JOURNAL OF CLINICAL MICROBIOLOGY, June 2001, p. 2206–2212 Vol. 39, No. 6
0095-1137/01/$04.00+0 DOI: 10.1128/JCM.39.6.2206–2212.2001

Outcome of Cephalosporin Treatment for Serious Infections Due to Apparently Susceptible Organisms Producing Extended-Spectrum β-Lactamases: Implications for the Clinical Microbiology Laboratory

DAVID L. PATERSON,[1,2] WEN-CHIEN KO,[3] ANNE VON GOTTBERG,[4] JOSE MARIA CASELLAS,[5] LUTFIYE MULAZIMOGLU,[6] KEITH P. KLUGMAN,[4] ROBERT A. BONOMO,[7] LOUIS B. RICE,[7] JOSEPH G. McCORMACK,[2] AND VICTOR L. YU[1]*

Infectious Disease Division, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania[1]; Department of Medicine, University of Queensland, Brisbane, Australia[2]; Department of Medicine, National Cheng Kung University Medical College, Tainan, Taiwan[3]; South African Institute of Medical Research, Johannesburg, South Africa[4]; Departmento de Infectologia y Microbiologia, Sanatorio San Lucas, Buenos Aires, Argentina[5]; Department of Microbiology, Marmara University, Istanbul, Turkey[6]; and Infectious Disease Section, VA Medical Center, Cleveland, Ohio[7]

Received 18 December 2000/Returned for modification 30 January 2001/Accepted 20 March 2001

Although extended-spectrum beta-lactamases (ESBLs) hydrolyze cephalosporin antibiotics, some ESBL-producing organisms are not resistant to all cephalosporins when tested in vitro. Some authors have suggested that screening klebsiellae or *Escherichia coli* for ESBL production is not clinically necessary, and when most recently surveyed the majority of American clinical microbiology laboratories did not make efforts to detect ESBLs. We performed a prospective, multinational study of *Klebsiella pneumoniae* bacteremia and identified 10 patients who were treated for ESBL-producing *K. pneumoniae* bacteremia with cephalosporins and whose infecting organisms were not resistant in vitro to the utilized cephalosporin. In addition, we reviewed 26 similar cases of severe infections which had previously been reported. Of these 36 patients, 4 had to be excluded from analysis. Of the remaining 32 patients, 100% (4 of 4) patients experienced clinical failure when MICs of the cephalosporin used for treatment were in the intermediate range and 54% (15 of 28) experienced failure when MICs of the cephalosporin used for treatment were in the susceptible range. Thus, it is clinically important to detect ESBL production by klebsiellae or *E. coli* even when cephalosporin MICs are in the susceptible range (≤ 8 μg/ml) and to report ESBL-producing organisms as resistant to aztreonam and all cephalosporins (with the exception of cephamycins).

Over the last 15 years, numerous outbreaks of infection with organisms producing extended-spectrum beta-lactamases (ESBLs) have been observed worldwide (16). The advent of ESBL producers has represented a great threat to the use of many classes of antibiotics, particularly cephalosporins. It has been well recognized that poor outcome occurs when patients with serious infections due to ESBL-producing organisms are treated with antibiotics to which the organism is frankly resistant. The mortality rate in such patients is significantly higher than in patients treated with antibiotics to which the organism is susceptible (21) and has ranged from 42 to 100% (11, 14, 21). In the majority of instances in which "inappropriate" therapy was given, the therapy was ceftazidime for an ESBL-producing organism for which MICs of ceftazidime were elevated (often >256 μg/ml).

Much more controversy exists as to whether cephalosporin therapy is appropriate for ESBL-producing organisms for which cephalosporin MICs are in the susceptible range (4). Such a scenario is relatively common—of 141 American isolates of ESBL-producing *Klebsiella pneumoniae* examined by Jacoby et al. (7), only 23% would have been reported as cefotaxime resistant when examined using the NCCLS breakpoints existing at that time. In a recent study from Europe, of 91 ESBL-producing klebsiellae, just 36% were reported by their referring clinical laboratories as cefotaxime resistant (1).

In a 1998 survey of 369 American clinical microbiology laboratories, only 32% (117 of 369) reported performing tests to detect ESBL production by *Enterobacteriaceae* (3). It was not reported why these laboratories did not make efforts to detect ESBLs. However, some authors have suggested that ESBL screening is not likely to affect patient outcome and hence is neither clinically necessary nor cost-effective for the laboratory (4). The purpose of this study was to examine the outcome of serious infections due to ESBL-producing organisms in patients who were treated with cephalosporins to which the organism was "susceptible" or "intermediate" in vitro.

MATERIALS AND METHODS

Patients. A prospective, observational study of consecutive patients with *K. pneumoniae* bacteremia was performed in 12 hospitals in the United States, Taiwan, Australia, South Africa, Turkey, Belgium, and Argentina. The study period was 1 January 1996 to 31 December 1997. Patients older than 16 years of age with blood cultures positive for *K. pneumoniae* were enrolled, and a 188-item study form was completed. Patients were monitored for 1 month after the onset of bacteremia to assess clinical outcome, including mortality. The study was observational in that administration of antimicrobial agents, and other therapeutic management, was controlled by the patient's physician, not the investigators.

The infection leading to bacteremia was identified as pneumonia, urinary tract infection, meningitis, peritonitis, or a primary bloodstream infection using Centers for Disease Control and Prevention definitions (6).

* Corresponding author. Mailing address: Infectious Disease Division, VA Medical Center, University Dr. C, Pittsburgh, PA 15240. Phone: (412) 688-6179. Fax: (412) 688-6950. E-mail: vly+@pitt.edu.

TABLE 1. In vitro susceptibilities of ESBL-producing *K. pneumoniae* bloodstream isolates to cephalosporins

Antibiotic	% of isolates (cumulative %) for which the MIC (μg/ml) was:						
	≤1	2	4	8	16	32	≥64
True cephalosporins							
Cefotaxime	5.6 (5.6)	18.1 (23.6)	5.6 (29.2)	19.4 (48.6)	13.9 (62.5)	15.3 (77.8)	22.2 (100)
Ceftriaxone	4.2 (4.2)	5.6 (9.7)	15.3 (25.0)	11.1 (36.1)	16.7 (52.8)	15.3 (68.1)	31.9 (100)
Ceftazidime	4.2 (4.2)	4.2 (8.3)	5.6 (13.9)	5.6 (19.4)	8.3 (27.8)	5.6 (33.3)	66.5 (100)
Cefepime	23.6 (23.6)	22.2 (45.8)	23.6 (69.4)	9.7 (79.2)	4.2 (83.3)	9.7 (93.1)	6.9 (100)
Cephamycins							
Cefoxitin	0 (0)	2.8 (2.8)	59.7 (62.5)	18.1 (80.6)	9.7 (90.3)	4.2 (94.4)	5.6 (100)
Cefotetan	65.3 (65.3)	19.4 (84.7)	8.3 (93.1)	1.4 (94.4)	1.4 (95.8)	2.8 (98.6)	1.4 (100)

The interpretation of MICs (in micrograms per milliliter) of cephalosporin antibiotics against klebsiellae and *E. coli* is as follows: for cefotaxime and ceftriaxone, susceptible, ≤8, intermediate, 16 to 32, and resistant, ≥64; for ceftazidime, cefepime, and cefoxitin, susceptible, ≤8, intermediate, 16, and resistant, ≥32; and for cefotetan, susceptible, ≤16, intermediate, 32, and resistant, ≥64.

Antibiotic susceptibility testing. The antibiotic susceptibility of each blood culture isolate was determined at each study site by disk diffusion or automated broth microdilution methods. The method of determining antibiotic susceptibility and ESBL production and the combination of antibiotic susceptibility results reported to physicians was at the choice of individual laboratories. Each isolate was frozen at −80°C. At the conclusion of the study the stored isolates were sent to a central study laboratory in Pittsburgh. There, the identity of each isolate as *K. pneumoniae* was confirmed using standard methods (9). MICs of cefotaxime, ceftriaxone, ceftazidime, cefepime, cefotetan, and cefoxitin were determined for each isolate by Etest methodology (AB Biodisk, Solna, Sweden). The MICs which were considered to indicate susceptibility were ≤8 μg/ml for cefepime, cefotaxime, cefoxitin, ceftazidime, ceftizoxime, and ceftriaxone and ≤16 μg/ml for cefotetan. MICs of 16 to 32 μg/ml for cefotaxime, ceftizoxime, or ceftriaxone, 16 μg/ml for ceftazidime, cefepime, and cefoxitin, and 32 μg/ml for cefotetan were interpreted as intermediate results.

ESBL production was phenotypically determined at the central study laboratory by broth dilution using NCCLS performance standards, current as of January 2000 (12). In brief, the MICs for *K. pneumoniae* isolates of cefotaxime and ceftazidime alone and in combination with 4 μg of clavulanic acid/ml were determined. A decrease of three or more twofold concentrations in an MIC for either cefotaxime or ceftazidime tested in combination with clavulanic acid compared to its MIC when tested alone was considered phenotypic confirmation of ESBL production.

Inclusion criteria and definition of failure of therapy. Patients receiving cephalosporins (to which their ESBL-producing organism had tested susceptible or intermediate using NCCLS definitions [12]) as therapy within the first 5 days after onset of bacteremia were included in this analysis. In addition to these cases, an additional case of bacteremic infection with ESBL-producing *K. pneumoniae* occurring at one of the participating institutions shortly after the conclusion of the study is reported separately in this paper.

Failure of antibiotic therapy was defined as death of the patient within 14 days of the blood yielding a positive culture being drawn or persistence of fever or bacteremia despite 48 h of cephalosporin usage.

Genotypic analysis. The genotypic relationships of ESBL-producing isolates were determined by using pulsed-field gel electrophoresis (PFGE). The *K. pneumoniae* isolates were grown on blood agar plates for 16 h at 37°C. Genomic DNA was prepared as previously described (9). Overnight digestion was performed with 30 U of the restriction endonuclease *Xba*I (New England Biolabs, Beverly, Mass.). PFGE was performed using a CHEF-DRII system (Bio-Rad, Hercules, Calif.). The DNA was electrophoresed for 22 h at 14°C in a 1% agarose gel at 6 V/cm with a linear gradient pulse time of 5 to 35 s. Bacteriophage lambda concatemers (48.5 kb; New England Biolabs) were used as molecular weight standards. Gels were stained with ethidium bromide and photographed under UV illumination; interpretation was done according to the criteria of Tenover et al. (24).

Characterization of beta-lactamases. Beta-lactamases were liberated from *K. pneumoniae* isolates by the use of lysozyme. Initial characterization of the beta-lactamases was performed by analytical isoelectric focusing using a modification of the method of Vecoli et al. (27). Briefly, 10 μl of crude beta-lactamase extract was loaded onto a precast gel (Ampholine PAG plate; Pharmacia, Uppsala, Sweden); running conditions were 200 V, 30 mA, and a constant power of 8 W. Isoelectric focusing was usually completed within 2 h. Isolates with previously characterized beta-lactamases (TEM-1, TEM-2, TEM-12, K-1, SHV-1, P99, and ACT-1) (kindly provided by P. Bradford, Wyeth Ayerst Pharmaceuticals, Pearl River, N.Y.) were used as controls. Beta-lactamase detection was performed by overlaying the gel with nitrocefin-soaked filter paper.

Review of the literature. Treatment of all previously reported cases of serious infection (defined as bacteremia, meningitis, peritonitis, or nosocomial pneumonia) with ESBL-producing *K. pneumoniae*, *Klebsiella oxytoca*, or *Escherichia coli* was also reviewed. These cases were identified by a MEDLINE search using the key words "extended-spectrum beta-lactamase." The references of the retrieved articles were perused to find further reported cases. The abstracts of the programs of the Interscience Conference on Antimicrobial Agents and Chemotherapy (1990 to 1999) were also reviewed for further cases.

RESULTS

A total of 455 episodes of *K. pneumoniae* bacteremia were prospectively studied in 440 patients. Of these, 18.7% (85 of 455) episodes were due to ESBL producers and 81.1% (369 of 455) were due to non-ESBL producers. One additional episode involved an isolate for which the MICs of the oxyimino beta-lactam antibiotics were markedly elevated but no diminution of MICs with the addition of clavulanic acid was observed. MICs of cephamycin antibiotics for this isolate were in the resistant range, and the organism most likely possessed an AmpC-like enzyme. This episode was excluded from further analysis.

The percentage of ESBL-producing isolates which were susceptible (S), intermediate (I), or resistant (R) to cephalosporins (using the definitions above) were as follows: for cefotetan, 95.8% S, 2.8% I, and 1.4% R; for cefoxitin, 80.6% S, 9.7% I, and 9.7% R; for cefepime, 79.2% S, 4.2% I, and 16.7% R; for cefotaxime, 48.6% S, 29.2% I, and 22.2% R; for ceftriaxone, 36.1% S, 32.0% I, and 31.9% R; and for ceftazidime, 19.4% S, 8.3% I, and 72.2% R. Further details of the in vitro susceptibilities of the ESBL-producing strains are given in Table 1.

Six patients with an ESBL-producing strain were treated with a cephalosporin active in vitro; that is, one for which the MIC was ≤8 μg/ml. These patients received ceftriaxone (two patients), cefepime (two patients), cefotaxime (one patient), and ceftazidime (one patient). Two of these six patients died, and a further patient had continued fevers despite 72 h of cephalosporin therapy; these fevers resolved after therapy was changed to meropenem. The remaining three patients were cured of their infection with cephalosporin therapy. One of these patients had a repeat episode of bacteremia with ESBL-

producing *K. pneumoniae* after ceftriaxone monotherapy, but PFGE showed that the strains were not genotypically related.

A further three patients were treated with a cephalosporin, the MIC for which was in the intermediate range (16 to 32 μg/ml for cefotaxime and ceftriaxone and 16 μg/ml for ceftazidime). One of these patients died, and the two others required a change in therapy because of continued evidence of infection. These two patients were ultimately cured of their infection.

The clinical details of these nine patients and an additional patient from one of the participating hospitals are summarized in Table 2. The clinical details of 26 patients previously reported (2, 4, 8, 15, 17, 18, 19, 21, 22, 23, 28) are reported in Table 3. When the data for the 10 patients from the international *K. pneumoniae* bacteremia study were combined with those for the 26 previously reported patients, data for a total of 36 patients were available for analysis. Of the cases, 83% (30 of 36) were bacteremia; the remainder were nosocomial pneumonia (3 cases), empyema (1 case), peritonitis (1 case), and meningitis (1 case). The ESBL-producing organisms included *K. pneumoniae* (26 cases), *E. coli* (7 cases), *K. oxytoca* (2 cases), and mixed *K. pneumoniae* and *E. coli* (1 case). The cephalosporins which were used in these 36 cases of infection were cefotaxime or ceftriaxone (19 cases), ceftizoxime (6 cases), cefepime (6 cases), ceftazidime (3 cases), cefmetazole (1 case), and cefoxitin (1 case). The cases treated with cefoxitin and cefmetazole (cephamycins) were excluded from further analysis, since the cephamycins are resistant to the hydrolytic activity of ESBLs. Additionally, two patients who died within 48 h of commencing cephalosporin therapy were also excluded from further analysis.

Of the remaining 32 patients, 54% (15 of 28) had clinical failure while receiving a cephalosporin to which the organism was susceptible, and 100% (4 of 4) had clinical failure while receiving a cephalosporin to which the organism was intermediate. Four of the 15 patients with clinical failure with cephalosporins to which the organism was "susceptible" died within 14 days of beginning the cephalosporin treatment; of the 11 remaining patients with clinical failure, all were cured with a change in antibiotic therapy. The change was to a carbapenem in all cases except one.

Of patients with organisms which were "susceptible" to the cephalosporin used, clinical failure was observed in 9 of 16 patients receiving cefotaxime or ceftriaxone, 4 of 5 receiving cefepime, 2 of 6 receiving ceftizoxime, and 0 of 1 receiving ceftazidime (Tables 2 and 3). There was no relationship between the number of beta-lactamases present in the infecting organism and likelihood of failing cephalosporin therapy: 5 of 10 patients whose infecting organism had one beta-lactamase failed, compared to 5 of 12 whose infecting organism had two beta-lactamases ($P > 0.20$).

Further breakdown of clinical failure by MIC is given in Table 4 for the 23 patients for whose isolates a precise MIC was recorded. Failure rates were highest (100% [6 of 6]) in patients with infecting organisms for which the MIC of the cephalosporin used was 8 μg/ml and lowest in patients (27% [3 of 11]) with infecting organisms for which the MIC was <2 μg/ml; there was a statistically significant increase in failure rate as MICs rose within the susceptible range ($P = 0.004$).

DISCUSSION

The NCCLS established breakpoints for expanded-spectrum cephalosporin antibiotics shortly after the clinical release of these antibiotics in the early 1980s. Correlations of MICs to clinical outcome were excellent; indeed, an MIC of ≤8 μg/ml correlated with ≥92% clinical success for all relevant species, including *K. pneumoniae* and *E. coli* (R. Jones, personal communication). It is important to note that these breakpoints were established essentially prior to the era of the ESBLs.

In the late 1980s and early 1990s, it was recognized that MICs of some cephalosporins for isolates possessing ESBLs may be ≤8 μg/ml (that is, in the susceptible range). Brun-Buisson et al. (2) in a description of the first large outbreak of ESBL-producing organisms reported that the ceftriaxone and cefotaxime MICs for some ESBL-producing strains were 0.5 to 4 μg/ml. Although these cephalosporin MICs were in the susceptible range, they were substantially higher than the MICs for non-ESBL-producing strains at their hospital (ceftriaxone MICs, 0.03 to 0.06 μg/ml). Good clinical outcomes were observed when expanded-spectrum cephalosporins were used to treat urinary tract infections due to ESBL-producing organisms, but the outcome when serious infections were tackled was questionable.

Initial challenges to the notion that ESBL-producing organisms for which MICs of expanded-spectrum cephalosporins are in the susceptible range may not be truly susceptible (when serious infections are considered) came from in vitro studies of "inoculum effect" and animal studies. In vitro, the MICs of cephalosporins rise as the inoculum of ESBL-producing organisms increases (10, 20, 26). For example, for a *K. pneumoniae* strain producing TEM-26, at an inoculum of 10^5 CFU/ml the cefotaxime MIC was 0.25 μg/ml and the cefepime MIC was 1 μg/ml, but when the inoculum rose to 10^7 CFU/ml, the MICs rose to 64 and >64 μg/ml, respectively (26). Experience in experimental animal models of infection with ESBL-producing organisms has demonstrated failure when ceftriaxone or cefotaxime was used, despite levels of antibiotics in serum far exceeding the MIC of the antibiotic when tested at the conventional inoculum of 10^5 organisms per ml (5, 20).

In view of the in vitro data and animal data presented above, combined with case reports of failure of cephalosporin therapy in serious infections due to ESBL-producing strains (even in the presence of apparent susceptibility to cephalosporins), the NCCLS Subcommittee on Antimicrobial Susceptibility Testing convened a working party on detection of ESBLs in the late 1990s. The conclusions of this working party were that strains of clinical isolates of *Klebsiella* spp. and *E. coli* should be screened for ESBL production and that isolates suspected of ESBL production should be subjected to a phenotypic confirmatory test. These conclusions are part of the *Approved Standard for Methods for Dilution Antimicrobial Susceptibility Tests* published in January 2000 (12). In brief, MICs of ≥2 μg/ml for cefpodoxime, ceftazidime, aztreonam, cefotaxime, or ceftriaxone should be regarded as possibly indicating ESBL production. The phenotypic confirmatory test should be performed on suspicious isolates and consists of testing the MIC of cefotaxime and ceftazidime combined with clavulanic acid. A decrease in an MIC of three or more twofold concentrations for either antibiotic when tested in combination with clavulanic

acid compared to its MIC when tested alone indicates the presence of an ESBL. Similar guidelines are available for antimicrobial disk susceptibility testing (13). The NCCLS recommends that for all ESBL-producing strains, the test result should be reported as resistant for all penicillins, cephalosporins, and aztreonam (12, 13).

In the past, anecdotal reports have been published in which patients have had good clinical outcomes despite receiving cephalosporins as treatment of infections with ESBL-producing organisms, and such occurrences have been used as an argument against routine screening for ESBL production (4). However, when the results of our study were combined with previously published reports, we found that 54% (15 of 28) of patients treated with cephalosporins for serious infections due to ESBL-producing organisms for which the cephalosporin MIC was in the "susceptible" range experienced failure of this therapy. All patients with therapeutic failure either died or had continued signs of infection which necessitated a change in antibiotic therapy. Outcome was worst for patients in whom the cephalosporin MIC of the infecting organism was 8 μg/ml; all six of these patients experienced failure of this therapy, and two of them died. Such data are consistent with recommendations that ESBL-producing organisms be reported as resistant to all cephalosporins.

However, there appears to be a marked discrepancy between these clinical data and the recently reported inability (or unwillingness) of clinical microbiology laboratories to detect ESBL-producing organisms. Tenover et al. (25) sent three ESBL-producing organisms to 38 clinical microbiology laboratories in Connecticut for antimicrobial susceptibility testing; fewer than 10% of laboratories reported isolates possessing the ESBLs SHV-8 and SHV-4 as resistant to cefotaxime. In a large survey of 369 American clinical microbiology laboratories, just 32% (117 of 369) reported performing tests to detect ESBL production by *Enterobacteriaceae*. We believe that clinicians, whose laboratories do not perform tests for detection of ESBLs and do not report ESBL producers as resistant to cephalosporins, risk poor outcome for their patients with serious infections with ESBL producers.

There are several reports of urinary tract infections due to ESBL-producing organisms being successfully treated with cephalosporins, regardless of the results of in vitro susceptibility tests (2, 4, 11). This raises the question of whether clinical microbiology laboratories should test urinary tract isolates for the presence of ESBLs. There are not sufficient data in the literature regarding treatment of such less serious infections to determine if the presence of ESBLs in such settings has clinical significance. However, the detection of ESBLs in any clinical isolate has great potential significance from the point of view of infection control. More than 50 outbreaks of infection with ESBL-producing organisms have been reported thus far (16), and almost all indicate horizontal transfer of ESBL-producing strains. Such outbreaks have been curtailed by prompt introduction of infection control procedures or changes in antibiotic usage patterns (16). Therefore, we recommend that (i) laboratories screen all clinical isolates of klebsiellae and *E. coli* (regardless of the severity of clinical illness or site of infection) for the presence of elevated MICs or reduced zone diameters possibly indicating ESBLs and (ii) if ESBL production is con-

TABLE 2. Treatment of bacteremia with ESBL-producing *K. pneumoniae* with cephalosporins to which the organism is not resistant[a]

Patient age (yr) and sex[b]	Underlying disease or condition	Type of infection[c]	Enzyme(s)	Antibiotic	MIC (μg/ml)	Additional antibiotic (MIC [μg/ml])	Outcome
72, M	Intracerebral hematoma	Ventilator associated pneumonia	TEM (pI 5.4), SHV (pI 7.6)	Ceftazidime	16	Gentamicin (>256)	Failure; continued fevers despite 2 days of ceftazidime; changed to imipenem with cure
76, M	Hypertension	CVL related	SHV (pI 8.2)	Ceftriaxone	16		Failure; continued fevers despite 3 days of ceftriaxone; changed to imipenem but died on 14th day of therapy
58, M	Cirrhosis	Nosocomial pneumonia (not ventilator associated)	SHV (pI 7.6), SHV (pI 8.2)	Ceftriaxone	12		Failure; died (received 48 h of therapy)
39, M	Abdominal surgery	CVL infection	SHV (pI 8.2)	Ceftriaxone	8		Failure; died received 48 h of therapy
35, F	Caesarean section	Surgical wound infection	TEM (pI 5.4), SHV (pI 7.6)	Cefotoxime	4	Amikacin (32)	Failure; continued fevers after 72 h; changed to meropenem with cure
48, M[d]	Abdominal surgery	Unknown	Unknown	Cefepime	2		Failure; continued fevers after 4 days; changed to meropenem with cure
49, M	Cirrhosis	SBP	TEM (pI 5.4), SHV (pI 7.6)	Ceftriaxone	1.5		Cure; infection resolved but relapse with a new strain after antibiotics stopped
73, F	Neurosurgery	Ventilator-associated pneumonia	TEM (pI 5.4) SHV (pI 8.2)	Cefepime	1.5		Cure
25, M	Multiple trauma	Ventilator-associated pneumonia	SHV (pI 7.6)	Cefepime	0.5	Gentamicin (32)	Failure; died of sepsis despite 5 days of therapy
25, F	Bone marrow transplant	CVL infection	Unknown	Ceftazidime	0.5	Tobramycin (0.5)	Cure

[a] Data are from the international *Klebsiella* bacteremia study described in the text. Entries are in descending order of the MIC of the cephalosporin used.
[b] M, male; F, female.
[c] CVL, central venous line; SBP, spontaneous bacterial peritonitis.
[d] This patient was seen at a study site after the study had closed.

TABLE 3. Previously published or presented cases of treatment of serious infections with ESBL-producing *Klebsiella* or *E. coli* with cephalosporins to which the organism is not resistant[a]

Patient age (yr) and sex (reference)	Underlying disease[e]	Type of infection[f]	Blood culture result	Organism	Enzyme(s)	Antibiotic[g]	MIC (μg/ml)	Additional antibiotic (MIC [μg/ml])	Outcome
72, M (Casellas[b])	Esophageal surgery	Mediastinitis	Positive	*K. pneumoniae*	CTX-M2, PER-2, SHV-5	Cefepime	16	Amikacin (32)	Failure; continued fevers and bacteremia despite 3 days of therapy; changed to imipenem and ciprofloxacin with cure
58, F (Casellas)	Biliary tract surgery	Nosocomial pneumonia	Positive	*K. pneumoniae*	NS	Cefepime	8	Amikacin (16)	Failure; persistent fevers despite 3 days of therapy; cured with change to imipenem
68, M (Casellas)	Colon cancer surgery	Nosocomial UTI	Positive	*E. coli*	NS	Cefepime	8	Amikacin (8)	Failure; persistent fevers despite 3 days of therapy; cured with change to imipenem
Infant (28)	Low birth weight	Meningitis	Positive	*K. oxytoca*	SHV-5	Cefotaxime	8		Failure persistent bacteremia after 5 days of cefotaxime; cured with change to imipenem and ciprofloxacin
Infant (28)	Omphalocele repair	Nosocomial pneumonia		*K. oxytoca*	SHV-5	Cefotaxime	8		Failure; died (received 48 h of therapy)
75, M (Wong-Beringer et al.[c])		UTI	Positive	*E. coli*	TEM-28	Ceftizoxime	8	Gentamicin	Failure; relapse
47, M (15)[d]	AIDS	Nosocomial pneumonia		*K. pneumoniae*	TEM-3	Cefoxitin	4	Gentamicin	Initial improvement; then had recurrence of isolation of *K. pneumoniae* for which MIC was increased
48, F (Wong-Beringer et al.)	Kidney-pancreas transplant	UTI	Positive	*E. coli*	TEM-1 other not stated	Ceftizoxime	4		Cure
82, F (Wong-Beringer et al.)	From nursing home	UTI	Positive	*E. coli*	TEM-1, SHV-5	Ceftizoxime	4		Failure
14, F (22)[d]	Ewing's sarcoma	CVL related	Positive	*K. pneumoniae*	SHV-2	Cefmetazole	1	Aztreonam	Cure of *K. pneumonia* bacteremia; died of *Candida* fungemia 34 days later
21, F (Wong-Beringer et al.)	ESRD, ESLD	Primary bacteremia	Positive	*E. coli*	Non-TEM or -SHV	Ceftizoxime	1		Cure
NS (17)	NS	Meningitis		*K. pneumoniae*	TEM-10	Cefotaxime	1		Cure
NS (18)	NS	Nosocomial pneumonia		*K. pneumoniae*	NS	Ceftriaxone	<1		Failure; died
NS (4)[d]	Pancreatitis	Peritonitis		*K. pneumoniae* and *E. coli*	NS	Ceftazidime	≤1		Death within 24 h of therapy from bowel necrosis
14, M (8)	Multiple bowel fistulae	CVL infection	Positive	*K. pneumoniae*	NS	Cefotaxime	0.75		Failure; no improvement after 3 days of cefotaxime; cured with change to ciprofloxacin
61, F (Wong-Beringer et al.)	OLTX	UTI	Positive	*E. coli*	TEM (pI not stated)	Ceftizoxime	0.5		Cure had previously received cefoperazone for 3 days with partial response
45, M (Wong-Beringer et al.)	OLTX	Primary	Positive	*K. pneumoniae*	TEM-28, SHV (pI not stated)	Ceftizoxime	0.5		Partial response after 5 days of therapy
NS (19)	NS	NS	Positive	*E. coli*	TEM-12, TEM-26	Cefotaxime	0.5–1		Cure
44, M (23)	multiple injuries from MVA	Meningitis	Positive	*K. pneumoniae*	TEM-12	Cefotaxime (2 g q4h)	≤0.5–1	Amikacin	Cure (had previously been given 5 days of ceftazdime)
53, M (Wong-Beringer et al.)	OLTX	Peritonitis	Positive	*K. pneumoniae*	SHV-2	Cefotaxime	<0.12		Cure (had previously received cefoperazone for 3 days without success)
Child (21)[d]	Leukemia	NS	Positive	*E. coli*	TEM-10	Cefotaxime	<8		Death (received less than 24 h of therapy)
NS(2)	NS	UTI	Positive	*K. pneumoniae*	SHV-2, SHV-1	Cefotaxime or ceftriaxone	0.5–4		Cure
NS(2)	NS	UTI	Positive	*K. pneumoniae*	SHV-2, SHV-1	Cefotaxime or ceftriaxone	0.5–4	Aminoglycoside	Cure
NS(2)	NS	Empyema	Positive	*K. pneumoniae*	SHV-2, SHV-1	Cefotaxime or ceftriaxone	0.5–4	Aminoglycoside	Failure; relapse
NS(2)	NS	Empyema		*K. pneumoniae*	SHV-2, SHV-1	Cefotaxime or ceftriaxone	0.5–4	Aminoglycoside	Failure; relapse
NS(2)	NS	Mediastinitis	Positive	*K. pneumoniae*	SHV-2, SHV-1	Cefotaxime or ceftriaxone	0.5–4	Aminoglycoside	Failure; relapse

[a] Entries are in descending order of the MIC of the Caphalosporin used. NS, not stated.
[b] J. M. Casellas, Abstr. 36th Intersci. Conf. Antimicrob. Agents Chemother., abstr. E89, 1996.
[c] A. Wong-Beringer, N. Lee, and J. A. Hindler, Abstr. 39th Intersci. Conf. Antimicrob. Agents Chemother., abstr. 1478, 1999.
[d] The patient received a cephamycin or died within 24 h of starting cephalosporin therapy and was therefore, excluded from further analysis.
[e] ESRD, end-stage renal disease; ESLD, end-stage liver disease; OLTX, orthotopic liver transplant recipient; MVA, motor vehicle accident.
[f] UTI, urinary tract infection; CVL, central venous line.
[g] q4h, every 4 h.

TABLE 4. Outcome of serious infections due to ESBL-producing organisms is inferior when the MIC of antibiotics is 2 to 8 μg/ml

MIC (μg/ml)	% (no./total) of patients who:	
	Experienced failure of cephalosporin therapy	Died within 14 days of bacteremia
8	100 (6/6)	33 (2/6)
4	67 (2/3)	0 (0/3)
2	33 (1/3)	0 (0/3)
≤1	27 (3/11)	18 (2/11)
Total[a]	54 (15/28)	

[a] Includes five patients with whose isolates for which MICs were recorded simply as 0.5 to 4 mg/liter.

firmed, either infection control practitioners be notified or a comment appear on the laboratory report indicating the epidemiological significance of ESBL production.

MICs of some cephalosporins for a small number of ESBL-producing isolates will be ≤1 μg/ml. In this study we reviewed 11 cases of serious infections due to ESBL producers for which the MIC of the antibiotic which was used to treat the infection was ≤1 μg/ml. Death occurred in 18% (2 of 11) of these patients, and 9% (1 of 11) required a change in therapy to effect cure (Tables 2 to 4). The number of patients in this category is too small to accurately state whether cephalosporins can be reliably used in this setting.

The cephamycins (cefoxitin, cefotetan, and cefmetazole) are structurally different from the "true" cephalosporins and have enhanced stability to ESBLs. More than 90% of ESBL-producing organisms were "susceptible" to cephamycins (Table 1). However, there are only two reports in peer-reviewed literature of the use of cephamycins for the treatment of serious infections with ESBL-producing organisms (15, 22). In one case, relapse of infection occurred with a cefoxitin-resistant strain (15). Of the five patients evaluated in this report who were treated with cefepime, four experienced clinical failure. Further clinical experience with cephamycins and cefepime needs to be published in order to more fully evaluate the potential usefulness of these antibiotics against serious infections due to ESBL producers.

In summary, we have documented that suboptimal clinical outcome occurs when cephalosporins are used for the treatment of serious infections due to ESBL-producing organisms which may appear to be susceptible on the basis of cephalosporin MICs of 2 to 8 μg/ml. Clinical microbiology laboratories should take heed of current recommendations for detection of ESBLs in order to avoid potential treatment failure when cephalosporins are used.

ACKNOWLEDGMENTS

This work was supported in part by grants from the Cottrell Fellowship of the Royal Australasian College of Physicians, Wyeth Pharmaceuticals, and Merck Inc.

Marilyn Wagener is thanked for her statistical expertise. Herman Goossens, Sunita Mohapatra, and Gordon Trenholme are thanked for their participation in the clinical study and for provision of bacterial isolates.

REFERENCES

1. **Babini, G. S., and D. M. Livermore.** 2000. Antimicrobial resistance amongst *Klebsiella* spp. collected from intensive care units in Southern and Western Europe in 1997–1998. J. Antimicrob. Chemother. **45:**183–189.
2. **Brun-Buisson, C., A. Philippon, M. Ansquer, P. Legrand, F. Montravers, and J. Duval.** 1987. Transferable enzymatic resistance to third-generation cephalosporins during nosocomial outbreak of multiresistant *Klebsiella pneumoniae*. Lancet **i:**302–306.
3. **Centers for Disease Control and Prevention.** 2000. Laboratory capacity to detect antimicrobial resistance, 1998. Morb. Mortal. Wkly. Rep. **48:**1167–1171.
4. **Emery, C. L., and L. A. Weymouth.** 1997. Detection and clinical significance of extended-spectrum β-lactamases in a tertiary-care medical center. J. Clin. Microbiol **35:**2061–2067.
5. **Fantin, B., B. Pangon, G. Potel, F. Caron, E. Vallee, J.-M. Vallois, J. Mohler, A. Bure, A. Philippon, and C. Carbon.** 1990. Activity of sulbactam in combination with ceftriaxone in vitro and in experimental endocarditis caused by *Escherichia coli* producing SHV-2-like β-lactamase. Antimicrob. Agents Chemother. **34:**581–586.
6. **Garner, J. S., W. R. Jarvis, T. G. Emori, T. C. Horan, and J. M. Hughes.** 1988. CDC definitions for nosocomial infections. Am. J. Infect. Control **16:** 128–140.
7. **Jacoby, G. A., and P. Han.** 1996. Detection of extended-spectrum beta-lactamases in clinical isolates of *Klebsiella pneumoniae* and *Escherichia coli*. J. Clin. Microbiol. **34:**908–911.
8. **Karas, J. A., D. G. Pillay, D. Muckart, and A. W. Sturm.** 1996. Treatment failure due to extended spectrum β-lactamase. J. Antimicrob. Chemother. **37:**203–204.
9. **Maslow, J. N., S. Brecher, K. S. Adams, A. Durbin, S. Loring, and R. D. Arbeit.** 1993. Relationship between indole production and the differentiation of *Klebsiella* species: indole-positive and -negative isolates of *Klebsiella* determined to be clonal. J. Clin. Microbiol. **31:**2000–2003.
10. **Medeiros, A. A., and J. Crellin.** 1997. Comparative susceptibility of clinical isolates producing extended spectrum beta-lactamases to ceftibuten: effect of large inocula. Pediatr. Infect. Dis. J. **16:**S49–S55.
11. **Meyer, K. S., C. Urban, J. A. Eagan, and B. J. Berger.** 1993. Nosocomial outbreak of *Klebsiella* infection resistant to late-generation cephalosporins. Ann. Intern. Med. **119:**353–358.
12. **National Committee for Clinical Laboratory Standards.** 2000. Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically. Approved standard M7–A5, 5th ed. National Committee for Clinical Laboratory Standards, Wayne, Pa.
13. **National Committee for Clinical Laboratory Standards.** 2000. Performance standards for antimicrobial disk susceptibility tests. Approved standard M2–A7, 7th ed. National Committee for Clinical Laboratory Standards, Wayne, Pa.
14. **Naumovski, L., J. P. Quinn, D. Miyashiro, M. Patel, K. Bush, S. B. Singer, D. Graves, T. Palzkill, and A. M. Arvin.** 1992. Outbreak of ceftazidime resistance due to a novel extended-spectrum β-lactamase in isolates from cancer patients. Antimicrob. Agents Chemother. **36:**1991–1996.
15. **Pangon, B., C. Bizet, A. Bure, F. Pichon, A. Philippon, B. Regnier, and L. Gutmann.** 1989. In vivo selection of a cephamycin-resistant porin-deficient mutant of *Klebsiella pneumoniae* producing a TEM-3 β-lactamase. J. Infect. Dis. **159:**1005–1006.
16. **Paterson, D. L., and V. L. Yu.** 1999. Extended-spectrum beta-lactamases: a call for improved detection and control. Clin. Infect. Dis. **29:**1419–1422.
17. **Quinn, J. P., D. Miyashiro, D. Sahm, R. Flamm, and K. Bush.** 1989. Novel plasmid-mediated beta-lactamase (TEM-10) conferring selective resistance to ceftazidime and aztreonam in clinical isolates of *Klebsiella pneumoniae*. Antimicrob. Agents Chemother. **33:**1451–1456.
18. **Rice, L. B., E. C. Eckstein, J. DeVente, and D. M. Shlaes.** 1996. Ceftazidime-resistant *Klebsiella pneumoniae* isolates recovered at the Cleveland Department of Veterans Affairs Medical Center. Clin. Infect. Dis. **23:**118–124.
19. **Rice, L. B., S. H. Willey, G. A. Papanicolaou, A. Medeiros, G. M. Eliopoulos, R. C. Moellering, Jr., and G. A. Jacoby.** 1990. Outbreak of ceftazidime resistance caused by extended-spectrum β-lactamases at a Massachusetts chronic-care facility. Antimicrob. Agents Chemother. **34:**2193–2199.
20. **Rice, L. B., J. D. C. Yao, K. Klimm, G. M. Eliopoulos, and R. C. Moellering, Jr.** 1991. Efficacy of different β-lactams against an extended-spectrum β-lactamase-producing *Klebsiella pneumoniae* strain in the rat intra-abdominal abscess model. Antimicrob. Agents Chemother. **35:**1243–1244.
21. **Schiappa, D. A., M. K. Hayden, M. G. Matushek, F. Hashemi, J. Sullivan, K. Y. Smith, D. Miyashiro, J. P. Quinn, R. A. Weinstein, and G. M. Trenholme.** 1996. Ceftazidime-resistant *Klebsiella pneumoniae* and *Escherichia coli* bloodstream infection: a case-control and molecular epidemiologic investigation. J. Infect. Dis. **174:**529–536.
22. **Siu, L. K., P. L. Lu, P. R. Hsueh, F. M. Lin, S. C. Chang, K. T. Luh, M. Ho, and C. Y. Lee.** 1999. Bacteremia due to extended-spectrum beta-lactamase-producing *Escherichia coli* and *Klebsiella pneumoniae* in a pediatric oncology ward: clinical features and identification of different plasmids carrying both SHV-5 and TEM-1 genes. J. Clin. Microbiol. **37:**4020–4027.
23. **Smith, C. E., S. Tillman, A. W. Howell, R. N. Longfield, and J. H. Jogensen.** 1990. Failure of ceftazidime-amikacin therapy for bacteremia and meningitis due to *Klebsiella pneumoniae* producing an extended-spectrum β-lactamase. Antimicrob. Agents Chemother. **34:**1290–1293.

24. **Tenover, F. C., R. D. Arbeit, R. V. Goering, P. A. Mickelsen, B. E. Murray, D. H. Persing, and B. Swaminathan.** 1995. Interpreting chromosomal DNA restriction patterns produced by pulsed-field gel electrophoresis: criteria for bacterial strain typing. J. Clin. Microbiol. **33:**2233–2239.
25. **Tenover, F. C., M. J. Mohammed, T. S. Gorton, and Z. F. Dembek.** 1999. Detection and reporting of organisms producing extended-spectrum beta-lactamases: survey of laboratories in Connecticut. J. Clin. Microbiol. **37:** 4065–4070.
26. **Thauvin-Eliopoulos, C., M.-F. Tripodi, R. C. Moellering, Jr., and G. M. Eliopoulos.** 1997. Efficacies of piperacillin-tazobactam and cefepime in rats with experimental intra-abdominal abscesses due to an extended-spectrum β-lactamase-producing strain of *Klebsiella pneumoniae*. Antimicrob. Agents Chemother. **41:**1053–1057.
27. **Vecoli, C., F. E. Prevost, J. J. Ververis, A. A. Medeiros, and G. P. O'Leary.** 1983. Comparison of polyacrylamide and agarose gel thin-layer isoelectric focusing for the characterization of beta-lactamases. Antimicrob. Agents Chemother. **24:**186–189.
28. **Venezia, R. A., F. J. Scarano, K. E. Preston, L. M. Steele, T. P. Root, R. Limberger, W. Archinal, and M. A. Kacica.** 1995. Molecular epidemiology of an SHV-5 extended-spectrum beta-lactamase in enterobacteriaceae isolated from infants in a neonatal intensive care unit. Clin. Infect. Dis. **21:**915–923.