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Predictors of Mortality in Patients with Bloodstream Infections Caused by Extended-Spectrum-β-Lactamase-Producing *Enterobacteriaceae*: Importance of Inadequate Initial Antimicrobial Treatment▽

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Bloodstream infections (BSI) caused by extended-spectrum β-lactamase (ESBL)-producing organisms markedly increase the rates of treatment failure and death. We conducted a retrospective cohort analysis to identify risk factors for mortality in adult in-patients with BSI caused by ESBL-producing *Enterobacteriaceae* (ESBL-BSI). Particular attention was focused on defining the impact on the mortality of inadequate initial antimicrobial therapy (defined as the initiation of treatment with active antimicrobial agents >72 h after collection of the first positive blood culture). A total of 186 patients with ESBL-BSI caused by *Escherichia coli* ($n = 104$), *Klebsiella pneumoniae* ($n = 58$), or *Proteus mirabilis* ($n = 24$) were identified by our microbiology laboratory from 1 January 1999 through 31 December 2004. The overall 21-day mortality rate was 38.2% (71 of 186). In multivariate analysis, significant predictors of mortality were inadequate initial antimicrobial therapy (odds ratio [OR] = 6.28; 95% confidence interval [CI] = 3.18 to 12.42; $P < 0.001$) and unidentified primary infection site (OR = 2.69; 95% CI = 1.38 to 5.27; $P = 0.004$). The inadequately treated patients (89 of 186 [47.8%]) had a threefold increase in mortality compared to the adequately treated group (59.5% versus 18.5%; OR = 2.38; 95% CI = 1.76 to 3.22; $P < 0.001$). The regimens most commonly classified as inadequate were based on oxyimino cephalosporin or fluoroquinolone therapy. Prompt initiation of effective antimicrobial treatment is essential in patients with ESBL-BSI, and empirical decisions must be based on a sound knowledge of the local distribution of pathogens and their susceptibility patterns.

Bloodstream infections (BSI) caused by organisms that produce extended-spectrum β-lactamase (ESBLs) are associated with increased rates of treatment failure and death (1, 14, 15, 19, 22, 25, 28, 30–33, 38, 39, 41, 43, 46, 47, 50, 51). ESBLs are plasmid-mediated beta-lactamases that confer resistance to oxyimino cephalosporins and monobactams (7, 33). In most cases, they are the result of mutations involving the classical TEM-1/TEM-2 and SHV-1 type β-lactamase genes, although exceptions to this rule (e.g., CTX-M β-lactamases) are becoming more and more common (13, 27, 33, 39).

Patients at high risk for infection by ESBL-producing organisms are often seriously ill, with histories of lengthy hospital stays and prolonged exposure to invasive medical devices and/or procedures (3, 5, 13, 15, 25, 35, 41, 43, 49). Prior exposure to antimicrobial therapy is also a well-recognized risk factor for acquisition of an ESBL-producing organism (25, 35, 43, 47).

The presence of an ESBL determinant significantly reduces the number of antimicrobial agents to which the infecting organism is susceptible (9). In addition, because of their nosocomial origin and the frequent links between ESBL genes and other resistance genes on the mobile DNA elements that are involved in their dissemination, ESBL producers often present complex multidrug-resistant phenotypes (7, 27, 33, 42).

Inadequate initial antimicrobial therapy has been shown to predict mortality in patients with BSI and severe sepsis (24), and it is more likely to occur in BSI due to ESBL producers (43). Recent studies suggest that delaying adequate therapy in these cases can result in adverse outcomes, and mortality increases proportionally with the duration of the delay (1, 15, 19, 22, 25, 43, 47).

In this retrospective study, we attempted to identify risk factors for mortality in patients with BSI caused by ESBL-producing strains of *Escherichia coli*, *Klebsiella* spp., and *Proteus mirabilis*. Particular attention was focused on the adequacy of initial antimicrobial therapy. The hospital-based cohort we analyzed included 186 cases of BSI caused by organisms producing a variety of different ESBLs, and this picture is likely to increase the applicability of our findings.

MATERIALS AND METHODS

Setting. This study was conducted at the Catholic University Hospital, a 1,700-bed academic medical center located in Rome, Italy. It offers a full range of clinical services and admits approximately 60,000 patients per year.

Study design and patients. The computerized database of our microbiology laboratory was searched to identify all adult inpatient BSI caused by ESBL-producing strains of *E. coli*, *Klebsiella* spp., or *P. mirabilis* diagnosed between January 1999 and December 2004. Recurrent infections were excluded, and only one episode per patient (the first) was included in our analysis. The data were collected from patients' hospital charts and the laboratory database, which contains complete profiles for all patients with blood cultures positive for gram-

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TABLE 1. ESBLs identified in 186 bloodstream isolates of *E. coli*, *K. pneumoniae*, and *P. mirabilis*

Microorganism (no. of strains)	ESBL type(s) (no. of isolates)				
	CTX-M	SHV	TEM	SHV/TEM	CTX-M/SHV/TEM
E. coli (104)	CTX-M-1 (6) CTX-M-3 (3) CTX-M-4 (1) CTX-M-10 (4) CTX-M-15 (1) CTX-M-1/CTX-M-4 (8)	SHV-2 (1) SHV-2a (17) SHV-5 (8) SHV-12 (5)	TEM-20 (1) TEM-52 (5) TEM-72 (5) TEM-93 (2) TEM-117 (1) TEM-141 (9)	SHV-5/TEM-141 (1) SHV-12/TEM-52 (1) SHV-12/TEM-58 (7) SHV-12/TEM-72 (2)	CTX-M-3/SHV-12 (1) CTX-M-3/TEM-72 (7) CTX-M-4/TEM-58 (3) CTX-M-10/SHV-12 (1) CTX-M-10/TEM-52 (1) CTX-M-10/TEM-93 (1) CTX-M-4/SHV-12/TEM-58 (2)
K. pneumoniae (58)		SHV-2a (9) SHV-5 (9) SHV-8 (5) SHV-12 (24)		SHV-2a/TEM-116 (7) SHV-2a/TEM-93 (2) SHV-8/TEM-24 (1) SHV-12/TEM-93 (1)	
P. mirabilis (24)	TEM-52 (13) TEM-72 (10) TEM-93 (1)				

negative bacteria since 1999. A retrospective cohort study design was used. The outcome measured was death within 21 days of the first positive blood culture. Survivor and nonsurvivor subgroups were compared to identify predictors of 21-day mortality.

Variables. The following variables were explored as possible predictors of 21-day mortality, For patient variables, we considered age; gender; Charlson comorbidity index (8); underlying diseases; immunosuppressive therapy; the duration of hospitalization; an intensive care unit (ICU) stay at the time of infection; and a history of previous hospitalization (during the 12 months preceding BSI onset), surgery (30 days preceding BSI onset), invasive procedures (including the insertion of central venous catheters, nasogastric tube, or Foley catheters), endoscopy, endoscopic retrograde cholangiopancreatography, bronchoscopy, parenteral nutrition, mechanical ventilation (during the 72 h preceding BSI onset), or prior exposure to antimicrobial therapy on admission and/or after admission before BSI onset. For infection variables, we considered acquisition type (health care acquired versus community acquired), presentation with septic shock, severity of illness, and source of infection. For treatment variables, we considered the inadequacy of initial antimicrobial therapy. For pathogen variables, we considered species, multiple ESBL production, and multidrug resistance.

Definitions. The following terms were defined prior to data analysis. An ESBL-BSI was defined as a bloodstream infection documented by blood culture positivity (at least one specimen) for an ESBL-producing strain of *E. coli*, *Klebsiella* spp., or *P. mirabili*s in a patient with the systemic inflammatory response syndrome (e.g., fever, tachycardia, tachypnea, and leukocytosis) (40). BSI onset was defined as the date of collection of the first blood culture yielding the study isolate. The source of the BSI was an infection at a distant site caused by a microbial strain identical to the bloodstream isolate. It was determined on the basis of microbiological results and physicians' findings (16).

BSIs were classified as healthcare acquired when onset occurred >48 h after admission to the study hospital (16, 19). Earlier-onset infections, i.e., <48 h after hospital admission, were also considered healthcare acquired if the patients had been transferred directly from another hospital or nursing home or discharged from a hospital within the 30 days preceding admission to the study (19).

Septic shock was defined as sepsis associated with organ dysfunction and accompanied by persistent hypotension after volume replacement (40). Severity of illness at infection onset was expressed in terms of the acute physiology and chronic health evaluation (APACHE) III score (23). It was calculated on the basis of available clinical data relative to the first 24 h after BSI onset. Neutropenia was defined as an absolute neutrophil count <500 cells/mm^3.

Inadequate initial antimicrobial therapy was defined as the initiation of treatment with active antimicrobial agents (identified as such based on in vitro susceptibility testing) >72 h after BSI onset.

Microbiology, ESBL identification, and antimicrobial susceptibilities. Bloodstream isolates were identified at the species level with the VITEK 2 (bioMérieux, Inc., Hazelwood, MO) and/or Phoenix (Becton Dickinson Microbiology Systems) systems. The ESBL status of each isolate was determined by phenotypic analysis with molecular identification of ESBL genes (44, 46, 47). The phenotypic assay consisted in disk diffusion screening with cefotaxime (30 μg) and ceftazidime (30 μg) disks, followed by confirmatory testing with disks containing cefotaxime and ceftazidime combined with clavulanic acid (CA; 10 μg) (from Becton Dickinson). Assays were performed and interpreted in accordance with the Clinical Laboratory Standards Institute (CLSI) guidelines, and *K. pneumoniae* ATCC 700603 and *E. coli* ATCC 25922 were used as positive and negative controls, respectively (9). The β-lactamase profiles of all isolates were determined with isoelectric focusing analysis, as described elsewhere (44, 47), and results were interpreted by using published criteria (http://www.lahey.org/studies/wetb.htm). Each isolate then underwent PCR amplification of bla_{TEM}, bla_{SHV}, $bla_{CTX\text{-M}}$, bla_{PER}, $bla_{\text{OXA-10}}$, and $bla_{\text{OXA-2}}$ genes and sequencing of both strands of the PCR products, as previously described (11, 12, 26, 27, 29, 37, 47).

The presence of quinolone resistance genes (*gyrA*, *parC*, *qnrA*, *qnrB1*, and *qnrB2*) in isolates with reduced susceptibility to ciprofloxacin (MIC of 0.5 to 1 μg/ml) was determined by PCR using primers and protocols described elsewhere (20, 48, 51).

The MICs of amoxicillin-CA, amikacin, cefoxitin, ciprofloxacin, cefepime, cefotaxime, ceftazidime, gentamicin, imipenem, levofloxacin, meropenem, piperacillin-tazobactam, and trimethoprim-sulfamethoxazole were determined with the E-test (AB Biodisc, Solna, Sweden), as previously described (44). *E. coli* ATCC 25922, *E. coli* ATCC 35218, and *K. pneumoniae* ATCC 700603 were included as quality control strains in all sessions. MICs were classified according to CLSI guidelines (9). In accordance with the same guidelines, all ESBL-producing isolates of *E. coli*, *K. pneumoniae*, and *P. mirabilis* were reported to be resistant to all penicillins, cephalosporins, and aztreonam, regardless of the MIC that emerged for these drugs. Multidrug resistance (MDR) was defined as in vitro resistance to at least one aminoglycoside (i.e., amikacin or gentamicin) or both, to the fluoroquinolones (levofloxacin and ciprofloxacin), and to trimethoprim-sulfamethoxazole.

Statistical analysis. Continuous variables were compared by the Student *t* test for normally distributed variables and the Mann-Whitney U test for non-normally distributed variables. Categorical variables were evaluated by using the chi-square or the two-tailed Fisher exact test. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated to evaluate the strength of any association that emerged. Values are expressed as means ± the standard deviation (continuous variables) or as percentages of the group from which they were derived (categorical variables). Two-tailed tests were used to determine statistical significance; a P value of <0.05 was considered significant.

Multivariate analysis was used to identify independent risk factors for 21-day mortality. For this analysis, we used logistic regression and incorporated variables found to be significant in univariate testing.

All statistical analyses were performed by using the Intercooled Stata program, version 8, for Windows (Stata Corp., College Station, TX).

RESULTS

During the 6-year study period (1999 to 2004), there were 356,710 hospital admissions, and 191 patients were diagnosed for the first time with ESBL-BSI (overall incidence: 0.53 per

TABLE 2. Antimicrobial susceptibility test results for 186 bloodstream isolates of ESBL-producing *E. coli*, *K. pneumoniae*, and *P. mirabilis*

Antimicrobial agent	*E. coli* (n = 104)			*K. pneumoniae* (n = 58)			*P. mirabilis* (n = 24)		
	MIC (μg/ml)[a]		No. (%) susceptible[b]	MIC (μg/ml)		No. (%) susceptible	MIC (μg/ml)		No. (%) susceptible
	MIC_{50}	MIC_{90}		MIC_{50}	MIC_{90}		MIC_{50}	MIC_{90}	
Amikacin	2	8	102 (98.1)	2	16	53 (91.4)	2	4	24 (100)
Amoxicillin-clavulanic acid	16/8	128/64	48 (46.1)	8/4	128/64	32 (55.1)	2/1	4/2	24 (100)
Aztreonam	256	256	0 (0)	256	256	0 (0)	0.25	1	0 (0)
Cefoxitin	2	≥64	74 (71.1)	2	≥64	43 (74.1)	2	8	100 (0)
Cefepime	16	256	0 (0)	1	256	0 (0)	2	32	0 (0)
Cefotaxime	256	256	0 (0)	8	256	0 (0)	16	256	0 (0)
Ceftazidime	256	256	0 (0)	256	256	0 (0)	4	16	0 (0)
Ciprofloxacin	≥16	≥16	9 (8.6)	2	≥16	27 (46.5)	≥16	≥16	3 (12.5)
Gentamicin	0.5	≥32	59 (56.7)	0.25	≥32	40 (68.9)	≥32	≥32	0 (0)
Imipenem	0.25	0.25	104 (100)	0.25	0.25	58 (100)	1	4	24 (100)
Levofloxacin	≥32	≥32	9 (8.6)	2	≥32	28 (48.2)	≥32	≥32	3 (12.5)
Meropenem	0.03	0.25	104 (100)	0.03	0.25	58 (100)	0.03	0.25	24 (100)
Piperacillin-tazobactam	2/4	256/4	86 (82.7)	2/4	256/4	37 (63.8)	0.5/4	1/4	24 (100)
Trimethoprim-sulfamethoxazole	≥4/76	≥4/76	35 (33.6)	0.12/2.38	≥4/76	2 (55.2)	0.12/2.38	≥4/76	14 (58.3)

[a] MIC_{50} and MIC_{90} are the MICs at which 50 and 90% of isolates, respectively, are inhibited.
[b] In accordance with CLSI guidelines, all ESBL-producing isolates were considered resistant to all penicillins, cephalosporins, and aztreonam regardless of the MICs that emerged for these drugs during in vitro susceptibility testing (see reference 9).

1,000 admissions). Of these, 186 had complete medical records available for review.

Characteristics of ESBL-producing isolates. Isolated organisms included *E. coli* (n = 104, 55.9%), *K. pneumoniae* (n = 58, 31.2%), and *P. mirabilis* (n = 24, 12.9%). A total of 234 different ESBL genes were identified in these 186 isolates: 104 (44.4%) were bla_{SHV}, 83 (35.4%) were bla_{TEM}, and 47 (20%) were $bla_{CTX\text{-}M}$ genes. Forty-six strains carried multiple ESBLs (Table 1).

As shown in Table 2, almost all of the isolates were inhibited by carbapenems and amikacin; 79.3% were susceptible to piperacillin-tazobactam, 55.9% were susceptible to amoxicillin-CA, 53.2% were susceptible to gentamicin, 43.5% were susceptible to trimethoprim-sulfamethoxazole, and 21% were susceptible to ciprofloxacin. Resistance to gentamicin was significantly more common among *P. mirabilis* and *E. coli* isolates than among *K. pneumoniae* isolates. The same was true of ciprofloxacin resistance. Almost half of the *K. pneumoniae* and *E. coli* isolates displayed resistance to amoxicillin-CA. Resistance to piperacillin-tazobactam was less common. None of the *P. mirabilis* isolates were resistant to either of these drug combinations. A total of 49 (26.3%) of the 186 isolates were classified as MDR: 35 *E. coli*, 6 *K. pneumoniae*, and 8 *P. mirabilis* isolates.

Susceptibility findings were reported to physicians 48 to 150 h after BSI onset (74 ± 24 h [mean ± the standard deviation]).

Patient characteristics and initial antimicrobial treatment. The characteristics of the patients with BSI are presented in Table 3. Over half of the patients were suffering from neoplastic disease. A total of 90% had healthcare-acquired infections, and 113 of 186 (60.7%) had histories of recent antimicrobial therapy. The most commonly identified primary infection site was the urinary tract, but the source of the BSI remained obscure in almost half of all cases.

Within a few hours after the index blood culture was drawn, all patients were empirically treated with currently recommended doses (4, 18) of the following antimicrobials: β-lactam–β-lactamase inhibitor combinations (amoxicillin-CA or piperacillin-tazobactam; n = 45; 24.2%), fluoroquinolones (ciprofloxacin or levofloxacin; n = 45; 24.2%), oxyimino cephalosporins (cefotaxime, ceftriaxone, ceftazidime, or cefepime; n = 38, 20.4%), aminoglycosides (amikacin or gentamicin; n = 30, 16.1%), and carbapenems (imipenem or meropenem) (n = 28; 15.1%). In most cases, the choice of the empirical regimen was made by the physician in charge of the patient, and protocols were not used.

In vitro susceptibility testing revealed that the initial therapy was inadequate in 47.8% of the cases (89 of 186). Histories of prior exposure to antimicrobial therapy were significantly more common in this subgroup (67 of 89 [75.3%] versus 46 of 97 [47.4%] of those treated adequately from the outset; OR = 3.37; 95% CI = 1.73 to 6.64; $P < 0.001$), and in roughly one-third of these cases (23 of 67 [34.3%]), the drug prescribed for the BSI came from the same class of antibiotics previously administered. The ineffective drug was an oxyimino cephalosporin in 38 of 89 (42.7%) of the cases; 29 (32.6%) were treated with fluoroquinolones, 12 (13.5%) were treated with aminoglycosides, and 10 (11.2%) were treated with β-lactam–β-lactamase inhibitor combinations.

After a mean interval of 76 h (range, 72 to 120 h) from the index blood culture, 75 of the 89 patients on inadequate initial antimicrobial regimens were placed on active drugs; the remaining 14 of 89 had died before switching therapy. All decisions on definitive therapy were made with the aid of an infectious disease specialist. Of these 75 patients, 33 (44%) were changed to carbapenems; 22 (29.3%) were switched to a β-lactam–β-lactamase inhibitor combination; 10 (13.3%) were placed on an aminoglycoside; and 9 (12%) were changed to a fluoroquinolone.

21-day mortality rates. Twenty-one days after onset of ESBL-BSI, 71 of 186 (38.2%) of the patients had died: 31.7% (33 of 104) of those with *E. coli* BSI, 48.3% (28 of 58) with *K. pneumoniae* BSI, and 41.7% (10 of 24) with *P. mirabilis* BSI.

Univariate analysis revealed significant differences between the survivor and nonsurvivor subgroups (Table 4). A signifi-

TABLE 3. Characteristics of the 186 patients with ESBL-BSIs

Characteristics	No. (%)[a] of patients with BSI caused by:				*P*		
	Total (n = 186)	*E. coli* (n = 104)	*K. pneumoniae* (n = 58)	*P. mirabilis* (n = 24)	*E. coli* vs *K. pneumoniae*	*E. coli* vs *P. mirabilis*	*K. pneumoniae* vs *P. mirabilis*
Patient related							
Males	107 (57.5)	54 (51.9)	40 (69)	13 (54.1)	0.03	0.84	0.20
Mean age in yr ± SD	54 ± 19	51 ± 20	63 ± 15	45 ± 16	0.01	0.22	<0.001
Underlying disease							
Solid tumor	52 (27.9)	21 (20.2)	24 (41.4)	7 (29.1)	0.004	0.33	0.29
Diabetes	50 (26.8)	26 (25)	20 (34.5)	4 (16.7)	0.19	0.38	0.10
Hematological malignancy	45 (24.2)	30 (28.8)	12 (20.6)	3 (12.5)	0.72	0.09	0.38
Liver disease	26 (13.9)	14 (13.5)	9 (15.5)	3 (12.5)	0.71	0.90	0.72
Chronic renal failure	53 (28.4)	32 (30.7)	21 (36.2)	0 (0)	0.47	<0.001	<0.001
Mean days in the hospital ± SD	27 ± 16	24 ± 13	34 ± 20	21 ± 9	0.01	0.35	0.002
Prior exposure to antimicrobial therapy							
Cephalosporins	50 (26.8)	25 (24)	18 (31)	7 (29.2)	0.33	0.60	0.86
Quinolones	48 (25.8)	25 (24)	17 (29.3)	6 (25)	0.46	0.92	0.69
Aminoglycosides	19 (10.2)	8 (7.7)	10 (17.4)	1 (4.2)	0.06	0.54	0.11
β-Lactam–β-lactamase inhibitors	34 (18.3)	15 (14.4)	11 (18.9)	8 (33.3)	0.45	0.03	0.16
Infection-related							
Health care acquired	168 (90.3)	92 (88.5)	55 (94.8)	21 (87.5)	0.18	0.89	0.24
Source of infection							
Unknown	86 (46.2)	41 (39.4)	33 (56.9)	12 (50)	0.03	0.34	0.56
Urinary tract	53 (28.4)	29 (27.9)	15 (25.9)	9 (37.5)	0.78	0.35	0.29
Pancreatico-biliary tract	24 (12.9)	19 (18)	3 (5.2)	2 (8.3)	0.02	0.23	0.58
Surgical wound	29 (10.7)	16 (15.4)	2 (3.4)	2 (8.3)	0.02	0.37	0.35
Lower respiratory tract	6 (3.2)	1 (1)	4 (6.9)	1 (4.2)	0.03	0.25	0.63
Central venous catheter	5 (2.7)	4 (3.8)	1 (1.7)	0 (0)	0.45	0.32	0.51

[a] All values are presented as "no. (%) of patients" except as noted otherwise in column 1.

cantly higher percentage of the latter group had liver disease and histories of previous hospitalization. Nonsurvivors also had significantly higher mean APACHE III scores at infection onset and BSI presentation that included septic shock. Their infections were more frequently caused by *K. pneumoniae* and organisms that were MDR or carried multiple ESBL genes, the source of infection was more likely to remain obscure, and a higher percentage of the patients were initially treated with an inadequate antimicrobial regimen. In logistic regression analysis, the only two variables independently associated with 21-day mortality were inadequate initial antimicrobial therapy (OR = 6.28; 95% CI = 3.18 to 12.42; $P < 0.001$) and unidentified primary infection site (OR = 2.69; 95% CI = 1.38 to 5.27; $P = 0.004$).

In fact, the group that initially received inadequate treatment had a 21-day mortality rate (59.5% [53 of 89]) that was roughly three times higher than that of the group treated from the outset with an active drugs (18.5% [18 of 97]) (OR = 2.38; 95% CI = 1.76 to 3.22; $P < 0.001$). Within the inadequate-treatment group, the mortality rate among those treated with an oxyimino cephalosporin (22 of 38 patients [57.9%]) was not significantly different from that observed among patients placed on other ineffective antimicrobial regimens (31 of 51 patients [60.8%]) ($P = 0.78$). Within the former subgroup, higher mortality was observed when the MIC of the oxyimino cephalosporin used for treatment was ≥16 μg/ml than when the MIC was indicative of susceptibility (i.e., ≤8 μg/ml) (60% [21 of 35] versus 33.3% [1 of 3]) ($P = 0.36$). The three patients in the latter category included one treated with ceftazidime (MIC of 8 μg/ml), who died. The remaining two, who survived, were treated with cefotaxime and cefepime, which displayed MICs of 2 μg/ml for the infecting pathogens, and subsequently they were switched to carbapenems.

For the subgroup of patients whose inadequate initial treatment was corrected based on in vitro susceptibility data, the 21-day mortality rate was 52% (39 of 75), as opposed to only 18% in the subgroup that received adequate treatment within a few hours of BSI onset (OR = 2.18; 95% CI = 1.58 to 3.01; $P < 0.001$). Analysis of the 97 patients in the adequate treatment group revealed that the 21-day mortality rate was highest among the 16 patients treated from the start with fluoroquinolones (44.4%; OR = 4.05; 95% CI = 1.89 to 8.65; $P < 0.001$), and the lowest rate was associated with carbapenem therapy (5.5%; OR = 0.14; 95% CI = 0.02 to 1.03; $P = 0.01$) (Table 5). The eight patients treated with a fluoroquinolone (ciprofloxacin in all cases) who died were infected by pathogens with ciprofloxacin MICs ranging from 0.5 to 1 μg/ml. Four of the eight isolates had a mutation at codon 83 of *gyrA*, and the *qnrB* gene was detected in the other four.

DISCUSSION

Our study highlights the high mortality associated with ESBL-BSI. At 21 days after infection onset, 38% of the 186 patients we investigated had died, and failure to provide adequate antimicrobial therapy within the first 72 h of infection emerged as an independent predictor of mortality. These findings are consistent with those of Anderson et al. (1), who

TABLE 4. Risk factors associated with 21-day mortality (univariate analysis)

Variable	No. (%) of patients[a]		OR (95% CI)	*P*
	Nonsurvivors (*n* = 71)	Survivors (*n* = 115)		
Patient-related				
Male sex	38 (53.5)	69 (60)	0.76 (0.40–1.45)	0.38
Mean age in yr ± SD	55 ± 20	54 ± 19		0.83
Baseline clinical characteristics				
Chronic renal failure	21 (29.6)	32 (27.8)	1.08 (0.53–2.19)	0.79
Dialysis	19 (26.7)	31 (26.9)	0.99 (0.47–2.02)	0.97
Diabetes	20 (28.2)	30 (26.1)	1.11 (0.53–2.26)	0.75
Hematological malignancy	12 (16.9)	33 (28.7)	0.50 (0.21–1.10)	0.06
Liver disease	15 (21.1)	11 (9%)	2.53 (1.00–6.51)	0.02
Solid tumor	20 (28.1)	32 (27.8)	1.01 (0.49–2.05)	0.95
Mean Charlson index ± SD	3.4 ± 2.1	3.2 ± 1.5		0.78
Intensive care unit stay at time of BSI	19 (26.8)	36 (31.3)	0.80 (0.39–1.61)	0.50
Invasive procedures	29 (40.8)	42 (36.5)	1.20 (0.64–2.29)	0.55
Immunosuppressive therapy	18 (25.3)	39 (33.3)	0.66 (0.32–1.33)	0.21
Neutropenia	6 (8.4)	16 (13.9)	0.57 (0.17–1.64)	0.39
Surgery	19 (26.8)	30 (26.1)	1.03 (0.49–2.12)	0.91
Mean days in hospital ± SD	27 ± 15	26 ± 6		0.97
Prior exposure to antimicrobial therapy	45 (63.3)	68 (59.1)	1.19 (0.62–2.31)	0.56
Previous hospitalization	45 (63.4)	49 (42.6)	2.33 (1.21–4.49)	0.005
Admission from a nursing home	6 (8.4)	5 (4.3)	1.46 (0.82–2.60)	0.24
Infection related				
Health care acquired	65 (91.5)	103 (89.6)	1.26 (0.41–4.30)	0.65
Mean APACHE III score ± SD	36 ± 18	31 ± 12	-	0.03
Presentation with septic shock	8 (11.3)	2 (1.7)	7.17 (1.35–70.63)	0.005
Unknown source of BSI	45 (63.4)	41 (35.6)	3.12 (1.61–6.06)	<0.001
Treatment related				
Inadequate initial antimicrobial treatment	53 (74.6)	36 (31.3)	6.46 (3.17–13.33)	<0.001
Microorganism related				
E. coli	33 (46.5)	71 (61.7)	0.53 (0.28–1.02)	0.04
K. pneumoniae	28 (39.4)	30 (26.1)	1.84 (0.93–3.64)	0.05
P. mirabilis	10 (14.1)	14 (12.2)	1.18 (0.74–2.68)	0.70
Multidrug resistant	31 (43.6)	18 (15.6)	4.17 (1.99–8.84)	<0.001
Multiple β-lactamase production	23 (32.3)	23 (20)	1.91 (0.92–3.97)	0.05

[a] All values are presented as "no. (%) of patients" except as noted otherwise in column 1.

reported that a delay in the initiation of effective therapy for >72 h after diagnosis of BSI caused by ceftazidime-resistant *K. pneumoniae* was an independent predictor of death, although no increased risk was associated with more limited delays. Similar findings have been reported by others (25).

Inadequate empirical treatment is a distinct risk in patients with ESBL-BSIs (43). Almost half (47.8%) of our patients initially received ineffective drugs, and rates of up to 66% have been reported by other investigators (1, 39, 43). The risk is substantially increased by additional forms of resistance (often mediated by genes found in the vicinity of the *bla* gene) (7, 33, 43). Approximately one out of four of our isolates were MDR. Prior antimicrobial therapy is a major risk factor for inadequate therapy (24) since it increases the probability of resistance. It was significantly more common in our inadequate-treatment group, and in many cases the drug prescribed for the BSI came from the class of antimicrobials used for the previous infectious episode.

Our findings confirm the low rate of failures reported by others in ESBL-BSIs treated with carbapenems (14, 15, 22, 32, 41). As for the oxyimino cephalosporins, current CLSI guidelines require that ESBL-producing isolates be reported as re-

TABLE 5. Mortality rates (21 day) in 97 ESBL-BSI patients initially treated with antimicrobial agents to which the infecting organism displayed in vitro susceptibility

Antimicrobial agents administered (*n*)	No. (%) of patients		OR (95% CI)	*P*
	Nonsurvivors (*n* = 18)	Survivors (*n* = 79)		
Aminoglycosides (20)	5 (27.8)	15 (19)	1.48 (0.59–3.66)	0.40
β-Lactam–β-lactamase inhibitors (33)	4 (22.2)	29 (36.7)	0.55 (0.19–1.55)	0.24
Carbapenems (28)	1 (5.5)	27 (34.2)	0.14 (0.02–1.03)	0.01
Ciprofloxacin (16)	8 (44.4)	8 (10.1)	4.05 (1.89–8.65)	<0.001

sistant to these drugs, regardless of the MICs that emerge from in vitro testing. Poor outcomes have been observed when severe ESBL infections are treated with these antibiotics, even when the MICs fall within the susceptible range (≤8 μg/ml) (9, 14, 15, 30, 50). In our cohort, empirical use of oxyimino cephalosporins was associated with a mortality rate of ca. 60%. The mortality rate when the MIC of drug used was ≥16 μg/ml was higher than it was among those three patients treated with a cephalosporin for which the MICs were of ≤8 μg/ml, but no conclusions can be drawn based on such a low number of cases.

In severe bacterial infections such as the ones examined in the present study, treatment may fail even when the infecting organism has displayed in vitro susceptibility to the antibiotics used. Indeed, 18.5% of the patients in our adequate-treatment group died, and the 21-day mortality rate was highest (50%) among the 16 patients treated with fluoroquinolones. Kang et al. (22) maintain that fluoroquinolones can be an alternative to carbapenems if the ESBL-producing isolate displays in vitro susceptibility to the drug, but other investigators have reported limited success with this approach (14, 32, 50). Resistance to ciprofloxacin (and piperacillin-tazobactam) has also emerged during treatment of endocarditis caused by an ESBL-producing strain of *K. pneumoniae*, which had initially appeared to be susceptible to both (51). In our study, the eight patients who died despite prompt and seemingly appropriate treatment with ciprofloxacin were infected by pathogens with ciprofloxacin MICs ranging from 0.5 to 1 μg/ml, which are well within the CLSI-defined range of susceptibility but clearly higher than those typically reported for fully susceptible *Enterobacteriaceae* (i.e., <0.25 μg/ml) (14). Consideration of a drug's pharmacokinetics can also improve the accuracy of outcome predictions (2). Failure to reach the pharmacodynamic targets correlated with quinolone efficacy is more likely when the MIC of the drug used is close to the susceptibility breakpoint, particularly when low doses are administered (32). For severely ill, hospitalized patients, a fixed dosage regimen of 400 mg twice daily (like those prescribed for our patients) has been estimated to provide optimal pharmacodynamic exposure to ciprofloxacin only for organisms with ciprofloxacin MICs of <0.03 μg/ml (34). For less susceptible pathogens (MICs of 0.25 to 0.5 μg/ml), substantial dose increases or the addition of a second active agent must be considered.

Clinical data are limited on the use of β-lactam–β-lactamase inhibitor combinations in the treatment of serious ESBL infections (33, 36, 38), so they are not regarded as suitable first-line options (33). Treatment may fail even when pathogens display in vitro susceptibility to these agents (14, 17, 32, 51). Of the 33 patients initially treated with these antimicrobials in our study, 4 died. The role of these agents in the treatment of ESBL-BSIs is still unclear.

The second independent risk factor for mortality that emerged from our study was failure to identify the source of the ESBL-BSI. Like Paterson et al. (31), we found that favorable outcomes were much more likely when the BSI originated from a urinary tract infection (data not shown) since many drugs reach levels in the urine higher than those attained in the blood. The source of a BSI is more likely to remain obscure in nosocomial infections, and the potential role of invasive procedures and recent surgery in these infections has been stressed (45). It is not surprising, therefore, that most of our patients had hospital-acquired infections and histories of invasive procedures and surgery. The risk of death also depends on the nature and severity of the underlying disease when antimicrobial therapy is initiated (10). Most of our patients had multiple underlying diseases (malignancies and liver disease were particularly frequent), and presentation with septic shock and high APACHE scores were common among the patients who died. Patients with these characteristics are probably less capable of tolerating substantial delays in the administration of effective therapy. The prognosis of ESBL-BSI may also depend on the infecting pathogen. Of particular interest are reports on the association between ESBL production and expression of pathogenicity factors (21).

Our study has certain limitations that must be acknowledged. For one thing, our analysis was retrospective, and it was performed at a single healthcare center, so the results are not necessarily applicable to other settings. However, this shortcoming is to some extent outweighed by the large size of the cohort and the fair variety of ESBLs we examined. In addition, the relationship between inadequate treatment of serious bacterial infections and poor outcome has been consistently demonstrated in other studies (1, 14, 15, 22, 24, 30–32, 47, 50).

In conclusion, decisions regarding the empirical treatment of ESBL-BSIs must be based on a sound knowledge of the local distribution of pathogens and their susceptibility patterns (24). It is worth recalling that healthcare-acquired infections are much more likely to be caused by resistant organisms. In a setting such as ours, where ESBL producers are fairly common, empirical treatment of nosocomial BSIs should ideally include drugs that will be effective against these pathogens. Even if the infection is present at admission, factors such as recent hospitalization, admission from a high-risk environment such as a nursing home, dialysis, and/or immunosuppression should alert physicians to the high risk of resistance (24). Histories of previous antibiotic therapy must also be taken into consideration when empirical antimicrobial therapy is being prescribed (24). The risk of inadequate treatment is higher if the BSI is treated with the same class of antimicrobials used recently for previous infectious episode. Awareness of changes in bacterial resistance patterns and an understanding of the risk factors for ESBL infection can improve the efficacy of empirical treatment protocols (24) and, in this context, close collaboration between physicians, clinical microbiologists, and infectious-disease consultants should produce significant positive effects (6).

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ERRATUM

Predictors of Mortality in Patients with Bloodstream Infections Caused by Extended-Spectrum-β-Lactamase-Producing *Enterobacteriaceae:* Importance of Inadequate Initial Antimicrobial Treatment

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Volume 51, no. 6, p. 1987–1994, 2007. Page 1990, Table 3: The values under the "Total" column for "Surgical wound" should read "20 (10.7)."