality rate by 14 days after onset: **24%** (61/253) • All-cause death within 14 days ○ Carbapenem: 1/27 ○ Ciprofloxacin: 4/11 ○ Cephalosporin: 2/5 ○ BL/BLIs: 2/4 ○ Amikacin: 0/2 • Carbapenem v non-carbapenem

	○ Mortality at 14 days: OR 0.048 (95% CI, 0.0009-0.688; p=0.009) • Previous administration of oxyimino β-lactams was associated with bacteremia due to ESBL-producing strains: RR 3.9 (95% CI, 1.1-13.8)
Author's conclusions	• Use of carbapenem (primarily imipenem) was associated with a significantly lower 14-day mortality than was use of other antibiotics active *in vitro*
Strengths	• Prospective study • International study conducted in 7 countries
Weaknesses	• Observational study with potential confounders • Propensity scores were not calculated • Bacteremia due to *E. coli* were not included • Minimum inhibitory concentrations (MICs) and dosing information unavailable • Supportive care in 1990s vs now
Take Home Points	• Carbapenems seem to be superior to non-carbapenem antibiotics for treatment of bloodstream infections caused by ESBL-producing *K. pneumoniae* • However, there were only 4 patients in the study receiving BL/BLIs • Bloodstream infections caused by ESBL-producing *E. coli* were not evaluated • The study was conducted in late 1990s when supportive care may have been different than it is today

v. CREs
    1. In 2001, the first case of *Klebsiella pneumoniae* carbapenemase (KPC)-producing Enterobacteriaceae in the U.S. was reported in North Carolina.[57]
    2. In 2002, a surveillance study in New York found that 9 of 602 known types of *Klebsiella pneumoniae* isolates produced KPC.[58]
    3. In 2004, there were two hospital outbreaks in New York, and an additional 20 KPC-producing isolates were identified.[59,60]
    4. Increased use of carbapenems resulted in increased incidence of CRE-related infections worldwide.[61]

vi. What are carbapenem-resistant Enterobacteriaceae (CREs)?
    1. Enterobacteriaceae resistant to carbapenems by producing carbapenemases and other resistance mechanisms.
    2. Increased use of carbapenems creates selection pressure for carbapenems resistance.[62]
    3. Carbapenemase-producing CRE carry antimicrobial resistance genes on mobile plasmids that can move between organisms.[61]

b. β-lactamase inhibitors:
    i. Avibactam[63,64]
        1. Avibactam belongs to the novel diazabicyclooctane class.
        2. It is a non-β-lactam β-lactamases inhibitor.

G. Timeline: 2010s
    a. ESBLs
        i. 2013 CDC report in the U.S.[65]
            1. 19% of all health-care-related infections caused by ESBL-producing Enterobacteriaceae.
            2. 23% of *Klebsiella* spp.: 17,000 infections and 1100 deaths yearly.
            3. 14% of *E. coli*: 9,000 infections and 600 deaths yearly.
            4. 26,000 infections and 1700 deaths every year.
        ii. ESBL-producing pathogens in the U.S. hospitals (SENTRY 2010):[31]
            1. *E. coli*: 81/195 (42%)
                a. CTX-M family: 41/81 (42%).
                b. CTX-M family is the predominant ESBL in Europe and the U.S.[28,29]
            2. *K. pneumoniae*: 71/195 (36%)
                a. CTX-M family: 24/71 (33.8%).
                b. SHV-type enzymes are common in *K. pneumoniae*.
                c. CTX-M-producing *K. pneumonia* used to be rare in the U.S., but seems to be increasing in prevalence to as high as 33.8%.[31]
                d. One institution in New York City reported CTX-M prevalence of 26.4% during 2010-2012, up from 1.7% during 2005-2009.[66]
        iii. ESBL producers are common in nosocomially acquired infections as well as in the community and especially in a health-care context, such as residential care facilities.[67-70]
    b. CREs
        i. Cases of *K. pneumoniae* carbapenemase (KPC)-producing CRE have been reported in almost every state.[61]
        ii. 2013 CDC report: 9,000 infections (88% *Klebsiella* spp.) and 600 deaths every year.[65]
        iii. Guh et al (2015) – Epidemiology of Carbapenem-Resistant Enterobacteriaceae in 7 US Communities, 2012-2013.[61]
            1. Metropolitan areas were in Georgia, Minnesota, Oregon, Colorado, Maryland, New Mexico, and New York.
            2. Among 599 CRE cases in 481 individuals, 520 (87%) were isolated from urine and 68 (11%) from blood.
            3. The overall annual CRE incidence rate per 100,000 population was **2.93** (95% CI, 2.65-3.23).
            4. Most cases occurred in individuals with prior hospitalization (75%) or indwelling devices (73%).
            5. Death occurred in 51 cases (9%; 95%CI, 6.6-11.4).
            6. Of 188 isolates tested, 90 (48%) produced a carbapenemase.
        iv. For comparison:
            1. MRSA: 25.1 per 100,000 population.[71]
            2. Invasive candidiasis: 13.3-26.2 per 100,000 population.[72]
            3. *Clostridium difficile*: 147.2 per 100,000 population.[73]

2. What is the controversy?

A. Problem

c. ESBLs in gram-negative bacteria have emerged as a major global public health concern in past decades.[23]

d. The rapid evolution and dissemination of β-lactamases is believed to have occurred via selection pressure because of the widespread use of antibiotics in human and veterinary medicine, and food production.[74]

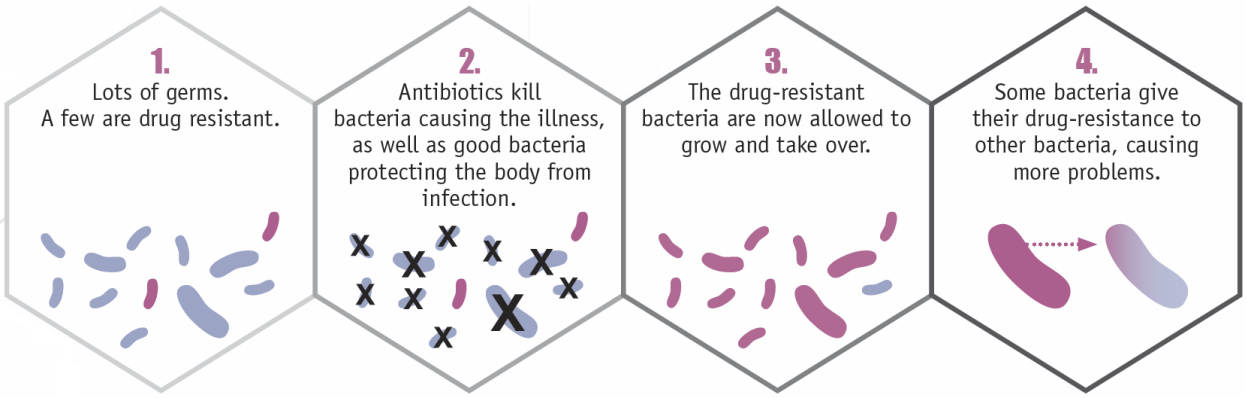

Figure 4: Selection pressure of antibiotics and the emergence of resistance.[65]

a. A strong risk factor for infection with carbapenems-resistant bacteria is previous use of a carbapenem.[75] Even brief exposure to a carbapenem increases the risk of colonization with imipenem-resistant gram-negative bacteria in patients in ICU.[76]

e. Use of carbapenem has been accompanied by the emergence of carbapenem resistance and increases in *Acinetobacter*[77] and *Stenotrophomonas*[78] infections.[79]

f. A new challenge of carbapenem resistance is emerging largely mediated by the efficient spread of carbapenemases.[80]

B. Proposed solution

a. Can we use β-lactam/β-lactamase inhibitors (BL/BLIs) for treatment of ESBL infections to spare carbapenems?

b. BL/BLIs might be a reasonable carbapenem-sparing option.

1. Some authors do not recommend their use.[45]
2. Others consider them a useful alternative.[81]

3. β-lactam/β-lactamase inhibitors

A. Spectrum of activity of β-lactamase inhibitors:[13]

Table 3: Spectrum of activity of β-lactamase inhibitors		
Inhibitor	**Spectrum**	**Intrinsic activity**
Clavulanic acid	Class A penicillinases	*H. influenzae* and *N. gonorrhoeae*
	Class A ESBLs	
Tazobactam	Class A penicillinases	*Borrelia burgdorferi*
	Class A ESBLs	
	Class C (some)	
Sulbactam	Class A penicillinases	*Bacteroides* spp., *Acinetobacter* spp., and *N. gonorrhoeae*
	Class A ESBLs	
Avibactam (NXL104)	Class A penicillinases	
	Class A ESBLs	
	Class A carbapenemases	
	Class C (some)	
	Class D (some)	
Relebactam (MK-7655)	Class A penicillinases	
	Class A ESBLs	
	Class A carbapenemases	
	Class C (some)	
RPX7009	Class A penicillinases	
	Class A ESBLs	
	Class A carbapenemases	
	Class C (some)	

B. Currently available β-lactam/β-lactamase inhibitors in the U.S.[14]
   a. Amoxicillin/clavulanate
   b. Ampicillin/sulbactam
   c. Piperacillin/tazobactam
   d. Ceftolozane/tazobactam
   e. Ceftazidime/avibactam

C. Pharmacokinetic-pharmacodynamic (PK-PD) target attainment
   a. There is concern that conventional dosing with BL/BLIs might not always achieve adequate PK-PD indices.[32]
   b. Why does PK-PD target attainment matter?
      i. For β-lactams, the time during which the free serum drug concentration exceeds the MIC of the drug for the organism (fT>MIC) appears to be the best predictor of outcomes.[82,83]

Table 4: PK-PD target for β-lactams[84-91]	
β-lactam	**PK-PD target**
Aztreonam	50% fT>MIC
Carbapenems	40% fT>MIC
Cephalosporins	60% fT>MIC
Penicillins	50% fT>MIC

ii. Near-maximal bactericidal effect (-3 log kill) is achieved when fT>MIC is approximately 40-50% of the dosing interval for the penicillins.[32,83]
iii. Animal model studies suggest that the PK-PD target associated with efficacy in treatment of ESBL-producing organisms is the same as that in therapy against non-ESBL-producing bacteria (50% fT>MIC).[92]
iv. ESBL production does not seem to alter PK-PD targets.

c. Prolonged infusion of piperacillin-tazobactam over 4 hours
i. May be necessary for critically ill patients.[93]
ii. May be associated with decreased mortality (RECEIPT Study).[94]

d. Shea et al compared pharmacodynamics of intermittent and prolonged infusions of piperacillin/tazobactam using Monte Carlo simulations and steady-state pharmacokinetic data from hospitalized patients.[95]

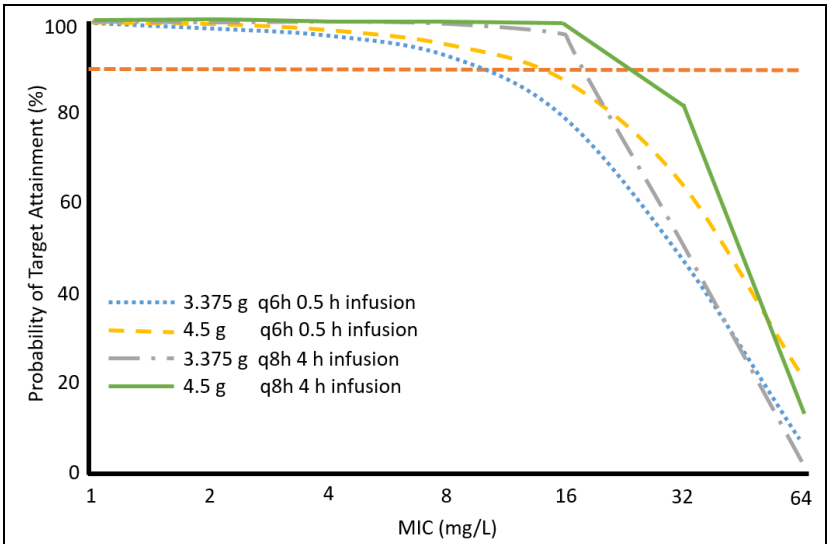

Figure 5: Probability of target attainment with various piperacillin-tazobactam dosing strategies.[95]

e. Lodise et al: Piperacillin-tazobactam 3.375g IV infused over 0.5h every 6 hours associated with >90% target attainment when MIC ≤ 8 mg/L. [82]

D. MIC distribution of piperacillin-tazobactam in *E. coli* and *K. pneumoniae* isolates

a. MICs of BL/BLIs might vary according to[96]
i. ESBL production
ii. Membrane permeability of strains
iii. Amount of β-lactamase produced
iv. The rate of enzyme synthesis

Table 5: Intra-abdominal Isolates from SMART – North America (2010-11)[48]

Organism	*E. coli* (non-ESBL)	*E. coli* (ESBL)	*K. pneumoniae* (non-ESBL)	*K. pneumoniae* (ESBL)
Isolates	1507	136	636	62
Susceptibility to piperacillin-tazobactam	96%	78%	93%	34%
MIC_{50}	≤2	4	≤2	>64
MIC_{90}	4	>64	16	>64

4. Evaluation of the Evidence

A. Systematic Reviews and Meta-Analyses

a. Vardakas et al (2012)[97]

Table 6: Carbapenems versus Alternative Antibiotics for the Treatment of Bacteraemia Due to Enterobacteriaceae Producing Extended-spectrum β-lactamases: A Systematic Review and Meta-Analysis.[97]	
Objective	• To study the comparative mortality associated with carbapenems and alternative antibiotics for the treatment of patients with ESBL-positive Enterobacteriaceae bacteremia
Design	• A systematic review and meta-analysis of 21 studies
Population	• 1584 patients with bacteremia due to ESBL-positive Enterobacteriaceae
Endpoints	• Primary analysis: Comparative all-cause mortality of patients receiving carbapenems or alternative antibiotics for bacteremia due to ESBL-positive Enterobacteriaceae as empirical or definitive treatment • Secondary analysis: BL/BLIs were compared with non-BL/BLIs
Methods	• Scopus and PubMed databases were searched until January 2012 • Any published article reporting data on mortality of patients with bacteremia due to ESBL-positive Enterobacteriaceae was eligible • Patients of all ages with community-, hospital- and healthcare-associated bacteremia were eligible • Studies in which all patients received only carbapenems were excluded • Studies that included infections other than bacteremia were excluded • Case reports and abstracts from conferences were excluded • Pooled risk ratios (RRs) and 95% confidence intervals (Cis) were calculated • Statistical heterogeneity between studies was assessed using a χ^2-test (P<0.10) and I^2 to denote the degree of heterogeneity • The Mantel-Haenszel (M-H) fixed-effect model (FEM) was used when no significant statistical heterogeneity between the studies; otherwise, the DerSimonian-Laird random-effect model (REM) was used • Publication bias was assessed by the funnel plot method • The Newcastle-Ottawa scale for assessment of risk of bias in non-randomized studies was used
Results	• Appropriate empirical treatment ranged from 22-100% • Mortality did not differ between patients treated with carbapenems and BL/BLIs ○ Definitive therapy: RR 0.52 (95% CI, 0.23-1.13) ○ Empiric therapy: RR 0.91 (95% CI, 0.66-1.25) • Carbapenem vs non-BL/BLI ○ Definitive: RR 0.65 (95% CI, 0.47-0.91) ○ Empiric: RR 0.50 (95% CI, 0.33-0.77) • Several patients who were treated empirically with a BL/BLI subsequently received a carbapenem
Author's Conclusion	• The role of BL/BLIs should be further evaluated for definitive treatment
Strengths	• Included studies from Asia, Europe, and America • Assessed risk of bias using the Newcastle-Ottawa scale

Weaknesses	• Analysis according to specific species lacking (e.g., *E. coli* vs *K. pneumoniae*) • MIC distribution of isolates unavailable • Breakdown of the BL/BLI group in terms of what proportion of patients received piperacillin/tazobactam or other BL/BLIs lacking • Dosing strategies unknown • Individual patient data unavailable • Most studies included were single-center studies • Limited by considerable heterogeneity in the trials included • Publication bias was present • Several studies included in the analysis reported mortality data unadjusted for potential confounders • Did not report outcomes on adequate treatment, correct dosing, and sufficient duration of administration
Take Home Points	• No difference in mortality was observed between carbapenems and BL/BLIs for definitive treatment • Difficult to draw a conclusion due to significant heterogeneity in the results of definitive therapy • It is not clear if the results are applicable to bacteremia caused by *K. pneumoniae* • Several studies included in the analysis reported mortality data unadjusted for potential confounders • Randomized clinical trials are desirable

b. Rodriguez-Bano et al (2012)[98]

Table 7: β-Lactam/β-Lactam Inhibitor Combinations for the Treatment of Bacteremia Due to Extended-Spectrum β-Lactamase-Producing *Escherichia coli*: A Post Hoc Analysis of Prospective Cohorts.[98]	
Objective	• To evaluate the outcomes of patients with bloodstream infections (BSIs) caused by ESBL-producing *E. coli* (ESBL-EC) who had been treated with BL/BLIs or carbapenems
Design	• A *post hoc* analysis of individual patients with BSI due to ESBL-EC • From 6 previously published prospective cohort studies carried out in Spain
Population	• Age > 17 years with clinically significant monomicrobial bacteremia (ESBL-EC alone) along with criteria for sepsis and therapy with a BL/BLI or a carbapenem for at least 48 hours
Endpoints	• The main outcome variable was mortality at 7, 14, and 30 days • Length of hospital stay after BSI was also evaluated
Methods	• The empirical therapy cohort (ETC) included patients who received empirical therapy with BL/BLI or carbapenem in monotherapy, whose first dose given during the first 24 hours after blood culture drawn and the isolate was susceptible • The definitive therapy cohort (DTC) included patients receiving definitive monotherapy with an active BL/BLI or carbapenem for at least 50% of total duration of antimicrobial therapy • Mortalities at days 7, 14, and 30 were compared using χ^2-test • To control for confounding, multivariate analysis was performed by Cox regression • Potential confounders and interactions were added using a forward method

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The propensity score-the probability of receiving carbapenem as empirical therapy-was calculated using a nonparsimonious multivariate logistic regression model
The validity of the model was assessed by estimating goodness-of-fit to the data with the Hosmer-Lemeshow test and its discrimination ability with the area under the receiver operating characteristic curve

</td></tr>
<tr><td>Baseline Characteristics</td><td>
<table>
<tr><th></th><th colspan="3">Definitive Therapy Cohort</th></tr>
<tr><th>Characteristic</th><th>BLBLI (n = 54)</th><th>Carbapenem (n = 120)</th><th>P</th></tr>
<tr><td>Age, median y (IQR)</td><td>67 (56–83)</td><td>70 (55–78)</td><td>.3</td></tr>
<tr><td>Male sex</td><td>34 (63)</td><td>70 (58.3)</td><td>.5</td></tr>
<tr><td>Nosocomial acquisition</td><td>18 (33.3)</td><td>67 (55.8)</td><td>.006</td></tr>
<tr><td>Charlson index, median, (IQR)</td><td>2.5 (1–5)</td><td>3 (1–5)</td><td>.5</td></tr>
<tr><td>Cancer</td><td>15 (27.8)</td><td>43 (35.8)</td><td>.2</td></tr>
<tr><td>Immunosuppression</td><td>3 (5.6)</td><td>15 (12.5)</td><td>.1</td></tr>
<tr><td>Neutropenia</td><td>0</td><td>7 (5.8)</td><td>.1</td></tr>
<tr><td>Urinary or biliary tract as source</td><td>42 (77.8)</td><td>79 (65.8)</td><td>.1</td></tr>
<tr><td>ICU admission</td><td>4 (7.4)</td><td>18 (15.4)</td><td>.1</td></tr>
<tr><td>Severe sepsis or shock at presentation</td><td>8 (14.8)</td><td>32 (26.7)</td><td>.08</td></tr>
<tr><td>Pitt score, median (IQR)</td><td>1 (0–2)</td><td>1 (1–2)</td><td>.04</td></tr>
<tr><td>CTX-M enzyme</td><td>43 (82.7)</td><td>95 (81.2)</td><td>.8</td></tr>
</table>
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<tr><td>Results</td><td>

Mortality

Empiric BL/BLIs: HR 1.14 (95% CI, 0.29-4.40;p=0.84)
Definitive BL/BLIs: HR 0.76 (95% CI, 0.28-2.07;p=0.5)

MIC of piperacillin-tazobactam linked to outcome: (Retamar et al[99,100])

39 patients analyzed
UTI: all 11 patients survived, irrespective of MIC
Non-UTI: Mortality decreased with MIC ≤ 2 mg/L (0/18 vs 7/17 [41.1%]; p=0.02)

Most isolates produced CTX-M-type
Urinary and biliary tract infections were predominant

</td></tr>
<tr><td>Author's Conclusion</td><td>

These results suggest that amoxicillin/clavulanate and piperacillin/tazobactam are suitable alternatives to carbapenems for treating patients with BSIs due to ESBL-EC if active in vitro and would be particularly useful as definitive therapy

</td></tr>
<tr><td>Strengths</td><td>

Included 6 studies which increased sample size
All included studies were prospective
Used a propensity score to control for confounding
Follow up MIC analysis by Retamar et al

</td></tr>
<tr><td>Weaknesses</td><td>

All studies were carried out in Spain
Limited to bacteremia due to E. coli alone
More severely ill patients tended to be prescribed carbapenems

</td></tr>
<tr><td>Take Home Points</td><td>

There does not seem to be an association between BL/BLI definitive therapy and increased mortality
This study only included bacteremia due to E. coli; the results may not apply to bacteremia due to K. pneumonia
The results may not apply to more severely ill patients
If active in vitro, BL/BLI may be considered a reasonable alternative to carbapenems for treating bacteremia due to ESBL-producing E. coli
Randomized clinical trials are desirable

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B. Observational studies

a. Harris et al (2015)[101]

Table 8: Comparable Outcomes for β-lactam/β-lactamase Inhibitor Combinations and Carbapenems in Definitive Treatment of Bloodstream Infections Caused by Cefotaxime-resistant *Escherichia coli* or *Klebsiella pneumoniae*.[101]

Objective	• To compare the efficacy of β-lactam/β-lactamase inhibitor combinations (BL/BLIs) to carbapenems for the treatment of bloodstream infections (BSIs) caused by cefotaxime non-susceptible (likely ESBL- or AmpC β-lactamase-producing) *Escherichia coli* and *Klebsiella pneumoniae*
Design	• A single-center, retrospective observational cohort study in Singapore
Population	• Adult patients 21 years of age or older with a BSI due to *E. coli* or *Klebsiella* spp. between May 2012 to May 2013 • Bacterial isolates confirmed as cefotaxime non-susceptible, but piperacillin-tazobactam and meropenem susceptible (EUCAST) • Patients with polymicrobial bacteremia were excluded
Endpoints	• Days to resolution of systemic inflammatory response syndrome (SIRS) • All-cause mortality at 30 days
Methods	• Definitive therapy with carbapenem vs BL/BLI ○ Piperacillin-tazobactam 4.5 g q6-8h ○ Amoxicillin-clavulanate 1.2 g q8h ○ Meropenem 1 g q8h ○ Ertapenem 1 g q24h ○ Imipenem 500 mg q6h ○ All renally adjusted per local guidelines
Baseline Characteristics	**Patient characteristic** / **Definitive treatment cohort** / **Total study population** **BLBLI (N = 24)** / **Carbapenem (N = 23)** / **N = 91** Age, median [IQR], years: 77 [61–83] / 77 [68–83] / 75 [62–83] Female: 13 (54%) / 12 (52%) / 49 (54%) Hospital acquired: 7 (29%) / 4 (17%) / 20 (22%) Community acquired: 7 (29%) / 9 (39%) / 42 (46%) Healthcare associated: 10 (42%) / 10 (43%) / 29 (32%) CCI, median [IQR]: 2 [1-4] / 2 [1-5] / 2 [1-4] Pitt score, median [IQR]: 1 [0–2] / 1 [0–3] / 1 [0–2] APACHEII (if ICU), median [IQR]: 26 / 20 / 24 [15-28] ICU admission: 2 (8%) / 5 (22%) / 11 (12.1) *E. coli*: 22 (92%) / 17 (74%) / 79 (87%)
Results	• 92/804 BSI caused by cefotaxime non-susceptible (likely ESBL or AmpC) ○ *E. coli* (86%) ○ *Klebsiella* spp. (14%) • 47 patients eligible for analysis of definitive therapy ○ BL/BLIs: 2/24 (8.3%) died ○ Carbapenem: 4/23 (17.4%) died

<table>
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<table>
<tr><th>Outcome</th><th>Crude HR (95% CI)</th><th>Adjusted HR (95% CI)*</th></tr>
<tr><td>30-day mortality</td><td>0.47 (0.09-2.59)</td><td>0.91 (0.13-6.28)</td></tr>
<tr><td>Resolution of SIRS</td><td>1.19 (0.44-3.19)</td><td>0.91 (0.32-2.59)</td></tr>
<tr><td>Hospital discharge</td><td>0.74 (0.38-1.41)</td><td>0.62 (0.27-1.42)</td></tr>
<tr><td colspan="3">*Adjusted for ICU admission, infecting organism, Pitt score</td></tr>
</table>
• Piperacillin-tazobactam MIC distributions: ≤4 (70.7%) and 8 (29.3%)
</td></tr>
<tr><td>Author's Conclusion</td><td>• BL/BLIs appear to have a similar efficacy to carbapenems in the treatment of cefotaxime-resistant E. coli and K. pneumoniae bloodstream infections
• Directed therapy with a BL/BLIs, when susceptibility is proven, may represent an appropriate carbapenem-sparing option</td></tr>
<tr><td>Strengths</td><td>• Provided dosing information
• Provided MIC distributions for piperacillin-tazobactam, although not separated by organism (e.g, E. coli vs K. pneumoniae)</td></tr>
<tr><td>Weaknesses</td><td>• Retrospective study
• Single-center study in Singapore with limited generalizability
• Study size was small (power of 55%)
• Did not use a propensity score to control confounding
• Underpowered to detect true differences in infrequent outcomes, particularly for mortality at 30 days</td></tr>
<tr><td>Take Home Points</td><td>• Use of a BL/BLIs as definitive treatment of cefotaxime non-susceptible E. coli or K. pneumoniae bacteremia was not associated with worse outcomes compared to carbapenems
• 86% of isolates were E. coli so the results may not be applicable to K. pneumoniae bacteremia
• Single center study in Singapore limits generalizability
• Randomized clinical trials are desirable</td></tr>
</table>

b. The INCREMENT Project[102]
    i. Large international (12 countries) retrospective observational study (January 2004 to December 2012).
    ii. Outcomes: cure rate at day 14 and 30-day mortality.
    iii. 656 pts with BSI were included.
        1. 129 received BL/BLIs.
            a. 61% piperacillin-tazobactam
            b. 38% amoxicillin-clavulanate
        2. 527 received carbapenem
            a. 23% imipenem
            b. 45% ertapenem
            c. 33% other
        3. 55% and 57% urinary or biliary tract source
        4. 78% and 73% caused by *E. coli* (p>0.2)
        5. 14-day clinical cure rates: 85% v 84%
        6. 30-day mortality: 12% v 14%
    iv. There was no difference in mortality between patients who received definitive therapy with BL/BLIs vs carbapenem given alone even after adjustment for comorbidity.

v. Adjusted HR 0.97 (95% CI, 0.48-2.03).
vi. Conclusions
    1. The results support hat BL/BLIs, if active *in vitro*, may be considered a reasonable alternative to carbapenems
    2. 73% of isolates were *E. coli*, so the results may not be applicable to *K. pneumoniae*
    3. Randomized clinical trials are desirable

C. Randomized Clinical Trials
    a. The MERINO Trial (ongoing)[103]
        i. Ongoing study in Australia, New Zealand, and Singapore.
        ii. Meropenem vs piperacillin-tazobactam
            1. Meropenem 1 g IV q8h.
            2. Piperacillin-tazobactam 4.5 g IV q6h.
        iii. This study is due in 2018.

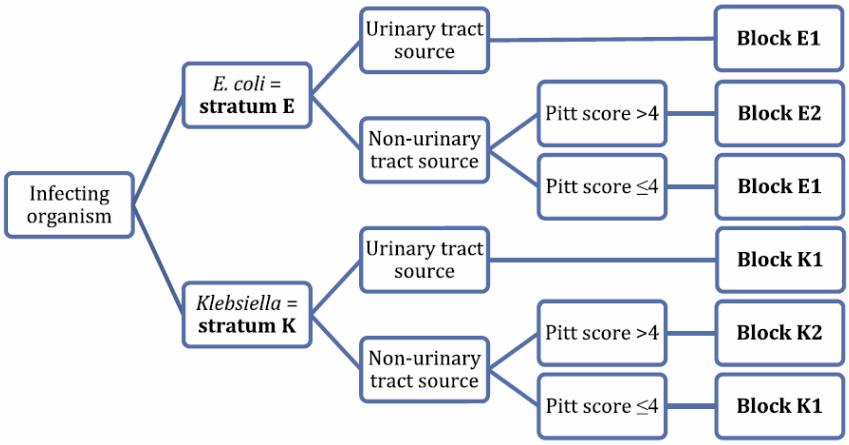

Figure 6: Design of MERINO Trial

5. Conclusions

A. The rapid evolution and dissemination of ESBLs is believed to have occurred via selection pressure.
B. Carbapenems are usually recommended as first-line therapy for serious infections caused by ESBL producers based on *in vitro* studies and observational studies.
C. Increased use of carbapenems has resulted in the emergence of carbapenem resistance and increases in *Acinetobacter* and *Stenotrophomonas* infections.
D. There are no randomized clinical trials to date comparing carbapenems and BL/BLIs.
E. Based on observational studies, it may be reasonable to use piperacillin-tazobactam, if active *in vitro*, for definitive treatment of ESBL-producing *E. coli* bloodstream infections using optimal dosing to maximize the probability of PK-PD target attainment.
F. There are limited data to support the use of piperacillin-tazobactam for definitive treatment of bloodstream infections due to ESBL-producing *K. pneumoniae*.
G. However, piperacillin-tazobactam may be an option for ESBL-producing *K. pneumoniae* if the MIC is known and a dosing strategy resulting in >90% probability of PK-PD target attainment is possible and safe.

6. Appendices

A. Breakpoints for susceptibility of Enterobacteriaceae to BL/BLIs and carbapenems

Table A: CLSI and EUCAST breakpoints for susceptibility of Enterobacteriaceae		
BL/BLIs	**CLSI 2015**	**EUCAST v5.0**
Amoxicillin-clavulanate	≤8/4	≤8
Ampicillin-sulbactam	≤8/4	≤8
Piperacillin-tazobactam	≤16/4	≤8
Carbapenems	**CLSI 2015**	**EUCAST v5.0**
Imipenem	≤1	≤2
Meropenem	≤1	≤2
Ertapenem	≤0.5	≤0.5
Doripenem	≤1	≤1

B. MIC distribution of imipenem in *E. coli* and *K. pneumoniae* isolates

Table B: Intra-abdominal Isolates from SMART North America (2010-11)				
Organism	***E. coli* (non-ESBL)**	***E. coli* (ESBL)**	***K. pneumoniae* (non-ESBL)**	***K. pneumoniae* (ESBL)**
Isolates	1507	136	636	62
Susceptibility to imipenem	100%	99%	97%	73%
MIC_{50}	0.12	0.12	0.25	0.25
MIC_{90}	0.25	0.25	0.5	>8

C. Bush-Jacoby-Medeiros classification (1995)[38]

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: CA[b]	Inhibited by: EDTA	Representative enzymes
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*

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