Efficacy and Safety of Cefepime in Pediatric Patients: A Systematic Review and Meta-Analysis

Elisabeth E. Adderson, MD, Patricia M. Flynn, MD,* and James M. Hoffman, PharmD*

Objectives We systematically reviewed clinical trials on the safety and efficacy of cefepime in pediatric patients in view of recent reports, which suggested that cefepime is associated with increased 30-day all-cause mortality rates.

Study design We searched the Cochrane Central Registry of Controlled Trials (CENTRAL), MEDLINE, EMBASE, and other published and unpublished sources. Randomized clinical trials of cefepime in patients <19 years of age were selected.

Results Sixteeen clinical trials were included. All-cause mortality rates did not differ between cefepime and comparator groups (risk difference, 0.00; 95% CI, -0.01-0.02). The risks of overall clinical failure (relative risk, 0.93; 95% CI, 0.82-1.04; $P > .05$) and failure in microbiologically confirmed infections (relative risk, 0.91; 95% CI, 0.68-1.22; $P > .05$) were not greater in subjects treated with cefepime. Rates of adverse events were similar in each group in all trials except 1. All studies had significant methodological flaws.

Conclusions Comparisons of the safety and efficacy of cefepime relative with other antimicrobial agents in pediatric patients are limited by small numbers of trials and enrolled subjects and poor study methodology. This review, however, suggests that cefepime therapy in pediatric patients is not associated with an increased risk of adverse outcomes. *(J Pediatr 2010;157:490-5)*.

Cefepime is a semi-synthetic fourth-generation cephalosporin with good activity against both Gram-positive and Gram-negative bacteria, including *Pseudomonas aeruginosa*.[1,2] It is generally more active against Gram-negative pathogens because of its rapid penetration of the bacterial cell membrane, high affinity for the penicillin binding proteins involved in bacterial cell wall synthesis, and resistance to hydrolysis by many β-lactamases.[3] After parenteral administration, cefepime is widely distributed in tissues and body fluids.[1,3] In 1999, the United States Food and Drug Administration (FDA) approved cefepime for the treatment of patients >2 years of age with moderate to severe pneumonia, urinary tract infections, skin and skin structure infections, and complicated intra-abdominal infections and in the empiric therapy for febrile neutropenic patients.[2]

In 2006, Paul et al[4] published the results of a structured review and meta-analysis of the efficacy and safety of cefepime as empiric monotherapy for febrile neutropenia. This reported an overall risk ratio for all-cause mortality at 30 days of 1.44 (95% CI, 1.06-1.94) in patients treated with cefepime compared with patients treated with other β-lactam antibiotics in 17 clinical trials.[4] Infection-related mortality also was more common with cefepime, and bacterial superinfection developed in a larger number of subjects treated with cefepime. In 3 studies recruiting only pediatric subjects, mortality was also higher in children treated with cefepime compared with children treated with ceftazidime (risk ratio [RR], 2.28; 95% CI, 0.53-9.79).[4] A subsequent systematic review of randomized clinical trials with cefepime for any indication revealed a overall higher RR for all-cause mortality for cefepime compared with other β-lactam agents (RR, 1.26; 95% CI, 1.08-1.49), but pediatric data were not reported separately.[5] In November 2007, the FDA issued a request for additional data to further evaluate the risk of death in patients treated with cefepime.[6] FDA meta-analyses reported in June 2009 found no statistically significant increase in mortality when cefepime was compared with other comparators.[7] The FDA concluded that cefepime was safe for its approved indications, but noted that it continues to review the safety of cefepime. Pending the results of this ongoing evaluation, health care professionals were advised to consider the risks and benefits of the use of cefepime.

Although these reviews included data on pediatric patients treated with cefepime, the relative risks of this treatment were not analyzed in detail for important clinical subgroups or all outcomes, and certain unpublished data were not in-

ANC	Absolute neutrophil count
FDA	United States Food and Drug Administration
RD	Risk difference
RR	Risk ratio
UTI	Urinary tract infection
VAP	Ventilator-associated pneumonia

From the Departments of Infectious Diseases (E.A., P.M.) and Pharmaceutical Sciences (J.H.), St. Jude Children's Research Hospital, Memphis, TN; and Departments of Clinical Pharmacy (J.H.) Pediatrics (E.A., P.M.), Preventative Medicine (P.M.) and Molecular Sciences (E.A.), The University of Tennessee Health Sciences Center, Memphis, TN

*These authors contributed equally to this work.

Supported by the National Cancer Institute Cancer Center CORE Support Grant (CA 21765) and the American Lebanese Syrian Associated Charities. The authors declare no conflicts of interest.

 10.1016/j.jpeds.2010.03.023

cluded in these reviews. Because pediatric patients may differ from adults in the etiologic agent of infections, preferred therapies, the risk of poor outcomes, and rates of adverse events, we systematically reviewed all randomized clinical trials in children and adolescents that compared cefepime with other conventionally used antibiotic regimens. The primary end points were all-cause mortality and efficacy. Patients' baseline characteristics and rates of adverse events also were evaluated.

Methods

All randomized controlled comparisons of cefepime with another comparator in pediatric (<19 years of age) subjects were included. Trials that included both adults and children as study subjects were excluded when data from children were not reported independently from those of adult subjects. The addition of other antimicrobial agents, including aminoglycosides and glycopeptides, was permitted when this was consistent with generally accepted clinical practice. The primary outcomes assessed were overall mortality rate and clinical failure, defined as incomplete resolution of infection without treatment modification. When 30-day all-cause mortality data were not available, mortality at the end of the study follow-up period (as long as 30 days) was used. Secondary outcomes included microbiologic failure and adverse effects.

Two reviewers independently searched for studies, applied inclusion criteria, extracted data, and assessed the validity of included studies. Disagreements between reviewers were resolved with consensus. We searched the Cochrane Central Registry of Controlled Trials (CENTRAL, The Cochrane Library, Issue 3, 2008), MEDLINE (January 1966-January 2009), and EMBASE (January 1980-January 2009) databases by using the search terms "cefepime," "cefepim," and "BMY-28142." No language restrictions were used. Unpublished trials were sought in new drug applications to the FDA, regulatory reviews, references of published clinical trials, abstracts of relevant scientific conferences, and through personal contact with clinical trials investigators, the FDA, and pharmaceutical companies. The last search was performed on Aug 3, 2009.

Outcomes were extracted preferentially by intention-to-treat when these data were available. Otherwise, per protocol data were extracted, and sensitivity analyses were performed to compare the data with intention-to-treat analyses. For clinical failure, a modified intention-to-treat analysis was conducted by imputing clinical failure for all enrolled subjects who did not complete the study. Subgroup analyses were planned to identify differences in outcomes in febrile neutropenia and in other suspected serious bacterial infections. Clinical heterogeneity was analyzed qualitatively, taking into account differences in the baseline characteristics of the studied population and type of infection. The baseline characteristics of subjects that may have influenced treatment outcomes were also compared. For studies of therapy for febrile neutropenia, the proportion of patients with an absolute neutrophil count (ANC) <100/mm^3, proportion of patients with acute leukemia, proportion of patients not in cancer remission, and proportion of patients with microbiologically confirmed and clinically documented infections were assessed. For other infections, the proportion of patients with microbiologically confirmed and clinically documented infections were determined. The group (cefepime or comparator) with the highest prevalence of a particular risk factor was assigned 1 point, as described by Yahav, and study groups in all trials were compared.[5]

Quality assessment was performed independently by each reviewer with 2 instruments, a 3-item scale that assessed randomization, allocation concealment, and attrition of subjects and a 9-item scale that evaluated enrollment and randomization methods, concealment of allocation, blinding, baseline characteristics, and data analysis.[8,9] Sensitivity analyses were performed to assess the effect of patient characteristics on outcomes.

Quantitative Data Synthesis

Mantel-Haenszel risk differences (RD) were calculated for each study for the primary outcome of all-cause mortality rate and combined to derive pooled estimates of the overall RD. Mantel-Haenszel RRs and their 95% CIs were calculated for all outcomes for each study and combined when this was deemed appropriate. Heterogeneity was assessed with the χ^2 test for heterogeneity and the I^2 measure of inconsistency by using Review Manager software version 5.0.15 (The Nordic Cochrane Center; The Cochrane Collaboration, Copenhagen, Denmark).[10] Small study bias was assessed with funnel plots.

Results

A total of 5467 records were retrieved, including 98 that described randomized clinical trials (**Figure 1**). In 79 of these studies, children were not enrolled or data from pediatric subjects were pooled with that of adults. Three additional studies were excluded because the study design was not explicitly stated or because data were reported incompletely and efforts to obtain clarification were not successful.[7,11] Data from 16 randomized clinical trials were included in the analysis. Data from only a subset of patients were available in the case of 1 trial that compared the efficacy of cefepime and ceftazidime for respiratory tract infections and pyelonephritis/complicated urinary tract infections (UTI).[12,13]

The efficacy of cefepime compared with other beta-lactam antibiotics for the empiric therapy of febrile neutropenia in pediatric oncology patients was addressed in 8 randomized clinical trials (**Table I**).[13-21] Patients with leukemia were excluded from 3 of these trials; otherwise, inclusion criteria did not differ considerably. Eight studies compared the efficacy of cefepime with other beta-lactam agents for

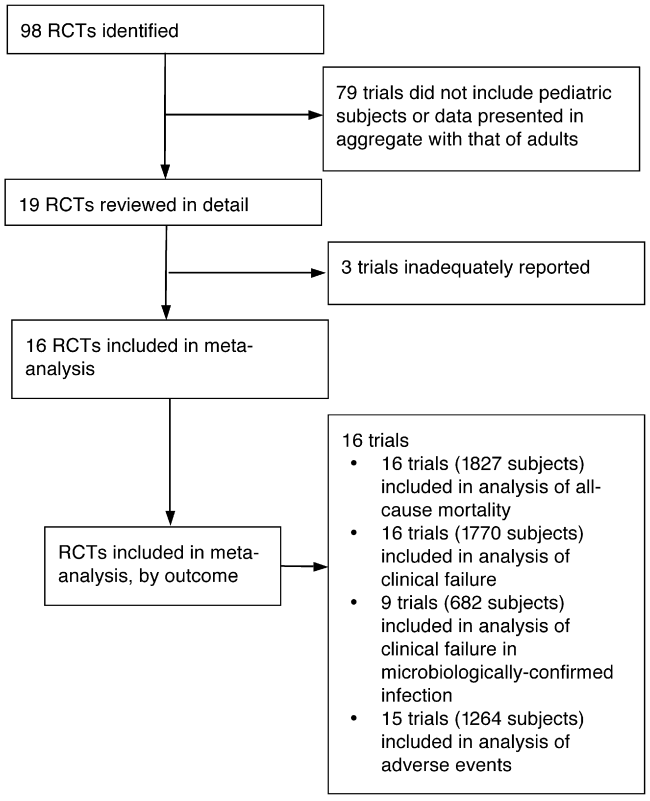

Figure 1. Study flow.

suspected or proven serious bacterial infections.[12,13,22-26] The addition of other antimicrobial agents was permitted in 7 trials when symptoms persisted, resistant pathogens were identified, new infections emerged, or at the treating physician's discretion.[14-20]

Methodologic Quality of Included Studies

Overall, the quality of studies was poor. Although all studies were described as randomized, no report described the exact method of randomization. Only 1 study reported a strategy for allocation concealment.[23] All reports explicitly described inclusion criteria. In studies describing the baseline characteristics of patients, they were well matched between cefepime and comparator groups. The mean score for baseline patient risk factors did not differ significantly for cefepime compared with other antimicrobial agents overall (cefepime, 1.36; 95% CI, 1.07-1.65; comparator, 1.21; 95% CI, 0.71-1.73) or for trials in patients with febrile neutropenia (cefepime, 2.00; 95% CI, 1.58-2.42; comparator, 1.75; 95% CI, 1.16-2.35). Nine reports adequately described withdrawals and subjects lost to follow-up. Primary outcomes were analyzed by using an intention-to-treat strategy in 10 studies. In 7 studies, the final analysis was limited to a subset of participants who were considered evaluable, excluding those subjects with unspecified protocol violations,[15,16,20] who failed to meet eligibility criteria,[16,17,24] who received improper doses of the study drug,[25] who had non-bacterial or no documented bacterial infection,[12,15,20,24,25] fever attributed to malignancy,[16,17] and who discontinued therapy prematurely[12,15,24,25] or had early modification of therapy without adequate reason[15] or because of adverse events,[20,24] therapeutic failure,[12] or death attributed to chemotherapy toxicity,[16] or who failed to meet defined criteria for therapeutic success or failure.[20] Although point estimates of effect for most important outcomes were provided in all reports, none reported a measure of variability of the estimate of the treatment effect.

Of the studies included in this review that were published in peer-reviewed journals, only one disclosed industry sponsorship, although it is likely that other studies received financial support. No authors described financial or other potential conflicts of interests in these publications.

Table I. Characteristics of included studies

Study	Years	Participant age (years)	Indication	Interventions
Agaoglu 2001[14]	1998-99	0.8-18.0	FN	cefepime + netilmicin versus ceftazidime + amikacin versus meropenem
Arrieta 2001[7,13,24]	no data	0.1-12.0	SBI	cefepime versus ceftazidime
Bradley 2001a[7,12,13]	1990-91	2.0-15.0	SBI	cefepime versus cefuroxime
Bradley 2001b[7,12,13]	1991-93	0.2-18.0	SBI	cefepime versus cefotaxime
Bradley 2001c[7,12,13]	no data	0.1-12.0	SBI	cefepime versus ceftazidime
Corapcioglu 2005[16]	2003-04	<18	FN	cefepime + amikacin versus ceftazidime + amikacin
Corapcioglu 2006[17]	2004-05	<18	FN	cefepime versus piperacillin/tazobactam
Chuang 2002[15]	2000-01	0.2-15.0	FN	cefepime versus ceftazidime
Huang 2005[22]	no data	0.1-9.0	pneumonia	cefepime versus cefoperazone/sulbactam
Kebudi 2001[18]	1998	0.1-14.0	FN	cefepime versus ceftazidime
Kutluk 2004[19]	no data	<16	FN	cefepime versus meropenem
Mustafa 2001[7,12,20]	1991-93	0.2-18.0	FN	cefepime versus ceftazidime
Oguz 2006[21]	2003-04	0.25-16.0	FN	cefepime versus meropenem
Saez-Llorens 2001[7,12,25]	1991-93	0.2-14.0	meningitis	cefepime versus cefotaxime versus ceftriaxone
Schaad 1998[7,12,26]	1996-97	0.1-12.0	UTI	cefepime versus ceftazidime
Shahid 2008[23]	2004-05	<1	VAP	cefepime versus ceftazidime

FN, Febrile neutropenia; *SBI,* serious bacterial infection.

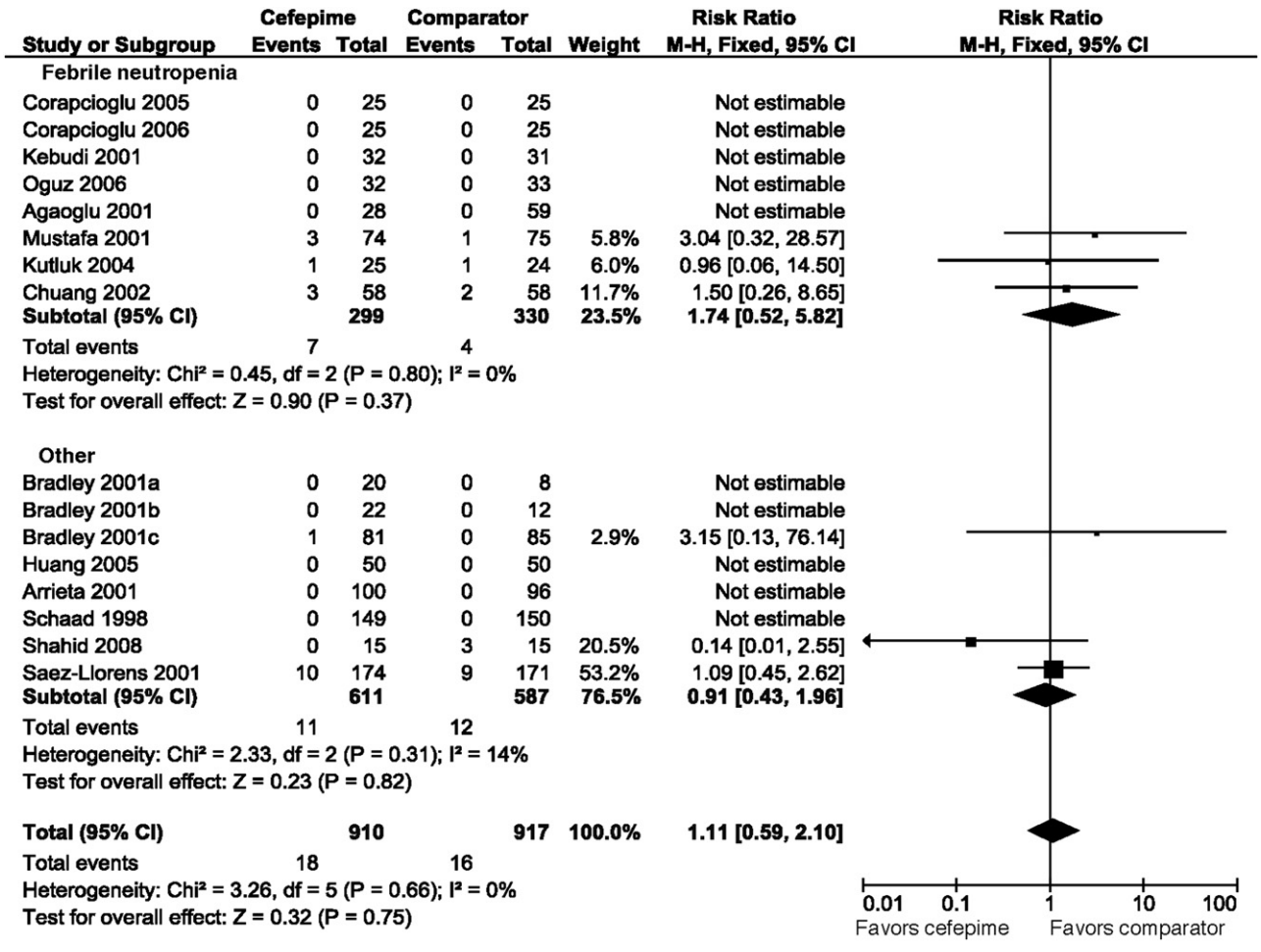

Figure 2. Cefepime versus comparator: all-cause mortality rate.

Treatment Outcomes

Mortality was reported for 16 trials involving 1827 patients. The time point at which mortality and efficacy was evaluated was not specified in 8 studies. Overall mortality rate for cefepime was similar to that of its comparators (RR, 1.1; 95% CI, 0.59-2.10; $P > .05$; Figure 2). The overall RD was 0.00 (95% CI, -0.01-0.02). All antibiotic comparators had mortality rates comparable with cefepime. Patients receiving cefepime for therapy of febrile neutropenia had an increased risk of death (7 of 299 patients versus 4 of 330 patients receiving comparators), but this was not significant. The RD for patients receiving cefepime compared with other antimicrobial agents for therapy of febrile neutropenia was 0.01 (95% CI, -0.02-0.03).

Clinical failure was reported for 16 trials and 1770 patients. Overall, clinical failure rates and clinical failure rates in febrile neutropenia did not differ between cefepime and comparators (Figure 3). Microbiologic failure was reported in 9 trials involving 682 patients. Overall failure in microbiologically confirmed infections was similar for cefepime and comparators (RR, 0.91; 95% CI, 0.68-1.22; $P > .05$). Patients with febrile neutropenia who were treated with cefepime were less likely to experience treatment failure than patients treated with comparators (RR, 0.70; 95% CI, 0.46-1.07; $P > .05$), but this difference was not statistically significant (data not shown).

No reports explicitly described the nature and timing of evaluations for adverse events, and adverse events were reported comprehensively in only 3 studies. A meta-analysis of the RR for adverse events was not performed because of clinical and statistical heterogeneity in both the nature and rates of adverse events reported in individual studies (Table II; available at www.jpeds.com). Rates of adverse events were comparable for cefepime and comparators, except in 1 study, which reported 10 adverse events in 20 subjects in the cefepime group and none in 8 patients receiving cefuroxime.[12, 13]

Discussion

Although our search strategy was comprehensive and our analysis included studies not evaluated in earlier systematic reviews, the number of reported trials in pediatric patients

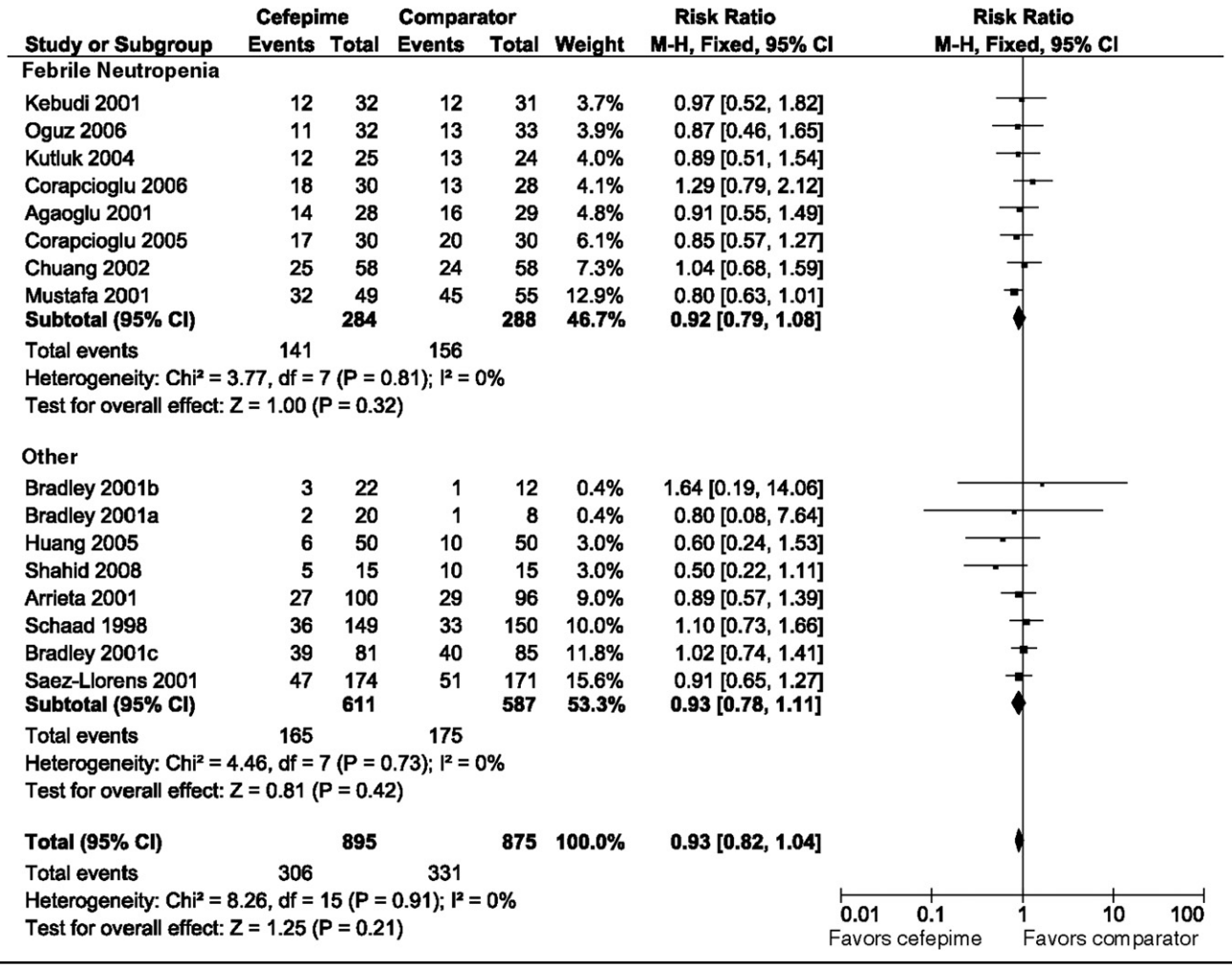

Figure 3. Cefepime versus comparator: clinical failure.

is small, and most trials enrolled relatively few subjects. Further analysis of data in special subgroups of interest, therefore, was not feasible. The considerable methodological shortcomings of the studies included in this review are aforementioned. Although these relationships are inconsistent, some studies have demonstrated that clinical trials that do not make use of adequate randomization procedures or allocation concealment and trials that are not double-blinded, particularly small trials, may overestimate the benefits of an intervention.[27] Only 10 reports included in this review seemed to analyze according to an intention-to-treat strategy, but few reports explicitly stated their methods. In general, losses to follow-up and missing data were poorly or not described. Some studies explicitly excluded subjects from analysis because of adverse events or lack of treatment response.

Our analyses contradict those of Yahav and collaborators.[4,5] These findings may reflect the inclusion of more data (16 versus 5 randomized clinical trials) and differences in inclusion criteria. The earlier reviews included only studies comparing monotherapy with ß-lactam and carbapenem agents and those that permitted the addition of a glycopeptide to both study arms. We were more liberal in our inclusion criteria, permitting other acceptable antimicrobial options, on the basis of current professional society recommendations.[28,29] Other authors have criticized the conclusions of Yahav et al, noting some discrepancies in their analysis and potentially excessive heterogeneity in infection-attributable mortality between study groups.[30]

Our findings support the recommendation of the FDA, based on trial- and patient-level meta-analyses, that cefepime remains acceptable therapy for approved indications. This conclusion must be tempered, however, by the understanding that small numbers of patients were included in these studies and that methodological flaws or other sources of partiality might impact on outcomes. More appropriately designed clinical trials are required to establish definitively the safety and efficacy of cefepime in children. Vigorous post-marketing surveillance and ongoing analysis of existing data should consider important clinical subgroups and the

differences between children and adults in treatment outcomes and adverse events. ■

Submitted for publication Oct 5, 2009; last revision received Feb 24, 2010; accepted Mar 17, 2010.

Reprint requests: Elisabeth Adderson, Department of Infectious Diseases, MS 320, St Jude Children's Research Hospital, 262 Danny Thomas Pl, Memphis TN 38105. E-mail: elisabeth.adderson@stjude.org.

References

1. Bodey GP, Ho DH, LeBlanc B. In vitro studies of BMY-28142, a new broad-spectrum cephalosporin. Antimicrob Agents Chemother 1985; 27:265-9.
2. Elan Biopharmaceuticals. Maxipime (cefepime hydrochloride) for Injection - prescribing information. (Revised March 2009.) Available at: http://www.elan.com/therapies/products/default.asp. Accessed Sep 30, 2009
3. Sanders CC. Cefepime: the next generation? Clin Infect Dis 1993;17: 369-79.
4. Paul M, Yahav D, Fraser A, Leibovici L. Empirical antibiotic monotherapy for febrile neutropenia: systematic review and meta-analysis of randomized controlled trials. J Antimicrob Chemother 2006;57:176-89.
5. Yahav D, Paul M, Fraser A, Sarid N, Leibovici L. Efficacy and safety of cefepime: a systematic review and meta-analysis. Lancet Infect Dis 2007;7:338-48.
6. United States Food and Drug Administration. Early communication about an ongoing safety review:cefepime (marketed as Maxipime). (Updated 06/18/2009.) Available at: www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/ucm070496.htm. Accessed Sep 30, 2009.
7. United States Food and Drug Administration. Cefepime (marketed as Maxipime) Update of Ongoing Safety Review. (Updated 06/17/2009.) Available at: www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm167427.htm. Accessed Sep 30, 2009.
8. Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials 1996;17:1-12.
9. Verhagen AP, de Vet HC, de Bie RA, Kessels AG, Boers M, Bouter LM, et al. The Delphi list: a criteria list for quality assessment of randomized clinical trials for conducting systematic reviews developed by Delphi consensus. J Clin Epidemiol 1998;51:1235-41.
10. The Cochrane Information Management System. Review Manager (RevMan) 5.0.15 ed. Available at: www.cc-ims.net. Accessed Sep 30, 2009.
11. Gulsun BS, Canpolat C, Cebecci D. Cefepim and ceftazidime in conbination with amikasin in febrile neutropenia of childhood: which regimen is more effective? In: Joint Congress of the 6th TRANSMED Pediatric and 34th Turkish Pediatric Association Congress. Istanbul; 1998.
12. Bradley JS, Arrieta A. Empiric use of cefepime in the treatment of lower respiratory tract infections in children. Pediatr Infect Dis J 2001;20:343-9.
13. Food and Drug Administration Center for Drug Evaluation and Research. Medical officer review of pediatric use supplement NDA 50-679/SLR-007. Available at: www.fda.gov/Cder/foi/nda/99/50679S007_Maxipine_medr.pdf. Accessed Dec 7, 2008.
14. Agaoglu L, Devecioglu O, Anak S, Karakas Z, Yalman N, Biner B, et al. Cost-effectiveness of cefepime + netilmicin or ceftazidime + amikacin or meropenem monotherapy in febrile neutropenic children with malignancy in Turkey. J Chemother 2001;13:281-7.
15. Chuang YY, Hung IJ, Yang CP, Jaing TH, Lin TY, Huang YC. Cefepime versus ceftazidime as empiric monotherapy for fever and neutropenia in children with cancer. Pediatr Infect Dis J 2002;21:203-9.
16. Corapcioglu F, Sarper N. Cefepime versus ceftazidime + amikacin as empirical therapy for febrile neutropenia in children with cancer: a prospective randomized trial of the treatment efficacy and cost. Pediatr Hematol Oncol 2005;22:59-70.
17. Corapcioglu F, Sarper N, Zengin E. Monotherapy with piperacillin/tazobactam versus cefepime as empirical therapy for febrile neutropenia in pediatric cancer patients: a randomized comparison. Pediatr Hematol Oncol 2006;23:177-86.
18. Kebudi R, Gorgun O, Ayan I, Gurler N, Akici F, Toreci K. Randomized comparison of cefepime versus ceftazidime monotherapy for fever and neutropenia in children with solid tumors. Med Pediatr Oncol 2001; 36:434-41.
19. Kutluk T, Kurne O, Akyuz C, Ceyhan M, Kanra G, Buyukpamukcu M, et al. Cefepime vs meropenem as empirical therapy for neutropenic fever in children with lymphoma and solid tumours. Pediatr Blood Cancer 2004;42:284-6.
20. Mustafa MM, Carlson L, Tkaczewski I, McCracken GH Jr., Buchanan GR. Comparative study of cefepime versus ceftazidime in the empiric treatment of pediatric cancer patients with fever and neutropenia. Pediatr Infect Dis J 2001;20:362-9.
21. Oguz A, Karadeniz C, Citak EC, Cil V, Eldes N. Experience with cefepime versus meropenem as empiric monotherapy for neutropenia and fever in pediatric patients with solid tumors. Pediatr Hematol Oncol 2006;23: 245-53.
22. Huang JJ, Zeng Q, Yu JL. [Therapeutic effects of cefepime and sulbactam/cefoperazone on moderate and severe respiratory tract infection in children] (in Chinese). Di Yi Jun Yi Da Xue Xue Bao 2005;25:1199-200.
23. Shahid SK. Efficacy and safety of cefepime in late-onset ventilator-associated pneumonia in infants: a pilot randomized and controlled study. Ann Trop Med Parasitol 2008;102:63-71.
24. Arrieta AC, Bradley JS. Empiric use of cefepime in the treatment of serious urinary tract infections in children. Pediatr Infect Dis J 2001;20: 350-5.
25. Saez-Llorens X, O'Ryan M. Cefepime in the empiric treatment of meningitis in children. Pediatr Infect Dis J 2001;20:356-61.
26. Schaad UB, Eskola J, Kafetzis D, Fishbach M, Ashkenazi S, Syriopoulou V, et al. Cefepine vs ceftazidime treatment of pyelonephritis: a European, randomized, controlled study of 300 pediatric cases. European Society for Paediatric Infectious Diseases (ESPID) Pyelonephritis Study Group. Pediatr Infect Dis J 1998;17:639-44.
27. Kjaergard LL, Villumsen J, Gluud C. Reported methodologic quality and discrepancies between large and small randomized trials in meta-analyses. Ann Intern Med 2001;135:982-9.
28. Dellinger RP, Levy MM, Carlet JM, Bion J, Parker MM, Jaeschke R, et al. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock: 2008. Intensive Care Med 2008; 34:17-60.
29. Rolston KV. The Infectious Diseases Society of America 2002 guidelines for the use of antimicrobial agents in patients with cancer and neutropenia: salient features and comments. Clin Infect Dis 2004;39(Suppl. 1): S44-8.
30. Nguyen TD, Williams B, Trang E. Cefepime therapy and all-cause mortality. Clin Infect Dis 2009.

Table II. Adverse events reported in clinical trials comparing cefepime with other antimicrobials

Study	Number of adverse events (rate/patient)	
	Cefepime	Comparator
Agaoglu 2001	0 (0.00)	3 (0.05)
Arrieta 2001*	–	–
Bradley 2001a	10/20 (0.50)	0/8 (0.00)
Bradley 2001b	9/22 (0.41)	7/12 (0.58)
Bradley 2001c	96/80 (1.20)	103/84 (1.23)
Corapcioglu 2005	0/25 (0.00)	1/25 (0.04)
Corapcioglu 2006	3/25 (0.12)	1/25 (0.04)
Chuang 2002	1/48 (0.02)	0/48 (0.00)
Huang 2005	1/50 (0.02)	1/50 (0.02)
Kebudi 2001	0/32 (0.00)	0/31 (0.00)
Kutluk 2004	0/25 (0.00)	0/24 (0.00)
Mustafa 2001	63/46 (1.37)	74/54 (1.37)
Oguy 2006	0/32 (0.00)	0/33 (0.00)
Saez-Llorens 2001*	–	–
Schaad 1998	41/149 (0.28)	37/150 (0.25)
Shahid 2008	0/15 (0.00)	0/15 (0.00)
Total	224/597 (0.38)	227/618 (0.37)

*Not reported.