## CLSI Cefepime Ad Hoc Working Group

Members:

Paul Schreckenberger, Rapporteur

Howard Gold

Mike Dudley

David Nicolau

Brandi Limbago

Steve Jenkins

## 5 Meetings by Conference Call

- October 29, 2012
- November 20, 2012
- January 3, 2013
- February 5, 2013
- May 13, 2013

## M23-A2: Situations in Which Reassessment of Interpretive Criteria May Be Considered

- When new resistance mechanisms emerge (eg, new carbapenamases) and resistance may not be reliably detected using established interpretive criteria
- When new PK-PD data indicate that existing interpretive criteria may have been set inappropriately high or low
- When prevailing antimicrobial dosage regimens differ substantially from dosage regimens used to establish initial interpretive criteria

## M23-A2: Situations in Which Reassessment of Interpretive Criteria May Be Considered

- When clinicians, laboratory practitioners, or public health agencies suggest poor prediction of clinical response using existing susceptibility interpretive criteria

## Currently three Sponsors for New Drug Applications (NDAs) for cefepime.

- B. Braun- Cefepime and Dextrose in duplex container (NDA 050821)
- Baxter- Cefepime in plastic container (NDA 050817)
- Hospira- Maxipime (NDA 050679)
- In addition, there are generic manufacturers of cefepime.

## Cefepime v. Enterobacteriaceae

| Cefepime | S | I | R | Dosage |
|---|---|---|---|---|
| Current CLSI/FDA | ≤8 | 16 | ≥32 | 1 g every 8 h or 2 g every 12 h (3-4 g/day) |
| EUCAST* | ≤1 | 2-4 | ≥8 | 1 g x 3 or 2 g x 3 (3-6 g/day) |
| Proposal | ≤2 | 4 | ≥8 | Covers all dosage ranges outside the urinary tract |

*EUCAST PK/PD breakpoint for Cefepime stated to be 4/8/16 however, cefepime susceptible clinical breakpoint was adjusted from 4 to 1 ug/ml to ensure that Enterobacteriaceae with clinically important ESBLs were not reported as susceptible

Kahlmeter G *Clin Microbiol Infect.* 2008 Jan;14 Suppl 1:169-74. Review

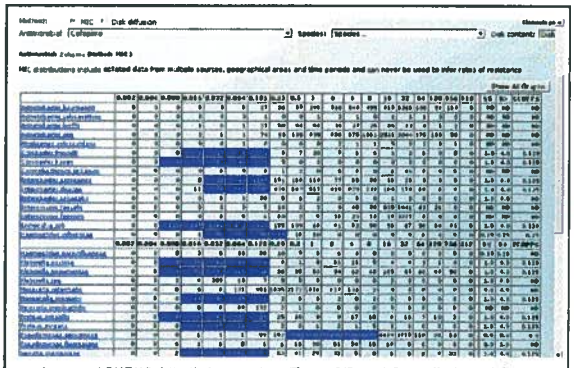
## M23-A2: Data to Be Examined in Reassessment of IC

- Microbiological Data
  - Data should be provided showing the MIC distributions for antimicrobial agents against the genera and species of interest
- Pharmacological Data
  - PK-PD indices and results of modeling should be provided using criteria that clearly describes the sources of data, assumptions, and details of simulations used to support BP

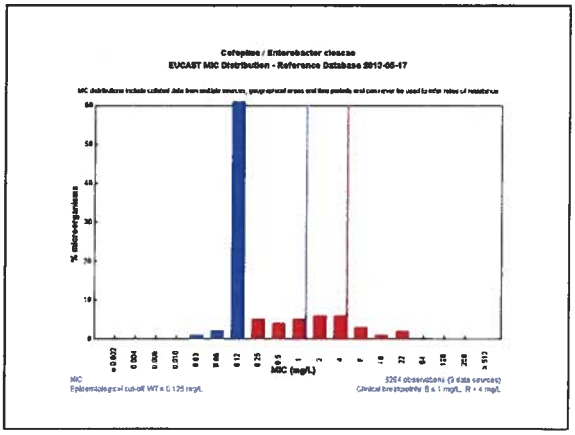
## M23-A2: Data to Be Examined in Reassessment of IC

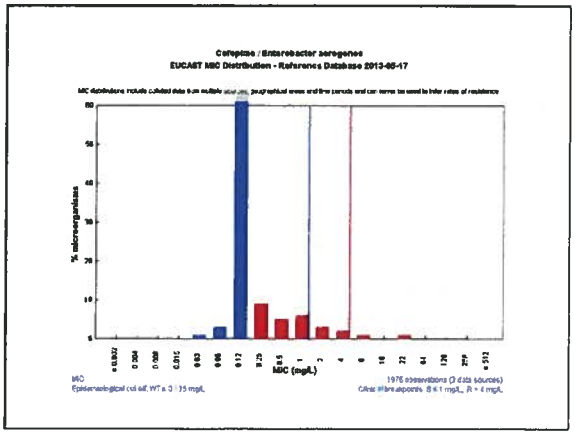
- Clinical Data
  - Data sources include results of nonsponsored clinical trials, observational studies, case-control studies, meta-analyses, and case series

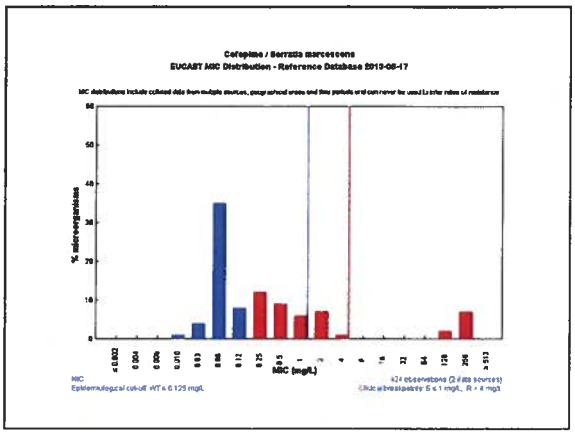
## Microbiologic Data

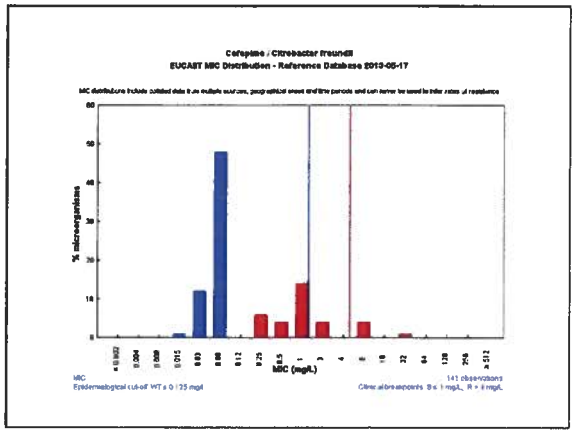


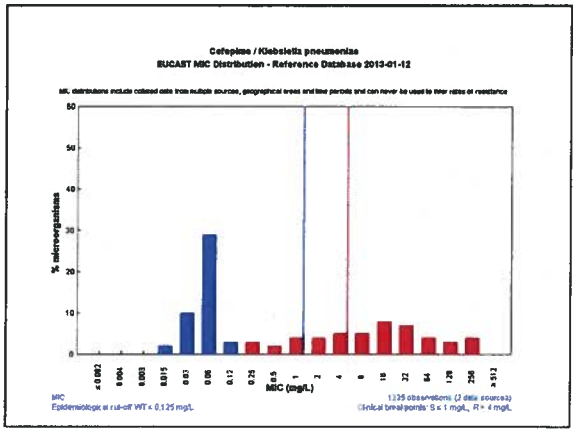
Accessed 5/17/13: http://mic.eucast.org/Eucast2/SearchController/search.jsp?action=performSearch&BeginIndex=0&Micdif=mic&NumberIndex=50&Antib=192&Specium=-1

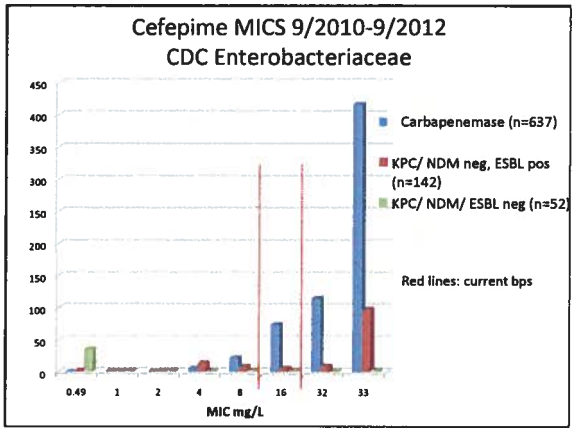


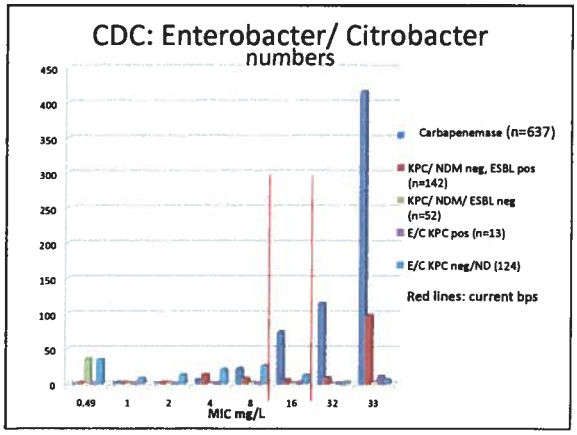



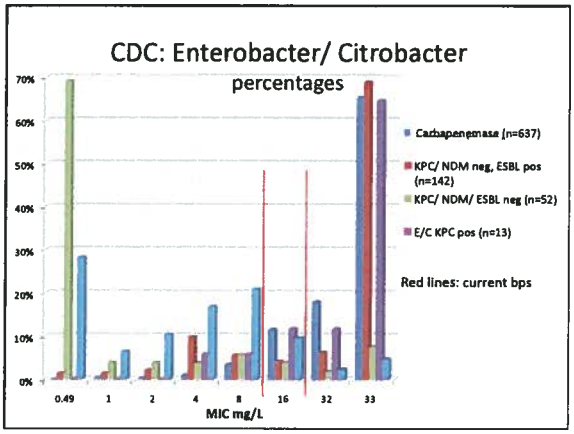

Cefepime / Serratia marcescens
EUCAST MIC Distribution - Reference Database 2013-05-17
% microorganisms
MIC (mg/L)


Cefepime / Citrobacter freundii
EUCAST MIC Distribution - Reference Database 2013-05-17
% microorganisms
MIC (mg/L)

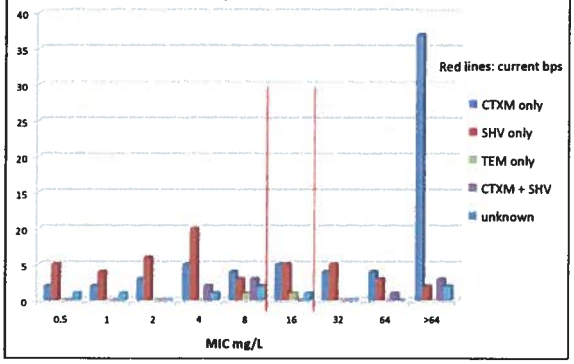

Cefepime / Klebsiella pneumoniae
EUCAST MIC Distribution - Reference Database 2013-01-12
% microorganisms
MIC (mg/L)


Cefepime MICS 9/2010-9/2012
CDC Enterobacteriaceae
Carbapenemase (n=637)
KPC/ NDM neg, ESBL pos (n=142)
KPC/ NDM/ ESBL neg (n=52)
Red lines: current bps
MIC mg/L


CDC: Enterobacter/ Citrobacter
numbers
Carbapenemase (n=637)
KPC/ NDM neg, ESBL pos (n=142)
KPC/ NDM/ ESBL neg (n=52)
E/C KPC pos (n=13)
E/C KPC neg/ND (124)
Red lines: current bps
MIC mg/L


CDC: Enterobacter/ Citrobacter
percentages
Carbapenemase (n=637)
KPC/ NDM neg, ESBL pos (n=142)
KPC/ NDM/ ESBL neg (n=52)
E/C KPC pos (n=13)
Red lines: current bps
MIC mg/L

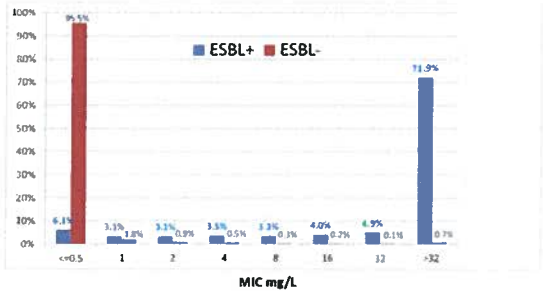
## Cefepime MICs
## ESBL producers, UTHSC




## Cefepime MIC Distributions of Beta-lactamase characterized *Enterobacteriaceae*

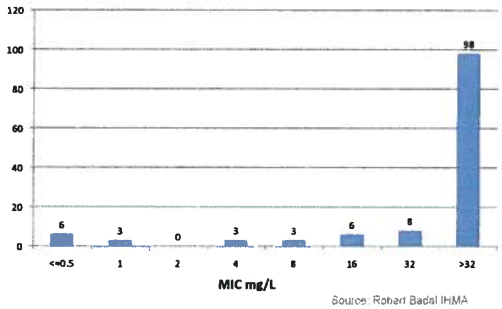
Global data from SMART 2002-2012
(The Study for Monitoring Antimicrobial Resistance Trends)
Source: Robert Badal IHMA

## Cefepime MIC Distribution of ***Phenotypically*** ESBL+ (14,263) and ESBL- (55,274) Ec/Kp/Ko/Pm




Source: Robert Badal IHMA

## Cefepime MIC Distribution of ***Genotypically*** ESBL-/AmpC-/Cb+ *Enterobacteriaceae* (n=127)




Source: Robert Badal IHMA

## Pharmacological Data

## Cefepime Package Insert

- Six FDA-approved indications

**Table 12: Recommended Dosage Schedule for Cefepime for injection in Patients with CrCL Greater Than 60 mL/min**

| Site and Type of Infection | Dose | Frequency | Duration (days) |
|---|---|---|---|
| **Adults** | | | |
| **Moderate to Severe** Pneumonia due to *S. pneumoniae**, *P. aeruginosa*, *K. pneumoniae*, or *Enterobacter* species | 1-2 g IV | Every 12 hours | 10 |
| Empiric therapy for febrile neutropenic patients (See **INDICATIONS AND USAGE** and **CLINICAL STUDIES.**) | 2 g IV | Every 8 hours | 7** |
| **Mild to Moderate** Uncomplicated or Complicated Urinary Tract Infections, including pyelonephritis, due to *E. coli*, *K. pneumoniae*, or *P. mirabilis** | 0.5-1 g IV/IM*** | Every 12 hours | 7-10 |
| **Severe** Uncomplicated or Complicated Urinary Tract Infections, including pyelonephritis, due to *E. coli* or *K. pneumoniae** | 2 g IV | Every 12 hours | 10 |

PI Sagent 2010

## Cefepime Package Insert

**Table 12: Recommended Dosage Schedule for Cefepime for Injection in Patients with CrCL Greater Than 60 mL/min**

| Site and Type of Infection | Dose | Frequency | Duration (days) |
|---|---|---|---|
| **Adults** | | | |
| **Moderate to Severe** Uncomplicated Skin and Skin Structure Infections due to *S. aureus* or *S. pyogenes* | 2 g IV | Every 12 hours | 10 |
| **Complicated Intra-abdominal Infections** (used in combination with metronidazole) caused by *E. coli*, viridans group streptococci, *P. aeruginosa*, *K. pneumoniae*, *Enterobacter species*, or *B. fragilis*. (See CLINICAL STUDIES.) | 2 g IV | Every 12 hours | 7-10 |

- FDA-approved doses for NON-UTI indications range from 1 g every 12h to 2 g every 8h (2-6 grams/day).
- Thus, the 1 g Q 12h would be the dose to consider in the simulations and thus is consistent with using a BP of <= 2ug/ml

PI Sagent 2010

## Efficacy and safety of cefepime: a systematic review and meta-analysis

*Lancet Infect Dis* 2007; 7: 338-48

Dafna Yahav, Meital Paul, Abigail Fraser, Nadav Sarid, Leonard Leibovici

- Systematic review of randomized trials that compared cefepime with another β-lactam antibiotic, alone or with the addition of a non-β-lactam antibiotic to both study groups
- Searched Central, PubMed, Embase, Lilacs, new US Food and Drug Administration drug applications, conference proceedings, and references of the included studies
- Two reviewers independently did the search and data extraction. 57 trials were included
- Baseline risk factors for mortality were similar
- No significant differences between groups in treatment failure, superinfection, or adverse events were found

Yahav, et al. Lancet ID 2007

## Efficacy and safety of cefepime: a systematic review and meta-analysis

*Lancet Infect Dis* 2007; 7: 338-48

Dafna Yahav, Meital Paul, Abigail Fraser, Nadav Sarid, Leonard Leibovici

- We found **all-cause mortality to be significantly higher with cefepime than with other β-lactams**
- The **RR of 1.26** denotes an **increase in all-cause mortality of 26%** (CI 95% **8%-49%**)
- Further analyses of the mortality outcome and assessment of secondary outcomes did not reveal a specific cause for the increased mortality, nor a specific patient population at risk
- Among subcategories of patients, significantly increased mortality with cefepime was seen only among neutropenic patients, but the RRs were similar for other types of patients and infections

Yahav, et al. Lancet ID 2007

## Efficacy and safety of cefepime: a systematic review and meta-analysis

*Lancet Infect Dis* 2007; 7: 338-48

Dafna Yahav, Meital Paul, Abigail Fraser, Nadav Sarid, Leonard Leibovici

- Authors conclude that a spurious finding is unlikely given the significance and homogeneity of results
- Authors offer two possible explanations for results
  - Unrecognized adverse event
    - Reports of neurotoxic effects of cefepime, including encephalopathy and non-convulsive status epilepticus
      - Most reports involve adults with acute or chronic renal failure
      - Cases of encephalopathy and status epilepticus have been reported in patients with normal renal
  - Inadequate antimicrobial efficacy in vivo
    - Discrepancies between results in vitro and in vivo have been described with cefepime
      - Inoculum effect
      - poor tissue concentrations
      - pharmacodynamic considerations that favor continuous administration of cefepime

Yahav, et al. Lancet ID 2007

## THE LANCET Infectious Diseases

Volume 9, Issue 1, January 2009, Pages 4–8

Infection and Review

### Efficacy and safety of cefepime

Trent G Towne, James S Lewis, Kelly Echevarria

- Method
  - Reviewed 19 studies collected for Yahav (Lancet ID 2007)
  - Complete cause of death information for 11 studies and partial cause of death information for 2 = 64% of the all -cause neutropenic deaths in Yahav (Lancet ID 2007)
- Results
  - A higher proportion of patients died d/t to progression of their underlying disease in the cefepime arm
  - No patients were determined to have died directly as a result of receiving therapy with any agent, including cefepime

Towne, et al. Lancet ID 2009

## Meta-Analysis of a Possible Signal of Increased Mortality Associated with Cefepime Use

**Peter W. Kim,[1] Yu-te Wu,[2] Charles Cooper,[2] George Rochester,[2] Thamban Valappil,[2] Yan Wang,[2] Cynthia Kornegay,[1] and Sumathi Nambiar[1]**

[1]Office of Antimicrobial Products, Office of Biostatistics, and [2]Office of Surveillance and Epidemiology, Center for Drug Evaluation and Research, US Food and Drug Administration, Silver Spring, Maryland

- FDA' s response to "concern regarding the possible increased risk of mortality associated with cefepime use"
- Methods - Meta-analyses
  - Trial-level analyses were performed using summary data from all patients in the trials
  - Patient-level analyses were performed on trials with available patient-level data
  - 30-day, all-cause mortality analyzed using Mantel-Haenszel adjusted risk difference (ARD) method
  - 7 comparative febrile neutropenia trials with patient-level data were reviewed in further detail to evaluate the cause(s) of death, including review of all CRFs from patients who died with particular attention to possible ADE

Kim, et al. CID 2010

## Meta-Analysis of a Possible Signal of Increased Mortality Associated with Cefepime Use

- Results
  - **Trial-level meta-analysis** based on 88 trials, 9467 cefepime patients and 8288 comparator patients
    - 30-day, all-cause mortality rate was 6.21% (588/9467) for the cefepime patients
    - 30-day, all-cause mortality rate was 6.00% (497/8288) for comparator patients
    - ARD per 1000 population, 5.38; 95% confidence interval (CI), -1.53 to 12.28
  - **Patient-level analysis** based on 35 trials, 5058 cefepime patients, and 3976 comparator patients
    - 30-day, all-cause mortality rate was 5.63% (285/5058) for cefepime patients
    - 30-day, all-cause mortality rate was 5.68% (226/3976) for comparator patients
    - ARD per 1000 population, 4.83; 95% CI, -4.72 to 14.38

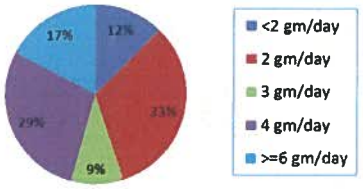
Kim, et al. CID 2010

## Meta-Analysis of a Possible Signal of Increased Mortality Associated with Cefepime Use

- Results (cont' d)
  - Sensitivity analysis based on 24 **febrile neutropenia trials** did not show a statistically significant increase in mortality with cefepime use (ARD per 1000 population, 9.67; 95% CI, **-2.87 to 22.21**)
  - Review of **patient-level data** from 7 comparative febrile neutropenia trials revealed:
    - 30-day, all-cause mortality rates for cefepime-treated patients were 7.86% (61/776)
    - 30-day, all-cause mortality rates for comparator-treated patients were 6.55% (41/626) (ARD per 1000 population, 18.10; 95% CI, -9.22 to 45.42)
    - No biologically plausible explanation for a mortality imbalance
- Conclusions. **Trial-level and patient-level meta-analyses did not identify a statistically significant increase in mortality among cefepime-treated patients**, compared with those treated with other antibacterials

Kim, et al. CID 2010

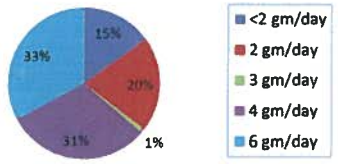
## Cefepime Regimens at ~120 US Hospitals (27,694/6 months)




CAVEAT: does not account for dose reduction due to renal function

Data c/o Vikas Gupta, Pharm.D., BCPS, Director, CareFusion MedMined™ services

## Cefepime Orders by Dose at Urban Tertiary Care Academic Medical Center (1181 orders/6 months)

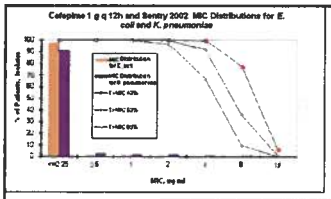



CAVEAT: does not account for dose reduction due to renal function

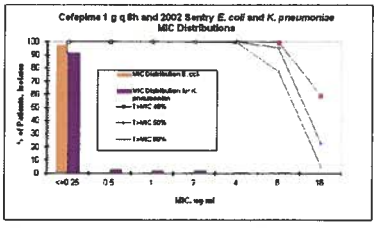
Data: Christopher McCoy, Pharm.D., BCPS, Clinical Pharmacy Coordinator Antimicrobial Stewardship, Beth Israel Deaconess Medical Center

## Cefepime: Why the BPs Were Not Lowered in the Re-Assessment of Ceph BPs in the 2005 Analysis

- PK-PD analysis showed high target attainment at an MIC <= 8 ug/ml
  - T>MIC of 50% using dosage regimens of 1 g every 8 hours or 2 g every 12h (3-4 g/day)
  - Comparable target attainment to other other cephalosporins with lowered BPs (e.g., cefotaxime MIC of 1 ug/ml)

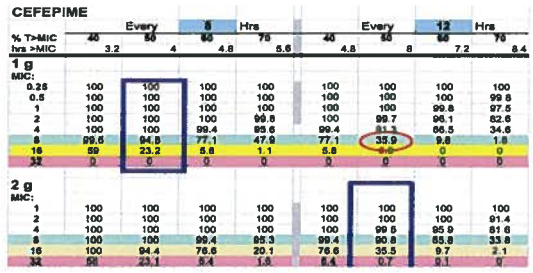



Cefepime 1 g every 8h (but not every 12h) supports a susceptibility BP of 8 ug/ml




CID 2013 (In Press)

## Cefepime Analysis from 2004




## Cefepime PK Data and Results From Patients

- Data in patients receiving cefepime, particularly those in ICU, show more variability and might suggest that cefepime breakpoints should be reduced using fT>MIC of 50% and 90% TAR
  - Results from recent analyses of clinical data may also be consistent with low TAR with current cefepime 8Ps
- It is likely that patient data for all other cephalosporins would also suggest a need to be examined (and would also likely suggest lower breakpoints (e.g., cefotaxime BP <=0.25 to 0.5 ug/ml)

## Selection of Cefepime PD Target (*f*T>MIC)

- *f*T>MIC longstanding PD driver of B-lactams efficacy
- Target values of 30-70% quoted, 50% generally advocated as reasonable target based on:
  - Neutropenic animal models, ≥ 1 log reduction in CFU [Craig WA: *Scand J Infect Dis* 1991;74:179-184, *J Infect Dis* 1989;159:281-292]
  - Applying pharmacodynamic principles to cephalosporins, predicts acceptable clinical results occur when antibiotic concentrations exceed MIC for target organism for approximately 50 percent of dosing interval [Owens RC, Ambrose PG, Quintiliani R. *Conn Med* 1997;61:225-7]
  - Patients infected with ESBL and Non-ESBL producing Enterobacteriaceae treated with Cefepime, Eradication was 80% when *f*T > MIC was 50% compared with 0% when *f*T > MIC was less than 50% ($p < 0.05$) [Lee SY, Kuti JL, Nicolau DP. *J Infect 2007*;54:463-468]

## PK-PD Target Attainment Analyses to Evaluate Susceptibility BP for Labeled Cefepime Dosing

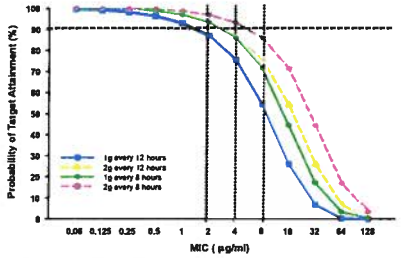
**Probability of PK-PD target attainment by Cefepime dosing regimen (0.5g Q12h / 1gQ12h / 2g Q12h / 2g Q8h)**

| MIC | T>MIC ≥ 40% | T>MIC ≥ 50% | T>MIC ≥ 60% | T>MIC ≥ 70% |
|---|---|---|---|---|
| 0.5 | 1.0/1.0/1.0/1.0 | 1.0/1.0/1.0/1.0 | 1.0/1.0/1.0/1.0 | 0.96/1.0/1.0 /1.0 |
| 1 | 1.0/1.0/1.0/1.0 | .99/1.0/1.0/1.0 | 0.82/1.0/1.0/1.0 | 0.34/0.96/1.0/1.0 |
| 2 | 0.97/1.0/1.0/1.0 | .49/.99/1.0/1.0 | .058/.82/1.0/1.0 | 0012/0.34/.96/1.0 |
| 4 | 0.1/0.97/1.0/1.0 | .0008/.49/.99/1.0 | 0/.058/.82/1.0 | 0/.0012/.34/1.0 |
| 8 | 0/0.10/0.97/1.0 | 0/.0008/0.49/1.0 | 0/0/ 0.058/0.98 | 0/0/0.0012/0.78 |
| 16 | 0/0/0.10/0.98 | 0/0/0.0008/0.66 | 0/0/0.0008/0.66 | 0/0/0/0.02 |
| 32 | 0/0/0/0.048 | 0/0/0/0.008 | 0/0/0/0.0008 | 0/0/0/0 |

Van Wart SA, Ambrose PG et al. 50th ICAAC, Boston, MA, Sept. 12-15, 2010

## Cefepime Susceptibility Breakpoints Based on Pharmacodynamic Endpoint

- Pharmacokinetics determined in ICU patient population
- V ~ 40 %CV and CL ~ 70 %CV
- PTA based upon a 50% *f*T>MIC target




Nicasio AM, et al. AAC 2009;53(4):1476-1481

## Cefepime Susceptibility Breakpoints Based on Pharmacodynamic Endpoints

- Most frequently utilized US regimens: 1g Q8h / 2g Q12h
- *f*T>MIC is nearly identical for 1g Q8h or 2g Q12h doses
- PTA based upon a 50% *f*T>MIC target

| MIC | % Attainment 1g q 12h ICU Patients[1] | % Attainment 1g q 8h ICU Patients[1] | % Attainment 2g q12h ICU Patients[1] | % Attainment 2g q12h Healthy Adults[2] |
|---|---|---|---|---|
| 1 | 93 | 97 | 96 | 100 |
| 2 | 87 | 93 | 93 | 100 |
| 4 | 75 | 86 | 87 | 99 |
| 8 | 55 | 71 | 75 | 49 |

[1]Nicasio AM, et al. AAC 2009;53(4):1476-1481, [2]Van Wart SA, et al. 50th ICAAC, Boston, MA, Sept 2010

# Clinical Data

## Clinical implications of extended spectrum β-lactamase (ESBL) producing *Klebsiella* species and *Escherichia coli* on cefepime effectiveness☆

Srividya Kotapati, Joseph L. Kuti, Charles H. Nightingale, David P. Nicolau*

- Retrospective, case-controlled study comparing responses of patients receiving cefepime for ESBL-producing *Klebsiella* species or *E. coli* (non-urine source) with matched controls receiving cefepime for non-ESBL strains
- Results
  - 10 patients receiving cefepime for ESBLs matched to 20 controls
  - Most patients received cefepime 1g q12h
  - Patients with ESBL-producing strains
    - **9.7 times as likely to have an unsuccessful clinical response** compared with those with non-ESBL infection
    - **28.5 times as likely to have an unsuccessful microbiological response** compared with those with a non-ESBL infection

Kotapati, et al. J Inf 2005

## Clinical implications of extended spectrum β-lactamase (ESBL) producing *Klebsiella* species and *Escherichia coli* on cefepime effectiveness☆

- Conclusions
  - **ESBL production among non-urinary *Klebsiella* species and *E. coli* negatively affected cefepime effectiveness** (most patients received cefepime 1g q12h)
  - Further studies required to evaluate if higher doses of cefepime may improve responses in ESBL producing strains

Kotapati, et al. J Inf 2005

## Failure of Current Cefepime Breakpoints To Predict Clinical Outcomes of Bacteremia Caused by Gram-Negative Organisms☆

Sunil V. Bhat,[1] Anton Y. Peleg,[2] Thomas P. Lodise, Jr.,[3] Kathleen A. Shutt,[1] Blair Capitano,[1] Brian A. Potoski,[1] and David L. Paterson[1,2]*

[1]Division of Infectious Diseases, University of Pittsburgh Medical Center, Suite 3A Falk Medical Building, 3601 Fifth Avenue, Pittsburgh, Pennsylvania 15213[1], Beth Israel Deaconess Medical Center, Boston, Massachusetts[2]; Albany Medical Center, Albany, New York[3]; and University of Queensland, Royal Brisbane & Women's Hospital, Brisbane, Australia[4]

Received 26 November 2006/Returned for modification 27 December 2006/Accepted 2 July 2007

- 204 episodes of bacteremia caused by gram-negative organisms treated with cefepime (typically 1 to 2 g every 12 h) as the primary therapy
- Patients with gram-negative organisms with
  - Cefepime MIC of ≥8 mcg/ml had a mortality rate of 54.8% (17/31 died)
    - 53.3% (8/15 died) for those treated with cefepime at a MIC of >8 mcg/ml.
    - 56.3% (9/16) died w/isolates having MIC of 8 g/ml
  - Cefepime MIC of <8 g/ml mortality rate of 24.1% (35/145 died)

Bhat, et al. AAC 2007

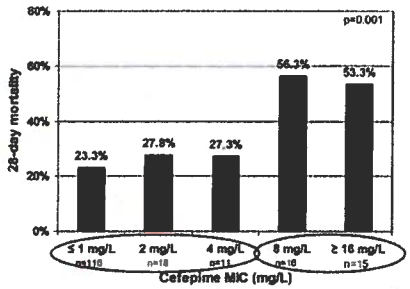



FIG. 1. Twenty-eight day mortality stratified by cefepime MIC.

- 24/34 (71%) isolates with MIC >= 8 were *Pseudomonas aeruginosa*
- 26/170 (16%) isolates with MIC < 8 were *P. aeruginosa*

Bhat, et al. AAC 2007

Antimicrobial Agents and Chemotherapy

## Impact of Cefepime Therapy on Mortality among Patients with Bloodstream Infections Caused by Extended-Spectrum-β-Lactamase-Producing Klebsiella pneumoniae and Escherichia coli

Teena Chopra, Dror Marchaim, Jennifer Veltman, Paul Johnson, Jing J. Zhao, Ryan Tansek, Denis Hatahet, Khamis Chaudhry, Jovan Ni, Pague, Nino Rahbar, Ting Yi Chen, Thientu Truong, Victor Rodriguez, Joseph Ellsworth, Ludgine Bernabela, Ashish Bhargava, Adnan Youcuf, George Alangaden and Keith S. Kaye

Antimicrob. Agents Chemother. 2012, 56(7):3856. DOI: 10.1128/AAC.06419-11
Published Ahead of Print 30 April 2012.

- Retrospective 5-hospital 2005-2007 study at the Detroit Medical Center on 145 adult patients with BSI due to ESBL-producing pathogens (*K. pneumoniae* (83%) and *E. coli* (16.5%)]
- Dose of cefepime not reported [data requested from PI]
- 53 patients (37%) died in the hospital and 92 survived to discharge

Chopra, et al. AAC 2012

Antimicrobial Agents and Chemotherapy

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

Teena Chopra, Drer Marchaim, Jennifer Veltman, Paul Johnson, Jing J. Zhao, Ryan Tarabek, Dario Hatahet, Khawar Chaudhry, Jason M. Pogue, Hiro Rahbar, Ting-Yi Chen, Thientu Truong, Victor Rodriguez, Joseph Ellsworth, Luigino Bernabela, Ashish Bhargava, Adnan Yousuf, George Alangaden and Keith S. Kaye
Antimicrob. Agents Chemother. 2012, 56(7):3838. DOI: 10.1128/AAC.05619-11
Published Ahead of Print 30 April 2012.

- In bivariate analysis, no significant associations between antimicrobial therapy and mortality
  - 40% who received cefepime monotherapy died compared to 35% who did not receive cefepime monotherapy (P = 0.7)
  - 38% who received carbapenem therapy (alone or in combination) died, compared to 36% of patients who did not receive a carbapenem (P = 1.0)
- Neither cefepime nor carbapenem consolidative therapy was associated with in-hospital mortality

Chopra, et al. AAC 2012

Antimicrobial Agents and Chemotherapy

Impact of Cefepime Therapy on Mortality among Patients with Bloodstream Infections Caused by Extended-Spectrum-β-Lactamase-Producing Klebsiella pneumoniae and Escherichia coli

- Subanalysis of 43 patients treated w/ empiric cefepime alone
- No association between increasing MIC of cefepime and mortality
  - 13 patients had cefepime MICs of <2 mcg/ml
  - 5/13 (39%) died

TABLE 4 Cefepime MIC and mortality among patients who received empirical therapy with cefepime alone

| Cefepime MIC (μg/ml) | In-hospital mortality rate (no. of deaths/total no. of patients) (%) |
|---|---|
| ≤2 | 5/13 (39) |
| 4 | 1/4 (25) |
| 8 | 1/2 (50) |
| ≥16 | 10/24 (42) |

Chopra, et al. AAC 2012

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

- 2-center retrospective study of monomicrobial bacteremia due to ESBL producers 2002-2007
- Patients definitively treated by in vitro active cefepime (MIC ≤8 mcg/mL, cases) compared with controls treated with a carbapenem (controls)
- Primary end point - 30-day crude mortality
- Patients received (adjusted for renal insufficiency)
  - ertapenem (1 g every 24 h)
  - imipenem (0.5 g every 6 h)
  - meropenem (1 g every 8 h)
  - cefepime (1 to 2 g every 8 h; 3-6 g/day)

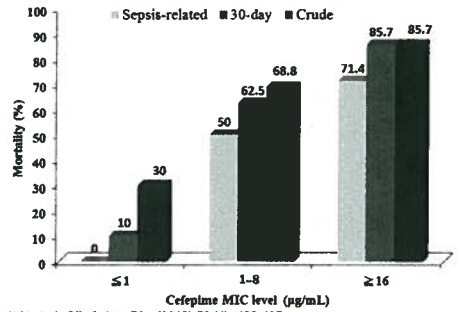
Lee N-Y et al. *Clin Infect Dis. (2013) 56 (4): 488-495.*

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

- Results - Cefepime (n=17) definitive therapy v. carbapenem (n=161)
  - more likely to have clinical failure (OR 6.2, 95% CI 1.7-22.5, P=0.002)
  - more likely to have microbiological failure (OR 5.5, 95% CI 1.3-25.6, P=0.04)
  - more likely to have 30-day mortality (OR 7.1, 95% CI 2.5-20.3, P<0.001)
- Conclusions - **By the current CLSI susceptible breakpoint of cefepime (MIC ≤8 mcg/mL), cefepime definitive therapy is inferior to carbapenem therapy in treating patients with so called "cefepime-susceptible" ESBL-producer bacteremia**

Lee N-Y et al. *Clin Infect Dis. (2013) 56 (4): 488-495.*

**Mortality rates of 3 subgroups of patients who received cefepime therapy (n = 33) stratified by the cefepime minimum inhibitory concentration.**



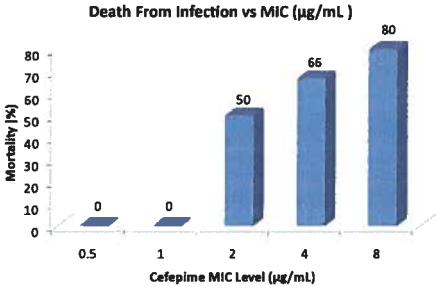

Lee N-Y et al. *Clin Infect Dis. (2013) 56 (4): 488-495.*



Clinical Infectious Diseases

| Patient ID# | Serum Creatinine | Age (yrs) | Cefepime Dose (g) | Dosing Interval (q h) | Daily dose (g) | Micro Response Persistence /Eradication | Clinical Response Success / Failure | Death Y / N | Infection-Related Death Y / N | MIC μg/mL |
|---|---|---|---|---|---|---|---|---|---|---|
| 3 | 0.5 | 23 | 1 | 8 | 3 | Persistance | Success | Y | N | 0.5 |
| 7 | 0.8 | 66 | 1 | 8 | 3 | Eradication | Success | N | N | 0.5 |
| 10 | 0.6 | 66 | 2 | 8 | 6 | Persistance | Success | N | N | 1 |
| 11 | 0.7 | 70 | 1 | 8 | 3 | Eradication | Success | N | N | 1 |
| 13 | 0.9 | 90 | 1 | 8 | 3 | Eradication | Failure | N | N | 1 |
| 2 | 0.8 | 23 | 1 | 8 | 3 | Eradication | Success | N | N | 2 |
| 5 | 1.2 | 49 | 2 | 12 | 4 | Eradication | Failure | Y | Y | 2 |
| 16 | 0.6 | 82 | 1 | 8 | 3 | Persistance | Success | Y | N | 2 |
| 12 | 8.2 | 88 | 2 | 12 | 4 | Eradication | Failure | Y | Y | 2 |
| 4 | 3.8 | 69 | 2 | 12 | 4 | Eradication | Failure | Y | Y | 4 |
| 9 | 0.8 | 69 | 1 | 8 | 3 | Eradication | Success | N | N | 4 |
| 1 | 2.5 | 73 | 2 | 12 | 4 | Eradication | Failure | Y | Y | 4 |
| 8 | 2.8 | 62 | 2 | 12 | 4 | Eradication | Failure | Y | Y | 8 |
| 15 | 0.8 | 70 | 1 | 8 | 3 | Eradication | Failure | Y | Y | 8 |
| 6 | 1.2 | 77 | 2 | 12 | 4 | Eradication | Failure | Y | Y | 8 |
| 17 | 5.1 | 81 | 2 | 12 | 4 | Eradication | Success | N | N | 8 |
| 14 | 0.8 | 86 | 1 | 8 | 3 | Eradication | Failure | Y | Y | 8 |

Unpublished data provided by Lee N-Y from *Clin Infect Dis. (2013) 56 (4): 488-495.*




Unpublished data provided by Lee N-Y from *Clin Infect Dis. (2013) 56 (4): 488-495.*

Chi Square = 5.12; P<0.023

| | Success | Failure | Marginal Row Totals |
|---|---|---|---|
| q8h | 7 (4.71)[1.12] | 3 (5.29) ]0.99) | 10 |
| q12 | 1 (3.29) [1.6[ | 6 (3.71) [1.42) | 7 |
| Marginal Column Totals | 8 | 9 | 17 (Grand Total) |

Unpublished data provided by Lee N-Y from *Clin Infect Dis. (2013) 56 (4): 488-495.*

## Cefepime Breakpoint Conclusions

- Epidemiologic Cutoff
  - Supports Susceptible BP of 1 ug/ml
- PK/PD
  - 2g/day – Support Susceptible BP of 1 or 2 ug/ml
  - 3-4 g/day – Support Susceptible BP of 2or 4 ug/ml
  - 6g/day – Support Susceptible BP of 8 ug/ml
- Clinical Data
  - Inconclusive – tendency for improved outcome when MIC's 1-4, Poorer outcome with MICs 8-16

## Cefepime v. Enterobacteriaceae

| Cefepime | S | I | R | Dosage |
|---|---|---|---|---|
| Current CLSI/FDA | ≤8 | 16 | ≥32 | 1 g every 8 h or 2 g every 12 h (3-4 g/day) |
| Proposal | ≤2 | 4 | ≥8 | Covers all dosage ranges outside the urinary tract |

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0066-4804/09/$08.00+0 doi:10.1128/AAC.01141-08

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# Population Pharmacokinetics of High-Dose, Prolonged-Infusion Cefepime in Adult Critically Ill Patients with Ventilator-Associated Pneumonia▽

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**A population pharmacokinetic model of cefepime was constructed from data from adult critical care patients with ventilator-associated pneumonia (VAP). A total of 32 patients treated with high-dose cefepime, 2 g every 8 h (3-h infusion) or a renal function-adjusted equivalent dose, were randomized into two groups—26 for the initial model and 6 for model validation. Serum samples of cefepime were collected at steady state. Nonparametric adaptive grid population modeling was employed using a two-compartment $K_{slope}$ pharmacokinetic model relating the elimination rate constant ($K_{10}$) to renal function, as defined by creatinine clearance ($CL_{CR}$), and central distribution volume ($V_1$) to total body weight (TBW). The final model was described by the following equations: $K_{10} = 0.0027 \times CL_{CR} + 0.071\ h^{-1}$ and $V_1 = TBW \times 0.21$ liter/kg. The median intercompartmental transfer constants $K_{12}$ and $K_{21}$ were 0.780 $h^{-1}$ and 0.472 $h^{-1}$, respectively. Using these median parameter estimates, the bias, precision, and coefficient of determination for the initial model were 11.3 μg/ml, 24.0 μg/ml, and 26%, respectively. The independent validation group displayed a bias, precision, and coefficient of determination of −1.64 μg/ml, 17.1 μg/ml, and 62%, respectively. Time-concentration profiles were assessed for various dosing regimens, using 5,000-patient Monte Carlo simulations. Among the regimens, the likelihoods of 2 g every 8 h (3-h infusion) achieving free drug concentrations above the MIC for 50% of the dosing interval were 91.8%, 78.1%, and 50.3% for MICs of 8, 16, and 32 μg/ml, respectively. This study provides a pharmacokinetic model capable of predicting cefepime concentrations in critically ill patients with VAP.**

Cefepime is a fourth-generation parenteral cephalosporin with activity against gram-positive and gram-negative organisms, including *Pseudomonas aeruginosa* and *Acinetobacter baumannii* (1, 6). Because of its broad coverage and favorable adverse event profile, cefepime is extensively used as an empirical antimicrobial therapy for serious infections in intensive care units (ICU). In patients with normal renal function, cefepime is typically dosed according to the manufacturer's recommendations: 1 g every 12 h in mild to moderate infections, 2 g every 12 h in severe infections, and 2 g every 8 h in neutropenic patients, all utilizing a 30-min infusion time.

With the rise of multidrug-resistant, gram-negative bacilli (10, 20), there is the potential for poor infection-related outcomes, particularly in high-risk patients, such as the critically ill whom are receiving mechanical ventilation. Moreover, various studies have illustrated that the manufacturer's recommended doses may fall short against less-susceptible gram-negative pathogens (2, 17, 23). This has led some investigators to explore or suggest alternative cefepime dosing strategies, including prolonged and continuous infusions (3, 4, 8, 22, 24). Like other β-lactams, cefepime displays time-dependent bactericidal activity whereby efficacy is optimized when free drug concentrations exceed the MIC for at least 50% of the dosing interval (50% *f*T>MIC) (19). As a result of these pharmacodynamic characteristics, prolonging the infusion duration from the standard 30 min to 3 to 4 h or administering β-lactam antibiotics as continuous infusions over 24 h will increase the probability of pharmacodynamic target attainment at higher MICs (9, 11, 13, 18, 21, 24).

Recently at our 840-bed tertiary care hospital, the high prevalence of resistant organisms, including *P. aeruginosa*, as a cause of ventilator-associated pneumonia (VAP) led to the development of a clinical pathway incorporating high-dose, prolonged-infusion antibiotic regimens (14). In this pathway, cefepime is empirically administered as a 2-g dose every 8 h, with each dose infused over 3 h, or a renal function-adjusted equivalent dose. The current population pharmacokinetic analysis was conducted to demonstrate that this new cefepime dosing regimen was effectively achieving the intended concentration-time profiles in patients treated for VAP at our institution, with the goal of empirically achieving 50% *f*T>MIC in the majority of patients infected with organisms harboring cefepime MICs of up to 32 μg/ml. The utility of this model not only allowed confirmation of dosing regimens in our patient population but also provided a means of estimating pharmacokinetic parameters for those patients receiving cefepime for the treatment of VAP who do not have concentration data available.

## MATERIALS AND METHODS

**Patient population and setting.** Blood sample collection was performed on patients who were admitted to the medical, surgical, or neurotrauma ICU at

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Hartford Hospital between April 2007 and December 2007 and received cefepime as part of the VAP clinical pathway (approved by the Pharmacy and Therapeutics and Medical Executive Committees) (14). Hartford Hospital, located in Hartford, CT, is a 840-bed tertiary care hospital, consisting of two 12-bed medical ICUs, a 12-bed surgical ICU, a 12-bed cardiothoracic ICU, and an 18-bed neurotrauma ICU. When placed on the clinical pathway, patients empirically received vancomycin, tobramycin (or a fluoroquinolone if tobramycin was contraindicated), and high-dose cefepime (2 g every 8 h, infused over 3 h). Doses were adjusted for renal function by using the Cockcroft-Gault equation, without the application of weight for estimating creatinine clearance ($CL_{CR}$) (7). Cefepime doses were originally developed based on a 5,000-patient Monte Carlo simulation, applying previously published pharmacokinetic data from patients with various degrees of renal function (23). A waiver of consent for the collection of blood samples was granted by Hartford Hospital's Institutional Review Committee, since these data were part of an ongoing quality assurance assessment of the VAP pathway. All information was kept confidential and secured by the Center for Anti-Infective Research and Development, Hartford, CT, in compliance with the Health Insurance Portability and Accountability Act of 1996, and patient identifiers were destroyed after data analyses were complete. Inclusion criteria consisted of adult patients (≥18 years old) in the ICU, who were placed on the VAP clinical pathway and prescribed cefepime. Patients with severely impaired renal function requiring dialysis and those deemed poor candidates for blood collection were excluded.

**Blood sampling.** Blood samples (2 to 3 per patient) were collected from an in situ venous line in a nonanticoagulant tube after at least three consecutive doses of cefepime in order to ensure steady-state concentrations. The blood samples were collected immediately after infusion, at 3 to 7 h after the start of infusion, and prior to the next dose, when possible. Once collected, blood samples were immediately centrifuged, and the serum was stored at −80°C until drug analysis.

**Analytic methods.** Cefepime concentrations in human serum were determined using a validated high-performance liquid chromatography assay (4). Intraday and interday coefficients of variation for the low (2 mg/liter) and high (40 mg/liter) quality control samples were all <6%.

**Pharmacokinetic analysis.** Population modeling of cefepime concentrations were performed using the nonparametric adaptive grid program in the MM-USC*PACK collection (5, 15). A two-compartment pharmacokinetic model with zero-order infusion and first-order elimination, applying creatinine clearance ($CL_{CR}$) as a function, was chosen based on log-likelihood values and Akaike's information criterion (25). The following parameters were estimated for each patient: volume of distribution in the central compartment ($V_1$ [liter/kg]), elimination rate constant ($K_{10}$ [$h^{-1}$]), and intercompartmental transfer constants ($K_{12}$, $K_{21}$ [$h^{-1}$]). Total body clearance ($CL_T$ [liter/kg/h and liter/h]) was then derived from the above-described estimates. Demographic variables were used to determine correlation with pharmacokinetic parameters. These variables included age, gender, ethnicity, body weight, APACHE II (*a*cute *p*hysiology *a*nd *c*hronic *h*ealth *e*valuation) score on the day of cefepime sampling (12), and $CL_{CR}$. A $K_{slope}$ population pharmacokinetic analysis was performed with $CL_{CR}$ for the elimination rate parameter ($K_{10}$) according to the following equation: $K_{10} = K_I + K_S \times CL_{CR}$, where $K_I$ is the intercept, $K_S$ is the slope parameter, and $CL_{CR}$ was calculated using an adjusted Cockcroft-Gault equation that excluded weight from the numerator and denominator [$CL_{CR}$ = (140 − age)/serum creatinine; the result of this equation is multiplied by 0.85 for females]. Body weight was considered a function of $V_1$. The overall assay error variance model with a gamma function ($\gamma$) was determined by fitting a first-order polynomial to the plot of the assay standard deviations (SD) versus the measured cefepime concentrations on an interday basis, generating the following formula: $SD = \gamma(0.0224 + 0.056 \times C)$, where $C$ was concentration and $\gamma$ was identified to be 1.07. The modeling procedure weighted the individual concentrations in the serum by the reciprocal of the assay error variance pattern, giving more influence to the precisely measured cefepime concentrations and less weight to the less-precise values. Measures of predictive performance and coefficients of determination were applied to observed-predictive plots. An independent group of randomly selected patients ($n = 6$) was withheld from the initial model-building process in order to test model bias and precision.

**Pharmacodynamic analysis.** A 5,000-patient Monte Carlo simulation (Crystal Ball version 2000; Decisioneering Inc., Denver, CO) using an open two-compartment model was conducted using the pharmacokinetic parameter median estimates, dispersion, and a lower triangular covariance matrix acquired from the final model to generate steady-state concentration-time profiles for various cefepime dosing regimens. Protein binding of 15% was applied by multiplying the cefepime dose by the fraction unbound before performing each simulation. The probability of target attainment (PTA) was calculated for each dosing regimen as a function of increasing MIC dilutions, using 50% $fT>MIC$ as the pharmacodynamic target (19). Cefepime dosage regimens, including package insert-recommended dosing as well as higher-dose prolonged 3-h infusion regimens, were simulated for three categories of renal function (based on $CL_{CR}$ ranges), as follows: 50 to 120 ml/min, 30 to 49 ml/min, and 10 to 29 ml/min, using the $K_{10}$ equation described above.

**Statistical analysis.** Dichotomous variables (e.g., gender, combination therapy, type of infection) were compared using a chi-square test. Continuous variables were compared using Student's $t$ test or the Mann-Whitney U test, where appropriate. An a priori $P$ value of <0.05 was statistically significant. All statistical tests were conducted on SigmaStat statistical software version 2 (SPSS Inc., Chicago, IL).

TABLE 1. Comparative demographics of patients receiving cefepime for VAP between the experimental and validation groups

| Characteristic[a] | Experimental group ($n$ = 26) | | | Validation group ($n$ = 6) | | |
|---|---|---|---|---|---|---|
| | Mean ± SD | Median (range) | No. (%) of patients | Mean ± SD | Median (range) | No. (%) of patients |
| Continuous variables | | | | | | |
| Age | 57.0 ± 21.3 | 60.5 (19–91) | | 62.0 ± 8.3 | 63.5 (49–72) | |
| Wt (kg) | 84.0 ± 23.2 | 78.6 (50.4–158.4) | | 86.9 ± 15.7 | 85.4 (70.5–106.8) | |
| APACHE II score[b] | 19.5 ± 4.6 | 19 (11–29) | | 18.3 ± 5.0 | 16.5 (15–28) | |
| SCr (mg/dl) | 0.9 ± 0.4 | 0.8 (0.4–2.3) | | 1.0 ± 0.5 | 0.9 (0.4–1.8) | |
| $CL_{CR}$ (ml/min)[c] | 100.5 ± 40.7 | 97.5 (26.1–186.7) | | 93.7 ± 56.2 | 80.7 (40.6–193.4) | |
| Dichotomous variables | | | | | | |
| Male gender | | | 17 (65) | | | 4 (67) |
| ICU type | | | | | | |
| SICU | | | 13 (50) | | | 3 (50) |
| NTICU | | | 13 (50) | | | 3 (50) |
| Concomitant treatment with: | | | | | | |
| Tobramycin | | | 19 (73) | | | 5 (83) |
| Vancomycin | | | 22 (85) | | | 5 (83) |
| Fluoroquinolone | | | 4 (15) | | | 0 (0) |
| Tobramycin + vancomycin | | | 18 (69) | | | 5 (83) |

[a] SICU, surgical intensive care unit; NTICU, neurotrauma intensive care unit; SCr, serum creatinine; $CL_{CR}$, creatinine clearance.
[b] APACHE II score was measured at the time of the first blood sample from the patient.
[c] $CL_{CR}$ was calculated using the Cockcroft-Gault equation, independent of weight.

TABLE 2. Pharmacokinetic parameters of the cefepime population model[a]

| Parameter | Mean | Median | SD |
|---|---|---|---|
| $K_i$ ($h^{-1}$) | 0.094 | 0.071 | 0.06 |
| $K_S$ ($h^{-1}$) | 0.006 | 0.003 | 0.011 |
| $K_{12}$ ($h^{-1}$) | 1.337 | 0.78 | 1.023 |
| $K_{21}$ ($h^{-1}$) | 1.046 | 0.472 | 1.082 |
| $V_1$ (liter/kg) | 0.263 | 0.206 | 0.187 |

[a] $K_{10} = K_i + (K_S \times CL_{CR})$. $CL_T$, total body clearance; $K_i$, $y$-intercept constant; $K_S$, slope constant; $K_{12}$, intercompartmental transfer rate constant from the central to the peripheral compartment; $K_{21}$, intercompartmental transfer rate constant from the peripheral to the central compartment; $V_1$, volume of distribution of the central compartment.

## RESULTS

**Population demographics.** Of the 32 total patients (88 collected serum samples), 26 patients (72 serum samples) were used to develop the cefepime population pharmacokinetic model (experimental group). The six remaining patients (16 collected serum samples) were used to validate the model (validation group). Not all patients had three blood samples collected, due to nursing shift changes or deterioration in the patient's clinical status. No significant differences were observed among the patient characteristics (Table 1). APACHE II scores were similarly high, suggesting that both groups of patients were severely ill at time of blood sample collection. One patient placed on the VAP pathway actually had an intra-abdominal infection, but the pharmacokinetics of this patient was similar to that of the others and, therefore, was kept in the analysis. High-dose cefepime of 2 g every 8 h (3-h infusion) or a dose consistent with renal adjustment was administered to 29 of the 32 critically ill patients (24 in the experimental group and 5 in the validation group); the remaining patients received package insert-recommended doses. In the experimental group, renal function was normal ($CL_{CR}$, 50 to 120 ml/min) in 22 patients and poor in four patients (three patients with $CL_{CR}$ values of 30 to 49 ml/min and one patient with a $CL_{CR}$ of 10 to 29 ml/min). Within the validation group, five patients had normal renal function, while one patient had a $CL_{CR}$ between 30 and 49 ml/min. In addition to cefepime, tobramycin or a fluoroquinolone was used concurrently in 28 of the 32 patients. Most patients ($n$ = 24) received tobramycin concomitantly with cefepime. No patient experienced adverse events attributed to the high-dose prolonged-infusion cefepime dosages.

TABLE 3. Covariance matrix in lower triangular form

| Parameter | Covariance | | | | |
|---|---|---|---|---|---|
| | $K_i$ | $K_S$ | $K_{12}$ | $K_{21}$ | $V_1$ |
| $K_i$ | 0.0037 | | | | |
| $K_S$ | −0.0001 | 0.0001 | | | |
| $K_{12}$ | −0.0370 | 0.0008 | 1.0466 | | |
| $K_{21}$ | −0.0136 | −0.0015 | 0.7208 | 1.1717 | |
| $V_1$ | 0.0026 | −0.0011 | −0.0455 | 0.0346 | 0.0348 |

$K_i$, the $y$ intercept of the elimination rate constant; $K_S$, the slope of the elimination rate constant; $K_{12}$, intercompartmental transfer rate constant from the central to the peripheral compartment; $K_{21}$, intercompartmental transfer rate constant from the peripheral to the central compartment; $V_1$, volume of distribution of the central compartment.

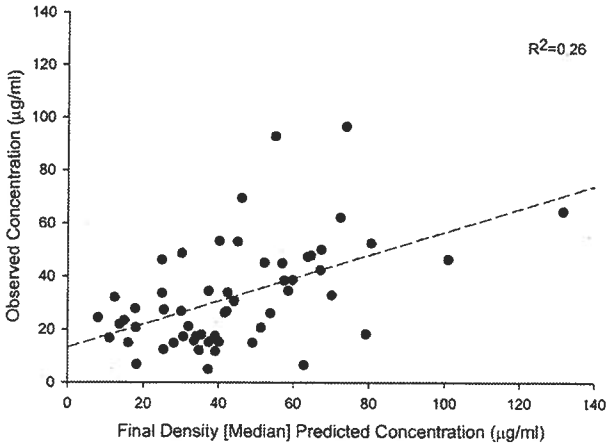


FIG. 1. Scatter plot of observed versus predicted cefepime concentrations, using the population pharmacokinetic model with covariates.

**Pharmacokinetic parameters.** Population pharmacokinetic parameters for cefepime for the 26 subjects are provided in Tables 2 and 3. Model building using log-likelihood values and Akaike's information criterion identified the optimal model, with $K_{10}$ as a function of $CL_{CR}$, whereby $K_{10}$ = 0.071 + 0.0027 × $CL_{CR}$, and with $V_1$ as a function of total body weight (TBW), whereby $V_1$ = TBW × 0.21 liter/kg. Other tested covariates had no identifiable influence on the pharmacokinetic parameters. Using these median parameter estimates, the bias, precision, and coefficient of determination for the initial model were 11.3 µg/ml, 24.0 µg/ml, and 26%, respectively (Fig. 1). Examining the data using the maximum a posteriori Bayesian estimation step as a reference, the bias, precision, and coefficient of determination for the model were 0.28 µg/ml, 7.39 µg/ml, and 98%, respectively. The independent validation group displayed a bias, precision, and coefficient of determination of −1.64 µg/ml, 17.1 µg/ml, and 62%, respectively (Fig. 2). This model was considered acceptable for predicting cefepime concentrations in our population. For comparisons with other research in the field, we also examined $CL_T$ as a function of $CL_{CR}$ and identified $CL_T$ by using the formula 0.048 × $CL_{CR}$ + 1.2. Our mean (SD) $V_1$ was 22.1 liters (6.1 liters), and our mean $CL_T$ was 7.6 liters/h (3.3 liters/h). The clearance parameter was calculated as the product of the elimination rate parameter and $V_1$.

**Pharmacodynamic analysis.** The probabilities of achieving a target of 50% $f$T>MIC for cefepime with various dosing regimens in three groups of critically ill patients with various renal functions ($CL_{CR}$ of 50 to 120, 30 to 49, and 10 to 29 ml/min) are shown in Fig. 3A to C. In patients with $CL_{CR}$ of 50 to 120 ml/min, the high-dose, prolonged-infusion regimen (2 g every 8 h, as a 3-h infusion) achieved 91.8%, 78.1%, and 50.3% PTAs at MICs of 8 µg/ml (susceptibility breakpoint), 16 µg/ml (intermediate), and 32 µg/ml (resistance breakpoint), respectively (Fig. 3A). Traditional 0.5-h infusion dosing regimens achieved significantly lower PTAs at these respective MICs. Among simulated patients with a $CL_{CR}$ of 30 to 49 ml/min, a 2-g dose every 12 h infused over 3 h achieved PTAs of 93.8%, 79.8%, and 50.7% at MICs of 8 µg/ml, 16, µg/ml, and 32 µg/ml, respectively (Fig. 3B). The same dose administered as a 0.5-h



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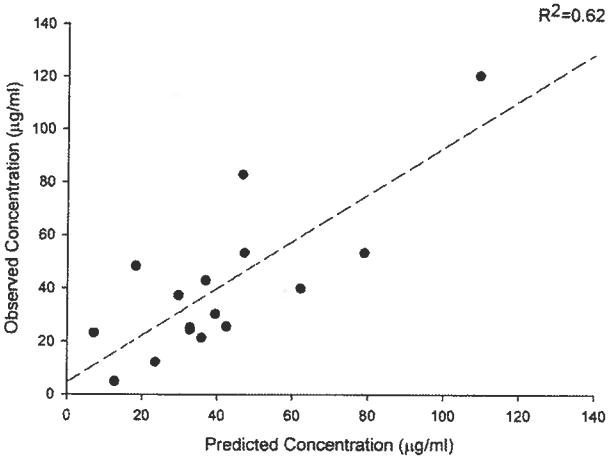


FIG. 2. Scatter plot of observed and predicted cefepime concentrations of the validation group, in accordance with the median parameter values of the pharmacokinetic population model.

infusion had slightly lower probabilities in this MIC range. In patients with $CL_{CR}$ of 10 to 29 ml/min, all regimens achieved similar PTAs across the tested MIC range (Fig. 3C); however, no regimen achieved a PTA against MICs of 16 μg/ml and 32 μg/ml as high as those of the other $CL_{CR}$ groups.

## DISCUSSION

Herein, we created a population pharmacokinetic model to describe the concentration data obtained in patients receiving a high-dose, prolonged-infusion cefepime dosing regimen (2 g every 8 h, infused over 3 h) according to our hospital's VAP pathway. The model was generated from critically ill patients predominately diagnosed with VAP. $CL_{CR}$ and body weight were shown to be the covariates most influential of $K_{10}$ and $V_1$, thus enabling for the prediction of individual cefepime serum concentrations. A unique characteristic of our model-building process was the use of a randomly selected independent population of VAP patients for validation. Compared with the population pharmacokinetic model that influenced the development of our hospital's VAP clinical pathway (23), our model had similar intercompartmental transfer and elimination rate constants. Although the intercept values and slopes are slightly different, the final regression equation published by Tam and colleagues ($CL_T = 0.055 \times CL_{CR} + 0.329$; median values) (23) produced values of drug clearance at 50 ml/min and 100 ml/min that were virtually identical to ours: 3.1 versus 3.6 liters/h and 5.8 versus 6.0 liters/h, respectively.

Although there have been several cefepime population pharmacokinetic models developed in the literature (16, 23), there are few that specifically observe an adult critically ill patient population (8, 22), and only one has explored the utilization of a prolonged infusion of cefepime (24). The importance of observing this patient population is centered upon the patient heterogeneity and the large interindividual pharmacokinetic parameters within the ICU populations. Additionally, our population model is believed to be the first generated using a prolonged-infusion cefepime dose. Recently, another

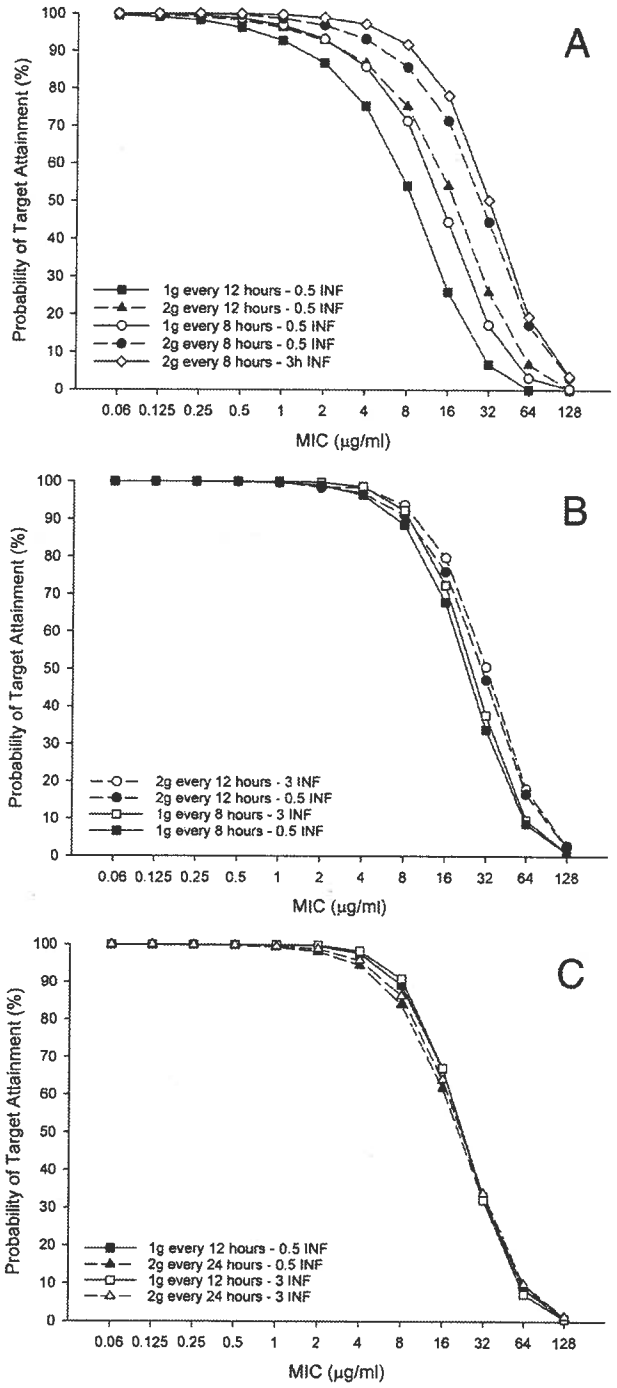


FIG. 3. PTA for cefepime regimens achieving 50% $fT>MIC$ at various $CL_{CR}$ levels: 50 to 120 ml/min (A), 30 to 49 ml/min (B), 10 to 29 ml/min (C). 0.5 INF, 0.5-h (30-min) infusion; 3h INF and 3 INF, 3-h infusion.

cefepime model with a similar population utilized doses of 4 g administered continuously over 24 h (8). Despite receiving a different dosing strategy and using a different parameter-covariant relationship ($CL_T$ to serum creatinine), $V_1$ and $CL_T$

rates were comparable to those in our assessment. Other cefepime pharmacokinetic studies have observed mean $V_1$ and $CL_T$ rates in critical care patients in the ranges of 23 to 27 liters and 6 to 7 liters/h, respectively, results which are similar to our mean values of 22.1 liters and 7.6 liters/h, respectively (17, 22, 23).

Because of the high prevalence of multidrug-resistant, gram-negative organisms as a cause of VAP in critically ill patients, the need for appropriate antibiotic therapy and optimal drug dosing is paramount. Although *P. aeruginosa* is considered susceptible to cefepime when the MIC is ≤8 μg/ml, a recent report noted increased mortality at this MIC in patients with bacteremia who were treated with standard cefepime dosages (2). Based on these data and the frequency of isolates nonsusceptible to this antibiotic at our institution, we employed a high-dose, prolonged-infusion (2 g every 8 h, with each dose infused over 3 h) aimed at achieving 50% *f*T>MIC for pathogens with cefepime MICs of up to 32 μg/ml (i.e., resistant). The actual pharmacokinetics observed in our patient population demonstrated that this dosage regimen did indeed achieve this pharmacodynamic exposure, with a high likelihood at MICs of 8 μg/ml, 16 μg/ml, and to a lower probability, 32 μg/ml. As shown in this study (Fig. 3A), as well as with other β-lactams, the prolonged-infusion regimen increased the *f*T>MIC against organisms with higher MICs compared to that of traditional 30-min infusion (9, 11, 13, 18). The prolonged-infusion strategy also permits ample time for other drugs to be administered through the same intravenous line during the breaks in infusion time.

We also evaluated different dosing regimens based on $CL_{CR}$ ranges to confirm that optimal exposure was maintained when doses were adjusted for renal dysfunction. Among simulated patients with a $CL_{CR}$ of 30 to 49 ml/min, 2-g doses administered every 12 h as either 0.5- or 3-h infusions achieved nearly identical PTAs at higher MICs as those achieved by the max dose (2 g every 8 h, as 3-h infusion) in patients with normal $CL_{CR}$. This suggests that the benefit of the prolonged infusion lessens as a patient's renal function declines; we currently advocate the administration of a 2-g dose every 12 h (0.5-h infusion) empirically for VAP patients with a $CL_{CR}$ of 30 to 49 ml/min at our hospital to target nonsusceptible organisms, reserving the prolonged infusion for those with normal renal function only. For patients with a $CL_{CR}$ range of 10 to 29 ml/min, all of the simulated dosage regimens achieved similar PTAs, but none were able to maintain high probabilities of achieving 50% *f*T>MIC at 16 μg/ml (~66%) or 32 μg/ml (~33%). We currently utilize a regimen of 1 g every 12 h (0.5-h infusion) for these patients, but further study is required to determine a dose that achieves higher PTAs at 50% *f*T>MIC at 16 or 32 μg/ml while retaining a low likelihood for toxicity.

In summary, this is the first cefepime population pharmacokinetic model developed and validated for critically ill patients with VAP treated with a high-dose, prolonged-infused regimen. These data demonstrate that cefepime dosed 2 g every 8 h as a 3-h prolonged infusion will improve the likelihood of pharmacodynamic target attainment over that of standard 30-min infusions. This report also provides suggestions for doses that are able to maintain these PTAs in patients with decreased renal function. Lastly, this covariate model will be useful in predicting cefepime exposures in VAP patients who do not have concentration data available.

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# Pharmacokinetic-pharmacodynamic rationale for cefepime dosing regimens in intensive care units

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***Objectives*: (i) To develop a population pharmacokinetics (PK) model for cefepime in patients in intensive care units (ICUs). (ii) To assess the pharmacokinetic-pharmacodynamic profile of various cefepime dosing regimens and to assess their expected probability of target attainment (= PTA expectation value) against common ICU pathogens such as *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa* and *Acinetobacter baumannii*.**

***Methods*: Thirteen ICU patients received cefepime 2 g 12 hourly intravenous (3 min). Twelve blood samples were taken on two occasions: (i) immediately after initial dose; and (ii) between days 3 and 6 after starting therapy. Population PK models were developed using NONMEM. Based on the final covariate model, Monte Carlo simulations were undertaken ($n$ = 1000) to simulate free-drug concentrations of cefepime for two administration methods: (i) intermittent bolus administration (IBA); and (ii) continuous infusion (CI). Concentration–time profiles were evaluated by the probability of achieving free-drug concentration above the MIC for >65% of the dosing interval. Finally, using local MIC distributions of *E. coli*, *K. pneumoniae*, *P. aeruginosa* and *A. baumannii* the PTA expectation values for each dosing administration method were evaluated.**

***Results*: A three-compartment model with zero-order input best described the concentration–time data. The PTA expectation values for *E. coli* and *K. pneumoniae* were >90% in all CI doses but only when administered as 1 g every 6 h and higher daily doses for IBA. For the current treatment protocol, 2 g every 12 h, *P. aeruginosa* and *A. baumannii* achieved target concentrations of only 54% and 28%, respectively. For *P. aeruginosa*, a CI of at least 4 g/day was required to achieve a PTA expectation value >90% while for *A. baumannii* a 6 g/day CI only achieved a PTA expectation value of 75%.**

***Conclusions*: When given as IBA or CI for *E. coli and K. pneumoniae*, cefepime should be successful in achieving the bactericidal target. For *P. aeruginosa* higher doses of cefepime (>4 g/day) are required to achieve the required PTA expectation value. Cefepime fails to achieve the bactericidal target even when administered at high doses, e.g. 6 g/day, for *A. baumannii*.**

Keywords: β-lactams, critically ill patients, probability of target attainment

## Introduction

Cefepime is a 'fourth-generation' cephalosporin with good activity against Gram-negative microorganisms, i.e. *Escherichia coli* and *Klebsiella pneumoniae*, and some activity against Gram-positive microorganisms, i.e. *Streptococcus* spp.[1] Cefepime belongs to the β-lactam class of antibiotics. The goal of β-lactam therapy is to achieve a free-drug concentration (indicated by the prefix $f$)[2] above the MIC. This is usually expressed as a fraction of the dosing interval ($f$T > MIC). It has been reported that the $f$T > MIC achieved directly impacts on the microbiological killing of β-lactams.[3,4] *In vivo* animal models of infection[5] have demonstrated that for β-lactams an $f$T > MIC of about 60–70% is required to achieve near-maximal bacterial killing.

The recommended dosage of cefepime for adults with normal renal function and mild to moderate infections is 1 g every 12 h. This cefepime dosing regimen has been shown to be effective

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against the majority of Enterobacteriaceae, streptococci and *Staphylococcus aureus*.[6] For critically ill patients such as those treated in intensive care units (ICUs) cefepime's broad spectrum of activity offers an advantage for empirical antibiotic therapy. In this critically ill patient group, the recommended dose is increased to 2 g every 12 h.[7] However, for pathogens such as *Pseudomonas aeruginosa* and *Acinetobacter* species, it has been suggested that higher doses of cefepime or different modes of administration may be required to achieve maximal bacterial killing.[8]

The current dataset has been previously published and analysed using a standard two-stage approach.[9,10] This pharmacokinetic (PK) analysis method has some limitations[11] and it is now preferred that population PK analysis via non-linear mixed effects model is utilized to provide more accurate estimates of the between-subject variability and therefore should provide more accurate estimation of the probability of target attainment (PTA).

The aims of this study were: (i) to develop a population PK model for cefepime in ICU patients; and (ii) to assess the pharmacokinetic-pharmacodynamic profile of various cefepime dosing regimens and to assess their expected PTA (= PTA expectation value) against common ICU pathogens such as *E. coli*, *K. pneumoniae*, *P. aeruginosa* and *Acinetobacter baumannii*.

## Materials and methods

### *Subjects*

Full details on the current dataset have been presented elsewhere.[9,10] The study protocol was approved by the Ethics committee of the Royal Brisbane Hospital, Brisbane, Australia. Informed consent was obtained from patients or next of kin.

In summary, 13 ICU patients (11 males) received cefepime 2 g every 12 h as a 3 min intravenous (iv) infusion. Patients were enrolled if they had a serum creatinine concentration of <0.1 mmol/L.

### *Sampling schedule and determination of cefepime in plasma by HPLC*

All blood samples (10 mL) were taken from an *in situ* arterial line immediately prior to dose administration (time [*T*] = 0 at the start of the 3 min infusion) and at 5, 10, 20, 30, 60, 90, 120, 240, 360, 480, 600 and 720 min post-start of infusion. The subjects received the same dose of 2 g cefepime twice daily as a 3 min infusion for at least 3–6 days. Occasion 2 started between 60 and 120 h after the first dose. The HPLC assay for measurement of cefepime in plasma was linear from 1 to 200 μg/mL and the intra-day and inter-day imprecision values were under 6%.[9,10] For the PK analysis, the values below the limit of quantification (BLQ) of the assay (1 μg/mL) have been substituted by half the quantification limit, as described by Beal.[12]

### *Population pharmacokinetics modelling*

The concentration versus time data for cefepime in plasma were analysed by a non-linear mixed effects modelling approach[13] using NONMEM (Version 5, Level 1.1, GloboMax LLC, Hanover, MD, USA) with double precision with the G77 FORTRAN compiler. The NONMEM runs were executed using Wings for NONMEM (WFN 408b). Data were analysed using the first order conditional estimation (FOCE) method with INTERACTION.

For the population PK analysis, the plasma cefepime concentrations were fitted to one, two or three-compartment models using subroutines from the NONMEM library.[13] The concentration–time profile can be described as (Equation 1):

$$y_{ij} = f_{ij}(\theta_i, x_{ij}) \cdot e^{\varepsilon 1ij} + \varepsilon_{2ij}, \quad (1)$$

where $y_{ij}$ is the $j$th observed concentration at time points $x_{ij}$ for the $i$th subject. Also, $\theta_i$ represents fixed effects parameter of the structural model to be estimated. $f_{ij}$ is the function for the prediction of the $j$th response for the $i$th subject. Finally, $\varepsilon_{ij}$ denotes the $j$th measurement error for the $i$th subject. In other words, $\varepsilon_{ij}$ is the difference of the observed concentration from the predicted concentration. It is assumed to be independent and identically distributed with a normal distribution around the mean zero and variance $\sigma^2$.

### *Between-subject variability (BSV) and between-occasion variability (BOV)*

BSV was modelled using an exponential variability model (Equation 2):

$$\theta_i = \theta \cdot e^{\eta i}, \quad (2)$$

where $\theta_i$ is the value of the parameter for the $i$th subject, $\theta$ is the typical value of the parameter in the population and finally $\eta_i$ is a random vector with normal distribution, zero mean and variance–covariance matrix of BSV $\Omega$ to be estimated.

BOV is the variability of a parameter within a subject during treatment and includes between-occasion variability and within-occasion variability. BOV was assumed to be log normally distributed and modelled over the two PK study occasions (Equation 3):

$$\theta_{i,k} = \theta \cdot e^{\eta i + \eta i,k}, \quad (3)$$

where $\theta_{i,k}$ is the value of the parameter for the $i$th subject on the $k$th occasion.

### *Model diagnostics*

Statistical comparison of nested models was based on a $\chi^2$ test of the difference in the objective function. A decrease in the objective function of 3.84 units ($P < 0.05$) was considered significant.

Goodness-of-fit was evaluated by visual inspection of diagnostic scatter plots, including observed and predicted concentrations versus time, weighted residual versus time and residual versus predicted concentrations.

### *Bootstrap*

A non-parametric bootstrap method[14] ($n$ = 1000) was used to study the uncertainty of all PK parameter estimates. From the bootstrap empirical posterior distribution we have been able to obtain the 95% confidence interval (2.5–97.5% percentile) for the parameters, as described previously.[15]

### *Covariate screening*

The covariates analysed were age, weight, serum creatinine, creatinine clearance measured by 8 h urine collection, creatinine clearance estimated via C&G equation using total body weight and APACHE II scores. The individual covariates were centred by the median or standard values of occasion one and occasion two. Individual empirical Bayesian (POSTHOC) parameters were plotted against covariate values to assess relationships. If a trend between covariates and PK parameter was observed, then it was considered for inclusion in the population model.





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Possible covariates were added in a stepwise fashion into the model. Covariates were kept in the model if there was improvement in the fit over the base model, i.e. decrease in objective function and decrease in the BSV of the parameter.

### *Visual predictive checks*

Using the final covariate model a visual predictive check was performed by simulating 10 000 subjects to assess the predictive performance of the model. The visual predictive checks were generated using a Perl Script (version 1e).[16] The visual checks and representative percentiles [10th, 50th (median) and 90th percentile] were visually assessed using Prism® 2005 (Version 4.03).

### *Dosing simulations*

Five intermittent bolus administration (IBA) and three continuous infusion (CI) dosing regimens were simulated using Monte Carlo simulations. The five bolus dose regimens evaluated were 2 g every 12 h (same treatment regimen as in this study protocol), 2 g every 8 h, 1 g every 12 h, 1 g every 6 h and 1 g every 4 h, while the three CI regimens evaluated were 2, 4 or 6 g over 24 h with a loading dose of 0.5 g. Each Monte Carlo simulation generated free-concentration time profiles for 1000 subjects per dosing regimen using the parameters from the final covariate model. A value of 10% protein binding was used in all simulations.[17,18] From this data the $fT > MIC$ was calculated for each simulated subject using linear interpolation. The PTA was obtained by counting the subjects who achieved free-cefepime concentrations for at least 65% of the dosing interval.[3,19]

### *MIC distributions*

MIC distributions were derived from cefepime $MIC_{50}$, $MIC_{90}$ and range collected from Australian laboratories provided by the Queensland Health Pathology Service (QHPS) for *E. coli*, *K. pneumoniae*, *P. aeruginosa* and *A. baumannii* isolates. The MIC distributions were estimated from 2794 strains of *E. coli*, 896 strains of *K. pneumoniae*, 1853 strains of *P. aeruginosa* and 234 strains of *A. baumannii*.

The PTA expectation values were calculated by multiplying the PTA at each MIC by the fraction of organisms susceptible at that concentration of the respective MIC distribution. The sum of those individual products is the PTA expectation value for the respective MIC distribution. The PTA expectation value can be interpreted as the probability of successful treatment of infections caused by bacteria with a specific susceptibility pattern (MIC distribution) in the studied patient population. These calculations were performed for the first 12 h of treatment (occasion 1). Calculations were performed on the first 12 h as it represents the worst case scenario of PTA expectation as the free-concentrations approach steady-state with the different dosing regimens and that likely onset of sepsis treatment can be ascertained.

## Results

### *Subjects*

The patients' age ranged from 34 to 75 years (median, 60 years); estimated total body weight ranged from 56 to 128 kg (median, 75 kg); APACHE II scores ranged from 4 to 24 (median, 11); and the 8 h urine collection resulted in a creatinine clearance that ranged from 2.3 to 11.7 L/h (median, 7.1 L/h). The dataset comprises a total of 307 quantifiable samples. Five measurements were below the limit of quantification.

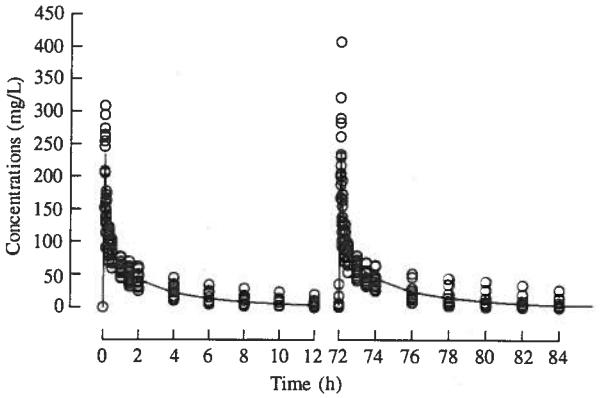


**Figure 1.** Scatter plot of observed (open circles) and predicted (continuous line) cefepime concentrations versus time.

### *Model building*

The best base model based on the model building criteria consisted of a three-compartment model with a full variance-covariance matrix between clearance (CL) and central volume of distribution (V1), a diagonal BSV for peripheral volume of distribution (V2) and a combined residual unknown variability (RUV). The model supported between-occasion variability on CL and V1. The values of inter-compartmental clearance between the third and first compartment (Q3) and the peripheral volume of distribution (V3) were fixed. The final objective function for this model was 1227.391.

Figure 1 shows the plot of the observed cefepime concentrations versus time overlaid by the predicted typical cefepime concentrations versus time. The values of the parameters for the final base model are given in Table 1. Table 1 presents the 95% confidence interval for the parameters computed from all bootstrap runs.

Creatinine clearance measured by 8 h urine collection was the only covariate to describe cefepime clearance. The final model was represented by Equation 4:

$$TVCL = \theta_1 \cdot \left(\frac{CLCr}{CLCr_{Std}}\right), \quad (4)$$

where TVCL is the typical value of clearance and $CLCr_{Std}$ is the standard value of creatinine clearance for all patients and had a value of 7.0 L/h. Table 2 shows the changes in BSV after the addition of the covariate to the model.

Figure 2 (a and b) shows a plot of visual predictive check with the final covariate model for occasion 1 and occasion 2. These plots show that the final PK model describes the measured cefepime concentrations adequately on both occasions. All subsequent cefepime Monte Carlo simulations were then based on this model.

### *Dosing simulations*

*Intermittent bolus administration.* Figure 3(a) shows the PTA versus MIC profiles for the different intermittent short-term infusion regimens. The recommended dosing regimen for patients with mild to moderate infections, 1 g every 12 h, appears to provide a high PTA up to an MIC of 0.25 mg/L (inclusive).





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**Table 1.** Bootstrap parameter estimates of the final base model

| Parameter | Average | 95% Confidence interval | |
|---|---|---|---|
| **Fixed effects** | | | |
| Clearance CL (L/h) | 6.51 | 5.22 | 8.01 |
| Central volume of distribution V1 (L) | 5.74 | 4.95 | 6.56 |
| Deep peripheral volume of distribution V2 (L) | 9.57 | 7.86 | 11.7 |
| Deep peripheral volume of distribution V3 (L) | 7.3 | fixed | |
| Slow inter-compartmental clearance Q2 (L/h) | 33.8 | 29.4 | 38.4 |
| Slow inter-compartmental clearance Q3 (L/h) | 3.5 | fixed | |
| **Random effects** | | | |
| Between-subject variability ($\Omega_{BSV}$) (CV%) | | | |
| BSVCL | 38% | 22% | 48% |
| BSVV1 | 23% | 2% | 39% |
| BSVV2 | 34% | 20% | 44% |
| Between-occasion variability ($\Omega_{BOV}$) (CV%) | | | |
| BOVCL | 15% | 7% | 22% |
| BOVV1 | 30% | 21% | 35% |
| **Random error** | | | |
| Residual unknown variability | | | |
| CV CV% | 8% | 6% | 10% |
| SD mg/L | 0.452 | 0.136 | 0.798 |

**Table 2.** Change in objective function, between-subject variability and between-occasion variability, before and after the addition of covariates into the model

| Model components | OBJ | ΔOBJ | BSV (CV%) | BOV (CV%) |
|---|---|---|---|---|
| Final base model: TVCL = $\theta_1$ | 1227.391 | – | 38 | 15 |
| TVCL = $\theta_1 \cdot$ (CLCR/CLCR$_{Std}$) | 1205.012 | 22.379 | 4 | 19 |

However, the recommended ICU treatment protocol, 2 g every 12 h, provides a high PTA up to and including an MIC of 0.5 mg/L. In addition, the dosing regimens of 1 g every 4 h or 2 g every 8 h provide very similar and robust (>90%) PTA up to and including an MIC of 2 mg/L.

*Continuous infusion.* The PTA versus MIC profiles for the different CI dosing regimens with a loading dose is shown in Figure 3(b). The low-dose CI of 2 g cefepime per day provides a robust (>90%) PTA up to an MIC of 2 mg/L. However, a high-dose of cefepime (6 g CI) showed a robust (>90%) PTA up to an MIC of 8 mg/L (inclusive).

### *PTA expectation values*

The assessment of PTA expectation value versus the MIC distributions for the first occasion is shown in Table 3. When

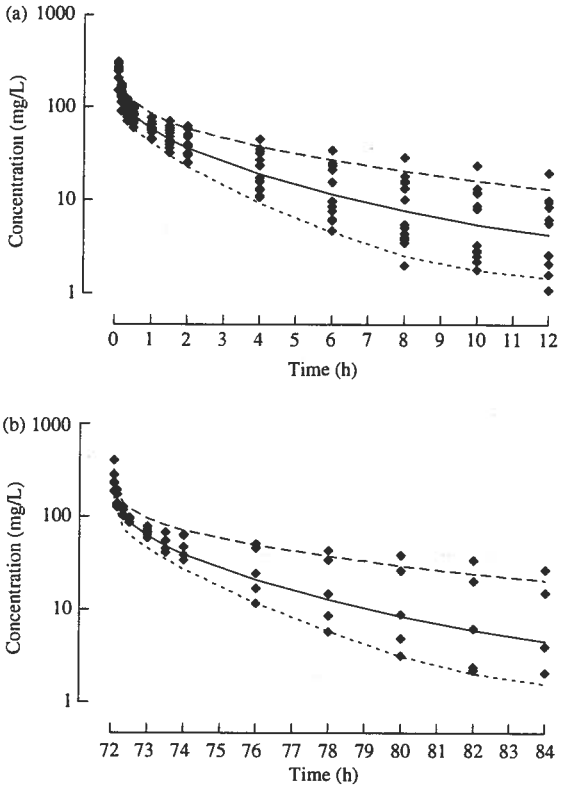


**Figure 2.** Visual predictive checks for (a) occasion 1 and (b) occasion 2 generated from Monte Carlo simulations ($n$ = 10000) and showing that the estimated population PK model has adequate predictive performance. 10th percentile, dotted line; 50th percentile, continuous line; 90th percentile, dashed line.

cefepime is administered as 1 g every 4 h, 1 g every 6 h or 2 g every 8 h, the population PTA expectation value is >90% for *E. coli* and *K. pneumoniae*. For the current treatment protocol of 2 g every 12 h, cefepime achieves a 54% and 28% PTA expectation value for *P. aeruginosa* and *A. baumannii*, respectively. This is further reduced for 1 g every 12 h, which would provide PTA expectation values of 35.5% and 11.6%, respectively.

The PTA expectation values for *E. coli* and *K. pneumoniae* when cefepime is given as a CI was >90% for all dose groups, i.e. 2, 4 or 6 g/day. To achieve a >90% PTA expectation value for *P. aeruginosa* a dose of at least 4 g/day of cefepime as a CI is required. However, at the maximum recommended cefepime dose of 6 g/day administered as a CI, the PTA expectation value for *A. baumannii* is at best only 75%.

## Discussion

The current study presents a population PK model for cefepime in ICU patients who had serum creatinine concentrations below the upper limit of normal. It includes stochastic simulations (often called Monte Carlo simulations) under various dosing regimens to assess the PTA for common ICU pathogens.

It is necessary to appreciate that the PTA for maximal bacterial cell killing of β-lactams following the administration of a fixed





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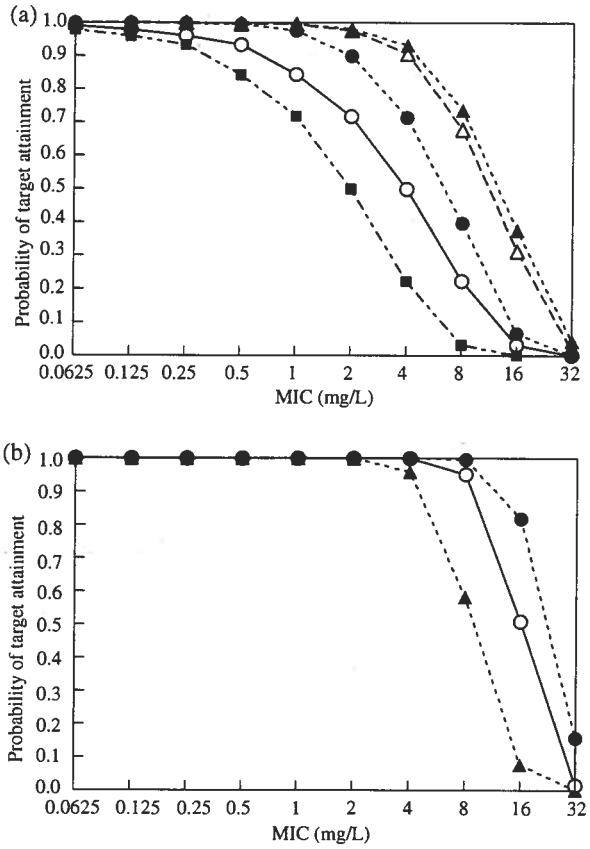


**Figure 3.** Probability of target attainment for 1000 simulated subjects given cefepime as (a) intermittent administration (2 g every 8 h, filled triangles; 1 g every 4 h, open triangles; 1 g every 6 h, filled circles; 2 g every 12 h, open circles; 1 g every 12 h, filled squares) and (b) continuous infusion with a loading dose of 0.5 g (2g/day, filled triangles; 4g/day, open circles; 6g/day, filled circles). The chosen target for the analysis was 65% of the dosing interval of free-cefepime plasma concentrations to be in excess of the MIC.

dose will depend on the between-subject variability of PK parameters, in particular clearance and volume of distribution.[20] This must be then incorporated with different MIC distributions for specific pathogens in various parts of the world. The current study used susceptibility patterns obtained from the QHPS. Therefore, our PTA expectation values apply for Australian resistance patterns, whereas our PTA versus MIC profiles apply for ICU patients worldwide. However, it is important to note that by using the PTA profiles given in Figure 3 (a and b), the PTA expectation values can be obtained for any given MIC distribution.

It should be noted that the inclusion criterion of the initial study[9] was a 'normal' serum creatinine and some of these patients had very high creatinine clearances.[9,10] As creatinine clearance was a predictor of cefepime clearance, the patients with the high creatinine clearance will result in low trough cefepime concentration. It is in these patients that our data show the need for higher than normal doses of cefepime either using IBA or CI to cover all PTA expectation values.

An important finding from the model building was that BSV was greater than BOV. This supports the concept that cefepime could be dose-individualized as there are only small changes in PK parameters from day to day. This could be achieved empirically by using creatinine clearance to predict the likely dose or via blood sampling and a target concentration intervention approach.[15]

More sensitive assays for cefepime have been published in the past years.[21] However, the area under the curve from time zero to the last quantifiable concentration was at least 91% of the area under the curve from time zero to infinity in our study. Therefore, our assay was sensitive enough for our objectives. The number of data points below the quantification limit was small (<2%). Therefore, we could not show that our BLQ handling method provided less bias in the model parameters as suggested previously.[12,22–24]

There is convincing data for penicillins from animal experiments that only the non-protein bound concentration is microbiologically active.[3,5,25] Also, the duration of unbound concentrations above the MIC is the key determinant to achieve optimum therapy for this class of antibiotics. The present study has shown that administration via CI with a loading dose offers

**Table 3.** Expected probabilities of target attainment (PTA expectation values) for intermittent administration versus continuous infusion of cefepime in ICU patients (the target chosen was 65% of unbound concentration above the MIC)

| | PTA expectation values (%) | | | |
|---|---|---|---|---|
| Dosing regimens | *E. coli* | *K. pneumoniae* | *P. aeruginosa* | *A. baumannii* |
| Intermittent administration | | | | |
| 1 g every 4 h (6 g/day) | 95.3 | 95.3 | 82.6 | 57.9 |
| 2 g every 8 h (6 g/day) | 95.8 | 95.8 | 84.9 | 61.1 |
| 1 g every 6 h (4 g/day) | 91.9 | 91.9 | 69.5 | 41.5 |
| 2 g every 12 h (4 g/day) | 78.9 | 78.9 | 53.6 | 28.2 |
| 1 g every 12 h (2 g/day) | 66.1 | 66.1 | 35.5 | 11.6 |
| Continuous infusion with loading dose (0.5 g) | | | | |
| 2 g/day | 95.2 | 95.2 | 81.3 | 56.3 |
| 4 g/day | 96.9 | 96.9 | 91.7 | 68.5 |
| 6 g/day | 97.9 | 97.9 | 94.8 | 74.6 |





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significant advantage when compared with IBA. This is based on achieving a higher PTA for the same daily dose per 12 h. Furthermore, the results of the present study suggest that CIs offer an advantage when treating *P. aeruginosa*.

However, against *A. baumannii*, at a dose of 6 g per 24 h, the CI achieved a PTA value of 75%, whereas intermittent regimens at best could only achieve a PTA expectation of 61% (see Table 3). What this means is that for this pathogen cefepime doses greater than 6 g per day via CIs may need to be considered to optimize therapy, as well as providing antimicrobial cover with other synergic agents, e.g. fluoroquinolones.[26]

While the use of CI therapy in ICU patients could possibly have disadvantages, for example, the extra iv line may be associated with a higher probability of a line infection, increasing costs and morbidity[27] and some drugs may be unstable at room temperature or incompatible with other simultaneously administered drugs, requiring the placement of a separate line, in our experience these potential problems are of nuisance value only. However, reconstituted solution of cefepime is stable for up to 24 h at room temperature or in a refrigerator (<5°C) for up to 7 days.[7] Thus, cefepime is ideally suited to CI administration.

Simulation of longer infusion times, e.g. 30 min, 3 or 5 h infusion, instead of CI, have been suggested to minimize the problems discussed above. For this mode of administration the optimal length of infusion is about the $fT > MIC$ target multiplied by the dosing interval. Thus the duration of infusion that achieves the highest PTAs is ~7.8 h (12 h × 65%) for every 12 h dosing and ~5.2 h (8 h × 65%) for every 8 h dosing. [27]

Nevertheless, CI clearly remains the optimal mode of administration if higher targets of an $fT > MIC$ above 70% of the dosing interval are required. However, further clinical studies on the exact target in critically ill sepsis patients are required. Furthermore, more clinical data about the effectiveness of continuous versus prolonged infusion should be collected in future clinical studies.

### *Conclusions*

Creatinine clearance measured by 8 h urine collection to assess ICU patients' renal function appears to be a useful predictor for cefepime clearance and potentially could be used to individualize cefepime therapy. Cefepime when administered as 1 g every 6 h has a >90% PTA expectation value for killing *E. coli* and *K. pneumoniae*. However for *P. aeruginosa*, a daily dose of 4 g/day of cefepime administered as CI is required to achieve a PTA expectation value of >90%, while for *A. baumannii* even a CI of 6 g/day cefepime only achieved a PTA expectation value of 75%.

## Acknowledgements

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## Transparency declarations

None to declare.

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# The Impact of Extended Spectrum Beta-Lactamase Production on the Pharmacodynamics of Cefepime

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Methodology:

1. 23-27g ICR Swiss mice were made neutropenic by 2 injections of cyclophosphamide (150 mg/kg and 100 mg/kg four and one day before study, respectively).

2. 4 strains of *E. coli* (3 ESBL producing) and 4 strains of *K. pneumoniae* (3 ESBL producing) were used for all studies. Cefpime MICs were determined by standard NCCLS methods (inoculum $10^5$ cfu/ml).

3. Multiple pairs of mice, infected with each of the strains cited above, were treated for 24 hours with cefepime at doses of 1.56-1600 mg/kg every 6 hours (total doses ranging > 1000-fold). These animals were sacrificed at 24 hours, and their thighs were removed and prepared as 10% homogenates. Pairs of untreated mice were sacrificed at 0 and 24 hours. CFU/thigh were determined from plating serial dilutions of thigh homogenates.

4. Sigmoid dose-response curves were analyzed by non-linear regression using the modified Hill equation. The static dose (the dose resulting in no net change in CFU over 24 hours) was calculated from the Emax model parameters.

5. Time above MIC (T>MIC) for each static dose was calculated from pharmacokinetic parameters in our ICR Swiss mice. Total drug levels were used in all calculations because of the low degree of protein binding in this animal model (<10%).

Results:

1. MICs against the ESBL producing *E. coli* were 8- to 33-fold higher than the susceptible strains. MICs against the ESBL producing *K. pneumoniae* were 2- to 16-fold higher than the susceptible strain.

| Organism | ESBL Type | MIC (µg/l) |
|---|---|---|
| E. coli ATCC 25922 | NA | 0.12 |
| E. coli 14714 | TEM-10 | 1.0 |
| E. coli 102-94090 | TEM-1, SHV-2A | 4.0 |
| E. coli SC15243 | SHV-2 | 4.0 |
| K. pneumoniae MCV2 | SHV-4 | 0.50 |
| K. pneumoniae UA-834 | SHV-2 | 8.0 |
| K. pneumoniae ATCC 43816 | NA | 0.25 |

NA = not applicable,

The 7 strains grew well in the thighs of neutropenic mice. The amount of growth over 24 hours in untreated mice varied from 1.20 to 3.36 $\log_{10}$.

2. The pharmacokinetics of cefepime in neutropenic mice is shown in Table 1. The half-life of cefepime is only 0.24-0.25 hours at doses of 10-50 mg/kg, respectively.

Table 1. Pharmacokinetics of Cefepime in Infected Mice

| Dose (mg/kg) | Peak Level (µg/kg) | Half-life (hours) |
|---|---|---|
| 10 | 10.0 | 0.24 |
| 50 | 39.5 | 0.25 |

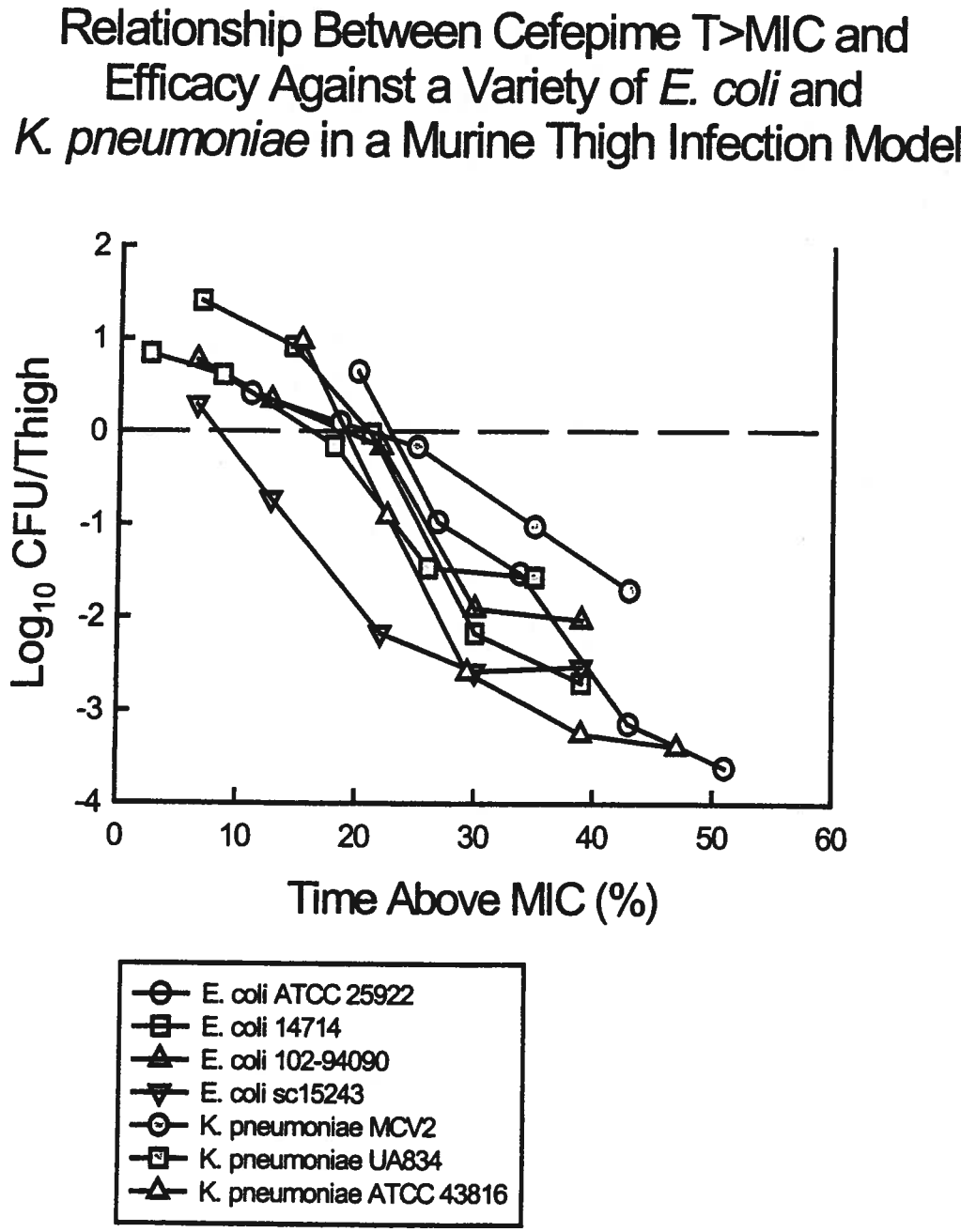
4. MICs for cefepime, the organism burden at the start of therapy, the calculated 6 hourly-static doses and times above MIC with the 7 strains are shown in Table 2. The duration of time serum concentrations needed to exceed the MIC varied from 9.1-32.6%. These values are slightly less than observed with other cephalosporins against gram-negative bacilli in this infection model (30-40%). Maximal organism killing was observed with T>MIC around 40%. The organisms with higher MICs (4-8 μg/ml) appeared to require less time above MIC than those with lower MICs. The production of various ESBLs did not appear to affect the time above necessary for cefepime efficacy in this neutropenic infection model. These relationships are demonstrated graphically in Figure 1.

Table 2. MICs, starting inocula, static dose and time above MIC with 7 strains of *E. coli* and *K. pneumoniae*

| **Organism** | **ESBL Type** | **MIC (mg/l)** | **Q 6 h Static Dose (mg/kg)** | ***T>MIC (%)** |
|---|---|---|---|---|
| E. coli ATCC 25922 | NA | 0.12 | 3.02 | 27.7 |
| E. coli 14714 | TEM-10 | 1.0 | 20.5 | 20.2 |
| E. coli 102-94090 | TEM-1, SHV-2A | 4.0 | 28.7 | 13.5 |
| E. coli SC15243 | SHV-2 | 4.0 | 9.15 | 9.1 |
| K. pneumoniae MCV2 | SHV-4 | 0.50 | 72.3 | 32.6 |
| K. pneumoniae UA-834 | SHV-2 | 8.0 | 71.3 | 20.0 |
| K. pneumoniae ATCC 43816 | NA | 0.25 | 3.51 | 24.2 |
| **Mean ± SD** | | | | 21.0 ± 8.0 |

*ANOVA p-value = 0.423, NA = not applicable.

Figure 1.


Relationship Between Cefepime T>MIC and Efficacy Against a Variety of E. coli and K. pneumoniae in a Murine Thigh Infection Model
Log10 CFU/Thigh
2
1
0
-1
-2
-3
-4
0
10
20
30
40
50
60
Time Above MIC (%)
E. coli ATCC 25922
E. coli 14714
E. coli 102-94090
E. coli sc15243
K. pneumoniae MCV2
K. pneumoniae UA834
K. pneumoniae ATCC 43816

Conclusions

1. To obtain a static effect with cefepime in the thighs of neutropenic mice, serum concentrations needed to exceed the MIC for 9.1-32.6% (mean 21%) of the dosing interval. This was true for susceptible strains of *E. coli* and *K. pneumoniae* as well as those with reduced susceptibility due to the production of extended-spectrum beta-lactamases.

2. These studies suggest that dosing regimens of cefepime that provide drug levels above the MIC for at least 40% of the dosing interval will show significant killing of ESBL producing strains.

3. With MICs performed using a standard inoculum of $10^5$, cefepime therapy with a standard dosing regimen of 2g every 12 h would be expected to be efficacious against organisms with MICs as high as 4 μg/ml.

# Activity of 4 Cephalosporins Against Various Gram-Negative Bacilli in the Murine Thigh-Infection Model

Cefepime – less than 20% binding in mice

| Strain | MIC (mg/L) | Static Dose (mg/kg) | T>MIC Total (Free) | 1 Log Kill (mg/kg) | T>MIC Total (Free) |
|---|---|---|---|---|---|
| E. coli ATCC 25922 | 0.12 | 3.02 q 6h | 27.7 | 6.81 q 6h | 32.6 |
| K. pneumoniae ATCC 43816 | 0.25 | 3.51 q 6h | 24.2 | 8.44 q 6h | 29.5 |
| K. pneumoniae MCV2 | 0.5 | 72.3 q 6h | 32.6 | 318 q 6h | 49.3 |
| E. coli 14714 | 1.0 | 20.5 q 6h | 20.2 | 53.7 q 6h | 32.3 |
| E. coli SC15243 | 4.0 | 9.15 q 6h | 9.15 | 41.7 q 6h | 22.4 |
| E. coli 102-94090 | 4.0 | 28.7 q 6h | 13.5 | 50.2 q 6h | 23.5 |
| K. pneumoniae HBMS 151 | 4.0 | 304 q 6h | 36.1 | 637 q 6h | 40.8 |
| K. pneumoniae UA-834 | 8.0 | 71.3 q 6h | 20.0 | 265 q 6h | 29.4 |
| K. pneumoniae HBMS 152 | 8.0 | 98.3 q 6h | 26.3 | 374 q 6h | 33.0 |
| K. pneumoniae HBMS 154 | 8.0 | 25.9 q 6h | 15.9 | 189 q 6h | 28.6 |
| K. pneumoniae HBMS 145 | 16.0 | >1600 q 6h | >37.9 | >1600 q 6h | >37.9 |
| K. pneumoniae HBMS 149 | 32.0 | 271 q 6h | 22.0 | 398 q 6h | 24.5 |
| K. pneumoniae HBMS 148 | 64.0 | 237 q 6h | 16.7 | 636 q 6h | 23.1 |
| Mean T>MIC | | | 23.9 | | 31.3 |

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Ceftazidime – binding less than 20% in mice

| Strain | MIC (mg/L) | Static Dose (mg/kg) | T>MIC Total (Free) | 1 Log Kill (mg/kg) | T>MIC Total (Free) |
|---|---|---|---|---|---|
| E. coli ATCC 25922 | 0.12 | 5.88 q 6h | 39.2 | 14.5 q 6h | 46.8 |
| K. pneumoniae R- | 0.12 | 7.48 q 6h | 41.2 | 14.7 q 6h | 46.9 |
| K. pneumoniae ATCC 43816 | 0.25 | 11.2 q 6h | 38.9 | 21.6 q 6h | 44.4 |
| K. pneumoniae Black | 0.25 | 48.0 q 6h | 49.6 | 98.3 q 6h | 55.4 |
| S. marcescens #1 | 0.25 | 16.9 q 6h | 41.9 | 37.8 q 6h | 48.1 |
| Enterobacter 2781 | 0.5 | 54.5 q 6h | 45.3 | 114 q 6h | 51.0 |
| K. pneumoniae HBMS 151 | 2.0 | 83.2 q 6h | 36.5 | 206 q 6h | 44.2 |
| K. pneumoniae TC-TEM 3 | 4.0 | 101 q 6h | 32.5 | 202 q 6h | 38.3 |
| K. pneumoniae HBMS 152 | 4.0 | 232 q 6h | 39.6 | 487 q 6h | 48.2 |
| K. pneumoniae TC-TEM 12 | 4.0 | 258 q 6h | 40.7 | 579 q 6h | 52.2 |
| Enterobacter 27798 | 4.0 | 491 q 6h | 48.3 | 788 q 6h | 50.4 |
| K. pneumoniae MCV2 | 16.0 | 644 q 6h | 40.2 | 1890 q 6h | 53.0 |
| K. pneumoniae HBMS 149 | 16.0 | 1156 q 6h | 48.0 | >2400 q 6h | - |
| K. pneumoniae HBMS 145 | 16.0 | 1335 q 6h | 49.4 | >2400 q 6h | - |
| K. pneumoniae TC-TEM 26 | 64.0 | 1296 q 6h | 34.9 | >2400 q 6h | |
| Mean T>MIC | | | 49.9 | | 48.2 |



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Cefotaxime – 30% binding in mice

| Strain | MIC (mg/L) | Static Dose (mg/kg) | T>MIC Total (Free) | 1 Log Kill (mg/kg) | T>MIC Total (Free) |
|---|---|---|---|---|---|
| E. coli ATCC 25922 | 0.06 | 25.7 q 6h | 38.1 (35.9) | 62.5 q 6h | 44.3 (42.0) |
| K. pneumoniae R- | 0.06 | 37.7 q 6h | 41.0 (38.7) | 115 q 6h | 53.0 (52.2) |
| K. pneumoniae ATCC 43816 | 0.12 | 44.2 q 6h | 37.9 (35.6) | 90.2 q 6h | 45.8 (43.4) |
| K. pneumoniae TC-TEM 12 | 0.12 | 72.5 q 6h | 41.7 (39.4) | 157 q 6h | 53.1 (50.6) |
| K. pneumoniae TC-TEM 7 | 0.25 | 105 q 6h | 41.8 (39.4) | 254 q 6h | 51.2 (48.7) |
| K. pneumoniae HBMS 154 | 0.5 | 105 q 6h | 37.1 (34.7) | 327 q 6h | 48.1 (45.6) |
| K. pneumoniae TC-TEM 26 | 0.5 | 341 q 6h | 48.4 (45.9) | 678 q 6h | 53.3 (50.8) |
| K. pneumoniae TC-TEM 3 | 4.0 | 287 q 6h | 32.1 (29.6) | 777 q 6h | 39.3 (36.8) |
| Mean T>MIC | | | 39.8 (37.4) | | 48.5 (46.3) |

Ceftriaxone – 75% binding in mice

| Strain | MIC (mg/L) | Static Dose (mg/kg) | T>MIC Total (Free) | 1 Log Kill (mg/kg) | T>MIC Total (Free) |
|---|---|---|---|---|---|
| K. pneumoniae R- | 0.06 | 1.86 q 6h | 65.8 (43.5) | 4.52 q 6h | 80.0 (57.8) |
| K. pneumoniae ATCC 43816 | 0.12 | 1.08 q 6h | 45.9 (23.7) | 2.97 q 6h | 62.1 (39.9) |
| K. pneumoniae TC-TEM 12 | 0.12 | 2.72 q 6h | 60.0 (37.8) | 8.50 q 6h | 79.0 (56.8) |
| K. pneumoniae TC-TEM 7 | 0.12 | 3.33 q 6h | 64.0 (41.7) | 9.31 q 6h | 81.5 (59.2) |
| K. pneumoniae TC-TEM 26 | 0.5 | 10.3 q 6h | 60.2 (38.0) | 28.3 q 6h | 85.4 (60.4) |
| K. pneumoniae TC-TEM 3 | 2.0 | 24.4 q 6h | 51.8 (29.6) | 40.4 q 6h | 67.9 (42.9) |
| K. pneumoniae MCV2 | 4.0 | 40.1 q 6h | 55.3 (30.3) | 138 q 6h | 86.9 (59.1) |
| K. pneumoniae HBMS 154 | 8.0 | 125 q 6h | 71.0 (43.2) | 211 q 6h | 81.5 (53.7) |
| K. pneumoniae HBMS 152 | 32.0 | 352 q 6h | 65.5 (34.9) | 620 q 6h | 82.4 (51.9) |
| Mean T>MIC | | | 59.9 (35.9) | | 78.5 (53.5) |

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## Summary of findings from neutropenic murine thigh model

- T>MIC not influenced by ESBL production
- T>MIC not influenced by bacterial inoculum size
- less T>MIC needed for cefepime (20-30%) than for other cephalosporins (40-50%)

| Compound | Target T>MIC (total free) | |
|---|---|---|
| | Static Dose | Maximal killing |
| Cefepime | 20% | 30% |
| Ceftazidime | 40% | 50% |
| Cefotaxime | 40% (40%) | 50% (50%) |
| Ceftriaxone | 60% (50%) | 80% (50%) |

- that not all β-lactams have the same target T>MIC is not new
  .....past examples: carbapenems & penicillins (eg amoxicillin-clavulanate)

- cefepime has unique mode of action among cephalosporins
  .....more rapid penetration across Gram-negative cell wall
  .....affinity for PBP2 (same PBP as for carbapenems)

- investigators' conclusion:
  .....cefepime T>MIC of 40% yields significant killing
  .....at the standard 2g q12h dosing regimen, cefepime expected to be efficacious against organisms with MICs ≤4 μg/ml



*

# Breakpoints for intravenously used cephalosporins in Enterobacteriaceae—EUCAST and CLSI breakpoints

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## ABSTRACT

It has long been acknowledged that the cephalosporin breakpoints used in most European countries and the USA fail to detect many or most extended spectrum β-lactamases (ESBLs) in Enterobacteriaceae and that all ESBLs are clinically significant. Therefore, microbiological laboratories have undertaken not only regular cephalosporin susceptibility tests based on breakpoints, but also special tests to detect all ESBLs. An increasing accumulation of clinical data implies that the clinical success of third generation cephalosporin therapy is related more to the minimum inhibitory concentration (MIC) than to the presence or absence of an ESBL. However, the breakpoints must be lower than those previously recommended by many breakpoint committees. In Europe, this adjustment has been achieved by EUCAST (European Committee on Antimicrobial Susceptibility Testing) through the ongoing process of harmonising European breakpoints. In the USA, the CLSI recently voted to adopt similar guidelines but are waiting to implement these while revising other β-lactam breakpoints. As Enterobacteriaceae are becoming increasingly resistant, a less 'diehard' interpretation of the relationship among MICs, ESBLs and clinical outcome may provide therapeutic alternatives in difficult situations.

**Keywords** breakpoints, cephalosporins, CLSI, Enterobacteriacae, EUCAST, review

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Both the European Committee on Antimicrobial Susceptibility Testing (EUCAST) [1] and the Clinical Laboratory Standards Institute (CLSI) [2] in the USA have recently revised breakpoints for third-generation cephalosporins. In Europe, this was part of the ongoing European harmonisation of clinical breakpoints for all existing antimicrobials and involves the national breakpoint committees in Europe, including the CA-SFM [3] in France, the DIN [4] in Germany, the CRG [5] in The Netherlands, the NWGA [6] in Norway, the SRGA [7] in Sweden, and the BSAC Working Party on Antimicrobial Susceptibility Testing [8] in the UK. EUCAST is organised through the European Society for Clinical Microbiology and Infectious Diseases (ESCMID) [9] and is financed by ESCMID, the national breakpoint committees and a 3-year (2005–2007) grant from DG Sanco of the European Union with a 1-year extension through the European Centre for Disease Control.

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The new European cephalosporin breakpoints were finalised on 31 March 2006 (alongside those for aztreonam and carbapenems). The cephalosporins for intravenous use that were dealt with were cefuroxime, cefotaxime, ceftriaxone, ceftazidime and cefepime. In the USA, the CLSI Working Group on Enterobacteriaceae made presentations to the CLSI, and a vote was called for, during several meetings (2003–2005). However, new CLSI breakpoints will not be operative until CLSI procedures for revising breakpoints, and their legal implications, have been resolved. The breakpoints recommended by CLSI and by national breakpoint committees in Europe prior to the revision are shown in Table 1.

A major issue in both committees has been whether new clinical Enterobacteriaceae MIC breakpoints could predict clinical success and failure even without ancillary tests or whether laboratories need to continue to screen for, and confirm the presence or absence of, extended spectrum β-lactamases (ESBLs) before issuing a susceptibility report. Having reviewed the available data, both EUCAST and the CLSI concluded

**Table 1.** Cephalosporin breakpoints prior to revision

| Breakpoint committee[a] | Country | Cefuroxime S≤/R> | Cefotaxime S≤/R> | Ceftriaxone S≤/R> | Ceftazidime S≤/R> | Cefepime S≤/R> |
|---|---|---|---|---|---|---|
| BSAC | UK | 8/16 | 1/1 | 1/1 | 2/2 | 1/1 |
| CA-SFM | France | 8/32 | 4/32 | 4/32 | 4/32 | 4/32 |
| CLSI | USA | 8/16 | 8/32 | 8/32 | 8/16 | 8/16 |
| CRG | The Netherlands | 4/16 | 4/16 | 4/16 | 4/16 | NA |
| DIN | Germany | 4/8 | 2/8 | 4/16 | 4/16 | 4/16 |
| EUCAST | Europe | – | – | – | – | – |
| NWGA | Norway | 0.5/8 | 1/4 | 1/4 | 1/8 | NA |
| SRGA | Sweden | 8/8 | 0.5/1 | 0.5/1 | 2/4 | 0.5/1 |

[a]See text for abbreviations.
NA, not available.
All breakpoints, including CLSI breakpoints, are expressed as X/Y, interpreted as S ≤ X, R > Y.

that: (i) there was a need for lowering of many of the current breakpoints; and (ii) correct clinical breakpoints could obviate the need for ESBL screening for the prediction of clinical outcome, whereas both detection and characterisation would continue to be of importance for infection control and surveillance purposes.

## BREAKPOINTS NEED REVISION

The history of breakpoints has shown that initial breakpoints are often overly optimistic. Almost without exception, revisions have resulted in a lowering of the initial breakpoint. New resistance mechanisms need to be assessed, doses and indications may change, and new drugs within the class provoke a need for re-evaluation of the breakpoints of existing drugs. As tools for determining breakpoints improve, older breakpoints can be subjected to re-examination using the new tools.

The proliferation of cephalosporin breakpoints in Europe highlighted the need for revision and harmonisation in itself. Some committees felt that their existing breakpoints did not allow detection of important resistance mechanisms and did not correlate well with clinical outcome. Recent studies and compilations of clinical data suggest that clinical outcome is better correlated with the MIC value than with the presence or absence of an ESBL enzyme [10–13]. Furthermore, the screening techniques used in addition to, or as a substitute for, relevant MIC breakpoints need constant adjustments to keep up with the rapidly increasing number of β-lactamases in a rapidly rising number of species [14]. Laboratories are currently required to make sure: (i) that the MIC is equal to or below (or the equivalent zone diameter is equal to or above) the breakpoint; and (ii) that the isolate is devoid of an ESBL. Thus, despite the fact that the isolate may be characterised as susceptible according to the breakpoint, the laboratory needs to exclude the presence of a resistance mechanism. When a resistance mechanism is detected (by use of a screening test), the laboratory needs to determine whether this is an ESBL, in which case the isolate should be automatically reported as resistant to that and other cephalosporins and to penicillins and aztreonam, even though the efficacy of β-lactamase inhibitors is debated. If the ESBL test is negative, a different resistance mechanism (e.g., AmpC, impermeability) is assumed, in which case the isolate may be categorised as susceptible to that cephalosporin. However, a separate test would be required in order to report on other cephalosporins. It is not surprising that the screening for and identification of ESBLs often delay the susceptibility report by one or more days and that many laboratories find it difficult to keep up with changing and complicated recommendations. The expensive, time-consuming and no less complicated alterna-

**Table 2.** Dosages of third-generation cephalosporins relevant for EUCAST revised cephalosporin breakpoints

| | Daily dosage | | |
|---|---|---|---|
| | Low | High | Maximum (g) |
| Cefuroxime | 0.75 g × 3 | 1.5 g × 3 | 4.5 |
| Cefotaxime | 1 g × 3 | ≥2 g × 3 | 12 |
| Ceftriaxone | 1 g × 1 | ≥2 g × 1 | 4 |
| Ceftazidime | 1 g × 3 | 2 g × 3 | 6 |
| Cefepime | 1 g × 3 | 2 g × 3 | 6 |

**Table 3.** Cephalosporin breakpoints following recent EUCAST and CLSI revisions

| Breakpoint committee | Location | Cefuroxime S≤/R> | Cefotaxime S≤/R> | Ceftriaxone S≤/R> | Ceftazidime S≤/R> | Cefepime S≤/R> |
|---|---|---|---|---|---|---|
| CLSI[c] | USA | 8[a]/8 | 1/2 | 1/2 | 4/8 | 8/16 |
| EUCAST[d] | Europe | 8[a]/8 | 1/2 | 1/2 | 1/8[b] | 1/8[b] |
| EUCAST PK/PD[e] | | 4/8 | 1/2 | 1/2 | 4/8 | 4/8 |

[a]The S breakpoint for cefuroxime was adjusted—the pharmacokinetics and pharmacodynamics suggest a breakpoint of S ≤4 mg/L. To avoid dividing the cefuroxime MIC distributions of wild-type Enterobacteriaceae (Fig. 1), both committees increased the S breakpoint to 8 mg/L and suggested that the higher cefuroxime dosage be used for infections with Enterobacteriaceae (Table 2).
[b]The ceftazidime and cefepime S breakpoints were adjusted from 4 to 1 mg/L to ensure that Enterobacteriaceae with clinically important extended spectrum β-lactamases (ESBLs) were not reported as susceptible.
[c]CLSI breakpoints will not be operative until other β-lactam breakpoints have also been revised.
[d]EUCAST breakpoints (31 March 2006) will be implemented during 2007 by national breakpoint committees in Europe.
[e]EUCAST pharmacokinetic/pharmacodynamic breakpoints—as part of the EUCAST breakpoint process, EUCAST determines the theoretical breakpoint for each antimicrobial agent. This is based primarily on the pharmacokinetic and pharmacodynamic properties of the drug.
All breakpoints were expressed as S ≤ X/R > Y.

tive is to subject each isolate to a wide range of tests upon initial evaluation.

Considering all these points, cephalosporin breakpoints were subjected to independent revision by the EUCAST and the CLSI, using modern tools such as pharmacokinetic and pharmacodynamic considerations [15], modern dosing (Table 2) and the results from several compilations of clinical outcome data, all indicating that the MIC value was the important factor in predicting clinical outcome [10–13].

## THE REVISED CEPHALOSPORIN BREAKPOINTS

The revised cephalosporin breakpoints are listed in Table 3 and the doses used by EUCAST in setting the new breakpoints are listed in Table 2.

Neither committee intended for the revised breakpoints to detect all ESBL-producing isolates of Enterobacteriaceae. The breakpoints were determined as clinical breakpoints, i.e., to predict clinical outcome. However, in the majority of cases, and in comparison with the majority of the hitherto recommended breakpoints, the new breakpoints will allow detection of isolates with ESBLs [16].

Both committees recommend that, for epidemiological reasons, laboratories should continue to characterise resistance to third-generation cephalosporins. Correct species identification, detection and characterisation of resistance mechanisms and, above all, the typing of isolates have obvious roles in infection control and resistance surveillance. In addition, with the rising incidence of ESBL-producing Enterobacteriaceae in and outside hospitals, it becomes increasingly important to submit all Enterobacteriaceae isolates, not only those from cases of septicaemia, to cephalosporin susceptibility testing, and to devise alert

**Table 4.** Enterobacteriaceae epidemiological cut-off values (wild-type (WT) ≤ X mg/L) for cephalosporins (see http://www.eucast.org)

| | *Escherichia coli* WT≤ (mg/L) | *Klebsiella pneumoniae* WT≤ (mg/L) | *Klebsiella oxytoca* WT≤ (mg/L) | *Proteus mirabilis* WT≤ (mg/L) | *Citrobacter freundii* WT≤ (mg/L) | *Enterobacter* spp. WT≤ (mg/L) | *Salmonella* spp. WT≤ (mg/L) |
|---|---|---|---|---|---|---|---|
| Cefuroxime | 8 | 8 | 8 | 4 | 8 | 8–16 | 16 |
| Cefotaxime | 0.25 | 0.12 | 0.12 | 0.06 | 0.5 | 0.5 | 0.5 |
| Ceftriaxone | 0.25 | 0.12 | 0.12 | 0.06 | NA | 0.5 | NA |
| Ceftazidime | 0.5 | 0.5 | 0.5 | 0.12 | 1 | 1 | 2 |
| Cefepime | 0.12 | 0.12 | 0.12 | 0.12 | 0.12 | 0.12 | NA |

NA, not available.
Isolates with WT MIC values should be devoid of extended spectrum β-lactamases (ESBLs) or other resistance mechanisms.

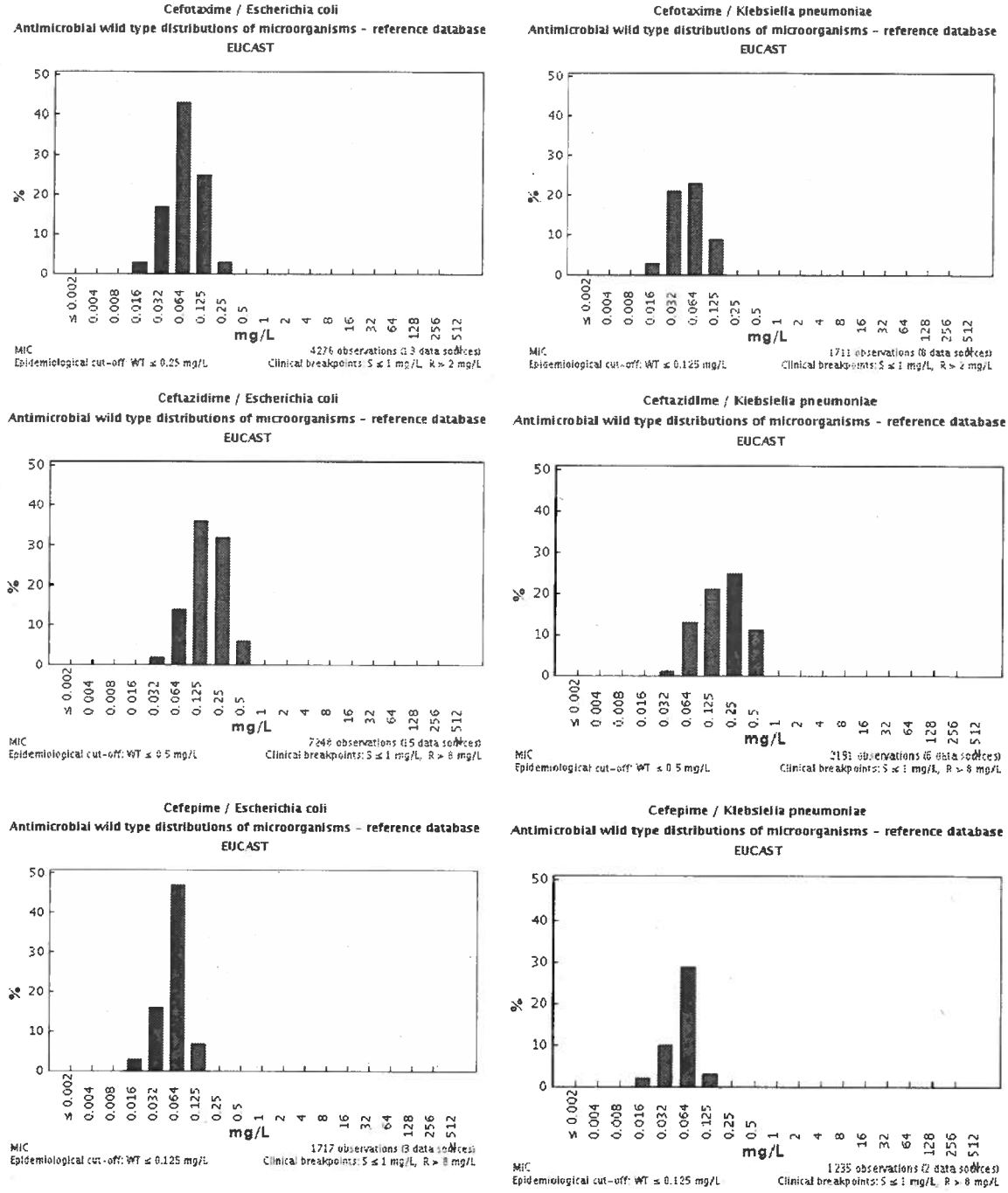


**Fig. 1.** MIC distributions for wild-type *Escherichia coli* and *Klebsiella pneumoniae* for cefotaxime (top), ceftazidime (middle) and cefepime (bottom) from the EUCAST website (http://www.eucast.org), last accessed on 28 December 2006. Epidemiological cut-off values are shown in the lower left corner and the clinical breakpoints in the lower right corner.

systems that will indicate clonal and polyclonal outbreaks of ESBL-producing Enterobacteriaceae in hospitals and the community.

The revised EUCAST cephalosporin breakpoints should ensure a clinically meaningful cephalosporin susceptibility categorisation of En-

terobacteriaceae. The frequent delay in reporting can be eliminated by recommending breakpoints that provide susceptibility categorisation without additional tests. If this is not the case, the breakpoint committees have failed.

In daily practice, the revised breakpoints will mean that if any of cefotaxime, ceftriaxone, ceftazidime or cefepime tests 'R', and no other cephalosporin tests were performed, the laboratory must report the tested cephalosporin as 'R', with a warning about the probability of other cephalosporins testing resistant. The same would apply, in the absence of other information, to a positive cefpodoxime ESBL screen test but, compared with a combination of cefotaxime and ceftazidime, this has a substantially higher percentage of 'false-positives' [17].

The issue that is now generating discussion is whether an isolate testing 'S' for one third-generation cephalosporin and 'R' for another (e.g., cefotaxime being 'R' and ceftazidime 'S') can be reported as tested, with (or even without) a warning about the possibility of an ESBL. The studies referred to earlier suggest that this is the case. Other investigators insist that there is enough evidence to the contrary. The controversy is difficult to resolve. To conduct a prospective clinical study would be difficult, and most available clinical evidence is anecdotal and/or generated with the high breakpoints and ESBL-screening strategies recommended by the CLSI. The discussion will go on for some time to come.

The EUCAST epidemiological cut-off values (Table 4, Fig. 1) offer an alternative to using cefpodoxime for sensitive screening for (and quantitation of) ESBLs in Enterobacteriaceae. Any isolate found to be outside the non-wild-type for either cefotaxime and/or ceftazidime and/or cefepime (Fig. 1) should be suspected of producing an ESBL and subjected to further analysis. Techniques to confirm and characterise ESBLs and other broad-spectrum β-lactamases are described elsewhere [18, internal reference].

To perform susceptibility testing and screening for ESBLs simultaneously, the revised EUCAST clinical breakpoints, in combination with the epidemiological cut-off values, can be used. To test *Escherichia coli* and *Klebsiella pneumoniae* (and, when relevant, *Proteus mirabilis*, *Citrobacter* spp. and *Salmonella* spp.), cefotaxime (or ceftriaxone) and ceftazidime should be used. The results, MIC values and inhibition zone diameters can be interpreted according to the clinical breakpoint and the epidemiological cut-off for each drug. The breakpoint will give the clinical susceptibility categorisation for the two cephalosporins, and the epidemiological cut-off will disclose the possible presence of an ESBL (or other resistance mechanisms). This provides, within 18–20 h, a clinical susceptibility report and a screen for ESBLs and other third-generation resistance mechanisms and allows these isolates to be subjected to further characterisation of the resistance mechanism.

In summary, an isolate with an MIC value above (or zone diameter correlate below) the epidemiological cut-off for that species should be suspected of having a resistance mechanism, which may be an ESBL. It is still controversial whether it is safe to classify isolates with MIC values below (or zone diameter correlates above) the revised EUCAST (or CLSI) clinical breakpoint as susceptible to the drug in question unless a specific ESBL-screening test has been performed. Old habits die hard, and many microbiologists will hesitate to report an *E. coli* or *K. pneumoniae* isolate as susceptible to a cephalosporin once an ESBL has been detected, even though studies show that failures are associated with cefotaxime, ceftriaxone or ceftazidime MICs of 4 mg/L or more.[12] Lowering the susceptiblity breakpoints of cefotaxime, cetriaxone, ceftazidime and cefepime to 1 mg/L should provide a wider margin of safety for those who wish to report cephalosporin susceptibilities in Enterobacteriaceae as tested. For epidemiological reasons, the revised breakpoints should be combined with screening techniques to detect ESBLs or other broad-spectrum β-lactamases [18]. However, susceptibility categorisation (S, I and R) must not be delayed by a desire to confirm and/or characterise resistance mechanisms.

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# Failure of Current Cefepime Breakpoints To Predict Clinical Outcomes of Bacteremia Caused by Gram-Negative Organisms[▽]

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**For commonly encountered gram-negative bacilli, a MIC of cefepime of 8 μg/ml or less was defined by the Clinical and Laboratory Standards Institute as "susceptible" prior to the commercial release of the antibiotic. We assessed 204 episodes of bacteremia caused by gram-negative organisms for which patients received cefepime (typically 1 to 2 g every 12 h) as the primary mode of therapy. The cefepime MIC breakpoint derived by classification and regression tree (CART) software analysis to delineate the risk of 28-day mortality was 8 μg/ml. Patients infected with gram-negative organisms treated with cefepime at a MIC of ≥8 μg/ml had a mortality rate of 54.8% (17/31 died), compared to 24.1% (35/145 died) for those treated with a cefepime MIC of <8 μg/ml. The rate of mortality for those treated with a cefepime MIC of 8 μg/ml was 56.3% (9/16 died), compared to 53.3% (8/15 died) for those treated with cefepime at a MIC of >8 μg/ml. A multivariable analysis including severity of illness indices showed that treating patients with bacteremia due to gram-negative organisms with a cefepime MIC of ≥8 μg/ml was an independent predictor of mortality ($P \leq 0.001$). There was no significant difference in outcome according to the dosage regimen utilized. Pharmacodynamic assessments that were presented previously would suggest that cefepime treatment (particularly a dosage of 1 g every 12 h) has a low probability of target attainment associated with successful in vivo outcome when the cefepime MIC is ≥8 μg/ml. It would appear reasonable, based on pharmacodynamic and clinical grounds, to lower the breakpoints for cefepime in countries where the cefepime dosage of 1 to 2 g every 12 h is the licensed therapy for serious infections, so that organisms with a cefepime MIC of 8 μg/ml are no longer regarded as susceptible to the antibiotic.**

Breakpoints for differentiating between organisms that are susceptible or resistant to antimicrobial agents are determined by several different organizations. These organizations, including the U.S. Food and Drug Administration (FDA), the Clinical and Laboratory Standards Institute (CLSI), the European Committee on Antimicrobial Susceptibility Testing (EUCAST), and various national organizations, determine breakpoints for antimicrobial susceptibility at the time an antibiotic is undergoing approval for clinical use. Such breakpoints may also be revised when microbiologic, pharmacodynamic, or clinical information suggests a medical necessity to do so. Cefepime breakpoints for gram-negative bacilli were determined prior to the drug's commercial release more than a decade ago. The current breakpoints determined by the FDA and CLSI for the cefepime MIC against infection by the *Enterobacteriaceae* family, *Pseudomonas aeruginosa*, and *Acinetobacter* spp. are ≤8 μg/ml (susceptible), 16 μg/ml (intermediate), and ≥32 μg/ml (resistant). In contrast, EUCAST breakpoints for cefepime MIC against the *Enterobacteriaceae* family are ≤1 μg/ml (susceptible), 2 to 8 μg/ml (intermediate), and >8 μg/ml (resistant); and EUCAST breakpoints for cefepime MIC against *Pseudomonas aeruginosa* are ≤8 μg/ml (susceptible) and >8 μg/ml (resistant). No EUCAST breakpoints exist for cefepime against *Acinetobacter* spp.

Given these disparities in breakpoints for such a commonly used antibiotic as cefepime, we examined the clinical outcomes of patients with bacteremia caused by gram-negative organisms (gram-negative bacteremia) treated with cefepime to determine whether current breakpoints need to be revised or harmonized.

## MATERIALS AND METHODS

**Patients.** We reviewed our hospital's clinical microbiology database to identify patients with gram-negative bacteremia. Next, we identified those patients who received cefepime as the primary mode of therapy. This mode was defined as cefepime therapy which was started within 1 calendar day of the date on which blood cultures were found to be positive. We included both those patients who received cefepime monotherapy and those who received it as a part of combination therapy. A total of 284 episodes of bacteremia from 269 patients were treated with cefepime. Secondary to a lack of MIC data, we excluded 43 episodes, leaving us with 241 episodes from 229 patients. We further excluded all episodes of patients who had concomitant bloodstream infection from a gram-positive organism or fungus. This left us with 204 analyzable episodes of gram-negative bacteremia from 197 patients.

**Microbiologic analysis.** Susceptibility testing by broth microdilution (Trek Diagnostics, OH) was performed on a routine clinical basis by the hospital's clinical microbiology laboratory, using CLSI standards (5). Cases in which a polymicrobial bloodstream infection was present, in which all organisms were gram-negative bacilli, were classified according to the isolate with the highest MIC.

**Clinical analysis.** We collected data including age, sex, presence of immunosuppression (neutropenia, history of solid-organ transplant, or AIDS), renal function (including the need for renal replacement therapy), and the source of bacteremia. The Acute Physiology and Chronic Health Evaluation (APACHE)-II score (6) was used to adjust for the severity of illness. The APACHE-II scores were stratified into quartiles in a manner that has been previously used in the literature (2).

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TABLE 1. Distribution and cefepime MICs of 204 bloodstream isolates from cefepime-treated patients

| MIC (μg/ml) | No. of isolates of: | | | | | | | | Total |
|---|---|---|---|---|---|---|---|---|---|
| | *Acinetobacter* spp. | *E. coli* | *Enterobacter* spp. | *Klebsiella* spp. | *Serratia* spp. | *P. aeruginosa* | Miscellaneous[a] | Polymicrobial[b] | |
| ≤1 | | 39 | 19 | 30 | 23 | 7 | 9 | 13 | 140 |
| 2 | 1 | 1 | 1 | 1 | | 12 | | 3 | 19 |
| 4 | | | 2 | 1 | | 7 | | 1 | 11 |
| 8 | 1 | | 1 | | 1 | 13 | | 1 | 17 |
| ≥16 | 2 | | 3 | | | 11 | | 1 | 17 |
| Total | 4 | 40 | 26 | 32 | 24 | 50 | 9 | 19 | 204 |

[a] Miscellaneous comprises *Citrobacter*, *Providencia*, and *Pantoea* spp. (one isolate from each with a MIC of ≤1 μg/ml), and *Proteus* spp. (six isolates, all with a MIC of ≤1 μg/ml).
[b] For polymicrobial infections, the highest cefepime MIC is recorded.

**Definitions.** Gram-negative bacteremia was defined as the presence of any aerobic gram-negative isolate in at least one blood culture. Cases were defined as discrete episodes of gram-negative bacteremia that were separated by at least 30 days. Polymicrobial infections were defined as those that consisted of two or more gram-negative isolates. Thus, the a priori primary endpoint was death from any cause by 28 days after the cefepime therapy was begun (2).

**Cefepime dosages.** The recommended dosages at the institution were 1 to 2 g given intravenously every 12 h, for patients with creatinine clearance of ≥50 ml/min; 1 to 2 g every 24 h, for creatinine clearance of 29 to 50 ml/min; 0.5 to 1 g every 24 h, for creatinine clearance of 10 to 29 ml/min; 250 to 500 mg every 24 h, for creatinine clearance of less than 10 ml/min; and 500 mg every 24 h, for patients on dialysis.

**Statistical analysis.** Analyses of each individual clinical outcome measure included only those cases in which a definitive endpoint could be identified. All variables were examined using PROC GENMOD (SAS software) in a univariate logistic regression. Factors that had a $P$ value of less than 0.20 in the univariate analysis were eligible for entry into a multivariable, stepwise logistic regression model. Variables with a two-sided $P$ value of $<0.05$ were considered significant.

The breakpoint in the distribution of cefepime MIC distribution was determined by classification and regression tree (CART; Salford Systems, San Diego, CA) analysis, a tool to identify breakpoints within ordinal and continuous variables where the outcome of interest is distinctly different between the resulting groups. Specifically, CART was used to identify the breakpoint in the cefepime MIC distribution that maximized the difference in 28-day mortality, thereby dividing the study population into two groups: those with a high likelihood of 28-day mortality and those with a low likelihood of 28-day mortality. Pruning and 10-fold cross-validation were used in the CART analysis to select the optimal nested subtree with the smallest misclassification cost.

## RESULTS

Analysis was performed with 197 patients with gram-negative bacteremia who were treated with cefepime. Seven patients had two episodes of bacteremia so that 204 episodes were analyzed in total. Patients treated with cefepime were infected predominantly with *P. aeruginosa* ($n$ = 50), *Escherichia coli* ($n$ = 40), *Klebsiella pneumoniae* ($n$ = 26), *Serratia marcescens* ($n$ = 24), and *Enterobacter cloacae* ($n$ = 21). Additionally, there were 24 cases of bacteremia caused by other gram-negative organisms and 19 cases of polymicrobial gram-negative organism infections (Table 1). The isolates were found to have the following MIC breakdown: 115 isolates with a MIC of ≤0.25, 11 with a MIC of 0.5, 14 with a MIC of 1, 19 with a MIC of 2, 11 with a MIC of 4, 17 with a MIC of 8, and 17 with a MIC of ≥16. The greatest number of isolates with a MIC against cefepime of ≤1 were *Escherichia coli* (39 isolates), *Klebsiella* species (30 isolates), *Serratia* species (23 isolates), and *Enterobacter* species (19 isolates). *Pseudomonas aeruginosa* was evenly distributed across the entire MIC spectrum (Table 1).

**Clinical outcome by cefepime MIC: cefepime-treated patients.** Twenty-one patients were discharged from the hospital within 28 days of culture-confirmed bloodstream infection and had no further contact with our hospital's health care system. We therefore could not analyze their outcomes at 28 days. The 28-day mortality rate for the remaining 176 patients with gram-negative bacteremia treated with cefepime was 29.5% (52/176). The rate of mortality varied by the cefepime MIC of the pathogen (Fig. 1); that is, the rate of mortality was 23.3% (27/116 died) for cefepime with a MIC of ≤1 μg/ml, 27.8% (5/18 died) with a MIC of 2 μg/ml, 27.3% (3/11 died) with a MIC of 4 μg/ml, 56.3% (9/16 died) with a MIC of 8, and 53.3% (8/15 died) with a MIC of ≥16 μg/ml.

The cefepime MIC breakpoint derived by CART analysis to delineate the risk of 28-day mortality was 8 μg/ml. Patients with cefepime MICs of ≥8 μg/ml had a twofold or greater increase in 28-day mortality over that of patients with MICs of <8 μg/ml (54.8% and 24.1%, respectively; $P$ = 0.001). The 28-day mortality rates were similar for all groups with a MIC of <8 μg/ml, and higher 28-day mortality rates were observed when the cefepime MIC was ≥8 μg/ml ($P$ = 0.001, using linear-by-linear association).

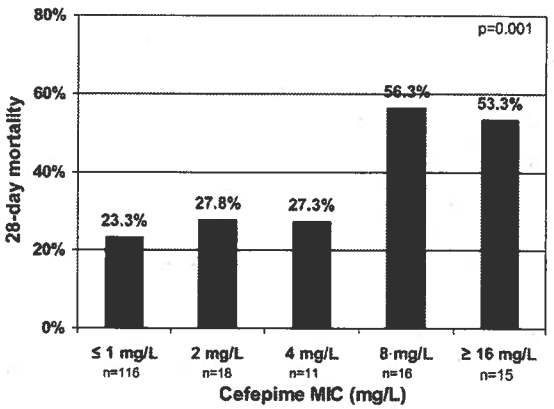


FIG. 1. Twenty-eight day mortality stratified by cefepime MIC.

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TABLE 2. Relationship between predictors of outcome and mortality at 28 days

| Patient data[a] | No. of patient deaths/total *n* (%) | *P* value | OR | 95% CI |
|---|---|---|---|---|
| Organism types | | | | |
| *E. coli* | 7/33 (21.2) | 0.25[b] | 0.6 | 0.2–1.5 |
| *P. aeruginosa* | 18/46 (39.1) | 0.10 | 1.8 | 0.9–3.7 |
| *Enterobacter* spp. | 5/23 (21.7) | 0.38 | 0.6 | 0.2–1.8 |
| *Klebsiella* spp. | 7/23 (30.4) | 0.92 | 1.05 | 0.4–2.7 |
| *Proteus* spp. | 1/4 (25) | 0.84 | 0.8 | 0.08–7.8 |
| *Serratia* spp. | 5/21 (23.8) | 0.54 | 0.7 | 0.3–2.1 |
| All others | 2/7 (28.6) | 0.95 | 0.95 | 0.2–5.1 |
| Polymicrobial | 7/19 (36.8) | 0.46 | 1.5 | 0.6–3.9 |
| APACHE-II scores | | | | |
| 3–19 | 12/85 (14.1) | | | |
| 20–24 | 10/38 (26.3) | 0.11[c] | 2.2 | 0.8–5.6 |
| 25–29 | 12/22 (54.5) | 0.0002 | 2.7 | 1.6–4.5 |
| 30–53 | 12/16 (75) | <0.0001 | 2.6 | 1.7–4.0 |
| Sources of bacteremia | | | | |
| CVC | 1/14 (7.1) | 0.09[d] | 0.2 | 0.02–1.3 |
| UTI | 5/26 (19.2) | 0.22 | 0.5 | 0.2–1.5 |
| Pneumonia | 13/34 (38.2) | 0.22 | 1.6 | 0.8–3.6 |
| Other | 2/9 (22.2) | 0.62 | 0.7 | 0.1–3.3 |
| Unknown | 31/93 (33.3) | 0.24 | 1.5 | 0.8–2.8 |
| Creatinine clearance rates | | | | |
| >100 ml/min | 4/28 (14.3) | | | |
| 60–100 ml/min | 7/41 (17.1) | 0.76[e] | 1.2 | 0.3–4.7 |
| <60 ml/min | 21/57 (36.8) | 0.039 | 3.5 | 1.1–11.5 |
| CVVHD | 12/18 (66.7) | 0.0007 | 12.0 | 2.8–50.8 |
| HD | 7/30 (23.3) | 0.28 | 2.1 | 0.6–7.9 |
| Immune status | | | | |
| Competent | 16/60 (26.7) | | | |
| Compromised | 36/116 (31) | 0.55[f] | 1.2 | 0.6–2.5 |
| Ages | | | | |
| ≤64 | 28/105 (26.7) | | | |
| ≥65 | 24/71 (33.8) | 0.31[g] | 1.4 | 0.7–2.7 |
| Modes of therapy | | | | |
| Monotherapy | 21/73 (28.8) | | | |
| Combination therapy | 31/102 (30.4) | 0.82[h] | 1.08 | 0.56–2.09 |

[a] Abbreviations: CVC, central venous catheter; UTI, urinary tract infection; CVVHD, continuous venovenous hemodialysis; HD, hemodialysis.
[b] *P* value compared to that of all other organisms.
[c] *P* value compared to that of score range 3–19.
[d] *P* value compared to that of all other sources.
[e] *P* value compared to that of creatinine clearance of >100 ml/min.
[f] *P* value compared to competent status.
[g] *P* value compared to those aged ≤64.
[h] *P* value compared to that of monotherapy.

**Other predictors of clinical outcome: univariate analysis.** Rising scores of severity of illness were highly correlated with 28-day mortality, as were renal impairment and the need for renal replacement therapy (Table 2). Specifically, those patients with an APACHE-II score of 3 to 19 had a mortality rate of 14.1%, whereas those with a score of 25 to 29 had a mortality rate of 54.5%, and those with a score of 30 to 53 had a rate of 75% (*P* values compared to 3 to 19 of 0.0002 and <0.0001, respectively). Patients who were receiving continuous renal replacement therapy had a mortality rate of 66.7% compared to 14.3% of those with a creatinine clearance of >100 ml/min ($P = 0.0007$). The univariate analysis of 28-day mortality in relation to the organism type showed that patients with bacteremia caused by *P. aeruginosa* infection had a trend toward an increased risk of dying (Table 2). There was no relationship between the organism type and the need for renal replacement therapy (data not shown). Neither age nor status of immune system was shown to be a predictor of death.

In order to determine the effect on mortality at 28 days of the use of combinations of antibiotics active against gram-negative bacilli plus cefepime, a comparison was made with monotherapy. A total of 73 patients received monotherapy with cefepime, and 102 received a combination therapy (Table 2). We found a 30.4% mortality rate with the combination therapy and a 28.8% rate with cefepime monotherapy (*P* value, 0.82; odds ratio[OR], 1.08; 95% confidence interval [CI], 0.56 to 2.09).

**Predictors of adverse clinical outcome: multivariable analysis.** In our multivariable model of predictors of 28-day mortality, we included all items that had a *P* value of ≤0.2 on the univariate analysis. This consisted of having an APACHE-II score of ≥25, a creatinine clearance of <60 ml/min, the use of continuous renal replacement therapy, a cefepime MIC of ≥8 μg/ml, a central venous line as the source of bacteremia, and an infection with *Pseudomonas aeruginosa*. We found that the use of cefepime against an isolate with a MIC of ≥8 μg/ml remained an independent risk factor for 28-day mortality ($P \leq 0.001$; adjusted OR, 8.2; 95% CI, 2.8 to 24.2). Other independent predictors of 28-day mortality on multivariable analysis included an APACHE-II score of ≥25 ($P < 0.0001$; OR, 5.9; 95% CI, 2.4 to 14.5), a creatinine clearance rate of <60 ml/min, and the use of continuous renal replacement therapy ($P = 0.009$; OR, 4.2; 95% CI, 1.4 to 11.4).

In a secondary analysis, patients with cefepime MICs of 8 and ≥16 μg/ml were included at model entry as distinct variables. Both cefepime MICs of 8 μg/ml ($P = 0.002$; adjusted OR, 9.1; 95% CI, 2.2 to 37.5) and ≥16 μg/ml ($P = 0.004$; adjusted OR, 7.5; 95% CI, 1.9 to 29.2) were independently associated with 28-day mortality when scores were adjusted for the other aforementioned univariate predictor variables.

**Outcomes of patients infected with *P. aeruginosa*.** Twenty-eight-day outcome data were available for 46 patients infected with *P. aeruginosa* as the sole bloodstream isolate. Mortality was higher from *P. aeruginosa* bacteremia treated with cefepime when isolates had a cefepime MIC of 8 μg/ml (66.7%; 8/12 died) than when isolates had a cefepime MIC of ≤4 μg/ml (20.8%; 5/24 died) ($P = 0.01$; OR = 7.6; 95% CI, 1.7 to 34.5) and higher when the mortality rate for those with a cefepime MIC of ≥8 μg/ml (59.1%; 13/22 died) was compared to that of a cefepime MIC of ≤4 μg/ml (20.8%; 5/24 died) ($P = 0.008$). Specifically, the 28-day mortality rate for patients with bacteremia due to *P. aeruginosa* infection was 33% (2/6 died) with a cefepime MIC of ≤1 μg/ml, 18% (2/11 died) with a cefepime MIC of 2 μg/ml, 14% (1/7 died) with a cefepime MIC of 4 μg/ml, 67% (8/12 died) with a cefepime MIC of 8 μg/ml, and 50% (5/10 died) with a cefepime MIC of ≥16 μg/ml. There were no differences between the proportion of patients with *P. aeruginosa* infection who received combination

therapy (52%; 26/50 died) and that of patients infected with other bacteria (61%; 93/153 died; $P = 0.32$).

**Outcomes of patients with beta-lactamase-producing *Enterobacteriaceae* infection.** Ten patients infected with organisms known to be capable of hyperproducing AmpC (e.g., *Enterobacter* and *Serratia* spp., etc.) died within 28 days of developing bacteremia. These patients had cefepime MICs of 0.25 μg/ml (nine patients) and 4 μg/ml (one patient). (One additional patient who died had a mixed infection with *Enterobacter cloacae* [a cefepime MIC of 8 μg/ml] and *Pseudomonas aeruginosa* [a cefepime MIC of 1 μg/ml]). Only one patient was infected at baseline with an organism which was resistant to ceftazidime; 0/9 patients with baseline ceftazidime MICs in the susceptible range had a documented selection of a mutant isolate resistant to ceftazidime.

Eleven patients were infected with extended-spectrum beta-lactamase (ESBL)-producing organisms (seven patients were infected with *E. cloacae*, one with *Klebsiella oxytoca*, one with *Enterobacter aerogenes*, and one with *E. coli*). A total of 5 of 10 (50%) patients for whom 28-day mortality was known died within 28 days of developing bacteremia. The cefepime MICs of the infecting organisms and patient outcomes were as follows: 2/3 died (MIC of 2 μg/ml), 2/3 died (MIC of 4 μg/ml), 1/2 died (MIC of 8 μg/ml), and 0/2 died (MIC of 16 μg/ml).

**Outcomes of patients with regard to cefepime dosing.** The dosing schedules given to patients whose infecting isolates had a MIC of 8 were 500 mg every 12 h (one patient with an unknown 28-day mortality), 1 g with dialysis (1/1 died), 1 g every 24 h (3/4 died), 2 g every 24 h (1/1 died), 1 g every 12 h (0/4 died), 2 g every 12 h (2/4 died), and 2 g every 8 h (2/2 died). No correlation was observed between dosing schedule and mortality rate in this group. However, the numbers were too limited for formal analysis. Finally, there were no significant differences in dosing regimens between patients with isolates whose MICs were less than 8, equal to 8, or greater than 16 (data not shown).

**Outcome of patients with gram-negative bacteremia treated with other antibiotics.** In order to determine whether bloodstream infection with an organism with a cefepime MIC of 8 μg/ml is in itself a marker for poor clinical outcome, we compared the outcome of patients treated with cefepime versus those treated with other antibiotics to which the bloodstream isolate was susceptible. For this comparison, we identified 53 bacteremic patients during the period January 2001 to April 2005 whose bacterial isolates showed a cefepime MIC of 8 and were treated with an antibiotic other than cefepime. We excluded cases in which the isolate was resistant to the chosen therapy or in which the isolate had no susceptibility result for the antibiotic chosen and patients who had a concomitant bloodstream infection with a gram-positive isolate or fungus. This left us with 19 cases from the same number of patients.

This study group consisted of 10 patients who were treated with either piperacillin or piperacillin-tazobactam (a piperacillin MIC of 4 μg/ml in one patient; a MIC of 32 μg/ml in seven patients; a MIC of 64 μg/ml in one patient; and one with no MIC but a disk diffusion result of susceptible), 3 who were treated with a quinolone (a ciprofloxacin MIC of 0.25 μg/ml in one patient; a levofloxacin MIC of ≤0.5 μg/ml in one patient; and a MIC of 1 μg/ml in one patient), 4 who were treated with an aminoglycoside (a tobramycin MIC of ≤1 μg/ml in two patients, an amikacin MIC of 16 μg/ml in one patient, and one with no MIC but a susceptible disk diffusion result), and 2 who were treated with a carbapenem (both with a MIC of 2 μg/ml). There were no significant differences between the population treated with cefepime and the population treated with another agent, in terms of organism type, APACHE-II scores, sources of bacteremia, creatinine clearance rates, immune status, age, or receipt of monotherapy versus combination therapy. The 28-day mortality rate was higher in those treated with cefepime (56.3%) than those treated with alternative antibiotics (38.9%), although this difference was not statistically significant ($P = 0.31$; OR, 2.0; 95% CI, 0.5 to 7.9).

## DISCUSSION

Antibiotic susceptibility breakpoints are determined typically by the integration of a variety of microbiologic, pharmacokinetic/pharmacodynamic (PK/PD), and clinical data (4). In the optimal situation, each of these data components show consistent results and strongly support a particular breakpoint. However, it is potentially naïve to think that such a situation will always occur or that all pieces of data will be both robust and consistent. This is particularly so when breakpoints are reconsidered after a particular antibiotic has been in clinical use for some years. In such a situation, new resistance mechanisms may have arisen, causing a "spread" of MICs away from wild-type distributions. Randomized clinical trials are difficult to perform after a drug has undergone requirements for registration as an approved drug. We believe that an examination of PK/PD and clinical data supports an alteration of the breakpoints for cefepime and gram-negative bacilli or a reexamination of dosing regimens of the drug, even though such data do not come from recently performed randomized trials.

Since the commercial release of cefepime, new mechanisms of antibiotic resistance have been detected. These include the production of ESBLs and metalloenzymes, many of which do hydrolyze cefepime (7, 11). While some of these organisms may have very high cefepime MICs (for example, more than 32 μg/ml), numerous examples now exist whereby such beta-lactamase-producing organisms have elevated cefepime MICs compared to that of wild-type organisms, yet the MICs are still in the susceptible range ("hidden resistance") (3, 8, 9). The CLSI currently recommends that ESBL-producing organisms be reported as resistant to cefepime. Small case series have suggested that the outcome for cefepime-treated patients is poor for serious infections with ESBL-producing organisms regardless of the MIC (10). In this study, we have too small a number to address this question specifically for ESBL producers, although mortality was substantial (50% [5/10] died).

Several studies have now assessed the PK/PD profile of cefepime and would support a change in cefepime breakpoints or an elimination of all but a dosage regimen of 2 g every 8 h for empirical therapy of serious infections. A 10,000-subject Monte Carlo simulation using published mean pharmacokinetic parameter estimates and PK/PD targets derived from a murine infection model has been presented (1). The FDA has not given a specific label for the use of cefepime in the treatment of bloodstream infections. However, for moderate to

severe pneumonia due to *P. aeruginosa*, *K. pneumoniae* or *Enterobacter* spp. infection, the recommended dosage is 1 to 2 g every 12 h; the empirical therapy for febrile, neutropenic patients is 2 g every 8 h. According to the model just described (1), the dosage regimen of 1 g of cefepime every 12 h has just a 35.9% probability of resulting in a percentage of time above a MIC of greater than 50% if the MIC is 8 μg/ml. Thus, these models would predict that a dose of 1 g every 12 h would most likely fail if the cefepime MIC is 8 μg/ml. However, this particular model would predict that a dosage regimen of 2 g every 12 h or 2 g every 8 h would have a greater than 90% probability of resulting in a percentage of time above a MIC of greater than 50% if the MIC is 8 μg/ml. In contrast, an alternative model showed a probability of the percentage of time above 50% if the MIC was 8 μg/ml of 2% for cefepime at 1 g every 12 h, 21% for 2 g every 12 h, and 88% for 2 g every 8 h (10). It would appear that the preponderance of evidence from PK/PD analyses suggests that the breakpoint of 8 μg/ml is too high for dosages of cefepime of 1 g every 12 h and quite possibly also for 2 g every 12 h.

From a clinical perspective, we have evaluated the outcome of almost 200 patients who received cefepime empirically for the treatment of gram-negative bacteremia. We found that the 28-day mortality of patients whose organisms had a MIC of 8 μg/ml (56.3%) approximated that of patients with MICs outside of the susceptible range (53.3%) and far exceeded that of patients whose organisms had a MIC of <8 μg/ml (24.1%). We chose 28-day mortality a priori as our endpoint since this was the definition in a large trial of patients with sepsis published in the *New England Journal of Medicine* (2). In order to account for important variables such as severity of illness, which may potentially confound this result, we used a multivariable analysis. This analysis showed that having a cefepime MIC of 8 μg/ml was an independent predictor of 28-day mortality in patients treated with cefepime for gram-negative bacteremia. Although 28-day mortality is widely used in other studies, a particular criticism of this endpoint is that variables other than antibiotic use may be responsible for the patient's death. In order to add another layer of rigor to our analysis, we compared outcomes of patients with bacteremia with cefepime MICs of 8 μg/ml treated with cefepime to those of patients treated with other antibiotics to which the organism was susceptible. This was done in order to exclude the hypothesis that some unforeseen variable leads to inferior outcomes for patients with bacteremia due to cefepime MICs of 8 μg/ml. If that hypothesis were correct, patients with bacteremia caused by an organism with a cefepime MIC of 8 μg/ml would have poor outcomes regardless of which antibiotic was chosen. In contrast, we found that patients infected with organisms at this MIC that were treated with alternative antibiotics had a trend toward superior outcomes compared to those treated with cefepime, suggesting that this potential hypothesis was incorrect.

Despite our rigorous clinical analysis of retrospective data, we would have preferred to have performed a prospective trial in which patients suspected of having gram-negative bacteremia were randomized to cefepime and an alternative antibiotic. Ideally, such a trial would include a pharmacokinetic analysis to determine if suboptimal cefepime "exposure" could be correlated with suboptimal clinical outcome. Unfortunately, the sample size of many hundreds of patients required to enroll sufficient patients with confirmed gram-negative bacteremia with organisms with a cefepime MIC of 8 μg/ml precludes the initiation of such a study. We are performing a more limited prospective, pharmacokinetic analysis of patients with serious gram-negative infections treated with cefepime.

In summary, our data add to the weight of data supporting a change of breakpoint for cefepime in countries where the cefepime dosage regimen of 1 to 2 g every 12 h is the licensed therapy for serious infections. First, two different PK/PD models strongly show that a cefepime dose of 1 g every 12 h has a low probability of reaching important PK/PD targets when the cefepime MIC is 8 μg/ml. It could be argued that higher doses are frequently used, but (i) some models question even the utility of 2 g every 12 h in treating organisms with a MIC of 8 μg/ml, and (ii) there are practical concerns about the communication of "dose-specific" breakpoints to prescribers. Second, our clinical data show that 28-day mortality, a widely used outcome measure in studies of sepsis, is higher in cefepime-treated patients with gram-negative bacteremia due to organisms with a cefepime MIC of 8 μg/ml than in patients infected with organisms with lower cefepime MICs. While inadequacies in this clinical study, such as its limited sample size and arbitrary outcome measures, are present, we believe the weight of data does support lowering the cefepime breakpoints so that a cefepime MIC of 8 μg/ml is no longer regarded as susceptible (if 1 to 2 g every 12 h is a licensed dosing regimen for serious infections, such as it is in the United States). We would propose that clinical data of the treatment of serious gram-negative infections with other antibiotics (for example, piperacillin-tazobactam) should also be investigated to determine if the breakpoints or dosing regimens of other commonly used antibiotics should also be changed.

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MAJOR ARTICLE

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

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***Background.*** Extended-spectrum ß-lactamase (ESBL)–producing *Enterobacteriaceae* isolates are important clinical pathogens. In addition, the efficacy of cefepime for such infections is controversial.

***Methods.*** We performed a retrospective study of monomicrobial bacteremia caused by ESBL producers at 2 medical centers between May 2002 and August 2007. The patients definitively treated with in vitro active cefepime (cases) were compared with those treated with a carbapenem (controls) in a propensity score–matched analysis to assess therapeutic effectiveness. The 30-day crude mortality is the primary endpoint.

***Results.*** A total of 178 patients were eligible for the study. Patients who received cefepime (n = 17) as definitive therapy were more likely to have a clinical failure (odds ratio [OR] 6.2; 95% confidence interval [CI], 1.7–22.5; $P = .002$), microbiological failure (OR 5.5; 95% CI, 1.3–25.6; $P = .04$), and 30-day mortality (OR 7.1; 95% CI, 2.5–20.3; $P < .001$) than those who received carbapenem therapy (n = 161). Multivariate regression revealed that a critical illness with a Pitt bacteremia score ≥4 points (OR 5.4; 95% CI, 1.4–20.9; $P = .016$), a rapidly fatal underlying disease (OR 4.4; 95% CI, 1.5–12.6; $P = .006$), and definitive cefepime therapy (OR 9.9; 95% CI, 2.8–31.9; $P < .001$) were independently associated with 30-day crude mortality. There were 17 case-control pairs in the propensity scores matched analysis. The survival analysis consistently found that individuals who received cefepime therapy had a lower survival rate (log-rank test, $P = .016$).

***Conclusions.*** Based on the current Clinical and Laboratory Standards Institute susceptible breakpoint of cefepime (minimum inhibitory concentration ≤8 μg/mL), cefepime definitive therapy is inferior to carbapenem therapy in treating patients with so-called cefepime-susceptible ESBL-producer bacteremia.

The presence of extended-spectrum β-lactamases (ESBLs) in various members of the *Enterobacteriaceae* family, particularly *Klebsiella pneumoniae* and *Escherichia coli*, is of great microbiological and clinical importance [1]. Bacteremia caused by ESBL-producing *Enterobacteriaceae* isolates compared with that caused by non-ESBL–producing isolates is associated with a delay in the institution of appropriate antimicrobial therapy [2]. The current standard of therapy for ESBL-producing organisms is a carbapenem [3, 4]. Increasingly empirical use of carbapenems in response to outbreaks of infections caused by ESBL producers has been accompanied by the rapid emergence of carbapenem resistance in nosocomial gram-negative pathogens [5]. Therapeutic options other than carbapenems, such as cefepime, would be attractive [4]. There have been anecdotal experiences of successful

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treatment of infections caused by ESBL-producing organisms with cefepime [6, 7]. However, cefepime has not been subjected to prospective randomized clinical trials to compare its efficacy and outcome with other active agents for infections caused by ESBL-producing *Enterobacteriaceae*. Because such trials present several practical challenges, the literature to date has been largely limited to observational analyses without comparators [3, 8].

Current documentation from the Clinical and Laboratory Standards Institute suggests that when using the new cephalosporin interpretive criteria for *Enterobacteriaceae*, routine testing for ESBLs is no longer necessary. However, the interpretive criteria of cefepime for *Enterobacteriaceae* remain unchanged [9]. The current susceptible breakpoint of cefepime (≤8 μg/mL) failed to identify all ESBL-producing *E. coli*, *K. pneumoniae*, or *Klebsiella oxytoca* isolates [10, 11]. The clinical role of cefepime therapy for infections caused by so-called cefepime-susceptible ESBL-producing organisms remains unclear. The aim of this study was to compare the clinical outcome of adults who have ESBL-producing *Enterobacteriaceae* bacteremia that was treated with cefepime with that of adults treated with a carbapenem.

## METHODS

### Study Design and Patients

A retrospective study among adults (age ≥18 years) with ESBL-producing *E. coli* and *K. pneumoniae* bacteremia at 2 hospitals, the National Cheng Kung University Hospital (NCKUH) in southern Taiwan and the National Taiwan University Hospital (NTUH) in northern Taiwan, was undertaken between May 2002 and August 2007 [12]. Individuals with ESBL-producing *Escherichia cloacae* bacteremia were identified from a previously described cohort at NCKUH between 2001 and 2008 [13]. If the patients experienced more than 1 bacteremic episode, only the first episode was included. The study was approved by the NCKUH Institutional Review Board. This analysis was reported using the format recommended by STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) [14].

Eligible patients fulfilled all of the following criteria: (1) clinically significant monomicrobial bacteremia demonstrated via the isolation of ESBL producer alone in blood cultures, compatible with sepsis syndrome; and (2) parenteral therapy with cefepime or a carbapenem for more than 48 hours until the end of antimicrobial therapy or death. The empirical therapy cohort (ETC) included patients who received empirical cefepime or carbapenem monotherapy, of which the first dose was administered during the first 24 hours after blood cultures had been drawn. The definitive therapy cohort (DTC) consisted of patients receiving definitive cefepime or carbapenem monotherapy if the causative isolate was in vitro–susceptible to the prescribed drug according to the current susceptible criteria of CLSI [15]. Antimicrobial therapy administered within 5 days after bacteremia onset was regarded as empirical therapy and administered afterward as definitive therapy.

In view of the differences in baseline characteristics among patients receiving cefepime and carbapenem therapy and based on the final parameter estimates in the multivariate model, a propensity score (an estimated probability of mortality) was assessed for each case. Subsequently, each patient receiving cefepime definitive therapy (the case group) was matched to a patient receiving carbapenem therapy (the control group) with a similar propensity score. A maximal difference of 5% in the likelihood of the mortality was allowed in the matching process. If there was more than 1 match with an identical propensity score, the one with a similar source of bacteremia (the initial secondary matching variable) or the closest date of bacteremia onset (the backup secondary matching variable) would have a higher priority in the matching process.

The clinical choice of antibiotics was at the discretion of the attending physician. Patients received the following intravenous doses or adjusted equivalents in cases of renal insufficiency: ertapenem (1 g every 24 hours), imipenem (0.5 g every 6 hours), meropenem (1 g every 8 hours), or cefepime (1–2 g every 8 hours; 3–6 g/day). In both hospitals, the prescriptions of carbapenems and cefepime were approved by infectious disease specialists and pharmacists for their indications and dosages.

### In Vitro Susceptibility Tests and ESBL Detection

ESBL production was detected using the phenotypic confirmatory test recommended by CLSI [9]. For *E. cloacae* isolates, the ESBL phenotype was determined using the Etest ESBL strip (AB Biodisk, Solna, Sweden) and confirmed by polymerase chain reaction and sequence analyses [13]. The minimum inhibitory concentrations (MICs) of carbapenems and cefepime were determined using the agar dilution method, and the interpretation followed the breakpoints recently recommended by CLSI in 2011 [9].

### Clinical Evaluation and Outcomes

Clinical information was retrieved from medical charts and collected in a case record form. Bacteremia was defined as the isolation of the organisms in 1 or more separately obtained blood cultures with compatible clinical features. Patients receiving cefepime or carbapenem therapy for more than 48 hours were included for assessment of outcome. The primary outcome was the crude 30-day mortality. Immunosuppression was referred to the receipt of corticosteroid (at least 10 mg or an equivalent dosage daily) for more than 2 weeks or of

antineoplastic chemotherapy or antirejection medication 4 weeks before the onset of bacteremia. The severity of underlying medical illness was stratified as being fatal, ultimately fatal, or nonfatal [16]. The severity of bacteremia was graded on the day of bacteremia onset using the Pitt bacteremia score [17].

Clinical failure was defined as follows: (1) for at least 5 days, the initial antimicrobial therapy failed to resolve sepsis symptoms or (2) signs or a fatal outcome ensued. The development of bacteremia due to the identical bacterial species with ESBL production during antimicrobial therapy for at least 72 hours was regarded as a microbiological failure.

### Statistical Analysis

Data were analyzed using the SPSS software for Windows, version 12.0. Continuous variables were expressed as mean values ± SDs and compared using the Mann-Whitney *U* test or Student *t* test. Categorical variables were expressed as percentages of total numbers of patients analyzed and compared using the Fisher exact test or $X^2$ test, as appropriate. Independent predictors for mortality were identified by means of logistic regression analysis. Variables with a *P* value of .1 or less, as determined using univariate analysis, were included in a multiple conditional logistic regression analysis. A Cox proportional hazard model was used to compare survival in both groups, adjusted for confounding variables. A *P* value less than .05 was considered statistically significant, and all tests were 2-tailed. Crude mortality rates of the 2 study groups were compared using the Kaplan-Meier curve and log-rank test.

## RESULTS

A total of 472 patients with bacteremia caused by ESBL-producing *E. coli*, *K. pneumoniae*, or *E. cloacae* were identified.

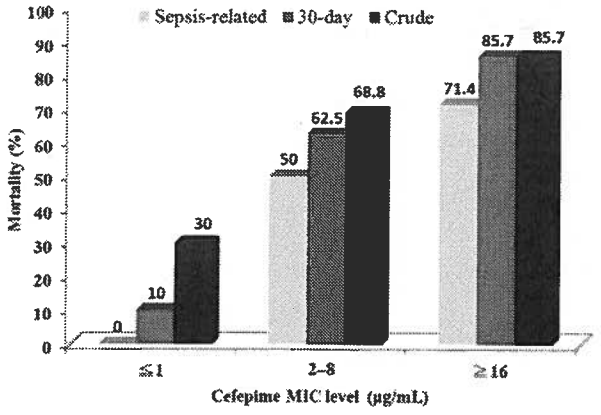


**Figure 1.** Mortality rates of 3 subgroups of patients who received cefepime therapy (n = 33) stratified by the cefepime minimum inhibitory concentration. Abbreviation: MIC, minimum inhibitory concentration.

Among them, 33 cases, including 18 cases with *E. cloacae* bacteremia, 8 with *E. coli* bacteremia, and 7 with *K. pneumoniae* bacteremia, were treated using cefepime for more than 48 hours. Of these cases, pneumonia (8 cases, 24.2%) and catheter-related infection (6 cases, 18.2%) were the major sources of infection, followed by urosepsis (6 cases, 18.2%), skin and soft infections (5 cases, 15.2%), and intraabdominal infections (2 cases, 6.0%). Eight cases had primary bacteremia. Males accounted for 57.5% (19 cases), and 36.4% (12 cases) had polymicrobial bacteremia.

The percentages of ESBL-producing isolates that were susceptible (MIC ≤8 μg/mL), intermediate (16 μg/mL), or resistance (≥32 μg/mL) to cefepime, according to CLSI 2011, were 78.8%, 9.1%, or 12.1%, respectively. Although there was a borderline significant difference in the mortality rates among 3 species (*E. cloacae*, 6/18 [33.3%]; *E. coli*, 6/8 [75.0%]; *K. pneumoniae*, 5/7 [71.4%]; *P* = .07), the proportions of cefepime-susceptible isolates varied significantly among the 3 species (18, 100% of *E. cloacae*; 4, 50.0% of *E. coli*; and 4, 57.1% of *K. pneumoniae*; *P* = .005). The mortality rate among bacteremia due to nonsusceptible *E. coli* or *K. pneumoniae* was 75% (3/4) and 100% (3/3), respectively.

Of 33 patients who received cefepime therapy, 25 (75.8%) experienced clinical failure and 13 (39.4%) died of sepsis. There was a significant increase in sepsis-related mortality because the cefepime MICs increased (*P* = .004, linear-by-linear association). The sepsis-related (*P* = .006), 30-day (*P* = .004), and crude mortality rates (*P* = .045) were lower in the causative isolates, with a MIC ≤1 μg/mL than those of other MIC categories (Figure 1).

According to our study criteria, there were 112 patients in the ETC and 178 in the DTC (Figure 2). Of those in the ETC, 21 patients were empirically treated with cefepime and 91 with a carbapenem (28 ertapenem, 13 meropenem, and 50 imipenem). Of 101 patients in the ETC, antimicrobial therapy did not change when the susceptibility results were available. However, the causative isolates from 11 patients were in vitro resistant to cefepime (4 isolates) or ertapenem (7), which were regarded as inappropriate empirical therapy. Of the ETC, the 30-day mortality rate was lower for the causative isolates, with a MIC ≤1 μg/mL (0/2, 0%) than those with other MIC categories (MIC 2–8 μg/mL: 6/15 [40%]; ≥16 μg/mL: 4/4 [100%]; *P* = .037). Mortality rates of those empirically, appropriately treated with cefepime were higher than those treated with a carbapenem, 47.1% vs 11.9% (sepsis-related mortality, *P* = .002), 58.8% vs 17.9% (30-day mortality, *P* = .001), or 64.7% vs 39.3% (crude mortality, *P* = .07).

A total of 178 patients were included in the DTC, and the 30-day mortality rate was lower in the isolates with a MIC ≤1 μg/mL (1/6, 16.7%) than those with a higher MIC (MIC 2–8 μg/mL: 5/11 [45.5%]; ≥16 μg/mL: 4/4, 100%; *P* = .035).

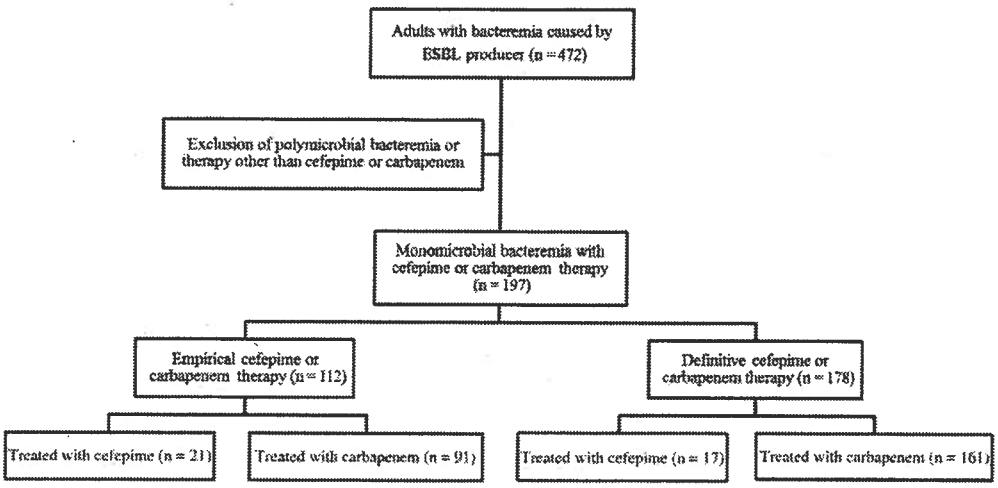


**Figure 2.** Study inclusion and exclusion criteria applied for patient identification. Abbreviation: ESBL, extended-spectrum ß-lactamase.

Seventeen patients treated with cefepime for cefepime-susceptible, ESBL-producer bacteremia were compared with 161 patients treated with a carbapenem (44 ertapenem, 25 meropenem, and 92 imipenem). There were no significant differences in terms of age, sex, comorbidity, source of bacteremia, or disease severity (Table 1). Patients who received cefepime therapy had more clinical failure (odds ratio [OR], 6.2; 95% confidence interval [CI], 1.7–22.5; $P = .002$), microbiological failure (OR, 5.5; 95% CI, 1.3–25.6; $P = .04$), and 30-day mortality (OR, 7.1; 95% CI, 2.5–20.3; $P < .001$) than those who received carbapenem therapy. However, the median hospital stay after bacteremia onset was 31 days (interquartile range [IQR], 27–55) or 30 days (IQR, 17–56), respectively, for the survivors receiving definitive cefepime or carbapenem therapy ($P = .3$).

In the multivariate analysis, definitive cefepime therapy (OR, 9.9; 95% CI, 2.8–31.9; $P < .001$), the presence of critical illness (a Pitt bacteremia score ≥4 points; OR, 5.4; 95% CI, 1.4–20.9; $P = .016$), and rapidly fatal underlying disease (OR, 4.4; 95% CI, 1.5–12.6; $P = .006$) were independently associated with 30-day mortality, after adjustment of other confounding variables (Table 2).

Seventeen patients who received definitive cefepime therapy could be matched on the basis of the propensity score. All patients were matched with less than 1% difference in their propensity score. After adjustment for confounding factors, including gender, hospital-onset bacteremia, urosepsis, rapidly fatal underlying disease, and a Pitt bacteremia score ≥4 points, cefepime treatment remained associated with a higher mortality (adjusted OR, 6.8; 95% CI, 1.5–31.2; $P = .01$; Cox regression model). The Kaplan-Meier survival analysis also revealed that the individuals who received cefepime therapy had a lower survival rate than those who received carbapenem therapy (log-rank test, $P = .016$; Figure 3). In the survivors, definitive cefepime therapy was not associated with a longer hospital stay (31 days vs 29 days; $P = .9$).

## DISCUSSION

In the present study, suboptimal clinical and microbiological outcomes were seen in patients who received cefepime therapy for bacteremia caused by ESBL-producing organisms that were apparently susceptible, according to current CLSI criteria [9]. A multivariable analysis showed that cefepime therapy was independently associated with a poor outcome. Moreover, there was an increasing risk of clinical failure and sepsis-related mortality as the cefepime MIC of the causative isolates increased. Revision of the susceptible breakpoint of cefepime to 1 μg/mL would provide a wider margin of safety. This was indicated in our subgroup analysis, which showed a favorable outcome in patients with bacteremia caused by ESBL-producing organisms with a cefepime MIC ≤1 μg/mL who were treated with cefepime.

Bhat et al warned that the current CLSI cefepime breakpoint, that is, MIC ≤8 μg/mL, might fail to predict a favorable outcome in patients with bacteremia caused by gram-negative organisms [18]. Although some organisms may have relatively high cefepime MICs in β-lactamase–producing organisms, the MICs are still in the susceptible range ("hidden resistance") [18, 19]. Because the *Enterobacteriaceae* isolates are becoming increasingly resistant, a less stringent interpretation of the relationships among MICs, ESBL producers and clinical outcome, may provide therapeutic alternatives in difficult situations [20]. It has been acknowledged that the cephalosporin breakpoints

**Table 1. Characteristics of Patients with Bacteremia Caused by Extended-Spectrum β-Lactamase–Producing Organisms Treated With Cefepime or a Carbapenem**

| Characteristic | Cefepime Group, n = 17 | Carbapenem Group, n = 161 | Matched Carbapenem Group, n = 17 | *P* Value[a] | *P* Value[b] |
|---|---|---|---|---|---|
| Age, median (IQR), years | 70 (54–82) | 70 (54–78) | 73 (45–85) | .9 | .9 |
| Gender, male | 12 (70.6) | 87 (54.0) | 8 (47.1) | .2 | .3 |
| Route of acquisition | | | | .004 | 1.0 |
| Hospital onset | 17 (100.0) | 110 (68.3) | 17 (100.0) | | |
| Community onset | 0 (0) | 51 (31.7) | 0 (0) | | |
| Length of hospital before bacteremia, median (IQR), days | 30 (7–53) | 12 (0–40) | 22 (10–63) | .07 | .7 |
| Comorbidity | | | | | |
| Diabetes mellitus | 9 (52.9) | 95 (41.6) | 10 (58.8) | .4 | 1.0 |
| Chronic kidney disease | 5 (29.4) | 58 (36.0) | 6 (35.3) | .8 | 1.0 |
| Malignancy | 3 (17.6) | 60 (37.3) | 5 (29.4) | .2 | .7 |
| Immunosuppression | 2 (11.8) | 43 (26.7) | 5 (29.4) | .3 | .4 |
| Liver cirrhosis | 4 (23.5) | 23 (14.3) | 4 (23.5) | .3 | 1.0 |
| None | 2 (11.8) | 23 (14.3) | 0 (0) | 1.0 | .5 |
| Severity of underlying disease (McCabe classification) | | | | .7 | 1.0 |
| Rapidly fatal | 1 (5.9) | 19 (11.8) | 1 (5.9) | | |
| None or nonrapidly fatal | 16 (94.1) | 142 (88.2) | 16 (94.1) | | |
| Pitt bacteremia score, ≥4 points | 12 (70.6) | 107 (66.5) | 12 (70.6) | 1.0 | 1.0 |
| Severe sepsis | 12 (70.6) | 96 (59.6) | 12 (70.6) | .4 | 1.0 |
| Source of bacteremia | | | | | |
| Vascular catheter-related infection | 5 (29.4) | 32 (19.9) | 7 (41.2) | .4 | .7 |
| Primary bacteremia | 4 (23.5) | 21 (13.0) | 3 (17.6) | .3 | 1.0 |
| Intraabdominal infection | 3 (17.6) | 25 (15.5) | 2 (11.8) | .7 | 1.0 |
| Pneumonia | 2 (11.8) | 41 (25.5) | 2 (11.8) | .4 | 1.0 |
| Skin and soft-tissue infection | 2 (11.8) | 9 (5.6) | 2 (11.8) | .3 | 1.0 |
| Urosepsis | 1 (5.9) | 38 (23.6) | 2 (11.8) | .1 | 1.0 |
| Length of hospital stay of survivor after bacteremia, median (IQR), days | 31 (27–55) | 30 (17–56) | 29 (12–54) | .3 | .9 |
| Sepsis-related mortality | 9 (52.9) | 18 (11.2) | 1 (5.9) | <.001 | .007 |
| 30-day mortality | 10 (58.8) | 27 (16.8) | 2 (11.8) | <.001 | .01 |
| Crude mortality | 11 (64.7) | 59 (36.6) | 9 (52.9) | .04 | .7 |

Data are given as numbers (percentages), unless otherwise specified.

Abbreviation: IQR, interquartile range.

[a] Crude analysis (cefepime group vs carbapenem group).

[b] Propensity score matched analysis (cefepime group vs matched carbapenem group).

used in most European countries and in the United States failed to detect all ESBLs in clinical *Enterobacteriaceae* isolates [20]. Recent studies and compilations of clinical data suggest that clinical outcome will be better correlated with the MIC values than with the presence or absence of an ESBL enzyme [1, 20–23] and that the MIC value is the important factor in predicting clinical outcome [20, 23]. Most of our patients with clinical failure under cefepime therapy were infected by the isolates with higher cefepime MICs; however, their outcomes will be more favorable if the MICs of the etiological isolates were ≤1 μg/mL.

It is not surprising that the screening and identification of ESBLs often delay the susceptibility report by 1 or more days and that many laboratories find it difficult to keep up with the changing and complicated recommendations. Our findings support the need for a shift in emphasis from a resistance-based mechanistic system to an MIC-based therapeutic outcome approach when ESBL producers have become endemic [20]. The unfavorable outcome may be related to inadequate antimicrobial efficacy in vivo [24]. It is well documented that clinical success with cefepime therapy correlates with the percentage of time that serum antibiotic

**Table 2. Multivariate Logistic Regression Analysis of Associations Between Different Variables and 30-Day Mortality in the Definitive Therapy Cohort**

| | | | Univariate Analysis | | Multivariate Analysis | |
|---|---|---|---|---|---|---|
| Variable | Survivors (n = 141) | Nonsurvivors (n = 37) | OR (95% CI) | *P* Value | OR (95% CI) | *P* Value |
| Age, years (mean ± SD) | 65.1 ± 17.1 | 69.7 ± 16.9 | ... | .15 | ... | ... |
| Male | 78 (55.1) | 21 (56.8) | 1.06 (.51–2.2) | 1.0 | ... | ... |
| Hospital-onset bacteremia | 96 (68.1) | 31 (83.8) | 2.42 (.94–6.22) | .07 | 1.46 (.47–4.48) | .51 |
| Urosepsis | 38 (27.0) | 1 (2.7) | 0.08 (.01–.57) | .001 | 0.18 (.02–1.43) | .1 |
| Pitt bacteremia score ≥4 points | 85 (60.3) | 34 (91.9) | 7.47 (2.19–25.49) | <.001 | 5.36 (1.37–20.91) | .016 |
| Rapidly fatal underlying disease | 9 (6.4) | 11 (29.7) | 6.21 (2.34–16.47) | <.001 | 4.42 (1.54–12.64) | .006 |
| Definitive therapy with cefepime | 7 (5.0) | 10 (27.0) | 7.09 (2.48–20.27) | <.001 | 9.93 (2.77–31.91) | <.001 |

Data are given as number (percentage) unless otherwise specified. Ellipses indicate not available.

Abbreviations: CI, confidence interval; OR, odds ratio; SD, standard deviation.

concentration exceeds the MIC (%T > MIC) for the infecting organism [25, 26]. Ambrose et al have suggested that the 2-g dose of cefepime every 12 hours has a high probability of achieving pharmacokinetic/pharmacodynamic (PK/PD) targets that have been previously correlated with clinical success [25]. However, clinical outcomes are contradictory for infections caused by the isolates, with MICs ranging from 2 mg/L to 8 mg/L [20, 26]. The analysis by Roos et al showed that the probability of target attainment among gram-negative organisms for which the cefepime MIC is 8 μg/mL is less than 30% when 1 g–2 g of cefepime is administered every 12 hours [27]. Otherwise, patients infected with ESBL-producing *Enterobacteriaceae*, *Pseudomonas aeruginosa*, or *Acinetobacter baumannii* had a much lower %T > MIC than patients infected with fully susceptible organisms [26]. This finding supports the concept that it is inappropriate to interpret a cefepime MIC of ≤8 mg/L as an indication of susceptibility for gram-negative organisms. Our study and several anecdotal reports revealed that patients would have therapeutic failure if cefepime were to be used for infections caused by ESBL-producing organisms [19, 21, 28]. The recommended dose of cefepime has the greatest likelihood of achieving PD targets against isolates of fully susceptible *Enterobacteriaceae* (ie, MIC ≤1 μg/mL) [25, 26], as found in our study. Furthermore, cefepime could be prescribed in prolonged or continuous infusion regimens with a greater probability of achieving the desired PK/PD targets [29].

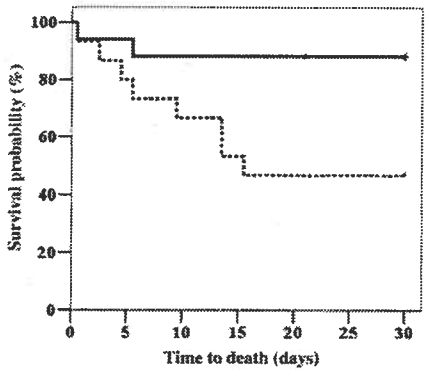


**Figure 3.** Kaplan-Meier survival analysis curves for patients with bacteremia caused by extended-spectrum ß-lactamase–producing organisms; bacteremia treated using a carbapenem (solid line) vs cefepime (broken line; log-rank test, *P* = .016).

There were no randomized controlled trials to evaluate the treatment effects of various comparator antibiotics for bacteremia caused by ESBL-producing organisms. However, if diagnostic microbiology laboratories cannot aggressively test for ESBL production, these cases of hidden resistance will go undetected by the microbiologists and clinicians, with a potential for negative consequences [18]. Currently, it is too early to consider cefepime a safe option for treating ESBL-producer infections, particularly those caused by isolates with MICs between 2 μg/mL and 8 μg/mL. Moreover, the discordance between the CLSI and EUCAST (European Committee on Antimicrobial Susceptibility Testing, http://www.eucast.org) guidelines may cause confusion among microbiologists and infectious disease specialists. With our clinical data, the role of cefepime in the treatment of ESBL-producer infections seems to be in compliance with the EUCAST guidelines, but only for infections caused by the isolates with a low MIC (≤1 μg/mL).

Our study did have several limitations. First, 3 gram-negative bacilli were unequally distributed, with a predominance of *E. cloacae* isolates. This is probably related to the clinical practice of not performing ESBL detection for bacteremic cefotaxime-resistant *E. cloacae* isolates, for which cefepime therapy often was initiated. It is unethical to conduct randomized controlled trials of cefepime therapy for infections

caused by ESBL-producing *E. coli* or *K. pneumoniae* [30]. However, the case and control groups were comparable in terms of baseline demographic characteristics and severity of illness. The difference in primary outcome between the case and control groups was statistically significant and consistent after adjusting confounding factors. Second, the outcome data on individuals with ESBL-producer bacteremia were combined for analysis. It is generally assumed that *E. coli*, *K. pneumoniae*, or *E. cloacae* behave similarly because such a combination was commonly adopted in the literature [21, 31]. Third, because only clinical data regarding the hospitalization period were available, we could only analyze the in-hospital outcome. It remains undetermined whether there is any difference in long-term outcome between the 2 study groups. Fourth, to date there is no study that suggests increasing invasiveness or lethality inherited in clinical isolates with a specific ESBL. Therefore, in our ESBL-producing isolates, molecular characterization of β-lactamases, though not done, may be of limited clinical significance.

In summary, a suboptimal clinical outcome ensues when parenteral cefepime is given for bacteremia caused by ESBL-producing organisms that are is susceptible to cefepime on the basis of the current susceptible breakpoint of CLSI. Cefepime therapy may be limited for bacteremia caused by ESBL-producing *Enterobacteriaceae* isolates with a cefepime MIC ≤1 μg/mL.

## Notes

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***Potential conflicts of interest.*** All authors: No reported conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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# Efficacy and safety of cefepime: a systematic review and meta-analysis

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**Cefepime is a broad-spectrum cephalosporin with enhanced coverage against Gram-positive and Gram-negative bacteria. We did a systematic review of randomised trials that compared cefepime with another β-lactam antibiotic, alone or with the addition of a non-β-lactam antibiotic to both study groups. We searched Central, PubMed, Embase, Lilacs, new US Food and Drug Administration drug applications, conference proceedings, and references of the included studies. Two reviewers independently did the search and data extraction. 57 trials were included. All-cause mortality—the primary outcome—was higher with cefepime than other β-lactams (risk ratio [RR] 1·26 [95% CI 1·08–1·49]). Sensitivity analyses by the trials' methodological quality revealed higher RRs for trials reporting adequate allocation-sequence generation (1·52 [1·20–1·92]) and allocation concealment (1·36 [1·09–1·70]). Baseline risk factors for mortality were similar. No significant differences between groups in treatment failure, superinfection, or adverse events were found. This Review provides evidence and offers possible explanations for increased mortality among patients treated with cefepime in randomised trials.**

## Introduction

The cephalosporins are currently among the most widely prescribed class of antibiotics in hospitals.[1] Their broad spectrum of activity both against Gram-positive and Gram-negative bacteria and a low toxicity profile contribute to their widespread use.

Cefepime is a semi-synthetic, broad-spectrum cephalosporin classified within the fourth generation class.[2,3] Compared with ceftazidime, cefepime has enhanced activity in vitro against Gram-positive bacteria, including meticillin-sensitive *Staphylococcus aureus* and *Streptococcus pneumoniae*.[4] Cefepime has better activity against Gram-negative bacteria that produce extended-spectrum β-lactamase than other commercially available oxyimino-cephalosporins.[4–7] Cefepime's superior activity is attributed to more rapid penetration into bacteria, the targeting of multiple penicillin-binding proteins, or lower affinity for several β-lactamases.[3] This drug may have a lower propensity for selection of resistant (derepressed) mutants, which results in a lower rate of resistant phenotypes during or after treatment,[8,9] although failures have been reported.[10] Cefepime is currently widely used in hospitals for its approved indications, including empirical monotherapy for febrile neutropenia, pneumonia, bacteraemia, and urinary tract, abdominal, and skin or soft-tissue infections.[1,2,11]

In a previous systematic review that assessed empirical monotherapy for febrile neutropenia, we found an increased rate of mortality with cefepime compared with other β-lactam antibiotics.[12] The cause of the increased mortality was not clear. Superinfections were more frequent with cefepime compared with other β-lactams, but the difference was not statistically significant. No differences were observed within other secondary outcomes, including treatment failure. Subgroup analyses and meta-regression did not detect an association with specific bacteria.

We therefore did a systematic review of all randomised controlled trials that compared cefepime with other β-lactam antibiotics. The primary outcome was all-cause mortality. We aimed to expand our previous analysis to all cefepime trials, including patients without neutropenia, and to systematically extract patients' baseline characteristics, adverse events, and efficacy data in the search for an explanation for the increased all-cause mortality.

## Methods

### Inclusion criteria and outcomes

We included randomised controlled trials that compared cefepime with a different β-lactam antibiotic. The addition of a non-β-lactam drug (eg, aminoglycoside) was allowed as long as the same antibiotic and dose were used in both study groups.

The primary outcome assessed was 30-day all-cause mortality. If all-cause mortality was unavailable, mortality at end of study follow-up and up to 30 days was used. Secondary outcomes were as follows: clinical failure (defined as non-resolved infection, treatment modification, or death as a result of infection); microbiological failure (defined as failure to eradicate the causative pathogens); bacterial, fungal, and any superinfections (defined as new, persistent, or worsening symptoms with or without signs of infection associated with the isolation of a new pathogen or the development of a new site of infection); and adverse events.

### Search strategy and selection criteria

We searched the Cochrane Central Register of Controlled Trials (Central), PubMed, Embase, and Lilacs databases. The search terms "cefepim*", "BMY-28142", "BMY-28142", "maxipime", "maxcef", "cepimax", "cepimex", or "axepim" were combined with the Cochrane filter for randomised controlled trials (except in Central).[13]

Unpublished trials were sought in references of all selected studies, relevant conference proceedings, trial registries and ongoing trial databases, new drug application documents of the US Food and Drug



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Administration, and through personal contact with the investigators and sponsoring pharmaceutical companies of the included studies. No language or date restrictions were imposed. The last search was done in October, 2006.

### Study selection and data extraction

Two reviewers (MP and DY, NS, or AF) independently did the search, applied inclusion criteria, and extracted the data. Outcomes were extracted preferentially by intention to treat, including all individuals randomised in the outcome assessment. If intention-to-treat data were not available, data per protocol were extracted and compared with intention-to-treat analysis through sensitivity analysis. For clinical failure, a modified intention-to-treat analysis was done by imputing failure for all dropouts. In all cases in which mortality data or randomisation methods were not reported in the primary reference, we requested the data from the investigators and the sponsor. Quality assessment was done using the individual component approach, which assessed allocation-sequence generation, allocation concealment, blinding, intention-to-treat analysis, and the number of patients excluded from the outcome assessment. Allocation concealment and generation were graded as adequate, unclear, or inadequate, by use of criteria suggested in the Cochrane handbook.[13] To assess the effect of study quality on outcomes, we did sensitivity analyses by individual components. Additionally, we compared patients' baseline characteristics that may have affected outcomes. For studies assessing patients with febrile neutropenia, we recorded age (in adults), neutrophil count, percentage of patients with acute leukaemia or bone-marrow transplantation, and percentage of patients with documented infections. For the other studies, we recorded age, temperature, percentage of patients with severe infection, and percentage with septic shock. We assigned 1 point for each risk factor to the group (cefepime *vs* comparator) in which it was more prevalent, and compiled the comparison between study groups for all trials.

### Statistical analysis

Risk ratios (RRs) and 95% CIs were calculated for individual studies. Heterogeneity in the results of the trials was assessed using the chi-squared test for heterogeneity and the $I^2$ measure of inconsistency.[14] If no heterogeneity was found, meta-analysis was done using the Mantel-Haenszel fixed-effects model (Review Manager 4.2, Nordic Cochrane Centre). RRs of less than 1·0 favour cefepime for all comparisons. Comparisons were subcategorised by the comparator antibiotic and main diagnosis (eg, pneumonia, febrile neutropenia). Subgroup analyses for mortality and clinical failure were planned for Gram-negative, Gram-positive, and *Pseudomonas* spp infections, and pneumonia. Because outcome data for most of these subgroups were not available, meta-regression analysis was done to assess the association between the percentage of these infections and individual study effect estimates (STATA 8). A funnel plot was used to assess small study effects (eg, publication bias).

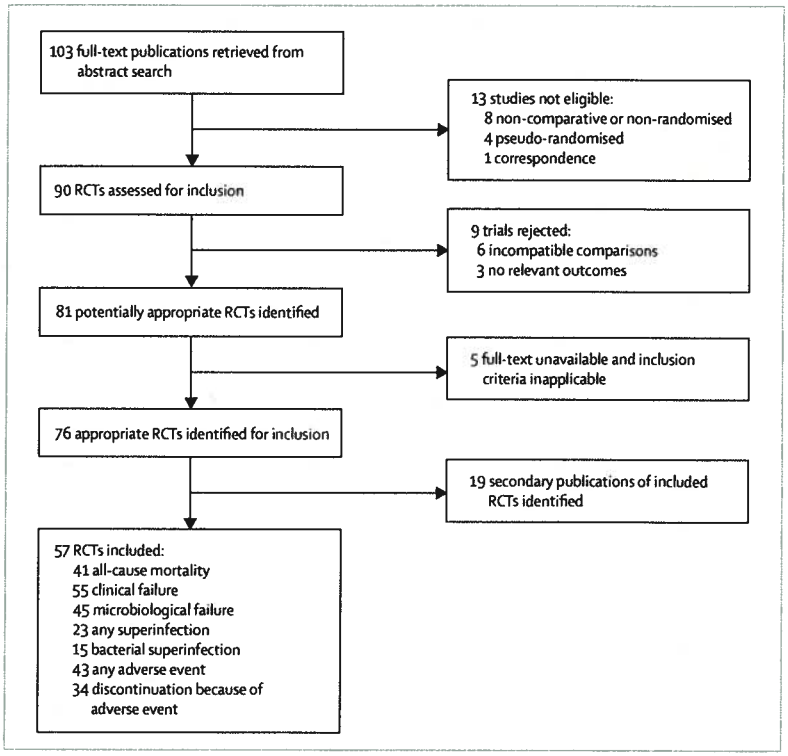


***Figure 1:*** **Trial profile**
Excluded studies and detailed reason for exclusion are shown in webtable 2. RCT=randomised controlled trial.

## Results

The trial profile is shown in figure 1. 103 publications were retrieved for full-text inspection, of which 46 were excluded. 57 randomised controlled trials that compared cefepime with a different β-lactam antibiotic were included in the Review[15–70] (webtable 1). One publication described two trials.[50] The excluded trials and reasons for exclusion are shown in webtable 2.

See Online for webtable 1 and webtable 2

The trials assessed cefepime for many different indications (webtable 1). For febrile neutropenia, cefepime was compared with ceftazidime,[15,23,26,28,32,36,43,45,51,57,67] imipenem-cilastatin or meropenem,[19,25,29,56,66] piperacillin-tazobactam,[20,22,37,61] or ceftriaxone.[30] Aminoglycosides were added to both study groups in six trials[28,30,32,37,43,61] and vancomycin in one trial.[15] For pneumonia or lower respiratory tract infections, cefepime was compared with ceftazidime,[16,18,21,31,44,47,48,50,59,60] cefotaxime,[17,27,68] ceftriaxone,[38,70] cefoperazone-sulbactam,[42] or imipenem-cilastatin.[69] Other trials that compared cefepime with ceftazidime included patients with urinary tract infections, sepsis, bacteraemia,

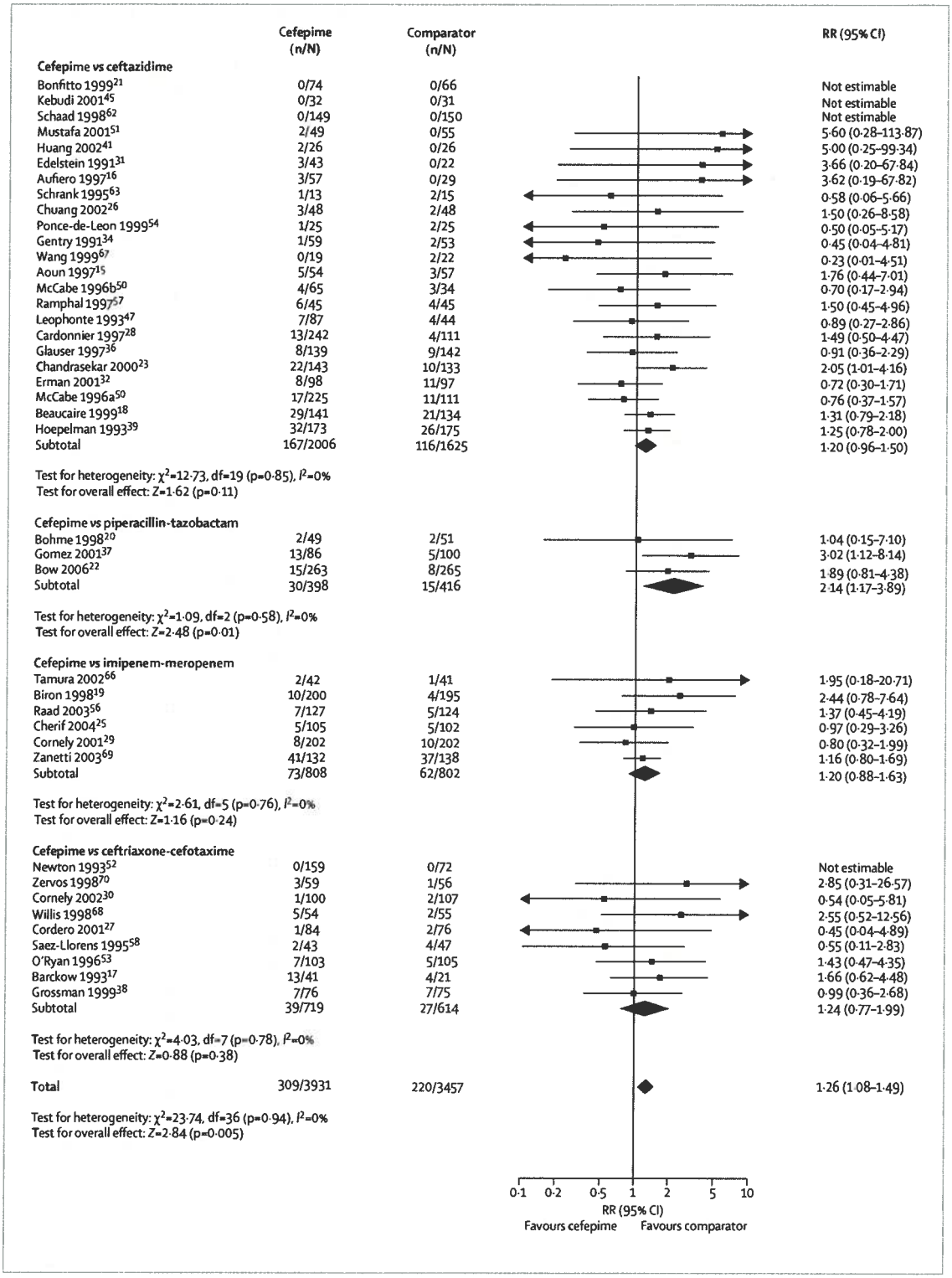


***Figure 2:*** **All-cause mortality by comparator drug**
Studies are identified by the name of the first author, year of publication, and reference. Fixed-effects meta-analysis used for estimation of combined risk ratio (RR; 95% CI). The comparison is subcategorised by the comparator antibiotic.



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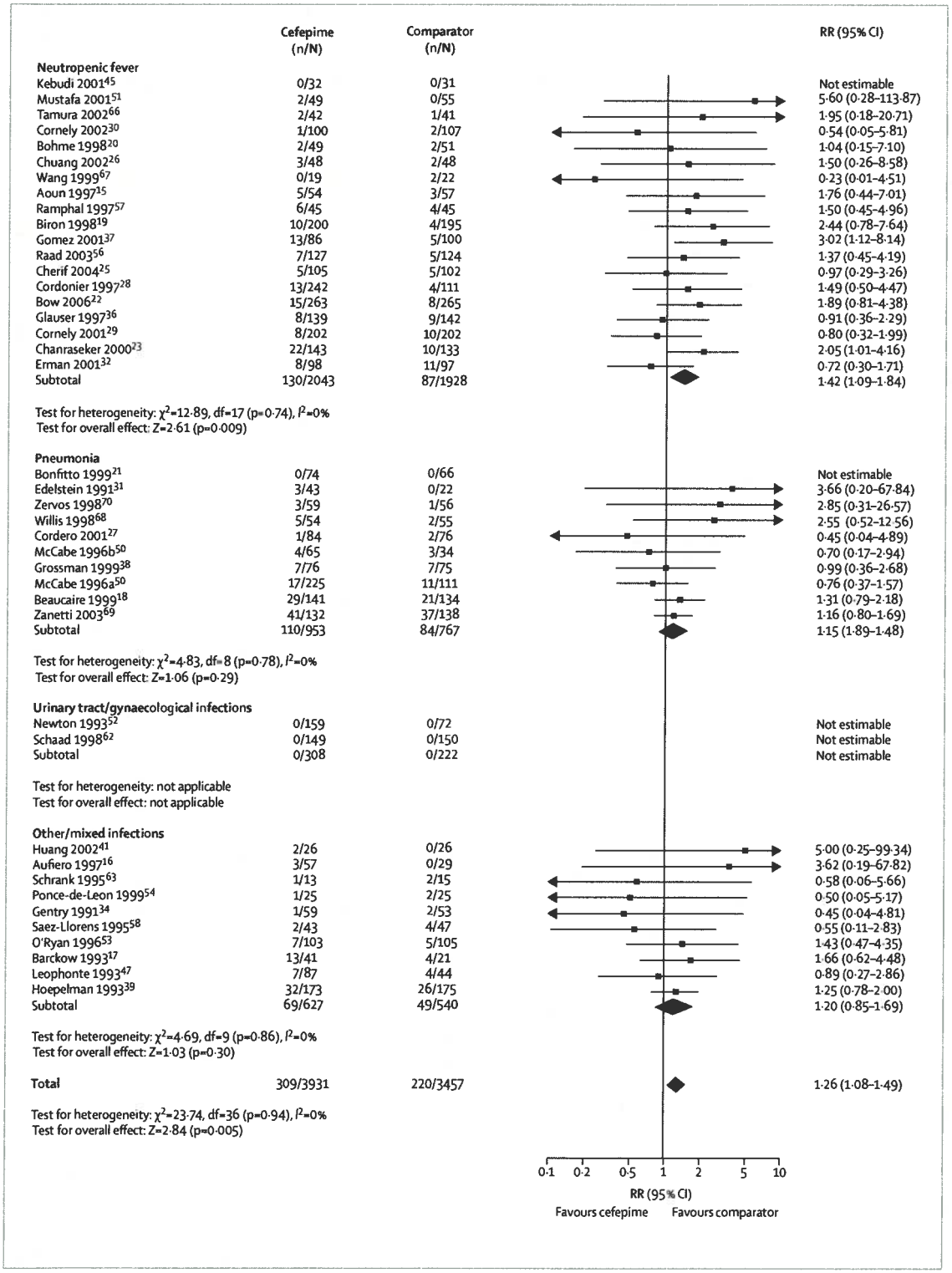


***Figure 3:*** **All-cause mortality by indication**
Studies are identified by the name of the first author, year of publication, and reference. Fixed-effects meta-analysis used for estimation of combined risk ratio (RR; 95% CI). The comparison is subcategorised by the main infectious diagnosis that defined patients for inclusion in the trial.



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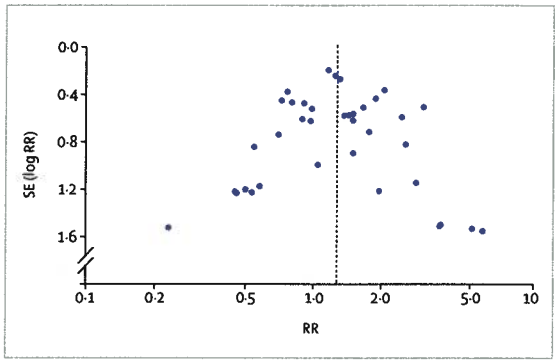


*Figure 4*: Funnel plot for all-cause mortality
A plot of the trials' precision (SE of log [risk ratio (RR)]), as a measure of trial size, against RR on a logarithmic scale. The graph shows a symmetric, inverted funnel shape. Dotted line indicates combined effect estimate.

or skin or soft-tissue infections.[24,33,34,39,40,41,46,54,55,62,63,64,65] Three trials compared cefepime with ceftriaxone or cefotaxime for children with meningitis,[49,53,58] and one trial compared cefepime with cefotaxime for gynaecological infections.[52] The full daily dose most commonly used for febrile neutropenia was 6 g and for pneumonia was 4 g, although lower doses were assessed. Overall, 11723 patients were randomised in these trials.

Adequate allocation concealment and allocation-sequence generation were described in 30 trials (webtable 3). One trial was triple blind,[23] five were double blind,[38,50,55,59,60] outcome assessors were blinded in eight trials,[18,19,29,36,51,56,62,69] and the remaining were open-label trials. The score for baseline patient risk factors did not differ significantly in trials assessing febrile neutropenia (1·12 [0·70–1·79]; 18 trials) or among other trials (1·15 [0·71–1·85]; 26 trials).

See Online for webtable 3

All-cause mortality data were available from 41 trials (webtable 3; 7388 patients).[15–23,25–32,34,36–39,41,45,47,50–54,56–58,62,63,66–70] Mortality was significantly higher for cefepime than its comparators (1·26 [1·08–1·49]; p=0·005). No significant heterogeneity was detected for the overall comparison (p=0·94, $I^2$=0%). All antibiotic comparators were associated with lower all-cause mortality (figure 2), with significance shown for piperacillin-tazobactam (2·14 [1·17–3·89]; p=0·01). All-cause mortality was higher for cefepime in all types of infections, except for the subgroup with urinary tract infections in which no deaths occurred (figure 3). The difference in all-cause mortality was significant for febrile neutropenia (1·42 [1·09–1·84]; p=0·009).

Studies of higher methodological quality were associated with greater mortality for cefepime. Studies reporting adequate allocation concealment yielded a slightly higher RR (1·36 [1·09–1·70]) than studies in which concealment was unclear (1·16 [0·91–1·47]). Similarly, studies with adequate allocation-sequence generation had higher effect estimates than those with unclear generation (1·52 [1·20–1·92] *vs* 1·07 [0·86–1·34]). Blinding and type of analysis (intention-to-treat *vs* per-protocol analysis) did not affect the results.

The proportion of patients with microbiologically documented Gram-negative and *Pseudomonas* spp infections was 17–97% and 0–40%, respectively. All-cause mortality for these subgroups of patients was not available. The association between the percentage of these infections and the studies' RRs by meta-regression analysis was not significant. Post-hoc analyses showed no significant associations between trial results and the percentage of adverse events in the cefepime group or the cefepime dose used in the study. Exclusion of studies that compared cefepime with carbapenems (of broader coverage spectrum) did not eliminate the disadvantage observed for cefepime (1·29 [1·06–1·56]). Re-analysis of all studies by use of a random-effects model gave results that were similar to the fixed-effects model (1·24 [1·05–1·46]). The funnel plot for all-cause mortality showed studies to evenly distribute within an inverse funnel shape around the combined RR (figure 4), which indicated that publication bias was unlikely.

Clinical failure was assessed in all but two trials,[29,49] and these analyses included 8911 patients. Overall, clinical failure was similar for cefepime compared with the comparator drugs (0·98 [0·93–1·03]), and for the different indications (figure 5). No significant difference was found among the subgroup of patients with pneumonia or lower respiratory tract infections (0·92 [0·82–1·04]; 2427 patients). No significant differences between cefepime and ceftazidime (0·94 [0·88–1·01]), carbapenems (0·92 [0·79–1·07]), and ceftriaxone or cefotaxime (0·92 [0·76–1·11]) were detected. Risk of clinical failure was significantly higher for cefepime versus piperacillin-tazobactam (1·09 [1·01–1·18]; p=0·04).

Studies with adequate allocation concealment yielded an RR for clinical failure of 1·01 (0·95–1·07), whereas studies of unclear concealment methods showed a non-significant advantage for cefepime (0·93 [0·86–1·01]). Results were similar for adequate allocation generation (1·00 [0·95–1·05]) and double-blinded studies (1·01 [0·82–1·23]). A modified intention-to-treat analysis included 10786 patients and yielded an RR of 0·98 (0·95–1·02).

Microbiological failure was not significantly different for cefepime compared with the comparator drugs (0·92 [0·84–1·02]; 45 trials, 4574 patients). The RR for the comparison with ceftriaxone or cefotaxime was 0·87 (0·63–1·22; 11 trials, 1023 patients).

New infections after treatment with cefepime versus comparator drugs occurred with similar frequency in both study groups (0·96 [0·79–1·17]; 23 trials, 4032 patients). Similarly, there was no significant difference overall between cefepime and comparator drugs in the comparison of documented bacterial superinfections (1·01 [0·74–1·38]; 15 trials, 2502 patients).



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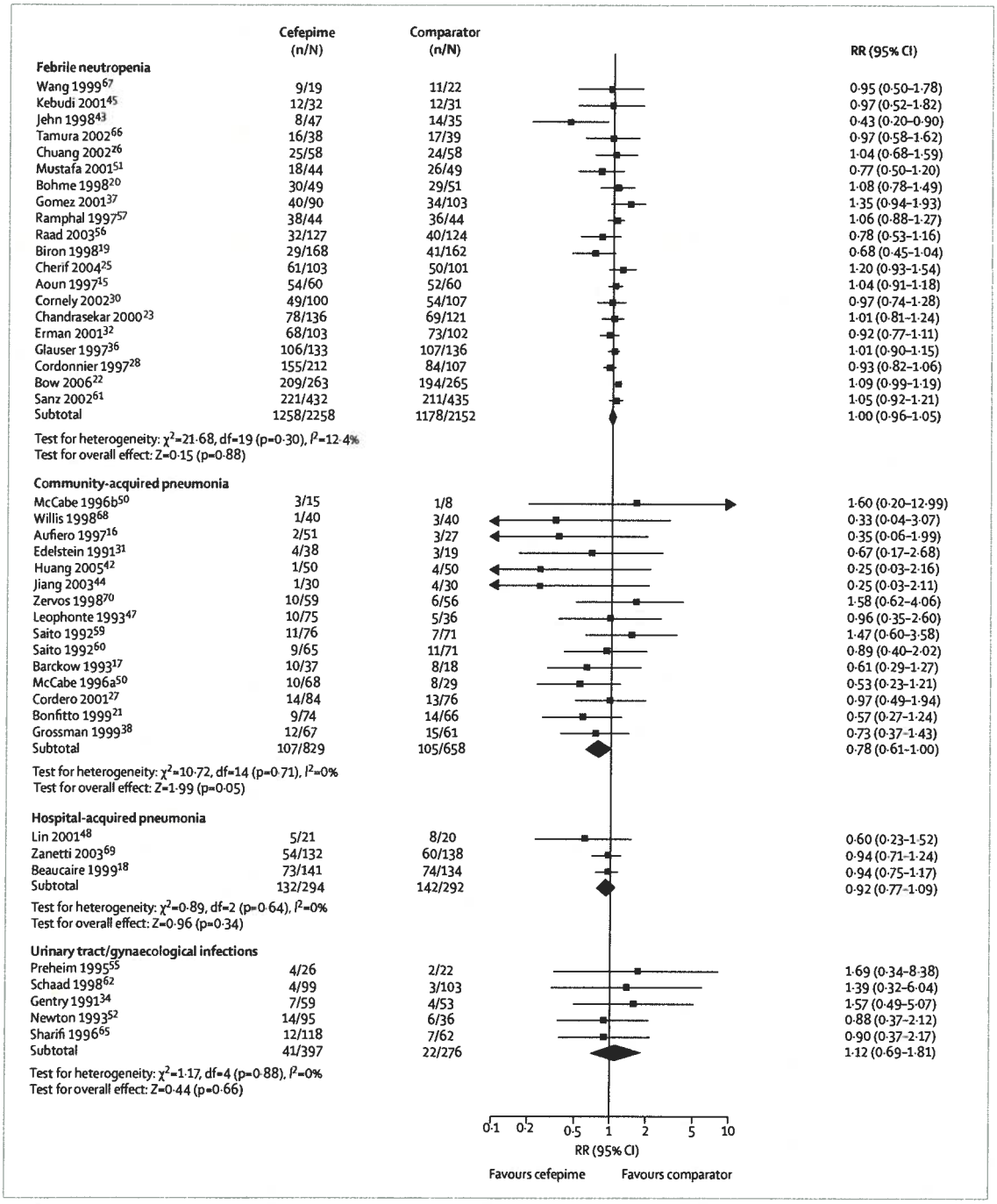


*Figure 5* **(continued on next page)**

The frequencies of any adverse event (0·99 [0·94–1·04]; 43 trials, 8806 patients) and adverse events requiring discontinuation (1·20 [0·94–1·52]; 34 trials, 7305 patients) were similar for cefepime versus comparator drugs. Neurological complications (other than headache) were reported in 19 trials[18,22,25,27,28,38–41,47,52,55,56,59–62,65,68] (1·16 [0·78–1·13]). Seizures were reported in one trial and occurred in the imipenem group.[56]

## Discussion

The objective of our systematic review was to assess the efficacy and safety of cefepime, nearly a decade after its



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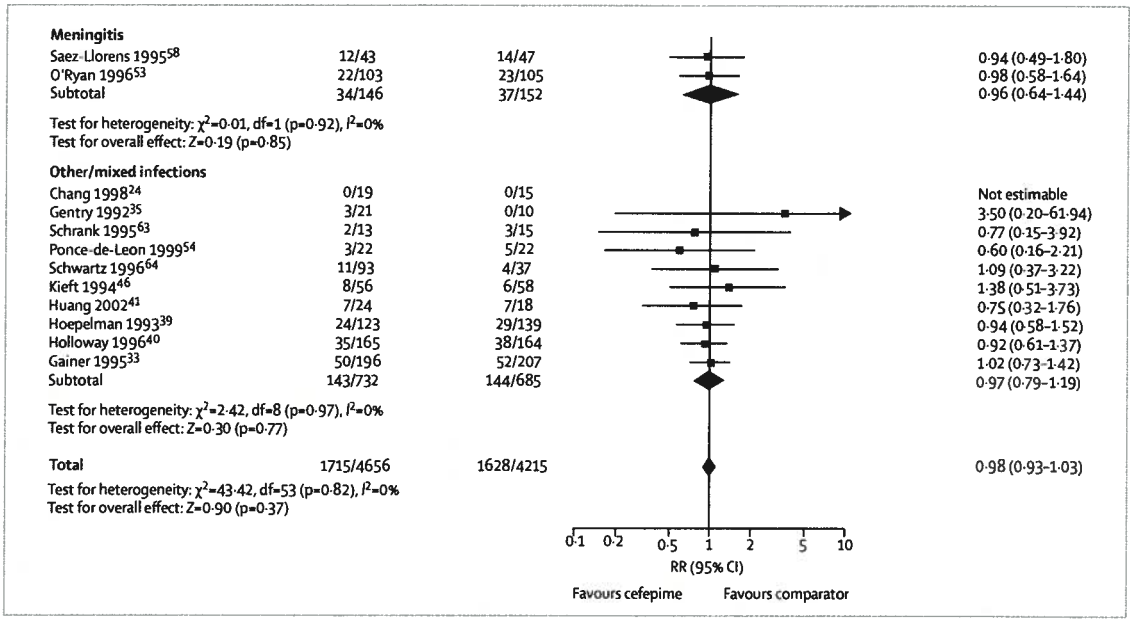


***Figure 5* (continued from previous page): Clinical failure by indication**
Studies are identified by the name of the first author, year of publication, and reference. Fixed-effects meta-analysis used for estimation of combined risk ratio (RR; 95% CI). Clinical failure is subcategorised by the main infectious diagnosis that defined patients for inclusion in the trial.

approval for clinical use.[2] We therefore compiled all randomised controlled trials that compared cefepime with a different β-lactam antibiotic. We allowed only the addition of a non-β-lactam antibiotic to both study groups, thus limiting the difference between study arms to the β-lactams compared.

We found all-cause mortality to be significantly higher with cefepime than with other β-lactams. The RR of 1·26 denotes an increase in all-cause mortality of 26%, with 95% CIs ranging from an increase of 8% to an increase of 49%. The corresponding number of patients needed to treat with comparator drugs in order to prevent one death with cefepime is 50 (33–100) patients, given a weight adjusted mortality rate in the comparator group of 5·8%. Further analyses of the mortality outcome and assessment of secondary outcomes did not reveal a specific cause for the increased mortality, nor a specific patient population at risk. Among subcategories of patients, significantly increased mortality with cefepime was seen only among neutropenic patients, but the RRs were similar for other types of patients and infections.

We selected all-cause mortality as the primary outcome because it is ultimately the most objective outcome and the main purpose of treating patients with infections. Other outcomes, such as clinical failure, are influenced by providers and outcome assessors, and may be prone to bias, especially in open trials that are assessing a novel broad-spectrum antibiotic. Even if assessed without bias, treatment failure is not a correlate of antimicrobial efficacy. Clinical failure is most often because of treatment discontinuation or modifications for various reasons by the treating physician. Microbiological eradication may represent antimicrobial efficacy more closely, but can be assessed only in the subgroup of patients with microbiologically documented infections, and does not always correlate with clinical improvement. Thus, the lack of a sensitive measure of efficacy in such trials requires all-cause mortality to be monitored and assessed.

In view of in-vitro and microbiological data from previous studies on cefepime, our results are somewhat surprising. Cefepime provides a broader spectrum of coverage in vitro than most comparator drugs assessed in these trials.[4] An advantage has also been claimed with regards to resistance induction, which should result in fewer secondary infections and better outcomes overall.[71] Therefore, how can our results be explained? A spurious finding is unlikely given the significance and homogeneity of our results. Moreover, several points support our findings on mortality. Studies of lower methodological quality tend to exaggerate spurious treatment effects.[72,73] In the case of our Review, studies of higher methodological quality were associated with the larger effect estimates. A 52% increase in mortality with cefepime was observed in studies reporting an adequate method for generation of the allocation sequence. To further assess the possibility that improper randomisation methods led to the assignment of sicker patients to the cefepime group (including studies in which randomisation methods were not reported) we compared patients' baseline characteristics. No significant differences were found. We combined studies comparing cefepime with different



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antibiotics for different infectious diagnoses. However, examination of the forest plots and formal statistical methods indicate that no evidence of heterogeneity of effect estimates was present. Finally, the funnel plot was symmetric, pointing against the existence of small study effects, such as publication bias.

We offer two possible explanations for our results. The first is an unrecognised adverse event. Recent reports have described neurotoxic effects with cefepime, including encephalopathy and non-convulsive status epilepticus, which have resulted in the addition of this adverse event in the drug application and postmarketing experience of cefepime.[74-80] Most reports involve adults with acute or chronic renal failure, but cases of encephalopathy and status epilepticus have been reported in patients with normal renal function.[81,82] Non-convulsive status epilepticus can be difficult to recognise in elderly patients, particularly if there is no history of seizures.[83] Delay in diagnosis may result in increased morbidity or mortality.[84] Therefore, increased mortality in the cefepime group might be explained by undiagnosed cases of non-convulsive status epilepticus or encephalopathy. The second possible explanation is inadequate antimicrobial efficacy in vivo. Discrepancies between results in vitro and in vivo have been described with cefepime, explained by an inoculum effect, poor tissue concentrations, or pharmacodynamic considerations that favour continuous administration of cefepime.[85-89] Randomised controlled trials are limited in their ability to assess rare and previously unrecognised outcomes. Trials of antibiotic treatment are further limited by imprecise efficacy outcome measures. Either of the possibilities may exist and should be pursued.

The main limitation of this Review is the lack of complete mortality data. All-cause mortality was not reported in all studies. We complemented published data through correspondence with the primary investigators, but did not achieve complete data for all trials. Nearly all trials that reported financial support were sponsored by Bristol-Myers Squibb, the producer of cefepime. Confronted with preliminary results from our Review, the company did not supply further data or results for unpublished trials.[90-93] We could also not determine the reasons for increased mortality in these trials. Data extraction was explicitly planned to search for its cause, given results of a previous meta-analysis.[12] We thus planned to extract data on mortality for patients with specific types of infections and pathogens, but these data were not reported.

## Conclusions

In view of the wide choice of alternative antibiotic treatments, the increased mortality observed with cefepime, whatever its reasons, should lead us to call for reconsideration of its use. Cefepime is currently recommended in several guidelines worldwide for the empirical treatment of febrile neutropenia,[94-97] severe community-acquired pneumonia,[98,99] and late-onset hospital-acquired pneumonia.[100] Interventions aimed at optimising antibiotic use in hospitals encourage the use of cefepime for these and other indications.[101-104] The new data presented in this report may necessitate a change in recommendations and in practice. Full mortality data must be obtained from all trials done to date. If mortality is indeed higher with cefepime, analysis of individual patients might clarify its reasons. Pending that, no new trials with cefepime for moderate to severe infections should be done.

**Search strategy and selection criteria**
These are described in detail in the Methods section on page 338.

**Conflict of interests**
We declare we have no conflicts of interests.

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investigation (figure 1) and 0·85 (0·81–0·89, $I^2$=95·6%) for passive case finding. Restricting pooled analysis to confirmed active tuberculosis, the pooled estimates would be 0·08 (0·05–0·12, $I^2$=93.5%) for household contact investigation and 0·92 (0·88–0·95, $I^2$=93·5%) for passive case finding. Such findings may highlight the key role of passive case finding in the control of tuberculosis.[3]

The public-health impact of household contact investigation is expected to be sustantially lower than that of passive case finding. The incubation period of tuberculosis varies from a few weeks to a few decades and household contact investigation focuses on examination at only one point of time. Additionally, most infected hosts do not develop disease. Thus, it may be more cost effective for low-income and middle-income countries to spend limited public-health resources on improving accessibility of a patient-friendly health-care infrastructure[4] and on increasing public awareness of tuberculosis, upon which passive case finding heavily relies. The feasibility of achieving the case detection target of 70% by passive case finding has been substantiated by early studies in India, which showed that 70% of people with smear-positive tuberculosis had symptoms and sought health care.[5]

In conclusion, although household contact investigation may be considered in low tuberculosis incidence, high-income countries,[6] the available evidence from meta-analysis does not favour household contact investigation in low-income and middle-income countries. The importance of improving case detection among symptomatic patients self-reporting to health services cannot be over-emphasised.[3]

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# Efficacy and safety of cefepime

A Review by Dafna Yahav and colleagues[1] found that cefepime compared with other beta-lactam antibiotics was associated with increased all-cause mortality, a difference driven by the febrile neutropenia subset of patients (risk ratio [RR] 1·26, 95% CI 1·08–1·49).

To better understand these differences and to determine if infectious or non-infectious causes impacted the mortality results, we reviewed the 19 studies comprising the neutropenic fever subset of these data. Whenever possible, the actual articles were obtained from the FDA website or through medical library holdings. Where abstracts were the only information available or data within the published literature were not adequate to answer all questions, every attempt was made to contact the original authors. Studies were specifically reviewed for data including number of deaths in each arm and causes of death.

For these 19 studies, complete cause of death information was obtained for 11 and partial cause of death information for two. These 13 studies included 64% of the all-cause neutropenic deaths in Yahav and colleagues' paper. Review of causes of death among these patients found no marked differences between cefepime and beta-lactam comparator for any infectious cause (table 1). A higher proportion of patients died secondary to progression of their underlying disease in the cefepime arm compared with the other beta-lactam arm. Furthermore, no patients were determined to have died directly as a result of receiving therapy with any agent, including cefepime (references 2–14, and personal communication with the lead author of reference 4).

| | Cefepime deaths (%) | Beta-lactam comparator deaths (%) |
|---|---|---|
| Progression of underlying disease | 27 (36) | 10 (22) |
| Invasive fungal infection | 6 (8) | 6 (14) |
| Bacterial infection | 9 (12) | 5 (11) |
| Unknown sepsis | 23 (31) | 19 (42) |
| Renal failure | 2 (3) | 0 |
| Hepatic failure | 1 (1) | 0 |
| Haemorrhage/cerebral vascular accident | 4 (6) | 3 (7) |
| Other (pulmonary embolism, heart failure, myocardial infarction) | 2 (3) | 2 (4) |
| Total | 74 | 45 |

***Table 1:*** **Causes of death for cefepime and beta-lactam antibiotic comparators[2–14]**

Yahav et al propose two explanations in their paper for increased deaths in the cefepime arm: unrecognised cases of non-convulsive status epilepticus/encephalopathy or inadequate antimicrobial effects. Our review of the available causes of death did not find unrecognised cases of non-convulsive status epilepticus/encephalopathy among the study patients. More substantial discussion of increased altered mental status would have been expected if these cases were more frequently reported; however, this was not seen. The second explanation on the potential for inadequate antimicrobial response is refuted by the authors' own statement earlier in the paper that microbiologic failure was not significantly different between the cefepime and comparator arms (RR 0·92, 95% CI 0·84–1·02).[1]

We believe that practitioners have the right and the responsibility to question and review data presented in a meta-analysis, especially if those data challenge our normal conceptions about medical practice. As evidenced by the recently released FDA memo concerning their safety review of cefepime, acquisition of the data used by Yahav and colleagues has been difficult and has yet to be completed. If a government body cannot obtain the necessary information to complete their analysis in a reasonable period of time, how is the everyday practitioner to make prescribing decisions based upon the meta-analysis?[15]

Taken without critical examination, the meta-analysis published by Yahav and colleagues seems to implicate cefepime as the cause of higher mortality compared with that among patients treated with other beta-lactam antibiotics. In an era with limited development of new antimicrobials for resistant Gram-negative organisms, agents like cefepime have a very important role. Losing cefepime as a major antimicrobial for the treatment and prophylaxis of complicated infections would have a profound impact on both pharmacy and medicine. Experience with cefepime is extensive and there is a considerable literature to support the safety and efficacy of this drug for many serious infections. We must be careful not to place too much weight on a meta-analysis without substantial biologic plausibility.

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We declare that we have no conflicts of interest.

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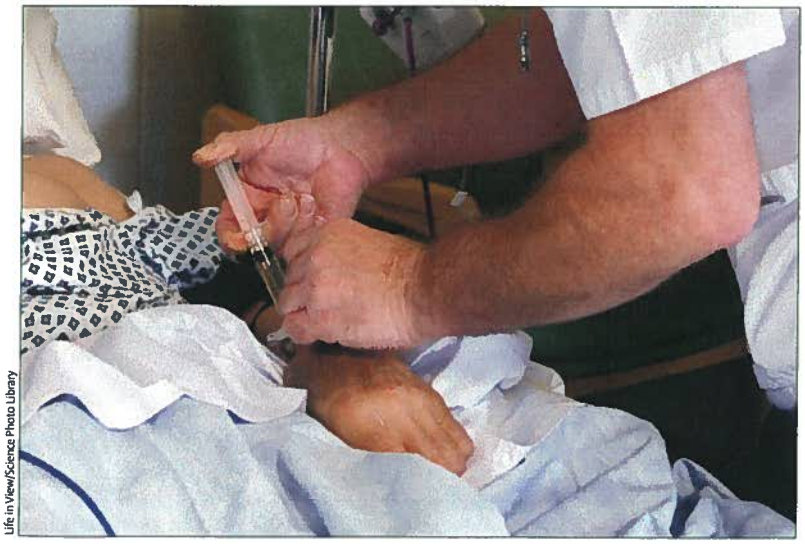
## Authors' reply

All-cause mortality is the primary outcome when assessing treatment of severe infections because it is the most objective outcome and encompasses efficacy, adverse events, and superinfections. The main purpose of treating patients with severe infections is to prevent death.

Cause-specific mortality might have delineated better differences between treatment regimens, avoiding dilution with outcomes that are unrelated to infection and its consequences. However, the cause of death cannot be established clinically in most cases. In cancer patients many causes of death commonly co-exist, including underlying malignancy, background diseases, thrombocytopenia, fungal infections, chemotherapy, and other drug-related adverse events. The final event remains mostly undiagnosed without post-mortem studies. In much less complex situations the correlation between clinical and post-mortem-established causes of death was poor.[1-3] Among patients with haematological malignancies, clinician's cause of death was reclassified by an expert panel in more than 50% of cases.[4] Infection-related mortality, frequently reported in trials of febrile neutropenia, is a subjective outcome, liable to impression and interpretation. We certainly welcome the quest for truth following our systematic review. However, clinical assessment of the cause for death is probably not the way. Rather, responsible recording of sponsored trials should provide all-cause mortality data for all trials conducted to date. All-cause mortality should be compared, accounting for the adequacy of allocation concealment and whether intention-to-treat analysis was done in the trial.



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Non-infection-related causes for death should be distributed equally between trial arms in randomised controlled trials. Trent Towne and colleagues claim that more patients treated with cefepime died due to their underlying disease. If this was true, patient allocation must have been unbalanced at baseline, since the only difference between trial arms was the antibiotic given. This can probably occur with imperfect allocation concealment in trials testing a new antibiotic. But then, where is the evidence on the efficacy and safety of cefepime?

We did not base our conclusions on the outcome of microbiological eradication, defined in the subgroup of patients with microbiologically documented infection. The outcome of microbiological eradication does not encompass all patients with the disease and the selection of patients may be biased. Within this subgroup, microbiological eradication does not well represent the outcome that is relevant to the individual patient, since adverse events and superinfections are ignored.

In summary, our Review[5] reported all-cause mortality data extracted from 41 trials including 7388 patients. All-cause mortality was significantly higher with cefepime (RR 1·26, 95% CI 1·08–1·49, p=0·005). Although we could not explain the increased mortality, considering the significance of the results and the wide variety of alternative antibiotic treatments, we believe that it is reasonable to reconsider the use of cefepime until the US Food and Drug Administration reaches a definite conclusion concerning the safety of cefepime.[6]

MAJOR ARTICLE

# Meta-Analysis of a Possible Signal of Increased Mortality Associated with Cefepime Use

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**(See the editorial commentary by Freifeld and Sepkowitz, on pages 390–391.)**

***Background.*** On the basis of meta-analyses, concern has been raised regarding a possible signal of increased mortality associated with the use of cefepime versus other β-lactam antibiotics. To further investigate this possible signal, we accessed findings and data from published and unpublished cefepime clinical trials.

***Methods.*** We performed meta-analyses using trial- and patient-level data from comparative trials. Trial-level analyses were performed using summary data from all patients in the trials, and patient-level analyses were performed on trials for which patient-level data were available. Thirty-day, all-cause mortality was analyzed using the Mantel-Haenszel adjusted risk difference (ARD) method.

***Results.*** The trial-level meta-analysis was based on 88 trials (9467 cefepime patients and 8288 comparator patients). The 30-day, all-cause mortality rates were 6.21% (588/9467) for the cefepime patients and 6.00% (497/8288) for comparator patients (ARD per 1000 population, 5.38; 95% confidence interval [CI], −1.53 to 12.28). In the patient-level analysis (35 trials, 5058 cefepime patients, and 3976 comparator patients), 30-day, all-cause mortality rates were 5.63% (285/5058) for cefepime patients and 5.68% (226/3976) for comparator patients (ARD per 1000 population, 4.83; 95% CI, −4.72 to 14.38). A sensitivity analysis based solely on the 24 febrile neutropenia trials did not show a statistically significant increase in mortality with cefepime use (ARD per 1000 population, 9.67; 95% CI, −2.87 to 22.21).

***Conclusions.*** In both trial-level and patient-level meta-analyses, we did not identify a statistically significant increase in mortality among cefepime-treated patients, compared with those treated with other antibacterials.

Cefepime was approved by the US Food and Drug Administration (FDA) in 1996 for the following indications: pneumonia (moderate to severe), uncomplicated and complicated urinary tract infections (including pyelonephritis), uncomplicated skin and skin structure infections, and complicated intra-abdominal infections. In 1997, cefepime was approved by the FDA as monotherapy for the empiric treatment of febrile neutropenia and is the only antibacterial agent approved as monotherapy for this indication in the United States. Cefepime is included as a recommended therapy in treatment guidelines for febrile neutropenia [1].

An increased risk of mortality associated with cefepime use has been reported in 2 previously published meta-analyses. Paul et al [2] published a trial-level meta-analysis in 2006 based on 17 publications reporting increased 30-day mortality with cefepime relative to other β-lactams when used for empiric antibacterial monotherapy for febrile neutropenia (risk ratio [RR], 1.44; 95% confidence interval [CI], 1.06–1.94). In 2007, the same group (Yahav et al [3]) published a trial-level meta-analysis based on 57 publications that showed increased 30-day mortality associated with cefepime, compared with other β-lactams (RR, 1.26; 95% CI, 1.08–1.49), for the following clinical conditions combined: febrile neutropenia, pneumonia, urinary tract or gynecologic infections, and other or mixed infections [3]. This finding was based on mortality data from 41 of the 57

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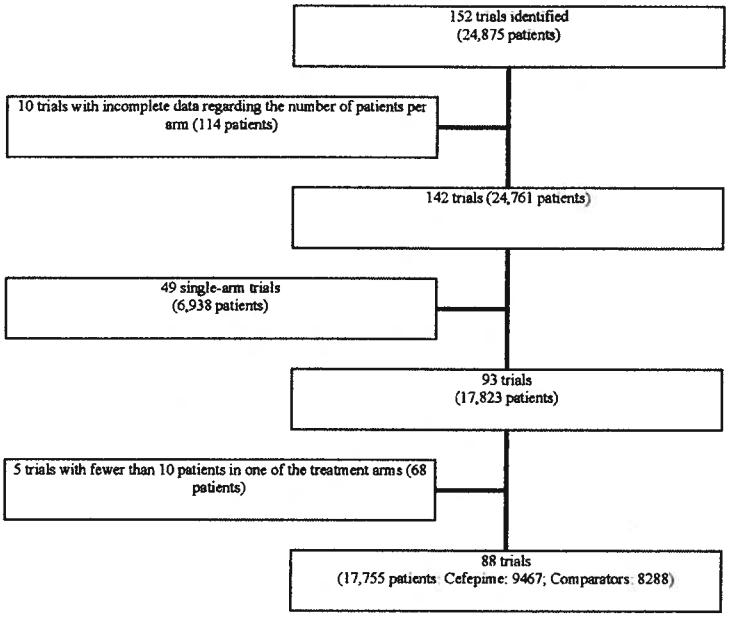


**Figure 1.** Flow diagram for the selection of trials in the trial-level analysis.

publications, because mortality data were missing from 16 publications; higher mortality rates were also noted in the subset of 19 febrile neutropenia publications (RR, 1.42; 95% CI, 1.09–1.84). The 2007 meta-analysis included 15 of the 17 cefepime publications from the 2006 meta-analysis; 2 publications were excluded because the trials were quasi-randomized.

Because of concern regarding the possible increased risk of mortality associated with cefepime use, we conducted a meta-analysis accessing both published and unpublished cefepime clinical trial data and findings. Our primary objective was to examine whether cefepime use was associated with an increased risk of mortality relative to the comparator drugs in randomized controlled trials. Our secondary objective was to examine whether the risk of mortality was associated with covariates such as clinical condition treated, comparator drug(s), and demographic and baseline risk factors (eg, presence of a microbiologically documented pathogen, baseline pathogen susceptibility, presence of renal failure, active malignant neoplasm, and bone marrow transplant). To gain a better understanding of the causes of death, including the possibility of lack of drug efficacy, we reviewed the case report forms (CRFs) of all patients who died in the febrile neutropenia trials that had previously been submitted to the FDA for registration purposes.

## METHODS

We attempted to develop a complete list of all clinical trials of cefepime encompassing all published and unpublished trials, including those not previously submitted to the FDA. We also attempted to obtain mortality data that were missing from 16 of the 57 publications included in the 2007 meta-analysis described herein [4–19]. Information gleaned from this process was used to define the set of trials included in our meta-analyses.

Both patient- and trial-level data were sought from the pharmaceutical sponsor and from the authors of the publications. Trial-level data included information by trial regarding number of patients, number of deaths, clinical condition treated, and comparator drug(s) used. In addition, the patient-level data included variables for patient and trial identification, age, sex, race, study location, and any of the following present at baseline: any pathogen recovered, all isolated pathogens susceptible to study therapy, presence of a fungal pathogen, whether an infection was monomicrobial or polymicrobial, presence of renal insufficiency or failure, active malignant neoplasm, and history of bone marrow transplantation.

Trials were characterized on the basis of level of data (patient vs trial), whether mortality data were based on the intent-to-treat (preferred due to randomization protection) or the clinically evaluable subset population, whether mortality rates were based on actual patients versus episodes of therapy (febrile neutropenia trials only), phase of trials, clinical condition treated, comparator agent(s) used, combination regimen used (if applicable), use of blinding, duration of follow-up, and inclusion in the 2007 meta-analysis.

A statistical analysis plan was developed before performing the meta-analysis. In our meta-analysis, we included the following: (1) all parallel-arm, randomized, active-controlled trials con-

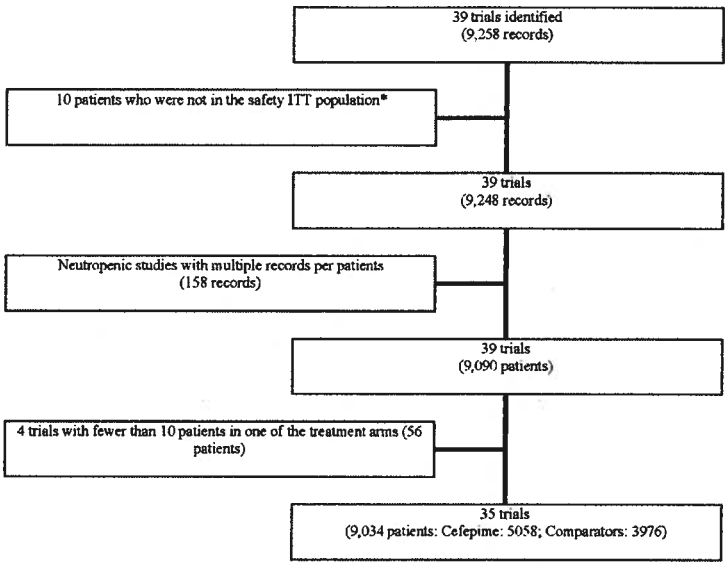


**Figure 2.** Flow diagram for the selection of trials in the patient-level analysis. *In the patient-level analysis, the safety intent-to-treat (ITT) population was defined as all patients who received at least 1 dose of study drug and whose 30-day, all-cause mortality status was known.

ducted with cefepime with or without adjunct therapy; (2) all US and non-US trials, including those not previously submitted to the FDA; and (3) trials with at least 10 patients per treatment arm. Figures 1 and 2 outline the process used to select trials included in the trial- and patient-level meta-analyses.

To include trials with no deaths in both treatment arms, meta-analysis was performed using the Mantel-Haenszel adjusted risk difference (ARD) method (Comprehensive Meta Analysis, version 2.2; BioStat), which uses a weighted average based on each trial's size and magnitude of point estimate [20]. The ARD and 95% CIs were calculated using a fixed-effects model. The primary endpoint was all-cause mortality 30-days after therapy. Several sensitivity analyses (eg, exact method for odds ratio and Cox proportional hazards model stratified by trial) were conducted to check the robustness of the findings [21]. A sensitivity analysis using a random-effects model was also performed.

The 7 comparative febrile neutropenia trials with patient-level data were reviewed in further detail to evaluate the cause(s) of death. This included the review of all CRFs from patients who died in the febrile neutropenia trials and analyses based on available clinical trial data. From these sources, we attempted to identify the most likely cause(s) of death for each patient and potential contributing factors (comorbidities, adverse events, and documented pathogens). Adverse events of special interest were identified and reviewed, including those associated with death, such as neurologic impairment or seizure, renal toxic effects, liver toxic effects, study drug failure, and central nervous system hemorrhage.

## RESULTS

***Trial-level analysis.*** Eighty-eight randomized, comparative trials, comprising 9467 cefepime-treated patients and 8288 comparator patients, were included in the trial-level analysis. Table 1 gives the number of trials and patients in each of the treatment groups by clinical condition treated. The febrile neutropenia and pneumonia trials comprised 30.7% and 22.80% of the total trial-level study population, respectively. Overall, 588 (6.21%) of 9467 cefepime-treated patients died within 30 days, compared with 497 (6.00%) of 8288 comparator patients. Meta-analysis based on these 88 trials showed no significant difference in mortality between cefepime-treated and comparator patients with an ARD per 1000 population of 5.38 (95%

**Table 1. Trials by Clinical Condition Treated in the Trial-Level Data**

| Clinical condition | No. of trials | No. (%) of patients | |
|---|---|---|---|
| | | Cefepime | Comparator |
| Febrile neutropenia | 24 | 2791 (29.48) | 2658 (32.07) |
| Intra-abdominal infection | 7 | 628 (6.63) | 470 (5.67) |
| Pneumonia | 26 | 2228 (23.53) | 1821 (21.97) |
| Urinary tract infection | 7 | 763 (8.06) | 490 (5.91) |
| Skin structure infection[a] | 2 | 335 (3.54) | 165 (1.99) |
| Other | 22 | 2722 (28.75) | 2684 (32.38) |
| Total | 88 | 9467 (100) | 8288 (100) |

[a] Not differentiated by uncomplicated versus complicated skin and skin structure infections.

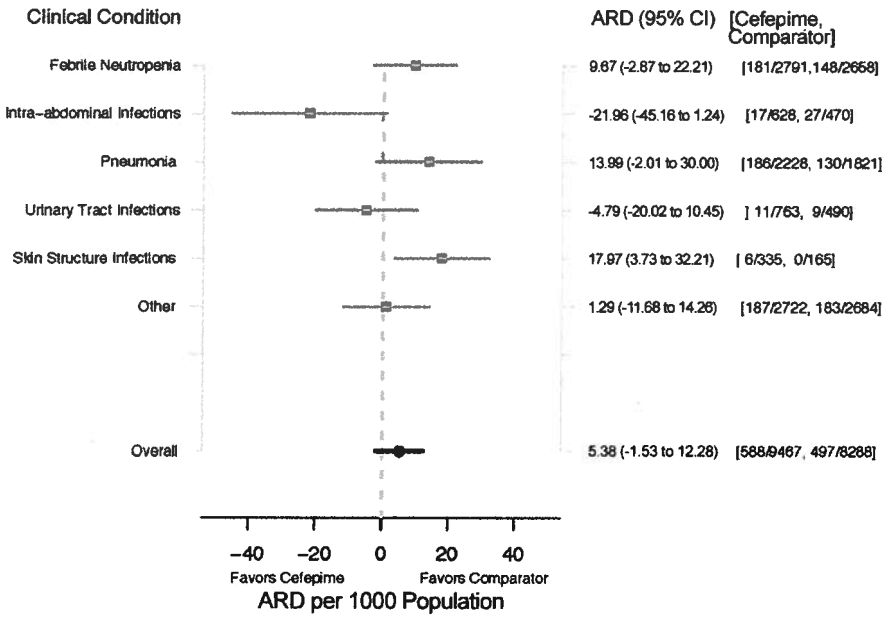


**Figure 3.** Trial-level meta-analysis (fixed-effects model) of randomized controlled trials of cefepime versus comparator in the overall population and in subgroups by the clinical condition treated. ARD, adjusted risk difference; CI, confidence interval.

CI, −1.53 to 12.28). A sensitivity analysis using a random-effects model was consistent with the primary analysis.

Figure 3 shows the ARDs per 1000 population and corresponding 95% CIs for the overall population and by the clinical conditions treated. The point estimates for mortality for the clinical conditions of febrile neutropenia, pneumonia, and skin and skin structure infections favored comparators. These were post hoc subgroup analyses, and the numbers of deaths and patients in some clinical conditions (eg, skin structure infections) were relatively small (6/335 for cefepime vs 0/165 for comparators). The point estimates for mortality for intra-abdominal infections and urinary tract infections favored cefepime.

For the subgroup analysis by comparator antibacterials, 5 groups were prespecified as follows: ceftazidime, piperacillin-tazobactam, imipenem-meropenem, ceftriaxone-cefotaxime, and "other" (eg, mezlocillin, mezlocillin-gentamicin, cefuroxime, sulbactam-cefoperazone, clindamycin-gentamicin, and amikacin). Results of this analysis are shown in Figure 4.

***Patient-level analysis.*** We were able to obtain patient-level data from 39 trials. Patient-level data from 4 of these trials were not used in the final patient-level meta-analysis per our statistical analysis plan because these trials included fewer than 10 patients in at least 1 of the treatment arms (Figure 2). Therefore, 35 randomized, comparative trials were available for the patient-level analysis, with a total of 5058 cefepime-treated patients and 3976 comparator patients.

Table 2 gives the number of trials and patients by treatment group and clinical condition treated. Patients with febrile neutropenia, intra-abdominal infection, and pneumonia were the largest groups, comprising 15.52%, 11.14%, and 10.13% of the study population, respectively. Cefepime- and comparator-treated patients were similar with respect to demographic characteristics (eg, age, sex, and race) and baseline study characteristics (eg, pathogen recovered at baseline, pathogen susceptibility, and malignant neoplasm type) (Tables 3 and 4).

Overall, 285 (5.63%) of 5058 cefepime-treated patients died within 30 days, compared with 226 (5.68%) of 3976 comparator patients. Meta-analysis of these 35 trials did not show a statistically significant increase in mortality in cefepime-treated patients (ARD per 1000 population, 4.83; 95% CI, −4.72 to 14.38). Subgroup analyses by demographic characteristics did not demonstrate significant mortality differences between cefepime- and comparator-treated patients.

Additional post hoc subgroup analyses were performed. Thirty-day, all-cause mortality in US trials with patient-level data was 4.36% (144/3299) for cefepime-treated patients and 4.70% (121/2593) for comparator patients (ARD per 1000 population, 1.59; 95% CI, −9.21 to 12.38). Thirty-day, all-cause mortality in non-US trials with patient-level data was 8.01% (141/1759) for cefepime-treated patients and 7.59% (105/1383) for comparator patients (ARD per 1000 population, 11.49; 95% CI, −6.77 to 29.75). Figure 5 displays an additional subgroup analysis for US and non-US trials according to whether the clinical condition treated was FDA approved or not.

***Febrile neutropenia trials.*** The ARD per 1000 population in the subset of 24 febrile neutropenia trials included in our

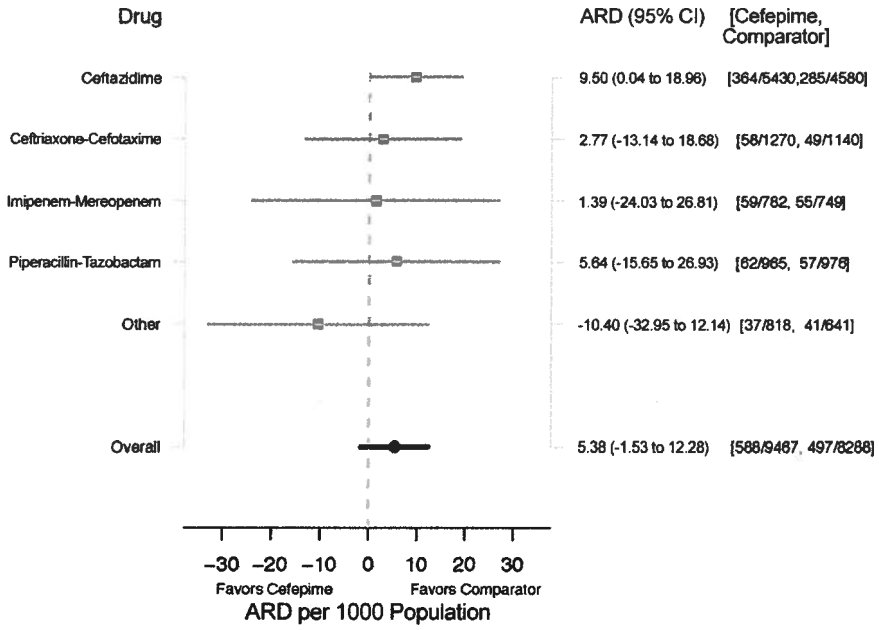


**Figure 4.** Trial-level meta-analysis (fixed-effects model) of randomized controlled trials of cefepime versus comparator, with mortality rate as a common endpoint. Figure shows the results by comparator drug. ARD, adjusted risk difference; CI, confidence interval.

trial-level meta-analysis was 9.67 (95% CI, −2.87 to 22.21). Because the Yahav et al [3] 2007 trial-level meta-analysis had reported relative risk rather than ARD per 1000 population, we estimated the ARD per 1000 population for the subset of febrile neutropenia trials (19 publications) in their meta-analysis to be 18.99 (95% CI, 4.96–33.02). Thirty-day, all-cause mortality rates for the 7 febrile neutropenia trials with patient-level data were 7.86% (61/776) for cefepime-treated patients and 6.55% (41/626) for comparator-treated patients (ARD per 1000 population, 18.10; 95% CI, −9.22 to 45.42). Exploratory subgroup analyses by baseline malignant neoplasm type showed that patients with solid tumors had greater mortality in the cefepime group, compared with comparators (ARD per 1000 population, 69.74; 95% CI, 8.13–131.35); however, the 95% CI is wide because of the low event rate and small number of patients (mortality rate, 10.45% [14/134] for cefepime and 3.70% [5/135] for comparators). No significant mortality differences were observed between cefepime and comparators for other malignant neoplasm types or baseline risk factors in the febrile neutropenia trials.

## DISCUSSION

Our analysis did not demonstrate statistically significantly higher 30-day, all-cause mortality rates in cefepime-treated patients, compared with those treated with other antibacterial drugs in randomized controlled trials. This finding was consistent in both trial-level and patient-level analyses. Although not statistically significant, the point estimates in the overall population and in several subgroups, notably the subset of febrile neutropenia trials, did not favor cefepime. The results of the subgroup analyses should be interpreted with caution given the caveats of post hoc subgroup analyses, the small numbers of patients, and the few deaths in these subgroups. On the basis of our analysis of patient-level data and CRFs, we did not identify a biologically plausible explanation for increased risk of mortality in cefepime-treated patients.

Our overall findings were not consistent with the trial-level meta-analyses published by Paul et al [2] in 2006 and Yahav et al [3] in 2007. The 41 publications in the Yahav et al [3] 2007 meta-analysis were based on 38 trials; our trial-level meta-analysis included these 38 trials plus 50 additional trials that

**Table 2. Trials by Clinical Condition Treated in the Patient-Level Data**

| Clinical condition | No. of trials | No. (%) of patients | |
|---|---|---|---|
| | | Cefepime | Comparator |
| Febrile neutropenia | 7 | 776 (15.34) | 626 (15.74) |
| Intra-abdominal infection | 5 | 585 (11.57) | 421 (10.59) |
| Pneumonia | 4 | 609 (12.04) | 306 (7.70) |
| Urinary tract infection | 4 | 426 (8.42) | 242 (6.09) |
| Skin structure infection[a] | 2 | 335 (6.62) | 165 (4.15) |
| Other | 13 | 2327 (46.01) | 2216 (55.73) |
| Total | 35 | 5058 (100) | 3976 (100) |

[a] Not differentiated by uncomplicated versus complicated skin and skin structure infections.

**Table 3. Baseline Demographic Characteristics in the Patient-Level Data**

| Characteristic | Cefepime ($n$ = 5058) | Comparator ($n$ = 3976) | Total ($n$ = 9034) |
|---|---|---|---|
| Age | | | |
| 0–17 years | 474 (9.37) | 448 (11.27) | 922 (10.21) |
| 18–54 years | 2114 (41.80) | 1547 (38.91) | 3661 (40.52) |
| 55–64 years | 820 (16.21) | 597 (15.02) | 1417 (15.69) |
| ≥65 years | 1650 (32.62) | 1384 (34.81) | 3034 (33.58) |
| Missing data | 0 | 0 | 0 |
| Mean ± SD (range), years | 49.32 ± 23.64 (0.09–100) | 49.59 ± 24.46 (0.13–101) | 49.44 ± 24.00 |
| Sex | | | |
| Female | 2299 (45.45) | 1772 (44.57) | 4071 (45.06) |
| Male | 2759 (54.55) | 2204 (55.43) | 4963 (54.94) |
| Missing data | 0 (0) | 0 (0) | 0 (0) |
| Race | | | |
| Asian | 10 (0.20) | 13 (0.33) | 23 (0.25) |
| Black | 727 (14.37) | 563 (14.16) | 1290 (14.28) |
| Hispanic | 785 (15.52) | 595 (14.96) | 1380 (15.28) |
| White | 3212 (63.50) | 2637 (66.32) | 5849 (64.74) |
| Other | 45 (0.89) | 24 (0.60) | 69 (0.76) |
| Unknown | 279 (5.52) | 144 (3.62) | 423 (4.68) |
| Region | | | |
| United States | 3299 (65.22) | 2593 (65.22) | 5892 (65.22) |
| Outside the United States | 1759 (34.78) | 1383 (34.78) | 3142 (34.78) |

**NOTE.** Data are no. (%) of patients, unless otherwise indicated. SD, standard deviation.

were not included in their analysis. These 50 trials included 5517 cefepime-treated patients and 4484 comparator-treated patients. We successfully obtained additional mortality data for 11 of 16 publications for which mortality data were not available in the 2007 Yahav et al [3] meta-analysis. Subset analysis of 38 trials included in our meta-analysis and the 2007 Yahav et al [3] meta-analysis showed an increased risk of mortality between cefepime-treated and comparator patients (ARD per 1000 population, 17.02; 95% CI, 5.54–28.50), whereas the subset analysis of the 50 trials that were included in our meta-analysis but not the Yahav et al [3] 2007 analysis did not show a statistically significant difference in mortality (ARD per 1000 population, −2.8; 95% CI, −11.47 to 5.80).

We examined the distribution of patients by clinical conditions treated to further understand the differences between the subset of 38 trials included in the Yahav et al [3] 2007 meta-analysis and the subset of 50 additional trials included only in our analysis. In the 38-trial subset (included in both the 2007 Yahav et al [3] and our meta-analyses), there was a larger proportion of patients with febrile neutropenia (53.4%), compared with 14.5% in the 50-trial subset (included only in our meta-analysis). The subset with 50 additional trials included 7 trials (628 cefepime-treated patients and 470 comparator patients) in which cefepime was evaluated for the treatment of intra-abdominal infections. The Yahav et al [3] 2007 meta-analysis did not include any intra-abdominal infection trials, probably because these trials did not meet their predefined inclusion criteria of either a $\beta$-lactam comparator alone or combination therapy that included the addition of the same antibacterial to both treatment groups [3]. We included these trials in our analyses because we were evaluating the overall risk and benefit of cefepime use across all clinical conditions. The additional 50-trial subset included 15 trials in patients with "other" infections, such as bacterial meningitis, bacterial endocarditis, and bloodstream infections (2162 cefepime-treated patients and 2122 comparator patients), accounting for 40% of the population in this data set. In contrast, in the Yahav et al [3] 2007 meta-analysis, the "other" infections category accounted for 15% of the total population (7 trials, 560 cefepime-treated patients, and 562 comparators).

Regarding the analysis of febrile neutropenia trials, the statistically significant result noted by Yahav et al [3] in their analysis of 19 febrile neutropenia publications was not observed in our meta-analysis of 24 febrile neutropenia trials. Of note, only 2 of the 19 febrile neutropenia publications included in the Yahav et al [3] 2007 trial-level meta-analysis had statistically significantly increased mortality with cefepime use [22, 23].

Other authors have explored the risk of mortality in cefepime clinical trials [23–27]. In September 2009, Gomez et al [24] noted that interim mortality data from a febrile neutropenia

**Table 4. Baseline Study Characteristics in the Patient-Level Data**

| Characteristic | Cefepime ($n$ = 5058) | Comparator ($n$ = 3976) | Total ($n$ = 9034) |
|---|---|---|---|
| Any pathogen recovered at baseline | | | |
| No | 1864 (36.85) | 1470 (36.97) | 3334 (36.91) |
| Yes | 3194 (63.15) | 2506 (63.03) | 5700 (63.09) |
| Unknown | 0 (0) | 0 (0) | 0 (0) |
| Pathogens isolated at baseline treatment (susceptible) | | | |
| No | 246 (4.86) | 180 (4.53) | 426 (4.72) |
| Yes | 2216 (43.81) | 1587 (39.91) | 3803 (42.09) |
| Unknown | 2596 (51.32) | 2209 (55.56) | 4805 (53.19) |
| Fungal pathogen recovered at baseline | | | |
| No | 4303 (85.07) | 3313 (83.32) | 7616 (84.30) |
| Yes | 133 (2.63) | 127 (3.19) | 260 (2.88) |
| Unknown | 622 (12.30) | 536 (13.48) | 1158 (12.82) |
| Baseline infection monomicrobial or polymicrobial | | | |
| Monomicrobial | 2217 (43.83) | 1665 (41.88) | 3882 (42.97) |
| Polymicrobial | 591 (11.68) | 446 (11.22) | 1037 (11.48) |
| Unknown or missing | 2250 (44.48) | 1865 (46.91) | 4115 (45.55) |
| Patient had central catheter at baseline | | | |
| No | 4374 (86.48) | 3421 (86.04) | 7795 (86.29) |
| Yes | 432 (8.54) | 319 (8.02) | 751 (8.31) |
| Unknown or missing | 252 (4.98) | 236 (5.94) | 488 (5.40) |
| Renal insufficiency or failure | | | |
| No | 2889 (57.12) | 2173 (54.65) | 5062 (56.03) |
| Yes | 1317 (26.04) | 1134 (28.52) | 2451 (27.13) |
| Unknown | 852 (16.84) | 669 (16.83) | 1521 (16.84) |
| Hepatic insufficiency or failure | | | |
| No | 4311 (85.23) | 3380 (85.01) | 7691 (85.13) |
| Yes | 6 (0.12) | 7 (0.18) | 13 (0.14) |
| Unknown | 741 (14.65) | 589 (14.81) | 1330 (14.72) |
| History of diabetes mellitus | | | |
| No | 3537 (69.93) | 2696 (67.81) | 6233 (68.99) |
| Yes | 585 (11.57) | 482 (12.12) | 1067 (11.81) |
| Unknown | 936 (18.51) | 798 (20.07) | 1734 (19.19) |
| Active cancer or malignant neoplasm (febrile neutropenic patients only) | | | |
| Solid tumor | 134 (2.65) | 135 (3.40) | 269 (2.98) |
| Hematologic malignant neoplasm | 544 (10.76) | 391 (9.83) | 935 (10.35) |
| Unknown or NA | 4380 (86.60) | 3450 (86.77) | 7830 (86.67) |
| Bone marrow transplantation (febrile neutropenic patients only) | | | |
| No | 400 (7.91) | 311 (7.82) | 711 (7.87) |
| Yes | 179 (3.54) | 128 (3.22) | 307 (3.40) |
| Unknown or NA | 4479 (88.55) | 3537 (88.96) | 8016 (88.73) |
| History of COPD | | | |
| No | 4461 (88.20) | 3548 (89.24) | 8009 (88.65) |
| Yes | 192 (3.80) | 159 (4.00) | 351 (3.89) |
| Unknown | 405 (8.01) | 269 (6.77) | 674 (7.46) |

**NOTE.** Date are no. (%) of patients. COPD, chronic obstructive pulmonary disease; NA, not applicable.

trial that they presented at a conference in 2001 were included in the Yahav et al [3] 2007 meta-analysis. In this trial, patients were randomized to receive either 2 g of cefepime every 12 h or 4 g of piperacillin-tazobactam every 8 h (both arms also received amikacin) [23]. Although, in the interim analysis, a statistically significantly higher mortality rate was seen in cefepime-treated patients, in their final analysis, no difference in 28-day, all-cause mortality was noted (7.8% [15/190] in the

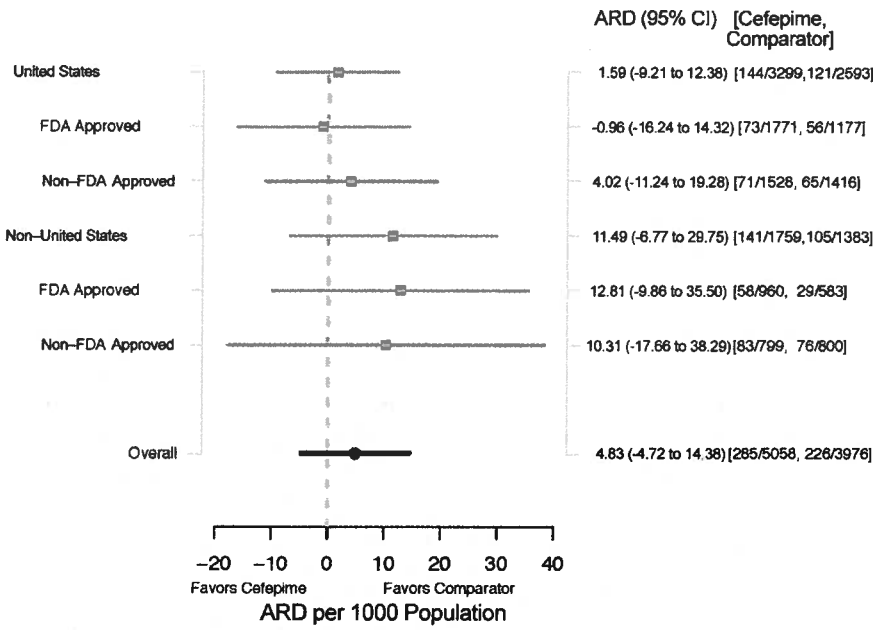


**Figure 5.** Subgroup analysis for US and non-US patients based on whether the clinical condition treated was approved by the Food and Drug Administration (FDA). ARD, adjusted risk difference; CI, confidence interval.

cefepime arm and 8.9% [17/190] in the piperacillin-tazobactam arm) [24]. Towne et al [25] reanalyzed mortality information from the 19 febrile neutropenia publications included in the 2007 Yahav et al [3] meta-analysis and were able to obtain information on the causes of death from 13 of these publications. They found no marked differences for infectious causes of death between cefepime-treated and comparator patients. They determined that none of the deaths were attributable to the antibacterial therapy administered and that more cefepime-treated patients died due to progression of underlying disease. In a retrospective cohort study of pediatric patients with acute myelogenous leukemia, Fisher et al [26] evaluated exposure to cefepime, ceftazidime, antipseudomonal penicillins, or carbapenems within the first year from acute myelogenous leukemia diagnosis. They found that cefepime exposure did not result in greater risk for in-hospital mortality when compared with other commonly used $\beta$-lactam antibacterials.

The strengths of our analysis included the following. First, because we were able to access data and results from unpublished trials submitted to the FDA for review and published studies, our meta-analysis included a larger number of clinical trials than did other published meta-analyses. Second, we obtained patient-level clinical trial data for a number of trials and were able to perform analyses based on these patient-level data in addition to those based on trial-level data. Third, the overall findings were consistent across both trial-level and patient-level analyses. For febrile neutropenia trials with patient-level data, we reviewed the CRFs of patients who died in an attempt to identify a biologically plausible explanation for the reported mortality difference. No biologically plausible explanation for a mortality imbalance was identified.

The limitations of our analysis included the following. First, most of the trials were open label. Second, the meta-analysis was not designed and did not have the power to assess mortality differences in several subgroups of interest, and as a result, the numbers of patients in subgroups with significant findings were small, making it difficult to interpret the results. Therefore, additional research will be necessary to explore potential differences in mortality for some of these subgroups. Third, because the "other" clinical conditions subset in the trial-level analysis included patients treated for a variety of infections, this population subgroup may have been more heterogeneous than others enrolled for treatment of specific conditions.

We did not find that the use of cefepime was significantly associated with increased mortality, compared with other antibacterial agents, for all trials included in our meta-analysis. Although the point estimate for the risk difference in the subset of trials including patients with febrile neutropenia did not favor cefepime, it was not statistically significant. Neither reviews of the CRFs nor analyses based on patient-level data identified a biologically plausible reason for an increased risk of mortality with cefepime use. Only adequately powered and well-controlled prospective trials may definitively answer the question of whether the use of cefepime, compared with other antibacterial agents, is associated with increased mortality.

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