Cefepime use for ESBL infections:
Usable or Inducible?

http://snippits-and-slappits.blogspot.com

Hansita B. Patel, Pharm.D.
PGY2 Pharmacotherapy Resident
University of the Incarnate Word Feik School of Pharmacy
San Antonio, Texas

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Learning Objectives

1. Identify the mechanism of resistance and clinical implications of ESBL production
2. Discuss the rationale for cefepime use for ESBL infections
3. Evaluate current literature regarding cefepime use for ESBL infections
4. Determine when it is appropriate to initiate cefepime use for ESBL infections

What are Extended Spectrum Beta Lactamases (ESBLs)?

- ESBLs are one of several emerging broad spectrum beta-lactamase enzymes in multidrug resistant *Enterobacteriaceae* [1]
  - Most often found in *E. coli* (ESBL-EC) *or K. pneumonia* (ESBL-K)
- **Classification[1]**
  - Based on molecular structure and spectrum of activity
    - Ambler Class A based on molecular structure
    - Bush-Jacoby class 2be based on spectrum of activity[2] (See Appendix A)

Molecular Class	Enzymes	Spectrum of Activity
A	ESBLs (TEM, SHV, CTX-M)	Penicillins, cephalosporins (except cefamycins), and monobactams
	K. pneumoniae Carbapenemases (KPC)	All β-lactams
B	Metallo b-lactamases (VIM, IMP, NDM)	All β-lactams except monobactams
C	AmpC type (CMY-2, DHA-1, FOX-1,	Penicillins, cephalosporins (except cefepime),and monobactams
D	Cloxacillinases, carbapenemases	All β-lactams

Adapted from Table 1 from Ther Adv Infect Dis 2013; 49-69.

- 3 main genotypes of Class A ESBLs: TEM, SHV, CTX-M
  - Genotypic analysis is rare outside of epidemiological research studies

Key characteristic differences amongst different types of class A ESBLs[2]

	Community Onset	Hospital Onset
Organism	E. coli	Klebsiella spp.
Infection	CTX-M	SHV, TEM
Molecular epidemiology	Most not clonally related	Clonally related
Type of Infection	▪ Usually UTI ▪ Bacteremia ▪ Intra-abdominal infections	▪ Bacteremia ▪ Intra-abdominal infections ▪ Respiratory ▪ Urinary tract infection

Adapted from Table 2 from Critical care research and practice 2011; 2012.

– **Identification**[1]
  - Resistant to 3rd generation cephalosporins (cefotaxime, ceftriaxone, ceftazidime)
    - Difficult to detect due to various levels of activity against each cephalosporin
    - Treatment failure may result even if causative organisms appear susceptible to these agents by susceptibility testing

– **Mechanism of Resistance**[1]

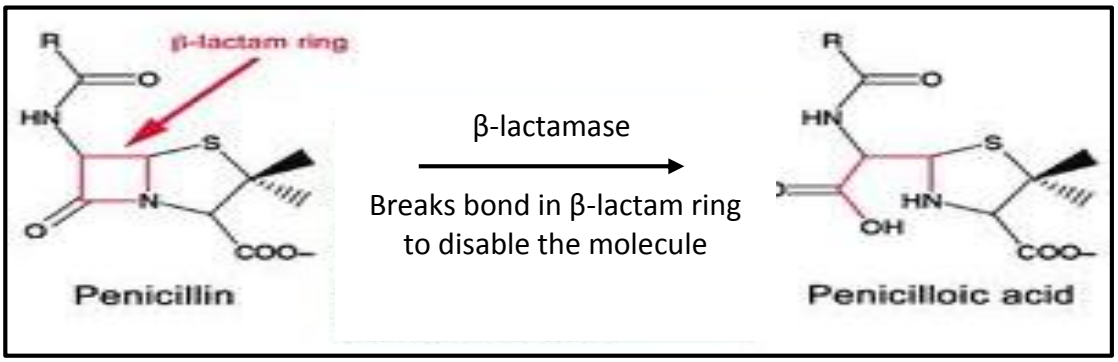
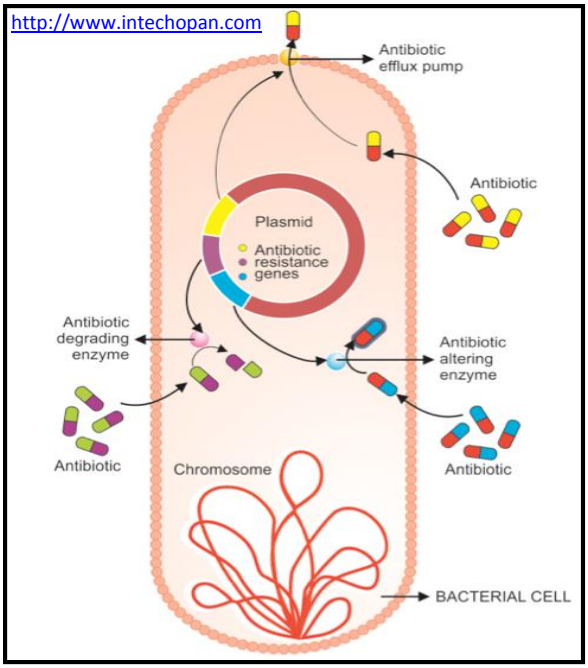


Image: http://www.wiley.com

  - Beta-lactamase enzymes inactivate β-lactam antibiotics by hydrolysis
    - Beta-lactamase inhibitors (clavulanate, sulbactam, tazobactam) inactivate beta-lactamases
  - Molecular class A beta-lactamases can be chromosomal or plasmid-mediated
  - Plasmid-mediated resistance
    - Antimicrobial-resistance genes carried on plasmids horizontally transferred from a donor to recombinant recipient during bacterial conjugation



- Plasmids carrying ESBL genes often carry additional resistance genes to other antimicrobial classes and resistance genes
- Other mechanisms of resistance for beta-lactams include:
  - Efflux pumps
  - Modified targets (eg. protein-binding proteins [PBPs])

– **Epidemiology**[2]
  - Prevalence ESBLs varies worldwide

Frequency of ESBL-producing E.coli and K. pneumoniae isolates in the TEST surveillance study (2004-2006) in different geographic areas

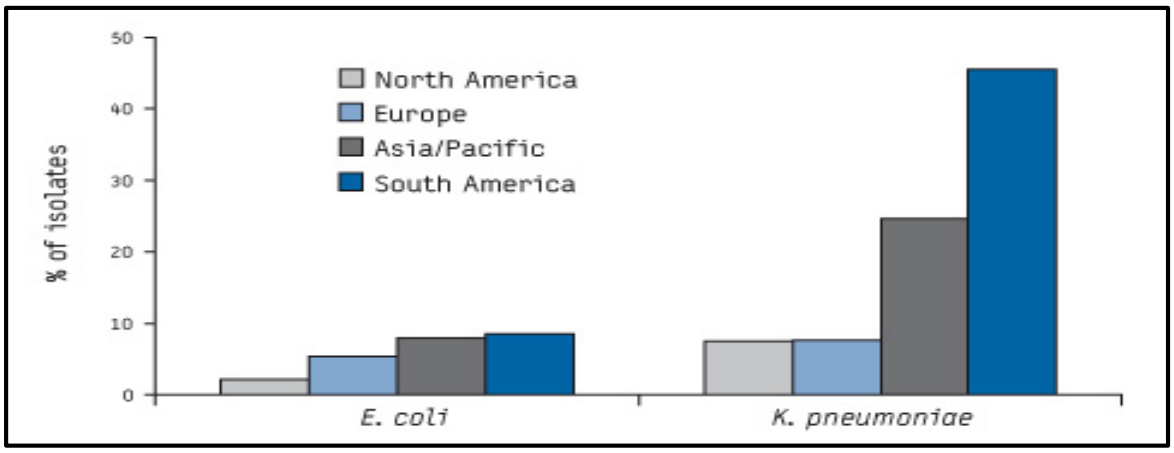


Image: http://www.eurosurveillance.org

  - Data from the Tigecycline Evaluation and Surveillance Trial (TEST) global surveillance database shows the rate of ESBL production was lowest among K. *pneumoniae* in North America (7.5%) compared to Latin America, followed by Asia, then Europe, (44.0%, 22.4%, 13.3%, respectively)[3]
  - MYSTIC surveillance study shows even lower level of prevalence of ESBL producing E.*coli* (1.5%) and K. *pneumoniae* (2.5-4.4%) in the United States[4]

– **Risk Factors**

Risk Factors for Community-Associated ESBL infections[5]

- Recurrent UTI
- Previous antibiotic usage
- Prior instrumentation to urinary tract
- Female sex
- Age (over 65 years)

Diabetes mellitus

Risk Factor for Hospital Associated ESBL[4]	Odds Ratio (95% Confidence Interval)
ICU admission	1.67 (1.16–2.40)
Renal failure	1.92 (1.21–3.04)
Burns	2.78 (1.92–4.01)
TPN	1.72 (1.18–2.49)
Urinary catheter	1.88 (1.25–2.83)
3rd Gen cephalosporin	2.99 (1.6–4.0)

- **Clinical Implications of ESBLs[2]**
  - Delay in detection and failure to treat with antibiotic active against ESBL producing organisms is associated with increased patient morbidity and mortality
    - The choice of appropriate antibiotic is crucial
    - Local surveillance data of prominent infective pathogens should closely be monitored
  - Lack of treatment options due to multiple-resistance genes on plasmids rendering many antibiotics inactive to ESBLs[7]
    - Eg. fluoroquinolones, aminoglycosides, trimethoprim, sulfonamides, and tetracyclines

- **Current Treatment**
  - Broad-spectrum carbapenems are the treatment of choice[8]
    - Associated with best outcomes of survival and bacteriologic clearance
    - However, overuse poses significant cause for concern for resistance, including development of carbapenem-resistant enterobacteriaceae (CREs)

Rationale for Cefepime Use

- Cephalosporins are class of bactericidal beta-lactams that inhibit cell wall synthesis
- Cefepime is 4th generation broad-spectrum cephalosporin
  - Frequently used as first-line empirical therapy for health care-associated infections, including those caused by suspected Gram-negative bacteria (GNB)
  - Relatively low propensity for degradation by ESBLs compared to that of other cephalosporins[9]
- **Latest CLSI Recommendations[10]**
  - **Previous Detection Recommendations**:
    - Test for ESBL production in enterbacteriaceae with reduced susceptibility to cephalosporins
    - Report ESBL-positive isolates as resistant to all cephalosporins

- **Current Detection Recommendations:**
  - In 2010, CLSI recommended to eliminate ESBL identification and report all broad-spectrum cephalosporins susceptibilities based on MIC alone
  - Thus, agents traditionally avoided in practice upon identification of ESBL-producing organisms are now being reconsidered
- **Current Breakpoints:**

CLSI Cefepime Breakpoints (mcg/mL)	
2006-2013	**2014-Present**
S ≤ 8 I: 16 R ≥ 32	S≤ 2 SDD: 4-8 R≥ 16

– **Incidence of ESBLs with New breakpoints[10]**
- McWilliams et al evaluated the rates of cephalosporin susceptibility that would be reported with new, lower 2014 CLSI breakpoints for ESBL producing E. *coli* and K. *pneumoniae*
  - Concluded that by eliminating confirmatory testing for ESBLs,, labs could report up to 20% to 30% of ESBL-producing E. *coli* and K. *pneumoniae* isolates, respectively, as susceptible to cefepime

Susceptibility Profiles of ESBL-producing E. coli and K. pneumoniae Isolates using 2010 and 2014 CLSI Breakpoints			
Bug/Year	**Susceptible**	**Intermediate**	**Resistant**
E. coli ▪ **2010** ▪ **2014**	19.7% 19.7%	8% ----	72.3% 80.3%
K. Pneumonia ▪ **2010** ▪ **2014**	29.3% 29.3%	8.7% ----	62% 70.7%

The Controversy

– Changes in the CLSI guidelines may lead to increased use of cefepime for ESBL-producing organisms[11]

– Increased rates of clinical failure have been associated with cefepime use in the past despite MIC breakpoints, but some data suggests cefepime may be more effective at lower MICs[1]

<table>
<tr><th colspan="2">Clinical Implications of Extended-Spectrum B-lactamase (ESBL) Producing Klebsiella species and Escherichia coli on Cefepime Effectiveness[14]
Kotapati S, Kuti, JL, Nightingale, CH, et al. J Infect 2005; 51, 211-217.</th></tr>
<tr><td>Objective</td><td>To compare clinical and microbiological responses of patients receiving cefepime for ESBL producing Klebsiella sp. and E. coli from non-urine source with matched controls receiving cefepime for non-ESBL producers</td></tr>
<tr><td>Methods</td><td>Study Design: Single center, retrospective, case-controlled study
Inclusion Criteria:
Initial cefepime monotherapy
ESBL producing Klebsiella sp. or E. coli from non-urine source
Non-ESBL controls on cefepime matched based on 4/5 criteria:
Age (+/- 5 yrs)
Site of infection
ICU stay
Pathogen species
Date of hospitalization (+/- 3 months)Clinically evaluable (≥ 3 days of cefepime therapy)
Regimen: Initial cefepime monotherapy; dose chosen at physician’s discretion
Outcomes:
Clinical cure (success or failure)
Microbiological cure (success or failure)
All-cause mortality
Infection-related mortality</td></tr>
<tr><td>Results</td><td>Baseline Characteristics (N=30; ESBL controls matched 2:1)→ 80-90% with pneumonia, LOS 11-14 days, duration of cefepime treatment 6-8 days, APACHE II 19-21

Outcomes (ESBL vs. non-ESBL)
Clinical cure: 40% vs 87%; P=0.028
Microbiological cure: 40% vs 95%; P=0.002.
Infection-related mortality: 20% vs 5%; P=0.251
All cause mortality: 40% vs. 25%; P=0.431
<table><tr><th colspan="2">Risk Estimates for Effect of ESBL Presence on Cefepime Outcomes</th></tr><tr><th>Variable</th><th>Odds ratio (95% CI)</th></tr><tr><td>Unsuccessful clinical response</td><td>9.7 (1.4–68.8)</td></tr><tr><td>Unsuccessful microbiological response</td><td>28.5 (2.6–306.6)</td></tr><tr><td>All-cause mortality</td><td>2.0 (0.396–10.1)</td></tr><tr><td>Infection-related mortality</td><td>4.7 (0.375–60.1)</td></tr></table></td></tr>
<tr><td>Author’s Conclusions</td><td>ESBL production among non-urinary Klebsiella sp. and E. coli negatively affected cefepime effectiveness even if initially susceptible. 60% of ESBL producing isolates had cefepime MICs within the susceptible range, yet only 50% had a positive clinical and microbiological response. All failures were pulmonary sources where penetration may be hindered, thus at low doses of 1 g every 12 or 24 h, appropriate exposure may not have been achieved and explain the poor response, even with lower MICs.</td></tr>
</table>

Limitations	• Small sample size • Single Center • Retrospective design • Clinical failure not clearly defined • Low cefepime dose for the majority of patients
Take-home Points	• Cefepime treatment in the presence of an ESBL was 9.7 and 28.5 times more likely to result in unsuccessful clinical and microbiological response, respectively. • All-cause and infection-related mortality were unaffected likely because therapy was changed to another anti-microbial if patient not improving (carbapenem) • Carbapenems should remain the drug of choice for ESBL producing Klebsiella sp and E. coli • Due to success in a small number of cases, further studies needed to evaluate if higher cefepime doses may improve responses to ESBLs that are initially susceptible

Use of cefepime for the treatment of infections caused by extended spectrum beta-lactamase-producing *Klebsiella pneumoniae* and *Escherichia coli*[14] LaBombardi VJ, Rotjman A, Tran K. Diag Microb and Infect Dis 2006; 56 313-315.	
Objective	To determine efficacy of cefepime in treating infections caused by ESBL-producing strains of K. *pneumoniae* and E. *coli*
Methods	**Study Design**: Single center, retrospective chart review **Inclusion Criteria:** ▪ Available charts from patients with infection caused by ESBL-producing bacteria ▪ Received cefepime within 72 hours of isolation of organism **Outcomes:** ▪ Clinical outcomes (therapeutic cure, improvement, or failure) ▪ Microbiological cure (eradication, persistence, or reinfection with same ESBL-producing species)
Results	**Baseline Characteristics** (N=13 with 15 disease episodes) ICU 8/13, sub-ICU 5/13 at time of initiation of cefepime therapy; 10/13 on mechanical ventilation; 10 PNA, 3 sepsis, 3 UTI, 1 Otit

Results

Age/Sex	ICU	INT	Infection	Isolate	MIC	Clinical Outcome	Microbial outcome
44/F	I	Y	Pneumonia	K. pneumo	≤1	Cure	Eradication
32/M	I	N	Pneumonia	K. pneumo	≤1	Failure	Persistent
67/F	I	Y	Sepsis/PNA	K. pneumo	>64	Failure	Persistent
59/F	I	Y	Sepsis	K. pneumo	≤1	Cure	Eradication
79/M	I	Y	Sepsis/BSI	E. coli	≤1	Cure	Eradication
72/F	S	Y	Pneumonia	K. pneumo	2	Cure	Eradication
74/M	S	Y	Pneumonia/ Urinary	K. pneumo	≤1	Cure	Eradication
83/M	S	Y	Urinary	E. coli	≤1	Cure	Eradication
59/M	I	Y	Pneumonia	K. pneumo	≤1	Cure	Eradication
81/M	S	Y	Urinary/PNA	K. pneumo	≤1	Cure	Eradication
46/M	I	N	Otitis	K. pneumo	≤1	Cure	Undetermined
76/F	S	Y	Pneumonia	K. pneumo	≤1	Cure	Eradication
46/M	I	N	Pneumonia	K. pneumo	≤1	Improved	Persistent

Author's Conclusions

Cefepime is a potential alternative to carbapenems for the treatment of infections caused by ESBL-producing bacteria.

Limitations

- Small sample size
- Retrospective design
- Single center
- Dosing of cefepime not specified,
- Not case-controlled or compared to carbapenem therapy

Take-home Points

- Only 1/10 clinical failures when MIC≤1.
- Although the doses of cefepime used were not reported, this study supports the potential use of cefepime for lower MICs, especially if MIC≤1 .

2/2 ICU patients with PNA with sepsis secondary to bacteremia experienced clinical failures

Impact of Cefepime Therapy on Mortality among Patients with Bloodstream Infections Caused by Extended-Spectrum-Beta-Lactamase-Producing *Klebsiella pneumoniae* and *Escherichia coli*[15]

Chopra T, Marchaim D, Veltman J et al. Antimicrob Agents Chemother 2012; 56: 3936–42.

Objective

To analyze the impact of antimicrobial therapy, focusing on cefepime, on clinical outcomes of patients with BSI due to ESBL producing *E. coli* and *K. pnuemoniae* and to examine associations between MICs of cefepime for ESBL-producing bloodstream pathogens and mortality

Methods

Study Design: Multicenter, 3-year, retrospective chart review

Inclusion Criteria:

- Blood culture positive for ESBL-producing *K. pneumoniae* or *E. coli*
- Empiric and consolidative therapy with cefepime alone, carbapenem alone, or either in combination with another antibiotic

Outcomes:

- In-hospital mortality rate
- Duration of hospitalization following initial culture (Number of days from culture to discharge)
- Number of hospital readmissions within 30 days following culture

Results

Baseline Characteristics: N=151; 83% *K. pneumoniae*, 16.5% *E. coli*; Age 66, 51% female

Empiric Therapy and Impacts on Outcome

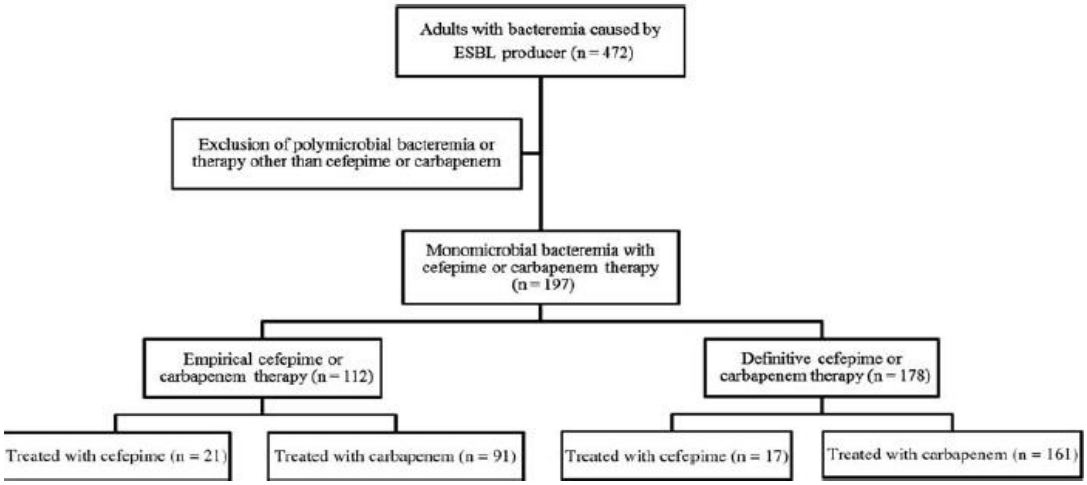
Treatment & Outcomes	Odds Ratio (95% CI)
Cefepime monotherapy	
Mortality	1.19 (0.57-2.49)
Readmission	1.14 (0.52-2.50)
Cefepime alone or in combination	
Mortality	1.09 (0.55-2.15)
Readmission	0.70(0.34-1.47)
Carbapenem alone	
Mortality	0.96 (0.30-3.03)
Readmission	0.39 (0.01-1.83)
Carbapenem alone or in combination	
Mortality	1.05 (0.49-2.24)
Readmission	0.44 (0.17-1.13)

<table>
<tr><td></td><td>Subgroup analysis showed no association between MIC of cefepime and mortality

<table>
<tr><th>Cefepime MIC (µmL)</th><th>Mortality</th></tr>
<tr><td>≤2</td><td>5/13 (39%)</td></tr>
<tr><td>4</td><td>1/4 (25%)</td></tr>
<tr><td>8</td><td>1/2 (50%)</td></tr>
<tr><td>≥16</td><td>10/24 (42%)</td></tr>
</table>

Length of stay (LOS) after culture:
– Median length of hospital stay 10 days (IQR 5-15 days)
– Shorter LOS for empirical cefepime 7 days (IQR 4-11 days) vs. carbapenems 12 days (IQR 9-16 days)</td></tr>
<tr><td>Author's Conclusions</td><td>In multivariate analysis, empirical cefepime therapy for BSI due to ESBL-producing pathogen was associated with a trend toward an increased mortality risk. Empirical carbapenem therapy was associated with a trend toward decreased mortality risk. The results support continued use of cefepime for empirical therapy for suspected BSI with gram-negative organisms. However, carbapenems should remain drug of choice for patients with confirmed bacteremia due to ESBL-producing pathogens.</td></tr>
<tr><td>Limitations</td><td>• Retrospective design; not case-controlled
• Cefepime dose not specified
• Unable to distinguish between patients with infections due to ESBL producers with cefepime MIC≤1 to those with MIC of >1 to ≤2
• Not powered to demonstrate association between increased MIC of cefepime and mortality</td></tr>
<tr><td>Take-home Points</td><td>• Because there was no significant difference in mortality, some review articles have used this study as supportive literature for cefepime use for ESBL infections.
• Caution should be used even with MIC ≤2.
• Unable to compare patients with infections due to ESBL producers with cefepime MIC≤1 to those with MIC of >1 to ≤2.</td></tr>
</table>

Cefepime Therapy for Monomicrobial Bacteremia Caused by Cefepime-Susceptible Extended-Spectrum Beta-Lactamase-Producing Enterobacteriaceae: MIC Matters[12] Lee N, Lee C, Huang W, Tsui K, Hsueh P, Ko W, et al. Clin Infect Dis 2013; 56:488–95.	
Objective	To compare the clinical outcome of adults who have ESBL-producing Enterobacteriaceae bacteremia that were definitively treated with in-vitro active cefepime with adults definitively treated with a carbapenem

	
Methods	**Study Design**: Multicenter, retrospective case-control study; propensity-score matched **Inclusion & Exclusion Criteria*:** **Regimen:** Choice of antibiotic at physician's discretion at the following doses (or renal-adjusted) approved by ID specialist or pharmacists per indications ▪ Ertapenem 1g q24h ▪ Imipenem 0.5g q6h ▪ Meropenem 1g q8h ▪ Cefepime 1-2g q8h; 3-6g/day **Primary Outcome**: 30-day crude mortality **Secondary Outcomes**: clinical failure, microbiological failure
Results	**Baseline Characteristics** (N=197; 33 treated with cefepime) with 24.2% PNA, 18.2% catheter-related, urosepsis 18.2%, SSTI 15.2%, IAA, 78.8% MIC ≤8 78.8% (susceptible according to 2011 CLSI); 18/33 E. cloacae, 8/33 E. coli, 7/33 K. pneumoniae No difference in terms of age, sex, comorbidity, source of bacteremia, or disease severity **Outcomes** (cefepime vs. carbapenem treatment): ▪ ETC: 30-D mortality 58.8% vs. 17.9% P=0.001 ▪ Lower rate in causative isolates with lower MIC as follows: ○ MIC≤1 (0%), MIC 2-8 (40%), MIC ≥16 (100%) ▪ Sepsis-related mortality 47.1% vs 11.9%; P=0.002 ▪ DTC: 30-D mortality (multivariate analysis) OR, 9.93; 95% CI, 2.7-31.91; P <0.01 ▪ Lower mortality rates in isolates with MIC ≤ 1 (16.7%), MIC 2-8 (45.5%), MIC≥16 (100%); P=0.035 ▪ Clinical failure: OR 6.2; 95% CI 1.3-25.6; P=0.04 ▪ Microbiological failure: OR 5.5; 95% CI 2.5-20.3%; P<0.001
Author's Conclusions	Suboptimal clinical outcomes ensue when cefepime is given ESBL producing organisms that are susceptible based on CLSI criteria of MIC≤8 mcg/mL. Cefepime may be limited for bacteremia caused by ESBL-producing Enterbacteriaceae isolates with cefepime MIC ≤1 mcg/mL.

Limitations	• Retrospective study • Relatively few number of patients on cefepime therapy compared to carbapenems • Only in-hospital data analyzed • Did not distinguish outcome data between individual species of ESBL-producers
Take-home Points	Too early to consider cefepime a safe option for ESBL infections at current recommended doses, particularly for isolates with MICs between 2-8 mcg/mL, but may be used for isolates with low MICs (≤1 mcg/mL) in concordance with EUCAST guidelines

Additional Studies

Study	Study Design	Population	Results
Paterson, et al (2001)	Multicenter International Prospective Observational	ESBL infections treated with cephalosporins (N=3 on cefepime)	Cefepime associated with poor outcomes (66% [2/3] clinical failures) despite MIC<2 in 3 patients with ESBL infections
Bhat, et al 2007)	Single-center Retrospective Case series Subgroup analysis	Gram (-) bacilli BSI treated with cefepime (N=10 with ESBL)	Cefepime associated with poor outcomes despite MIC Despite small sample size , mortality was substantial (50% [5/10] died)

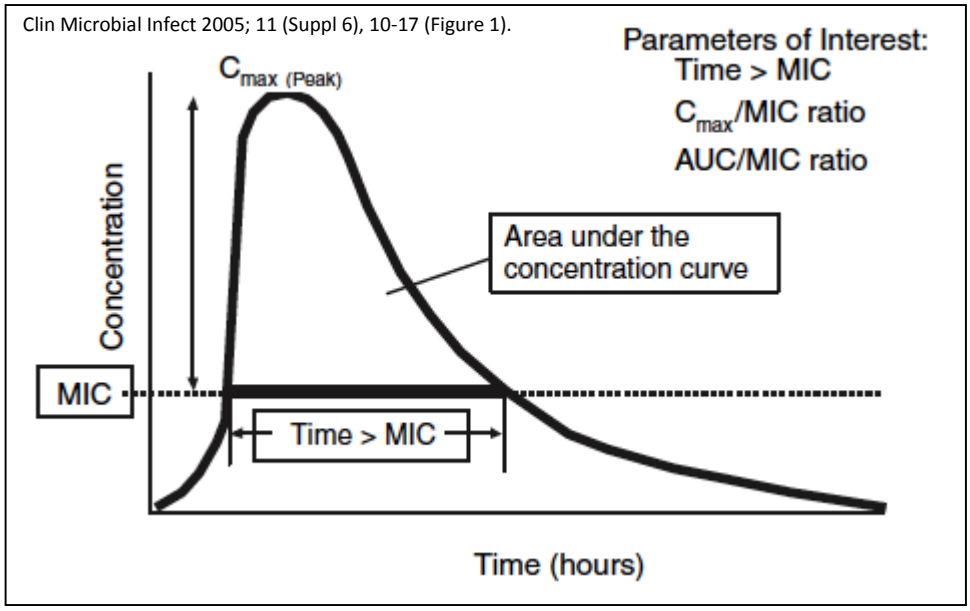
Does MIC Matter?

Rate of Clinical Failure or Mortality with Cefepime Use for ESBL infections							
MIC (mcg/mL)	**Chopra, et al (N=43)**	**Kotapati, et al (N=10)**	**Lee, et al (N=17)**	**Paterson, et al (N=3)**	**Bhat, et al (N=8)**	**LaBombardi, et al (N=13)**	**Total (N=94)**
≥8	11/26 (42%)	3/4 (75%)	3/5 (60%)	-----	1/2 (50%)	1/1 (100%)	**19/38 (50%)**
4	1/4 (25%)	2/4 (50%)	1/3 (33.3%)	-----	2/3 (66.7%)	-----	**6/14 (43%)**
2	5/13 (39%)	-----	1/3 (33.3%)	1/2 (50%)	2/3 (66.7%)	0/2 (0%)	**9/23 (39%)**
≤1	-----	1/2 (50%)	1/6 (16.7%)	1/1 (100%)	-----	1/10 (10%)	**4/19 (21%)**

- **Take Home Points**
  - Cefepime should NOT be used empirically
    - Majority of outcome data does not support use, especially at higher MICs
  - Cefepime may be still potentially be used for definitive therapy if isolates have MIC ≤1 with cefepime, but data is conflicting
    - If data is pooled from all studies with MIC data provided, there is a trend towards lower mortality with lower MICs
  - Limitation of outcome studies: dosing regimens and drug exposures not provided
    - It remains controversial if cefepime will be effective if MIC<1.0 if doses are optimized

Dosing

- **Rationale for using PK/PD data[18]**
  - Increasingly important in the development of susceptibility breakpoints
    - Clinical treatment trials most often do not include enough patients to allow determination of optimal antimicrobial therapy
    - PK/PD data can be useful to help design optimal therapeutic regimens
- **PK/PD Studies**
  - Analyze relationship between drug exposure, the antibiotic potency or MIC, and treatment efficacy[18]
  - PK values include:
    - Peak level in serum in relation to the MIC
    - Total amount of drug or area under the concentration curve relative to the MIC
    - Amount of time for which the drug levels remain above the MIC
  - PD analysis examines the relationship between PK values and outcomes
    - 50 % Time>MIC =PD target for optimal efficacy of beta-lactams, such as Cefepime



- **Monte Carlo Simulation Studies[18]**
  - Majority PK/PD data is based on Monte Carlo simulations
    - Simulate PK variation in up to 10, 000 patients
      - Account for 2 major sources of variation:
        - Distribution of MICs
        - Interpatient variability
    - Predict likelihood an antibiotic dosing regimen will achieve a PD target against organisms with varying MICs
    - Help establish breakpoints
      - Breakpoint=Highest MIC a dosing regimen is predicted to achieve the target the majority of the time (e.g., 95**%**)

Monte Carlo Simulations of ESBL Infections				
Study	**t½ (h)**	**MIC (mg/L)**	**Cefepime Regimen**	**PTA (%) for 50% T>MIC**
Ambrose, et al (US SENTRY)[19]	3.3	MIC_{50}: 0.5 MIC_{90}: 4	1g q12h 2g q12h	95 100
Reese, et al (single center)[20]	2.3	MIC_{50}: 8 MIC_{90}: 16	1g q12h 1g q8h 2g q12h	40 75 75

- **Take Home Points**
  - Empiric cefepime therapy should be NOT be used for suspected ESBL infections
  - Cefepime 2g q12h or 1g q8h may attain target attainment for the majority of ESBL-producing isolates if cefepime MIC≤4
  - Based on PK/PD data alone, cefepime appears to be a reasonable option, but the outcome data discussed above does NOT support this
  - Discordance between in-vitro PK/PD and outcome data are suggestive that there are additional concerning factors to consider[21]
    - Variable expression and efficiency of ESBL enzymes' abilities to hydrolyze particular extended-spectrum cephalosporins (eg, cefepime)
    - Inoculum effect

Conclusion & Recommendation

- Cefepime should NOT be used empirically for suspected ESBL infections over carbapenem therapy
    - Majority of outcome data does not support empiric use of cefepime for ESBL infections, especially for isolates with higher MICs
    - Outcome data that compared cefepime to carbapenems found higher mortality rates with cefepime use
- Cefepime should be avoided as definitive therapy for non-urinary, severe ESBL infections due to isolates with MIC >1 treated with traditional cefepime dosing
- Cefepime may potentially be used as definitive therapy for treatment, IF isolate has low MIC ≤1 to cefepime and doses are optimized
- Carbapenems drug of choice
    - 30-day mortality associated with imipenem, meropenem, or ertapenem therapy approximately 17%[22]
- Routine testing for ESBL producers should be continued, not just for epidemiology purposes, but for treatment purposes as well

Future Studies

- Cefepime use for ESBLs with optimized dosing
- Potential barriers and limitations:
    - Unethical to conduct prospective RCT with cefepime, versus carbapenem for ESBL infections
    - Difficult to obtain large enough sample size
    - Conducting a meta-analysis could be difficult if wanting to account for dosing
        - Dosing data not available in current literature regarding outcome data
        - Clinical failures and mortality data were not evaluated uniformly in all published studies

References

1. Delgado-Valverde, M, Sojo-Dorado, J, Pascual, A, et al. "Clinical management of infections caused by multidrug-resistant Enterobacteriaceae." Therapeutic Advances in Infectious Disease 2013; 1:49-69.
2. Dhillon, Rishi HP, and Clark, J. "ESBLs: A clear and present danger?" Critical care research and practice 2011; 2012.
3. Reinert, R, Low, D, Rossi, F, et al. “Antimicrobial susceptibility among organisms from the Asia/Pacific Rim, Europe and Latin and North America collected as part of TEST and the in vitro activity of tigecycline,” Journal of Antimicrobial Chemotherapy 2007; 60: 1018–1029.
4. Hidron, A, Edwards, J, Patel, J, et al., “Antimicrobialresistant pathogens associated with healthcare-associated infections: annual summary of data reported to the National Healthcare Safety Network at the Centers for Disease Control and Prevention, 2006-2007,” Infection Control and Hospital Epidemiology 2008; 29: 996–1011.
5. Pitout, J and Laupland, K, “Extended-spectrum β-lactamase-producing Enterobacteriaceae: an emerging publichealthconcern,” The Lancet Infectious Diseases 2008; 8: 159–166.
6. Paterson, D, Ko, W, Von Gottberg, A, et al., “International prospective study of Klebsiella pneumoniae bacteremia: implications of extended-spectrum β-lactamase production in nosocomial infections,” Annals of Internal Medicine 2004; 140: 26–32.
7. Sutton, S. “What are Extended-Spectrum Beta-Lactamases?” American Academy of Physician Assistants 2014; 27: 14-17.
8. Rawat, D, Nair, D. “Extended-spectrum β-lactamases in Gram Negative Bacteria,” Journal of Global Infectious Diseases 2010; 2: 263–274.
9. McWilliams, C, Condon, S, Schwartz, R, et al. "Incidence of Extended-Spectrum-β-Lactamase-Producing Escherichia coli and Klebsiella pneumoniae Isolates That Test Susceptible to Cephalosporins and Aztreonam by the Revised CLSI Breakpoints." Journal of Clinical Microbiology 52.7 (2014): 2653-2655.
10. Nguyen, H, Shier, K, Graber, C. “Determing a clinical framework for use of cefepime and Beta-lactam/Beta-lactamase inhibitors in the treatment of infections caused by extended-spectrum Beta-lactamase-producing Enterobacteriaceae.” Journal of Antimicrobial Chemotherapy 2014; 69:871-880.
11. Lee N, Lee C, Huang W, Tsui K, Hsueh P, Ko W, et al. “Cefepime therapy for monomicrobial bacteremia caused by cefepimesusceptible extended-spectrum beta-lactamase–producing Enterobacteriaceae: MIC matters.” Clin Infect Dis 2013; 56:488–95.
12. Kotapati S, Kuti, JL, Nightingale, CH, et al. “Clinical implications of extended spectrum beta-lactamase (ESBL) producing *Klebsiella* species and *Escherichia coli* on cefepime effectiveness. J Infect 2005; 51, 211-217.
13. LaBombardi VJ, Rotjman A, Tran K. “Use of cefepime for the treatment of infections caused by externded spectrum beta-lactamase-producing *Klebsiella pneumoniae* and *Escherichia coli*. Diag Microb and Infect Dis 2006; 56 313-315.

14. Chopra T, Marchaim D, Veltman J et al. Impact of cefepime therapy on mortality among patients with bloodstream infections caused by extended-spectrum-b-lactamase-producing Klebsiella pneumoniae and Escherichia coli. Antimicrob Agents Chemother 2012; 56: 3936–42.
15. Paterson DL, Ko WC, Von Gottberg A, et al. Outcome of cephalosporin treatment for serious infections due to apparently susceptible organisms producing extended spectrum beta-lactamases: implications for the clinical microbiology laboratory. J Clin Microbiol 2001; 39, 2206-12.
16. Bhat SV, Peleg AY, Lodise TP, et al. "Failure of current cefepime breakpoints to predict clinical outcomes of bacteremia caused by gram-negative organisms."Antimicrob Agents Chemother 2007; 51, 4390-4395.
17. Andes D, Craig WA. Treatment of infections with ESBL-producing organisms: pharmacokinetic and pharmacodynamic considerations. Clin Microbial Infect 2005; 11 (Suppl 6), 10-17.
18. Ambrose PG, Bhavanni SM, Janes RN. Pharmacokinetics-pharmacodynamics of cefepime and pipercillin-tazobactam against *Escherichia coli* and *Klebsiella pneumoniae* strains produing extended spectrum beta-lactamases report from the ARREST program. Antimicrob Agents Chemother 2003 47:1643–1646.
19. Reese, AM, Frei CR, Burgess DS. Pharmacodynamics of intermittent and continuous infusion pipercillin/tazobactam and cefepime against extended-spectrum beta-lactamase producing organisms. Int J Antimicrob Agents 2005; 26, 114-119.
20. Maglio D, Ong C, Banevicius MA. Determination of the in-vivo pharmacodynamic profile of cefepime against extended spectrum beta-lactamase *Escherichia coli* at various inocula. Antimicro Agent Chemother 2004; 48:1941-1947.
21. Lee NY, Huang WH, Tsui KC, Hsueh PR, et al. "Carbapenem therapy for bacteremia due to extended-spectrum beta-lactamase-producing *Escherichia coli* or *Klebsiella pneumoniae*.Diagn Microbiol Infect Dis. 2011; 70: 150-3

Appendix A

Bush-Jacoby Classifications[2]

TABLE 1

Bush-Jacoby-Medeiros Group	Molecular class (Ambler)	Preferred substrates	Representative enzymes	Resistance or susceptibility to β-lactamase inhibitors
1	C	Cephalosporins	AmpC	Resistant
2b	A	Penicillins, Cephalosporins	TEM, SHV	Susceptible
2be	A	Penicillins, extended-spectrum cephalosporins, monobactams	TEM, SHV	Susceptible
2d	D	Penicillins, cloxacillin	OXA	Resistant
2e	A	Cephalosporins	Inducible cephalosporinases from *Proteus vulgaris*	Susceptible
2f	A	Penicillins, cephalosporins, carbapenems	NMC-A from *Enterobacter cloacae*	Resistant
3	B	Most β-lactams including carbapenems	L1 from *Stenotrophomonas maltophilia*	Resistant

Amended from original Bush-Jacoby-Medeiros classification scheme for bacterial β-lactamases.