Cefepime use for ESBL infections:
Usable or Inducible?

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November 14, 2014

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)

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

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**\(^2\)

<table>
<thead>
<tr>
<th></th>
<th>Community Onset</th>
<th>Hospital Onset</th>
</tr>
</thead>
<tbody>
<tr>
<td>Organism</td>
<td>E. coli</td>
<td>Klebsiella spp.</td>
</tr>
<tr>
<td>Infection</td>
<td>CTX-M</td>
<td>SHV, TEM</td>
</tr>
<tr>
<td>Molecular epidemiology</td>
<td>Most not clonally related</td>
<td>Clonally related</td>
</tr>
<tr>
<td>Type of Infection</td>
<td>- Usually UTI</td>
<td>- Bacteremia</td>
</tr>
<tr>
<td></td>
<td>- Bacteremia</td>
<td>- Intra-abdominal infections</td>
</tr>
<tr>
<td></td>
<td>- Intra-abdominal infections</td>
<td>- Bacteremia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Intra-abdominal infections</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Respiratory</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Urinary tract infection</td>
</tr>
</tbody>
</table>

Adapted from Table 2 from *Critical care research and practice* 2011; 2012.
– **Identification**
  - 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**

![Image: http://www.wiley.com](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

![Image: http://www.intechopan.com](http://www.intechopan.com)
- 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 (e.g., protein-binding proteins [PBPs])

### Epidemiology
- 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**

- 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 States⁴

### Risk Factors

<table>
<thead>
<tr>
<th>Risk Factors for Community-Associated ESBL infections</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Recurrent UTI</td>
</tr>
<tr>
<td>- Previous antibiotic usage</td>
</tr>
<tr>
<td>- Prior instrumentation to urinary tract</td>
</tr>
<tr>
<td>- Female sex</td>
</tr>
<tr>
<td>- Age (over 65 years)</td>
</tr>
<tr>
<td>- Diabetes mellitus</td>
</tr>
</tbody>
</table>
Clinical Implications of ESBLs

- 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
  - Eg. fluoroquinolones, aminoglycosides, trimethoprim, sulfonamides, and tetracyclines

Current Treatment

- Broad-spectrum carbapenems are the treatment of choice
  - 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
- Latest CLSI Recommendations
  - Previous Detection Recommendations:
    - Test for ESBL production in enterbacteriaceae with reduced susceptibility to cephalosporins
    - Report ESBL-positive isolates as resistant to all cephalosporins

<table>
<thead>
<tr>
<th>Risk Factor for Hospital Associated ESBL</th>
<th>Odds Ratio (95% Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICU admission</td>
<td>1.67 (1.16–2.40)</td>
</tr>
<tr>
<td>Renal failure</td>
<td>1.92 (1.21–3.04)</td>
</tr>
<tr>
<td>Burns</td>
<td>2.78 (1.92–4.01)</td>
</tr>
<tr>
<td>TPN</td>
<td>1.72 (1.18–2.49)</td>
</tr>
<tr>
<td>Urinary catheter</td>
<td>1.88 (1.25–2.83)</td>
</tr>
<tr>
<td>3rd Gen cephalosporin</td>
<td>2.99 (1.6–4.0)</td>
</tr>
</tbody>
</table>
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:

<table>
<thead>
<tr>
<th>CLSI Cefepime Breakpoints (mcg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>2006-2013</strong></td>
</tr>
<tr>
<td>S ≤ 8</td>
</tr>
<tr>
<td>I: 16</td>
</tr>
<tr>
<td>R ≥ 32</td>
</tr>
</tbody>
</table>

Incidence of ESBLs with New breakpoints

- 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

<table>
<thead>
<tr>
<th>Bug/Year</th>
<th>Susceptible</th>
<th>Intermediate</th>
<th>Resistant</th>
</tr>
</thead>
<tbody>
<tr>
<td>E. coli</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2010</td>
<td>19.7%</td>
<td>8%</td>
<td>72.3%</td>
</tr>
<tr>
<td>2014</td>
<td>19.7%</td>
<td>----</td>
<td>80.3%</td>
</tr>
<tr>
<td>K. Pneumonia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2010</td>
<td>29.3%</td>
<td>8.7%</td>
<td>62%</td>
</tr>
<tr>
<td>2014</td>
<td>29.3%</td>
<td>----</td>
<td>70.7%</td>
</tr>
</tbody>
</table>

The Controversy

- Changes in the CLSI guidelines may lead to increased use of cefepime for ESBL-producing organisms.
- 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.
Clinical Implications of Extended-Spectrum B-lactamase (ESBL) Producing Klebsiella species and Escherichia coli on Cefepime Effectiveness


**Objective**
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.

**Methods**

**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)

**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

**Results**

**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>
<thead>
<tr>
<th>Variable</th>
<th>Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<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>
</tbody>
</table>

**Author’s Conclusions**
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.
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

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

**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*


**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. pneumoniae* 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

<table>
<thead>
<tr>
<th>Empiric Therapy and Impacts on Outcome</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Treatment &amp; Outcomes</strong></td>
<td></td>
</tr>
<tr>
<td>Cefepime monotherapy</td>
<td></td>
</tr>
<tr>
<td>Mortality</td>
<td>1.19 (0.57-2.49)</td>
</tr>
<tr>
<td>Readmission</td>
<td>1.14 (0.52-2.50)</td>
</tr>
<tr>
<td>Cefepime alone or in combination</td>
<td></td>
</tr>
<tr>
<td>Mortality</td>
<td>1.09 (0.55-2.15)</td>
</tr>
<tr>
<td>Readmission</td>
<td>0.70 (0.34-1.47)</td>
</tr>
<tr>
<td>Carbapenem alone</td>
<td></td>
</tr>
<tr>
<td>Mortality</td>
<td>0.96 (0.30-3.03)</td>
</tr>
<tr>
<td>Readmission</td>
<td>0.39 (0.01-1.83)</td>
</tr>
<tr>
<td>Carbapenem alone or in combination</td>
<td></td>
</tr>
<tr>
<td>Mortality</td>
<td>1.05 (0.49-2.24)</td>
</tr>
<tr>
<td>Readmission</td>
<td>0.44 (0.17-1.13)</td>
</tr>
</tbody>
</table>
Subgroup analysis showed no association between MIC of cefepime and mortality

<table>
<thead>
<tr>
<th>Cefepime MIC (μmL)</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<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>
</tbody>
</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)

Author’s Conclusions
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.

Limitations
- 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

Take-home Points
- 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.

Cefepime Therapy for Monomicrobial Bacteremia Caused by Cefepime-Susceptible Extended-Spectrum Beta-Lactamase-Producing Enterobacteriaceae: MIC Matters


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

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Design</th>
<th>Population</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bhat, et al 2007</td>
<td>Single-center Retrospective Case series Subgroup analysis</td>
<td>Gram (-) bacilli BSI treated with cefepime (N=10 with ESBL)</td>
<td>Cefepime associated with poor outcomes despite MIC. Despite small sample size, mortality was substantial (50% [5/10] died)</td>
</tr>
</tbody>
</table>

Does MIC Matter?

<table>
<thead>
<tr>
<th></th>
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<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>≥8</td>
<td>11/26 (42%)</td>
<td>3/4 (75%)</td>
<td>3/5 (60%)</td>
<td>-----</td>
<td>1/2 (50%)</td>
<td>1/1 (100%)</td>
<td>19/38 (50%)</td>
</tr>
<tr>
<td>4</td>
<td>1/4 (25%)</td>
<td>2/4 (50%)</td>
<td>1/3 (33.3%)</td>
<td>-----</td>
<td>2/3 (66.7%)</td>
<td>-----</td>
<td>6/14 (43%)</td>
</tr>
<tr>
<td>2</td>
<td>5/13 (39%)</td>
<td>-----</td>
<td>1/3 (33.3%)</td>
<td>1/2 (50%)</td>
<td>2/3 (66.7%)</td>
<td>0/2 (0%)</td>
<td>9/23 (39%)</td>
</tr>
<tr>
<td>≤1</td>
<td>-----</td>
<td>1/2 (50%)</td>
<td>1/6 (16.7%)</td>
<td>1/1 (100%)</td>
<td>-----</td>
<td>1/10 (10%)</td>
<td>4/19 (21%)</td>
</tr>
</tbody>
</table>
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\textsuperscript{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\textsuperscript{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

- 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%)

<table>
<thead>
<tr>
<th>Study</th>
<th>t½ (h)</th>
<th>MIC (mg/L)</th>
<th>Cefepime Regimen</th>
<th>PTA (%) for 50% T&gt;MIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ambrose, et al (US SENTRY)¹⁹</td>
<td>3.3</td>
<td>MIC&lt;sub&gt;50&lt;/sub&gt;: 0.5, MIC&lt;sub&gt;90&lt;/sub&gt;: 4</td>
<td>1g q12h, 2g q12h</td>
<td>95, 100</td>
</tr>
<tr>
<td>Reese, et al (single center)²⁰</td>
<td>2.3</td>
<td>MIC&lt;sub&gt;50&lt;/sub&gt;: 8, MIC&lt;sub&gt;90&lt;/sub&gt;: 16</td>
<td>1g q12h, 1g q8h, 2g q12h</td>
<td>40, 75, 75</td>
</tr>
</tbody>
</table>

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 consider²¹
  - 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%\(^\text{22}\)
- 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


# Appendix A

## Bush-Jacoby Classifications

### Table 1

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

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