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Bloodstream Infections Caused by Extended-Spectrum-β-Lactamase-Producing *Escherichia coli*: Risk Factors for Inadequate Initial Antimicrobial Therapy▽

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Extended-spectrum-β-lactamase (ESBL)-producing strains of *Escherichia coli* are a significant cause of bloodstream infections (BSI) in hospitalized and nonhospitalized patients. We previously showed that delaying effective antimicrobial therapy in BSI caused by ESBL producers significantly increases mortality. The aim of this retrospective 7-year analysis was to identify risk factors for inadequate initial antimicrobial therapy (IIAT) (i.e., empirical treatment based on a drug to which the isolate had displayed in vitro resistance) for inpatients with BSI caused by ESBL-producing *E. coli*. Of the 129 patients considered, 56 (43.4%) received IIAT for 48 to 120 h (mean, 72 h). Independent risk factors for IIAT include an unknown BSI source (odds ratios [OR], 4.86; 95% confidence interval [CI], 1.98 to 11.91; $P = 0.001$), isolate coresistance to ≥3 antimicrobials (OR, 3.73; 95% CI, 1.58 to 8.83; $P = 0.003$), hospitalization during the 12 months preceding BSI onset (OR, 3.33; 95% CI, 1.42 to 7.79; $P = 0.005$), and antimicrobial therapy during the 3 months preceding BSI onset (OR, 2.65; 95% CI, 1.11 to 6.29; $P = 0.02$). IIAT was the strongest risk factor for 21-day mortality and significantly increased the length of hospitalization after BSI onset. Our results underscore the need for a systematic approach to the management of patients with serious infections by ESBL-producing *E. coli*. Such an approach should be based on sound, updated knowledge of local infectious-disease epidemiology, detailed analysis of the patient's history with emphasis on recent contact with the health care system, and aggressive attempts to identify the infectious focus that has given rise to the BSI.

Extended-spectrum β-lactamases (ESBLs) are a heterogeneous group of plasmid-mediated bacterial enzymes that confer significant resistance to oxyimino cephalosporin and monobactam antimicrobials (8, 28, 30). Throughout the world, increasing attention is being focused on the growing involvement of ESBL-producing strains of *Escherichia coli* in serious infections of hospitalized and nonhospitalized patients (3, 26, 28–30, 34, 35, 39, 45). This trend is due largely to the emergence of CTX-M type ESBLs, a rapidly expanding group of enzymes that are being encountered with increasing frequency, especially in *E. coli* (24, 25, 35, 36, 48). They are encoded by transferable plasmid genes captured from the chromosomes of *Kluyvera* spp. (6, 36). Acquisition of any ESBL determinant reduces the number of antimicrobial agents to which the microorganism is susceptible (18, 25, 38). This problem is compounded by the fact that ESBL producers often carry other antimicrobial resistance genes, which are located near the *bla* gene on the mobile DNA elements that are involved in their dissemination. In these cases, there is a substantial risk that the infecting pathogen will be resistant to the empirically prescribed antimicrobial treatment.

In a previous study we found that failure to provide adequate antimicrobial therapy in the initial stages of bloodstream infections (BSI) caused by ESBL-producing *Enterobacteriaceae* was associated with a strong increase in the risk of 21-day mortality (45). These findings are consistent with those of other investigators (1, 18, 19, 35, 39, 40). However, much less is known about the specific factors that increase the likelihood of ineffective empirical treatment in these cases (18). Identification of risk factors that are predictive of resistance to empirically prescribed antimicrobials should facilitate attempts to define more-effective management strategies for these often life-threatening infections. To this end, we conducted a retrospective cohort study to define predictors of inadequate initial antimicrobial therapy (IIAT) for hospitalized adults with BSI caused by ESBL-producing *E. coli*.

MATERIALS AND METHODS

Study design and patient population. This retrospective cohort study was conducted at the Catholic University Hospital in Rome, Italy (1,700 beds; approximately 60,000 admissions/year). Hospital records were searched in order to identify all adult inpatients diagnosed with BSI caused by ESBL-producing *E. coli* between January 1999 and December 2005. Recurrent infections were excluded, and only the first episode recorded for each patient was included in our analysis. Patients whose infections were empirically treated with inadequate antibiotic regimens (defined below) were compared with those whose initial regimens were adequate in an attempt to identify factors capable of predicting inadequate initial treatment. The impact of IIAT on patient outcomes (21-day mortality and length of hospitalization after BSI onset) was also assessed.

Definitions. A BSI caused by ESBL-producing *E. coli* was defined as a bloodstream infection documented by growth of ESBL-producing *E. coli* in at least one blood culture specimen from a patient with systemic inflammatory response

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TABLE 1. ESBLs identified in 129 bloodstream isolates of *Escherichia coli*: distribution according to the epidemiological category of the infection

Epidemiological category of BSI (no. of isolates)	ESBL type (no. of isolates)				
	CTX-M	SHV	TEM	SHV/TEM	CTX-M/SHV/TEM
Nosocomial (109)	CTX-M-1 (6) CTX-M-3 (3) CTX-M-4 (1) CTX-M-10 (3) CTX-M-15 (13) CTX-M-1/CTX-M-4 (6)	SHV-2 (1) SHV-2a (16) SHV-5 (7) SHV-12 (14)	TEM-20 (1) TEM-52 (4) TEM-72 (4) TEM-93 (2) TEM-117 (1) TEM-141 (9)	SHV-5/TEM-141 (1) SHV-12/TEM-58 (7) SHV-12/TEM-72 (1)	CTX-M-3/SHV-12 (1) CTX-M-3/TEM-72 (3) CTX-M-4/TEM-58 (2) CTX-M-10/SHV-12 (1) CTX-M-15/SHV-12 (1) CTX-M-4/SHV-12/TEM-58 (1)
Health care associated (18)	CTX-M-10 (1) CTX-M-15 (1) CTX-M-1/CTX-M-4 (2)	SHV-2 (1) SHV-5 (1) SHV-12 (1)	TEM-52 (1) TEM-72 (1)	SHV-12/TEM-52 (1)	CTX-M-10/TEM-52 (1) CTX-M-4/TEM-58 (1) CTX-M-3/TEM-72 (4) CTX-M-10/TEM-93 (1) CTX-M-4/SHV-12/TEM-58 (1)
Community acquired (2)		SHV-5 (1)		SHV-12/TEM-72 (1)	

syndrome (e.g., fever, tachycardia, tachypnea, and leukocytosis) (37). The date of collection of the first blood culture yielding the study isolate (index culture) was regarded as the date of bacteremia onset. An infection at any site caused by the same microbial strain isolated from the blood was considered the source of the BSI (15). The impact of comorbidities was expressed by the Charlson comorbidity index (9), and the APACHE (acute physiology and chronic health evaluation) III score was used to rate the overall severity of the patient's illness (20). This score was calculated on the basis of available clinical data relative to the first 24 h following BSI onset. Septic shock was defined as sepsis associated with organ dysfunction and accompanied by persistent hypotension following volume replacement (37). BSI were classified as nosocomial if the index blood culture had been drawn >48 h after admission to our hospital (14); non-nosocomial infections were classified as health care associated or community acquired as defined by Friedman et al. (13). Prior hospitalization was defined as an inpatient stay of ≥2 days during the 12 months preceding the index hospitalization. Prior antimicrobial therapy was defined as the use of any antimicrobial for >48 h during the 3 months preceding the index admission. Documented recovery of ESBL-producing *E. coli* from a clinical sample(s) other than a blood sample ≤3 months before the onset of the index BSI (as defined above) was considered evidence of previous infections with ESBL-producing *E. coli*. Patients were classified as immunosuppressed if they had any of the following: neutropenia (absolute neutrophil count, <500 cells/mm^3), a history of organ transplantation requiring immunosuppressive therapy, a history of >14 days' treatment with prednisone (at least 10 mg per day or the equivalent) within the 45 days preceding BSI onset, or a history of cytotoxic chemotherapy during the same 45-day interval. The term "initial antibiotic treatment" refers exclusively to drugs with potential activity against *E. coli* (2, 11, 15) that were administered empirically before in vitro susceptibility test results were available (other types of antimicrobials used during this period, e.g., glycopeptides, antianaerobic agents, and antifungals, were excluded from all analyses). The initial treatment was classified as inadequate if the infecting pathogen displayed in vitro resistance (as defined below) to the drug being administered.

Microbiology studies. Bloodstream isolates recovered through December 2001 were identified at the species level with the Vitek 2 system (bioMérieux, Inc, Hazelwood, MO) alone. Thereafter, all isolates were identified with both the Vitek 2 and Phoenix (Becton Dickinson Microbiology Systems) systems. The ESBL status of each isolate was determined as described elsewhere (44, 45). MICs of antimicrobials were determined by the Etest (AB Biodisk, Solna, Sweden) as described previously (44, 45) and were classified according to Clinical and Laboratory Standards Institute (CLSI) breakpoints and guidelines (11). In accordance with these guidelines, all ESBL-producing *E. coli* strains were classified as resistant to all penicillins, cephalosporins, and aztreonam, regardless of the MICs determined for these drugs.

Statistical analysis. Statistical analyses were performed using the Intercooled Stata program, version 8, for Windows (Stata Corporation, College Station, TX). Normally and non-normally distributed continuous variables were evaluated with the Student *t* test and the Mann-Whitney U test, respectively. Categorical variables were evaluated using the chi-square or the Fisher exact test. Values are expressed as means ± standard deviations (SD) (continuous variables) or as group percentages (categorical variables). Univariate analysis was performed to identify factors associated with inadequate empirical therapy. Variables emerging from this analysis with *P* values of <0.2 were included in a multivariate model and subjected to logistic regression. The same approach was used to identify predictors of 21-day mortality. Two-tailed tests were used to determine statistical significance; a *P* value of ≤0.05 was considered significant.

RESULTS

We analyzed the records of 129 adult inpatients with BSI due to ESBL-producing *E. coli* diagnosed between January 1999 and December 2005. The number of cases per year increased threefold between 1999 and 2005 (from 8 to 25 cases). Most infections (109/129; 84.5%) were nosocomial. Of the 20 patients with BSI due to ESBL-producing *E. coli* diagnosed at hospital admission, 18 (13.9% of the total series) met the criteria for health care-associated BSI, and only 2 (1.6%) appeared to have true community-acquired infections.

Microbiological characteristics. A total of 167 different ESBL genes were identified in the 129 study isolates: 61 (36.5%) were $bla_{\text{CTX-M}}$ genes, 58 (34.7%) were bla_{SHV}, and 48 (28.7%) were bla_{TEM}. Thirty-six (27.9%) of the 129 isolates carried multiple ESBL genes (Table 1).

Table 2 shows the antimicrobial resistance phenotypes of the ESBL-producing *E. coli* isolates associated with nosocomial, health care-associated, and community-acquired BSI. All 129 isolates were susceptible to imipenem, meropenem, and amikacin. Fifty-five (42.6%) were coresistant to at least three of the following four drugs or drug classes: (i) ciprofloxacin, (ii) gentamicin, (iii) trimethoprim-sulfamethoxazole, and (iv) β-lactam–β-lactamase inhibitor combinations. Resistance within the last category involved amoxicillin-clavulanic acid and pipericillin-tazobactam in 12 cases and amoxicillin-clavulanic acid alone in the other 10 cases. Compared with isolates that caused health care-associated and community-acquired infections, the nosocomial isolates displayed a significantly higher rate of resistance to the β-lactam–β-lactamase inhibitor combinations ($P < 0.001$). Antimicrobial susceptibility findings were reported to physicians 48 to 120 h after the index blood culture was collected (mean ± SD, 72 ± 24 h).

Patient characteristics. As shown in Table 3, more than half of the patients had neoplastic disease, and almost 40% were immunosuppressed. Urinary tract infections were the most

TABLE 2. Resistance phenotypes of 129 ESBL-producing *E. coli* bloodstream isolates: distribution according to the epidemiological category of the infection

Epidemiological category of BSI (no. of isolates)	No. (%) of isolates[a] showing resistance to the following antimicrobial[b]:									
	AMC	TZP	IPM	MEM	AMK	GM	CIP	LEV	TMZ	≥3 drugs
Nosocomial (109)	36 (33.0)	20 (18.3)	0 (0.0)	0 (0.0)	0 (0.0)	37 (33.9)	100 (91.7)	100 (91.7)	63 (57.8)	48 (44.0)
Health care associated (18)	3 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	5 (27.8)	17 (94.4)	17 (94.4)	12 (66.7)	7 (38.9)
Community acquired (2)	0	0	0	0	0	1	2	2	1	0
Total (129)	39 (30.2)	20 (15.5)	0 (0.0)	0 (0.0)	0 (0.0)	43 (33.3)	119 (92.2)	119 (92.2)	76 (58.9)	55 (42.6)

[a] Values were not reported when fewer than 10 isolates were available.
[b] AMC, amoxicillin-clavulanic acid; TZP, piperacillin-tazobactam; IPM, imipenem; MEM, meropenem; AMK, amikacin; GM, gentamicin; CIP, ciprofloxacin; LEV, levofloxacin; TMZ, trimethoprim-sulfamethoxazole.

commonly identified sources of BSI, but no source could be identified in roughly one-third of the cases. Patients with nosocomial and non-nosocomial (i.e., health care-associated or community-acquired) BSI had similar characteristics, but some differences were found. More than half of the index blood cultures for patients with nosocomial BSI had been drawn in surgical units (51.4% versus 30% [$P = 0.07$]), while the majority of those related to non-nosocomial infections were drawn while the patient was hospitalized in a medical ward (65% versus 43.1% [$P = 0.07$]). Patients with non-nosocomial BSI (the vast majority of which were health care associated) had higher rates of previous hospitalizations (85% versus 50.4% [$P = 0.004$]), isolates that were CTX-M producers (60% versus 37.6% [$P = 0.06$]), and unknown BSI sources (65% versus 27.5% [$P < 0.001$]) and a higher 21-day mortality rate (45% versus 26.6% [$P = 0.09$]).

TABLE 3. Baseline characteristics of 129 patients with ESBL-producing *Escherichia coli* bloodstream infections: distribution according to the epidemiological category of the infection

Patient characteristic	Result[a] for patients in the following infection category with the indicated characteristic:			
	All infections ($n = 129$)	Nosocomial ($n = 109$)	Health care associated ($n = 18$)	Community acquired[b] ($n = 2$)
Demographic information				
Male sex	64 (49.6)	53 (48.6)	10 (55.5)	1
Mean age (yr) ± SD	52 ± 20	54 ± 29	50 ± 12	40 ± 25
Comorbidity				
Chronic liver disease	16 (12.4)	12 (11)	3 (16.6)	1
Chronic renal insufficiency	31 (24)	27 (24.7)	3 (16.6)	1
Diabetes mellitus	33 (25.6)	28 (25.6)	5 (27.7)	0
Hematological malignancy	31 (24)	24 (22)	6 (33.3)	1
Solid tumor	42 (32.5)	37 (33.9)	4 (22.2)	1
Immunosuppression	48 (37.2)	42 (38.5)	6 (33.3)	0
Prior antimicrobials[c]	73 (56.6)	59 (54.1)	12 (66.6)	2
Prior hospital admission[d]	72 (55.8)	55 (50.4)	15 (83.3)	2
Ward at BSI onset				
Medicine	60 (46.5)	47 (43.1)	13 (72.2)	0
Surgery	62 (48.1)	56 (51.4)	4 (22.2)	2
Intensive care unit	7 (5.4)	6 (5.5)	1 (5.5)	0
Source of BSI				
Pancreaticobiliary tract	32 (24.8)	26 (23.8)	6 (33.3)	0
Central venous catheter	4 (3.1)	4 (3.7)	0 (0)	0
Lower respiratory tract	1 (0.7)	0 (0)	1 (5.5)	0
Surgical wound	17 (13.2)	16 (14.6)	1 (5.5)	0
Urinary tract	40 (31)	37 (33.9)	3 (16.6)	0
Unknown	43 (33.3)	30 (27.5)	11 (61.1)	2
Presentation with septic shock	9 (6.7)	7 (6.4)	2 (11.1)	0
BSI caused by CTX-M-producing isolates	53 (41.1)	41 (37.6)	12 (66.7)	0
Inadequate initial antimicrobial treatment	56 (43.4)	44 (40.4)	11 (61.1)	1
21-day mortality	38 (29.4)	29 (26.6)	8 (44.4)	1

[a] Results are numbers (percentages) of patients except where indicated otherwise.
[b] The percentage was not calculated when fewer than 10 patients were evaluated.
[c] During the 3 months prior to the index blood culture.
[d] During the 12 months prior to the index blood culture.

Antimicrobial treatment. Within a few hours after the index blood cultures were collected, all patients were receiving empirical treatment with currently recommended doses (2, 15) of antimicrobials belonging to the following classes: trimethoprim-sulfamethoxazole ($n = 2$ [1.5%]), aminoglycosides (amikacin or gentamicin) ($n = 20$ [15.5%]), carbapenems (imipenem or meropenem) ($n = 25$ [19.4%]), fluoroquinolones (ciprofloxacin or levofloxacin) ($n = 25$ [19.4%]), oxyimino cephalosporins (cefotaxime, ceftriaxone, ceftazidime, or cefepime) ($n = 28$ [21.7%]), and β-lactam–β-lactamase inhibitor combinations (amoxicillin-clavulanic acid or piperacillin-tazobactam) ($n = 29$ [22.5%]). In most cases, the choice of the empirical regimen was made by the physician in charge of the patient, without an infectious-disease consultation. Specific preestablished treatment protocols were not used.

The results of in vitro susceptibility tests indicated that empirical therapy was inadequate in 56 (43.4%) of the 129 cases. Twenty-eight (50%) of these patients received oxyimino cephalosporins, 17 (30.3%) were treated with fluoroquinolones, 5 (8.9%) were treated with β-lactam–β-lactamase inhibitor combinations, 5 (8.9%) received aminoglycosides (amikacin and gentamicin), and trimethoprim-sulfamethoxazole was prescribed for 1 (1.8%). More than half of the inadequately treated patients (30 of 56) had histories of prior antimicrobial therapy with a drug belonging to the same class prescribed empirically for the BSI.

On average, the inadequate therapy was administered for 72 h (range, 48 to 120 h). When the results of susceptibility testing were reported, 10 of the 56 inadequately treated patients had already died. In the other 46 cases (82.1%), the original regimen was discontinued, and the patient was treated with a drug (or, in 10 cases, two drugs) to which his/her isolate had displayed susceptibility in vitro; these drugs comprised carbapenems ($n = 27$), aminoglycosides ($n = 14$), β-lactam–β-lactamase inhibitor combinations ($n = 11$), fluoroquinolones ($n = 2$), and trimethoprim-sulfamethoxazole ($n = 2$). All of the decisions on definitive therapy were made with the aid of an infectious-disease specialist.

Factors associated with IIAT. The 56 patients whose empirical treatment was inadequate were compared with the 73 who received adequate therapy from the onset, in an attempt to identify risk factors for IIAT (Table 4). The IIAT group was significantly older and had a higher mean Charlson comorbidity index. These patients were less likely to have hematological malignancies and more likely to have diabetes mellitus, chronic liver disease, and/or a recent history of invasive diagnostic or therapeutic procedures. A higher percentage of inadequately treated patients had histories (in most cases within the 90 days preceding BSI onset) of previous hospitalization and/or previous antimicrobial therapy. The ESBL-producing *E. coli* isolates from this subgroup were also more likely to be coresistant to three or more antimicrobials.

In multivariate analysis, independent associations with inadequate treatment emerged for the following factors: unknown BSI source (odds ratios [OR], 4.86; 95% confidence interval [95% CI], 1.98 to 11.91; $P = 0.001$), ESBL-producing *E. coli* coresistance to ≥3 antimicrobials (OR, 3.73; 95% CI, 1.58 to 8.83; $P = 0.003$), hospitalization during the 12 months preceding BSI onset (OR, 3.33; 95% CI, 1.42 to 7.79; $P = 0.005$), and exposure to antimicrobials during the 3 months preceding BSI onset (OR, 2.65; 95% CI, 1.11 to 6.29; $P = 0.02$).

Impact of IIAT on patient outcomes. Twenty-one days after BSI onset, 38 (29.4%) of the 129 patients had died, and one-third (13/38) of these deaths occurred within the first 72 h of infection. At both time points, significantly higher mortality was observed in the IIAT group than in the subgroup treated appropriately from the outset: mortality rates were 16.1% (9 of 56) versus 5.4% (4 of 73) 72 h after BSI onset ($P = 0.04$) and 51.8% (29 of 56) versus 12.3% (9 of 73) on day 21 ($P < 0.001$). By univariate analysis, mortality at 21 days was associated not only with inadequate empirical treatment but also with chronic liver disease, hematological malignancy, presentation with septic shock, and unknown source of the BSI (Table 5). Multivariate analysis confirmed that death within 21 days after infection onset was independently predicted by septic shock (OR, 5.88; 95% CI, 1.26 to 27.45; $P = 0.02$), unidentified BSI source (OR, 4.28; 95% CI, 1.71 to 10.69; $P = 0.002$), and, above all, inadequate empirical treatment (OR, 6.22; 95% CI, 2.33 to 16.61; $P < 0.001$).

The impact of inadequate antibiotic treatment on the length of hospitalization was studied for patients who were alive at day 21. Significantly longer stays were observed for inadequately treated patients (mean ± SD, 21.6 ± 8.9 days after BSI onset) than for those whose empirical treatment was adequate (mean ± SD, 16.7 ± 7.8 days) ($P < 0.001$). We repeated this analysis for all patients, regardless of survival. The duration of hospitalization remained longer for patients prescribed with IIAT (mean ± SD, 19.4 ± 8.9 days) than for those initially treated with adequate therapy (mean ± SD, 16.7 ± 7.9 days), but the difference did not reach statistical significance ($P = 0.07$).

DISCUSSION

The results of this 7-year retrospective analysis confirm that the initial treatment prescribed for BSI caused by ESBL-producing *E. coli* is frequently inadequate. Empirical antimicrobial treatment was started immediately after collection of the index culture in all of the cases we analyzed, but almost half of the patients (43.4%) received drugs that were ineffective. Even higher rates (up to 66%) have emerged from other studies of BSI caused by ESBL-producing organisms (1, 35, 39). Multivariate analysis pinpointed four factors as independent predictors of IIAT in this cohort: isolation of a strain displaying multiple-drug resistance (to ≥3 antimicrobials), previous hospitalization within the past year, previous antimicrobial therapy, and BSI with unknown sources.

Not surprisingly, the effectiveness of inadequate empirical treatment in this cohort was independently related to the antimicrobial susceptibility profile of the infecting ESBL-producing pathogen (18). The presence of coresistance to ≥3 antimicrobials more than tripled the likelihood of inadequate treatment (OR, 3.73). The antimicrobial susceptibility profile of the infecting organism is obviously not available when empirical therapy is being prescribed. In its stead, however, an epidemiological profile of the hospital unit itself can do much to improve the choice of an empirical regimen, even if the impact of this information on prescribing practices depends on the way it is used (5, 17, 22, 33). Awareness of local epidemi-

TABLE 4. Univariate and multivariate predictors of inadequate empirical antimicrobial therapy for 129 patients with bloodstream infections due to ESBL-producing *Escherichia coli*

Variable	Result[a] for patients with the indicated variable who received:		*P*	OR (95% CI)
	Inadequate initial antimicrobial treatment ($n = 56$)	Adequate initial antimicrobial treatment ($n = 73$)		
Univariate analysis				
Demographics				
Male sex	26 (46.4)	38 (52)	0.52	0.79 (0.37–1.69)
Mean age (yr) ± SD	56 ± 19	49 ± 20	0.03	
Comorbidity				
Chronic liver disease	13 (23.2)	3 (4.1)	0.001	7.05 (1.77–40.17)
Chronic renal insufficiency	13 (23.2)	18 (24.6)	0.84	0.92 (0.37–2.25)
Diabetes mellitus	21 (37.5)	12 (16.4)	0.006	3.05 (1.24–7.62)
Hematological malignancy	6 (10.7)	25 (34.2)	0.002	0.23 (0.07–0.64)
Solid tumor	23 (41.1)	19 (26)	0.07	1.98 (0.87–4.47)
Immunosuppression	17 (30.3)	31 (42.4)	0.15	0.59 (0.26–1.30)
Mean Charlson index ± SD	3.3 ± 2.1	2.5 ± 1.6	0.02	
History				
Invasive procedures[b]	27 (48.2)	22 (30.1)	0.03	2.15 (0.98–4.74)
Surgery[c]	13 (23.2)	25 (34.2)	0.17	0.58 (0.24–1.35)
Prior ESBL-producing *E. coli* infection[c]	11 (19.6)	11 (15.1)	0.49	1.37 (0.49–3.84)
Prior antimicrobials[d]	40 (71.4)	33 (45.2)	0.002	3.03 (1.36–6.83)
Aminoglycosides	6 (10.7)	7 (9.5)	0.83	1.13 (0.29–4.20)
β-Lactam–β-lactamase inhibitor combinations	8 (14.2)	7 (9.5)	0.40	1.57 (0.46–5.45)
Fluoroquinolones	18 (32.1)	13 (17.8)	0.05	2.18 (0.89–5.43)
Oxyimino cephalosporins	18 (32.1)	16 (21.9)	0.19	1.68 (0.71–4.00)
Prior hospital admission[e]	40 (71.4)	32 (43.8)	0.001	3.20 (1.43–7.23)
Epidemiological category				
Nosocomial	44 (78.5)	65 (89)	0.10	0.45 (0.14–1.32)
Health care associated	11 (19.6)	7 (9.5)	0.10	2.30 (0.74–7.53)
Community acquired	1 (1.8)	1 (1.4)	0.84	1.30 (0.01–104.16)
Ward at BSI onset				
Medicine	26 (46.4)	34 (46.5)	0.98	0.99 (0.46–2.11)
Surgery	25 (44.6)	37 (50.6)	0.49	0.78 (0.36–1.69)
Intensive care unit	5 (8.9)	2 (2.7)	0.12	3.48 (0.53–37.54)
Clinical presentation				
Mean APACHE III score ± SD	32 ± 15	29 ± 11	0.16	
Presentation with septic shock	3 (5.3)	6 (8.2)	0.52	0.63 (0.09–3.13)
Primary source of infection				
Pancreaticobiliary tract	11 (19.6)	21 (28.7)	0.23	0.60 (0.23–1.48)
Central venous catheter	1 (1.7)	3 (4.1)	0.45	0.42 (0.07–5.48)
Lower respiratory tract	1 (1.7)	0 (0)	0.25	
Surgical wound	3 (5.3)	14 (19.1)	0.02	0.23 (0.04–0.93)
Urinary tract	13 (23.2)	27 (36.9)	0.09	0.51 (0.21–1.19)
Unknown	30 (53.5)	13 (17.8)	<0.001	5.32 (2.24–12.86)
ESBL-producing *E. coli* bloodstream isolate				
CTX-M type ESBL production	27 (48.2)	26 (35.6)	0.14	1.68 (0.77–3.64)
Coresistance to ≥3 antimicrobials[f]	32 (57.1)	23 (31.5)	0.003	2.89 (1.32–6.37)
Multivariate analysis				
Unknown source of BSI			0.001	4.86 (1.98–11.91)
Coresistance to ≥3 antimicrobials[f]			0.003	3.73 (1.58–8.83)
Prior hospital admission[e]			0.005	3.33 (1.42–7.79)
Prior antimicrobials[d]			0.02	2.65 (1.11–6.29)

[a] Results are numbers (percentages) of patients except where indicated otherwise.
[b] Includes the presence of central venous catheters, nasogastric tubes, or Foley catheters, endoscopy, endoscopic retrograde cholangiopancreatography, bronchoscopy, administration of parenteral nutrition, or mechanical ventilation during the 72 h before the index blood culture.
[c] During the 30 days before the index blood culture.
[d] During the 3 months before the index blood culture.
[e] During the 12 months preceding the index hospitalization.
[f] Coresistance to three or more of the following antimicrobials: amoxicillin-clavulanic acid, piperacillin-tazobactam, ciprofloxacin, gentamicin, and trimethoprim–sulfamethoxazole.

TABLE 5. Risk factors associated with 21-day mortality (by univariate and multivariate analyses) for 129 patients with bloodstream infections due to ESBL-producing *Escherichia coli*

Variable	Result[a] for patients who:		*P*	OR (95% CI)
	Died (n = 38)	Survived (n = 91)		
Univariate analysis				
Demographics				
Male sex	16 (42.1)	48 (52.2)	0.27	0.65 (0.28–1.49)
Mean age (yr) ± SD	54 ± 20	51 ± 20	0.44	
Comorbidity				
Chronic liver disease	9 (23.6)	7 (7.6)	0.01	3.72 (1.10–12.78)
Chronic renal insufficiency	8 (21)	23 (25.2)	0.60	0.78 (0.27–2.09)
Diabetes mellitus	11 (28.9)	22 (24.1)	0.57	1.27 (0.48–3.20)
Hematological malignancy	5 (13.1)	26 (28.5)	0.06	0.37 (0.10–1.13)
Solid tumor	10 (26.3)	32 (35.1)	0.32	0.65 (0.25–1.62)
Immunosuppression	13 (34.2)	35 (38.4)	0.64	0.83 (0.34–1.95)
Mean Charlson index ± SD	2.9 ± 1.9	2.8 ± 1.8	0.76	
History				
Invasive procedures[b]	19 (50)	30 (32.9)	0.06	2.03 (0.87–4.71)
Surgery[c]	9 (23.6)	29 (31.8)	0.35	0.66 (0.24–1.68)
Prior ESBL-producing *E. coli* infection[d]	9 (23.6)	13 (14.2)	0.19	1.86 (0.62–5.28)
Prior antimicrobials[d]	26 (68.4)	47 (51.6)	0.07	2.02 (10.85–4.95)
Aminoglycosides	6 (15.7)	7 (7.6)	0.16	2.25 (0.57–8.44)
β-Lactam–β-lactamase inhibitor combinations	5 (13.1)	10 (10.9)	0.72	1.22 (0.30–4.31)
Fluoroquinolones	10 (26.3)	21 (23.1)	0.69	1.19 (0.44–3.05)
Oxyimino cephalosporins	12 (31.5)	22 (24.1)	0.38	1.44 (0.56–3.57)
Prior hospital admission[e]	24 (63.1)	48 (52.7)	0.27	1.53 (0.66–3.63)
Epidemiological category				
Nosocomial	29 (76.3)	80 (87.9)	0.09	0.44 (0.55–1.35)
Health care associated	8 (21.1)	10 (10.9)	0.13	2.16 (0.66–6.69)
Community acquired	1 (2.6)	1 (1.1)	0.52	2.43 (0.03–19.3)
Ward at BSI onset				
Medicine	14 (36.8)	46 (50.5)	0.15	0.57 (0.24–1.32)
Surgery	21 (55.2)	41 (45)	0.29	1.50 (0.65–3.46)
Intensive care unit	3 (7.8)	4 (4.4)	0.42	1.86 (0.25–11.58)
Clinical presentation				
Mean APACHE III score ± SD	32 ± 15	29 ± 11	0.16	
Presentation with septic shock	5 (13.1)	4 (4.3)	0.07	3.29 (0.65–17.48)
Primary source of infection				
Pancreaticobiliary tract	6 (15.7)	16 (28.5)	0.12	0.46 (0.14–1.32)
Central venous catheter	0	4 (4.4)	0.18	
Lower respiratory tract	1 (2.6)	0	0.12	
Surgical wound	4 (10.5)	13 (14.2)	0.56	0.70 (0.15–2.51)
Urinary tract	4 (10.5)	36 (39.5)	0.001	0.17 (0.04–0.57)
Unknown	24 (63.1)	19 (20.8)	<0.001	6.49 (2.62–16.25)
ESBL-producing *E. coli* bloodstream isolate				
CTX-M type ESBL production	15 (39.4)	38 (41.7)	0.81	0.90 (0.38–2.10)
Coresistance to ≥3 antimicrobials[f]	14 (36.8)	41 (45)	0.38	0.71 (0.30–1.65)
Inadequate initial antimicrobial treatment	29 (76.3)	27 (29.6)	<0.001	7.63 (2.97–20.58)
Multivariate analysis				
Inadequate initial antimicrobial treatment			<0.001	6.22 (2.33–16.61)
Unknown source			0.001	4.28 (1.71–10.69)
Presentation with septic shock			0.02	5.88 (1.26–27.45)

[a] Results are numbers (percentages) of patients except where indicated otherwise.
[b] During the 72 h before the index blood culture.
[c] During the 30 days before the index blood culture.
[d] During the 3 months before the index blood culture.
[e] During the 12 months preceding the index hospitalization.
[f] Coresistance to ≥3 of the following antimicrobials: amoxicillin clavulanic acid, piperacillin-tazobactam, gentamicin, ciprofloxacin, and trimethoprim-sulfamethoxazole.

ology among the different clinicians working on a ward may vary widely, and if initial treatment decisions are made ad hoc by the physician managing the case (as they were in our cohort), there is likely to be considerable variation in the appropriateness of these prescriptions. Alternatively, ward clinicians can rely on specific, preestablished protocols based on careful analysis of current local resistance profiles.

The empirical regimen was also much more likely to be ineffective when the patient history included hospitalization within the past year or recent antimicrobial therapy. Prior hospitalization is a well-recognized risk factor for infection with drug-resistant (or multidrug-resistant) organisms and colonization by these microbes, which can then persist for months or even years (21). Around half of the patients with nosocomial BSI and more than three-quarters of those with non-nosocomial infections had histories of previous hospitalization, and this factor was associated with an OR for IIAT of 3.33. These patients are more likely to have been exposed to carriers harboring resistant bacteria, owing to the selective pressure of antibiotic therapy (7). Fecal carriage of ESBL-producing *Enterobacteriaceae* is much more common in nosocomial settings than in the community (46), and higher rates of colonization by ESBL-producing strains have been reported in high-risk units characterized by intensive antibiotic use (16).

In accordance with the findings of Kollef (22), our multivariate analysis revealed that the risk of inadequate empirical therapy is significantly increased by a history of recent antimicrobial therapy. Previous antimicrobial use appears to be a major risk factor for the subsequent occurrence of an antibiotic-resistant infection (22, 31, 44). Antibiotic therapy promotes colonization or infection by resistant organisms by eradicating susceptible rival strains and modifying the host's resistance. Its negative effects on the normal flora can also increase the host's vulnerability to assaults by new strains, elevating the risk of colonization by resistant organisms encountered during or shortly after antibiotic treatment. The frequency of rectal colonization with ESBL-producing *Enterobacteriaceae* is increasing rapidly in both inpatient and outpatient settings (3, 10, 21, 32, 46). If the colonizing organism is a multiresistant ESBL-producing *E. coli* strain, it is quite likely that the subsequent infection will be treated inadequately in the empirical phase. Previous antimicrobial therapy, particularly that based on the use of fluoroquinolones, was a more common finding for the IIAT group. The fact that more than half of the patients in this group were treated for BSI with an antimicrobial belonging to the same class of drugs used for the previous infectious episode suggests that a more careful review of the patient history might have helped reduce the rate of IIAT in this group of patients.

The strongest independent predictor of IIAT that emerged from our study was failure to identify the source of the bacteremia. This is a well-known risk factor for mortality among bacteremic patients (19, 45, 50), but its association with inadequate treatment is less clear. Zaragoza and colleagues (50) found that the only factor associated with IIAT of BSI for intensive-care patients was the presence of a nonabdominal, nonrespiratory-tract focus of infection (including infectious foci whose location was never defined). They speculated that BSI stemming from pulmonary or abdominal infections were more likely to be treated effectively because, unlike bacteremia from other sources, these infections are treated with a standardized treatment regimen in their intensive care unit. This factor cannot explain the strong association we observed between unknown sources of the BSI and IIAT, since none of the patients we examined were treated with standard protocols. Nevertheless, these authors' conclusions (50) highlight once again the potential advantages of a standardized empirical regimen based on careful analysis of local antimicrobial susceptibility and resistance data. Our finding also indicates that location of the infectious focus in patients suffering from BSI caused by ESBL-producing *E. coli* should be a high priority.

Delaying effective antimicrobial therapy had a considerable impact on the case outcome. In our cohort, the 21-day mortality rate in the group that initially received inadequate treatment (51.8%) was four times higher than that associated with active drug therapy (10.9%). Other factors, including the primary site of infection, the presence and severity of underlying diseases when antibiotic therapy was started, and the infecting pathogen itself (19, 23, 45), admittedly played important roles in determining the outcome of a BSI. However, our multivariate analysis indicated that IIAT was the strongest independent predictor of mortality at 21 days. In addition, for patients who survived the first 3 weeks, the initial delay in administering effective treatment increased the mean hospital stay by almost 30% (approximately 22 days versus 17).

The size of the cohort and the variety of the ESBLs analyzed are undeniably strong points of our study. However, our analysis was retrospective and was confined to a single health care center, so the results are not necessarily applicable to other settings, particularly hospitals with very low rates of infection caused by ESBL-producing *E. coli* strains and those that use preestablished protocols for prescribing empirical antibiotic therapy (17). In this study 15.5% of the BSI caused by ESBL-producing *E. coli* (20 of 129) were non-nosocomial. In all 20 cases, the index culture was drawn upon admission from patients hospitalized with fevers that had developed at home, and most of the bloodstream isolates recovered from these patients were found to produce CTX-M type enzymes. However, in 18 of the 20 cases, the patient met the criteria for health care-associated BSI, and the only 2 cases that appeared to be true community-acquired infections were caused by non-CTX-M-producing strains. The discrepancies between these findings and those recently reported in Israel and Spain (3, 35), where CTX-M-producing *E. coli* proved to be an important cause of community-acquired BSI, might be related to several factors, including hospital-related and regional differences in the patient populations analyzed. A recent nationwide survey in Italy (25) revealed that ESBL-producing *E. coli* strains represented 1.9% of the *E. coli* isolates in the community, and this finding is consistent with the figures we observed for our cohort of bacteremic patients.

In conclusion, any delay in the initiation of adequate antibiotic therapy is potentially lethal (12, 22). Microbiology laboratories play an important role in detecting ESBL producers, since poor outcomes have been observed when severe infections with ESBL-producing organisms are treated with oxyimino cephalosporins and aztreonam, even when the MICs fall within the susceptible range ($\leq$8 μg/ml) (27, 47). Overexpression of a chromosomally encoded AmpC enzyme or acquisition of plasmid-encoded AmpC enzymes in ESBL-producing or-

ganisms is an additional concern, because the CLSI ESBL confirmatory tests may miss ESBLs in such isolates (11, 42, 43, 49). This could lead to inappropriate therapy with cefepime (4, 41). In a hospital like ours, where ESBL producers are fairly common, empirical treatment of BSI potentially caused by *E. coli* should be reviewed. Our findings indicate that when empirical treatment for these infections is prescribed in an ad hoc fashion, the risk of prescribing an ineffective drug is highest when the isolate proves to be resistant to multiple drugs, when the patient has been hospitalized within the past 12 months or given antimicrobial therapy within the previous 3 months, and when the source of the bacteremia cannot be identified. These results underscore the need for a systematic approach to the management of patients with serious infections caused by ESBL-producing *E. coli*. In addition to host-related factors and the severity of disease at presentation, treatment choices should be based on a sound, updated knowledge of local infectious-disease epidemiology, a detailed analysis of the patient history with special emphasis on recent contact with the health care system, and aggressive efforts to identify the infectious focus that has given rise to the BSI.

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