MAJOR ARTICLE

Community-Onset Bacteremia Due to Extended-Spectrum β-Lactamase–Producing *Escherichia coli*: Risk Factors and Prognosis

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Background. There is little clinical information about community-onset bloodstream infections (COBSIs) caused by extended-spectrum β-lactamase (ESBL)-producing *Escherichia coli* (ESBLEC). We investigated the prevalence and risk factors for COBSI due to ESBLEC, and described their clinical features and the impact of COBSI caused by ESBLEC on 14-day mortality.

Methods. Risk factors were assessed using a multicenter case-control-control study. Influence of ESBL production on mortality was studied in all patients with COBSI due to *E. coli*. Isolates and ESBLs were microbiologically characterized. Statistical analysis was performed using multivariate logistic regression. Thirteen tertiary care Spanish hospitals participated in the study.

Results. We included 95 case patients with COBSI due to ESBLEC, which accounted for 7.3% of all COBSI due to *E. coli*. The ESBL in 83 of these (87%) belonged to the CTX-M family of ESBL, and most were clonally unrelated. Comparison with both control groups disclosed association with health care (odds ratio [OR], 2.1; 95% confidence interval [CI], 1.2–3.8), urinary catheter use (OR, 3.1; 95% CI, 1.5–6.5), and previous antimicrobial use (OR, 2.7; 95% CI, 1.5–4.9) as independent risk factors for COBSI due to ESBLEC. Mortality among patients with COBSI due to ESBLEC was lower among patients who received empirical therapy with β-lactam/β-lactam inhibitor combinations or carbapenems (8%–12%) than among those receiving cephalosporins or fluoroquinolones (24% and 29%, respectively). Mortality among patients with COBSI due to *E. coli* was associated with inappropriate empirical therapy irrespective of ESBL production.

Conclusions. ESBLEC is an important cause of COBSI due to *E. coli*. Clinicians should consider adequate empirical therapy with coverage of these pathogens for patients with risk factors.

Escherichia coli is the leading cause of community-onset gram-negative bloodstream infections (BSIs) [1, 2]. Fluoroquinolones, cephalosporins, and β-lactam/β-lactam inhibitor combinations are frequently recommended as empirical therapy for invasive infections due to *E. coli* [3–5]. Antimicrobial resistance in *E. coli* has significant implications in empirical therapy, because it is associated with worse outcomes for patients with bacteremia [6]. Extended-spectrum β-lactamases (ESBLs) are usually plasmid-mediated enzymes conferring resistance to all penicillins and cephalosporins (except for cephamycins). ESBL-producing organisms are also frequently resistant to non–β-lactam antibiotics, such as fluoro-

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quinolones, trimethoprim-sulfamethoxazole, and aminoglycosides [7, 8].

During recent years, community-onset infections due to ESBL-producing *E. coli* (ESBLEC) have emerged worldwide [7, 9], related to the rapid spread of ESBLs from the CTX-M family [9]. Although most patients with community-onset infections caused by these organisms have lower urinary tract infections [10], some patients present with bacteremia [11, 12]. Despite this, there is still little clinical information about ESBLEC as a cause of community-onset BSIs (COBSIs). Our aim was to investigate the epidemiology, risk factors (in particular, the importance of previous antimicrobial use), and the mortality rate for patients with COBSI caused by ESBLEC.

METHODS

We followed the recommendations of the STROBE statement for reporting the results of observational studies [13].

Design overview, setting, and participants. The study was carried out in 13 tertiary care Spanish hospitals attending a population of >6 million people during the period from October 2004 through January 2006. The risk factors for COBSI due to ESBLEC were studied using a case-control-control design. A case patient was define as an adult (>14 years old) with COBSI due to ESBLEC. Case patients were prospectively recruited by daily review of blood culture results in the participating centers. Two base populations were considered (Figure 1). The first was made up of patients with community-onset sepsis (hereafter referred to as the sepsis population); from this population, 2 control patients per case patient were chosen from among patients in the same hospital who had had a blood culture performed in the month following the corresponding case patient because of suspected community-acquired sepsis (typically, blood cultures performed in the emergency department), provided that the blood culture did not yield ESBL-producing *E. coli*. The second base population was constituted of patients with COBSI due to *E. coli* (hereafter referred to as the COBSI due to *E. coli* population); for this population, 2 control patients per case patient in each center were chosen from among patients in the same hospital with COBSI due to non-ESBLEC, diagnosed during the month following the corresponding case patient. Control patients from both populations were matched to case patients on the basis of hospital and time period, and were randomly selected from among eligible patients by a computerized method using the blood culture register numbers in the microbiology laboratory of each participating hospital.

With regard to prognosis, we compared the 14-day mortality rate between case patients and control patients from the COBSI due to *E. coli* population, because the latter are a representative sample of that population. To control for confounders, an analysis of the variables potentially associated with mortality (including ESBL production) was carried out for all patients included with COBSI (Figure 1). All patients were followed until discharge or death. The study was approved by the local ethics committees of the participating centers.

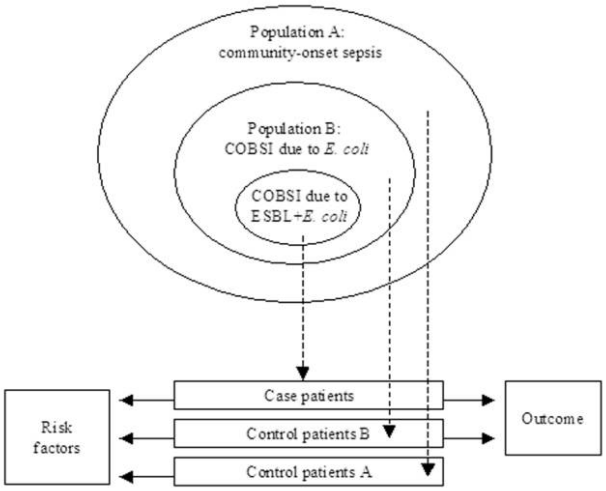

Figure 1. Base populations of the study. COBSI, community-onset bloodstream infection; ESBL, extended-spectrum β-lactamase.

Variables and definitions. Cases of sepsis or BSI were defined as community-onset when the infection occurred among nonhospitalized patients or <48 h after hospitalization. Episodes were considered health care–associated according to the criteria of Friedman et al [2] and were modified as follows, in accordance with the epidemiology of BSI due to ESBLEC [11]: the patient received intravenous therapy, wound care, or specialized nursing care at home or in a day hospital during the 30 days before bacteremia (including the performance of urinary or digestive tract endoscopy or other invasive procedures); the patient was attending a hospital or hemodialysis clinic, or had been hospitalized for ⩾2 days in an acute care hospital or resided in a nursing home or long-term care facility during the year before bacteremia.

The following variables were collected by reviewing the medical charts: age and sex; comorbidities and severity of underlying conditions according to the Charlson index [14]; surgery during the previous year; invasive procedures performed during the preceding 4 weeks; receipt of antimicrobial agents during the preceding 2 months and source of bacteremia (according to both clinical and microbiological criteria); presence of severe sepsis or septic shock [15] at presentation; severity of illness at presentation, according to Pitt score [8]; antimicrobial treatment; and mortality at day 14. Because previous antimicrobial

Table 1. Univariate Analysis of Risk Factors for Case Patients with Community-Onset Bacteremia Due to Extended-Spectrum β-Lactamase (ESBL)–Producing *Escherichia coli,* Compared with Patients with Community-Onset Sepsis (Control Group A) and Patients with Community-Onset Bacteremia Due to Non-ESBL–Producing *E. coli* (Control Group B)

Risk factor	Case patients (n = 95)	Control group A (n = 190)	OR (95% CI)	P	Control group B (n = 188)	OR (95% CI)	P
Age >65 years	69 (73)	96 (51)	2.5 (1.5–4.3)	<.001	120 (64)	1.5 (0.8–2.5)	.1
Female gender	42 (44)	80 (42)	1.0 (0.6–1.7)	.7	105 (56)	0.6 (0.3–1.0)	.06
Health care–associated bacteremia	72 (76)	102 (54)	2.6 (1.5–4.6)	<.001	99 (53)	2.8 (1.6–4.8)	<.001
Previous admission	45 (47)	63 (33)	1.8 (1.0–2.9)	0.02	57 (30)	2.0 (1.2–3.4)	0.005
Nursing home residency	10 (11)	3 (2)	7.2 (1.9–27.1)	.001	5 (3)	4.3 (1.4–12.9)	.005
Hemodialysis	4 (4)	4 (2)	2.0 (0.4–8.3)	.3	0 (0)	…	.005
Day hospital	37 (39)	59 (31)	1.4 (0.8–2.4)	.1	49 (26)	1.8 (1.0–3.0)	.02
Home care	2 (2)	2 (1)	2.0 (0.2–14.5)	.4	1 (1)	4.0 (0.3–44.9)	.2
Transplant	0 (0)	1 (1)	…	.4	6 (3)	…	.07
Charlson index >2	46 (48)	71 (38)	1.5 (0.9–2.5)	.08	58 (31)	2.1 (1.2–3.4)	.004
Diabetes mellitus	24 (25)	36 (19)	1.4 (0.7–2.5)	.2	40 (21)	1.2 (0.7–2.3)	.4
Chronic pulmonary disease	18 (19)	33 (18)	1.1 (0.5–2.0)	.7	13 (7)	3.1 (1.4–6.7)	.002
Heart failure	11 (12)	19 (10)	1.1 (0.5–2.5)	.6	22 (12)	0.9 (0.4–2.1)	.9
Neoplasia	24 (25)	35 (19)	1.4 (0.8–2.6)	.1	44 (23)	1.1 (0.6–1.9)	.7
Cirrhosis of liver	10 (11)	6 (3)	3.5 (1.2–10.1)	.01	8 (4)	2.6 (1.0–6.9)	.04
Chronic renal insufficiency	10 (11)	14 (7)	1.4 (0.6–3.4)	.3	11 (6)	1.8 (0.7–4.6)	.1
Use of immunosuppressive drugs	7 (7)	25 (13)	0.5 (0.2–1.2)	.1	19 (10)	0.7 (0.2–1.7)	.4
Obstructive urinary disease	26 (27)	16 (9)	4.0 (2.0–8.0)	<.001	43 (23)	1.2 (0.7–2.2)	.4
Obstructive biliary disease	8 (8)	7 (4)	2.3 (0.8–6.8)	.09	21 (11)	0.7 (0.3–1.7)	.4
Neutropenia	4 (4)	7 (4)	1.1 (0.3–4.0)	.8	12 (6)	0.6 (0.2–2.0)	.4
Venous catheter use	8 (8)	10 (5)	1.6 (0.6–4.3)	.3	10 (5)	1.6 (0.6–4.2)	.3
Urinary catheter use	23 (24)	17 (9)	3.2 (1.6–6.4)	.001	17 (9)	3.2 (1.6–6.3)	.001
Surgery	12 (13)	10 (5)	2.5 (1.0–6.2)	.02	7 (4)	3.7 (1.4–9.8)	.005
Previous antimicrobial use	39 (41)	44 (23)	2.2 (1.3–3.8)	.002	34 (18)	3.1 (1.8–5.4)	<.001
Aminopenicillins	7 (7)	22 (12)	0.6 (0.2–1.4)	.2	13 (7)	1.0 (0.4–2.7)	.8
Cephalosporins	12 (13)	17 (9)	1.4 (0.6–3.2)	.3	2 (1)	13.4 (2.9–61.4)	<.001
Fluoroquinolones	23 (24)	15 (8)	3.7 (1.8–7.5)	<.001	10 (5)	5.6 (2.5–12.5)	<.001

Note. Date are no. (%) of patients. CI, confidence interval; OR, odds ratio.

use might not have been available from the medical charts, patients or relatives were asked about this specifically using a previously defined questionnaire [10]. Empirical treatment was considered appropriate when an antimicrobial regimen that included an active antimicrobial (ie, one to which the organism causing the bacteremia was susceptible in vitro) at recommended doses was initiated during the first 24 h after the blood sample was obtained; otherwise, it was considered inappropriate.

Microbiological studies. The first isolate (recovered from a blood sample) per case patient was studied. All ESBLEC isolates were sent to a reference microbiology laboratory (Hospital Universitario Virgen Macarena, Seville, Spain), where identification to species level was confirmed using the API 20E system (bioMérieux) and where the production of ESBLs was done by the broth microdilution method, following Clinical and Laboratory Standards Institute guidelines [16]. Antibiotic susceptibility was evaluated by microdilution [16]. ESBL-producing isolates showing resistance to at least 1 representative of 2 other families of antibiotics (fluoroquinolones, β-lactam/β-lactam inhibitor combinations, trimetoprim-sulfamethoxazole, or aminoglycosides) were considered multidrug resistant. The characterization of β-lactamase was determined by isoelectric focusing (Pharmacia Phastsystem), by polymerase chain reaction (PCR) testing of the *bla* genes, and by sequencing [17]. Clonal relatedness was determined by use of the repetitive extragenic palindromic (REP)–PCR method, according to standard criteria [10]. Isolates with similar REP-PCR patterns were also studied using pulsed-field gel electrophoresis with *Xba*I endonuclease [18, 19].

Statistical analysis. Conditional logistic regression was used to compute crude odds ratios (ORs) and 95% confidence intervals (CIs). Multivariate analysis was also performed by conditional logistic regression. Variables introduced into the

Table 2. Multivariate Analysis of Risk Factors for Community-Onset Bacteremia Due to Extended-Spectrum β-Lactamase (ESBL)-Producing *Escherichia coli*

Control group, model, risk factor	OR (95% CI)	*P*
Patients from the community-onset sepsis population		
General model		
Age >65 years	2.3 (1.2–4.3)	.005
Female sex	1.9 (1.07–3.5)	.02
Health care–associated bacteremia	2.1 (1.2–3.8)	.008
Cirrhosis of liver	4.7 (1.4–15.4)	.008
Obstructive urinary tract disease	3.5 (1.5–7.8)	.001
Urinary catheter use	2.3 (1.05–5.0)	.03
Recent antimicrobial use	1.9 (1.03–3.5)	.03
Model with specific types of health care contact[a]		
Resident in long-term care facility	8.6 (2.0–36.2)	.003
Model with specific antimicrobials[a]		
Fluoroquinolones	2.8 (1.2–6.5)	.01
Patients from the community-onset bacteremia due to non-ESBL–producing *E. coli* population		
General model		
Health care–associated bacteremia	2.1 (1.2–3.8)	.008
Chronic obstructive pulmonary disease	3.1 (1.3–7.0)	.005
Urinary catheter use	3.1 (1.5–6.5)	.001
Recent antimicrobial use	2.7 (1.5–4.9)	<.001
Model with specific types of health care contact[a]		
Resident in long-term care facility	5.3 (1.6–17.3)	.005
Model with specific antimicrobials[a]		
Fluoroquinolones	4.7 (2.0–11.1)	<.001
Cephalosporins	10.3 (2.1–50.3)	.003

[a] The rest of the risk factors included in the general models are not shown because the odds ratios (ORs; 95% confidence intervals [CIs]) and *P* values did not change significantly.

multivariate analysis included those with a crude *P* value of <.1, those that were biologically sound, and those found in previous studies of ESBL-producing Enterobacteriaceae. Interactions between paired variables had previously been globally tested, but these were not introduced into the models because no significant association was shown (and also to prevent overfitting). Variables were selected using a stepwise backward process. To investigate the risk factors, we first developed models that included health care association and recent antimicrobial treatment, but not their constituent factors. After checking for selection of these variables, we repeated the models by introducing the individual constituent factors instead (eg, different types of previous health care relation and different families of antimicrobials). Data were analyzed using the Stata, version 9.2 (StataCorp), software package.

RESULTS

During the study period, 191 episodes of bacteremia due to ESBLEC occurred in the participating centers; 95 episodes (50%) were considered to be community-onset episodes and were included. The median percentage of cases of COBSI due to *E. coli* caused by ESBL-producing isolates was 7.3% (range, 3%–18%). The characteristics of the case patients are shown in Table 1.

***Risk factors for community-onset bacteremia due to ESBL-producing* E. coli.** The 2 control groups were made up of 190 and 188 patients, respectively (for 2 case patients, 1 control patients could not be found). The results of the univariate analysis are shown in Table 1. The interactions tested for both populations were: age and sex, recent antimicrobial use and chronic obstructive pulmonary disease, recent antimicrobial use and cirrhosis of the liver, and recent antimicrobial use and obstructive disease of the urinary or biliary tract. With regard to the sepsis population, the following variables were introduced into the multivariate analysis: age; sex; health care association; Charlson index; diabetes mellitus; cirrhosis of the liver; obstructive disease of the urinary tract; obstructive disease of the biliary tract; urinary catheter use; surgery; and recent antimicrobial use. The variables independently associated with COBSI due to ESBLEC are shown in Table 2. With regard to the COBSI due to *E. coli* population, the following variables

Table 3. Clinical and Prognostic Characteristics of Patients with Bacteremia Due to Extended-Spectrum β-Lactamase (ESBL)–producing and non-ESBL–producing *Escherichia coli*

Characteristic	Case patients (n = 95)	Control patients[a] (n = 187)	P
Source of bacteremia			
Not determined	7 (7)	24 (13)	.1
Urinary tract	55 (58)	119 (63)	.3
Intra-abdominal infection[b]	25 (26)	35 (19)	.1
Respiratory tract	4 (4)	8 (5)	.6
Other[c]	4 (4)	2 (1)	.1
Pitt score >1	40 (42)	42 (22)	<.001
Severe sepsis or septic shock	23 (24)	40 (21)	.5
Inappropriate empirical therapy	55 (58)	22 (12)	<.001
14-day mortality	16 (17)	15 (8)	.02

[a] From the community-onset bloodstream infection due to *E. coli* population; 1 patient was excluded because of lack of data.
[b] Spontaneous peritonitis (6 case patients and 1 control patient); secondary peritonitis (6 case patients and 11 control patients); enteritis (1 case patient and 2 control patients); cholangitis (12 case patients and 21 control patients).
[c] Soft tissue infection (1 case patient); catheter-related infection (1 case patient); genital tract infection (1 case patient and 2 control patients); osteomyelitis (1 case patient).

were introduced into the multivariate analysis: age; sex; health care association; Charlson index; diabetes mellitus; chronic obstructive pulmonary disease; cirrhosis of the liver; urinary catheter use; surgery; recent antimicrobial use. The variables independently associated with bacteremia due to ESBLEC are shown in Table 2.

When the 3 risk factors found in the 2 populations were considered (health care–associated bacteremia, urinary catheter use, and recent antimicrobial use), 75 case patients (79%) were found to have been exposed to ⩾1 of them, 34 (36%) to ⩾2, and 6 (20%) to 3; 20 (21%) were not exposed to any of them.

Clinical features and prognosis. The clinical and prognostic characteristics of the case patients are shown in Table 3. For the most frequently used empirical antimicrobials in monotherapy, mortality rates among patients with COBSI due to ESBLEC were as follows: amoxicillin-clavulanate, 8% (2/26 patients died); cephalosporins, 24% (5/21); fluoroquinolones, 29% (2/7); and carbapenems or piperacillin-tazobactam, 12% (1/8 in both cases). None of the case patients with a susceptible isolate treated with amoxicillin-clavulanate (14 patients) or piperacillin-tazobactam (4 patients) died; these patients were treated with intravenous doses of amoxicillin-clavulanate (2–0.125 g every 8 h) or piperacillin/tazobactam (4–0.5 g every 6 h).

The source of bacteremia did not differ significantly between case patients and control patients with COBSI caused by *E. coli* (Table 3). The 14-day mortality rate was significantly higher for bacteremic patients due to ESBL producers; however, the severity of illness, as measured by the Pitt score, was also higher, and empirical antimicrobial treatment was more frequently inappropriate (Table 3). To control for confounders, an analysis of variables associated with mortality was performed that included all patients with bacteremia due to *E. coli* (case patients and control patients from the COBSI due to *E. coli* population). A stratified analysis showed that inappropriate empirical therapy was associated with mortality, for both ESBL and non-ESBL producers, whereas ESBL production was not associated with mortality when empirical therapy was taken into account. Variables shown by multivariate analysis to be independently associated with mortality were as follows: a Pitt score of >1; source other than the urinary tract; and inappropriate empirical therapy (Table 4). Only when inappropriate empirical therapy was excluded from the model was ESBL production selected as being associated with mortality.

Microbiological results. Of the 95 ESBLEC isolates, 83 (87%) produced ESBLs from the CTX-M family (CTX-M-14, 51 isolates; CTX-M-15, 13 isolates; CTX-M-9, 12 isolates; CTX-M-32, 6 isolates; CTX-M-1, 1 isolate; and CTX-M-19, 1 isolate), 15 (16%) produced SHV-type ESBL (SHV-12, 13 isolates; SHV-2a, 2 isolates), and 1 isolate produced a TEM-type ESBL (TEM-52). Five isolates produced 2 ESBLs. We found no significant differences in epidemiological or clinical characteristics by type of ESBL produced (data not shown). Susceptibility results are shown in Table 5. Only 13 isolates (14%) showed resistance to penicillins and cephalosporins only; 57 isolates (60%) were considered to be multidrug resistant, and 13 (14%) were resistant to ciprofloxacin, amoxicillin-clavulanate, trimetoprim-sulfamethoxazole, and either tobramycin or gentamycin.

With regard to clonality, 88 isolates were clonally unrelated. Three small clusters of clonally related isolates were found by

Table 4. Univariate and Multivariate Analysis of Variables Associated with Death among 282 Patients with Community-Onset Bacteremia Due to *Escherichia coli*

Variable	No. of patients who died/no. of patients in the category (%)	RR (95% CI)	*P*	Adjusted OR	*P*
Sex					
Female	16 /147 (11)	1.0 (0.5–1.9)	.9	…	
Male	15/135 (11)				
Age					
>65 years	25/188 (13)	2.0 (0.8–5.0)	.08	…	
≤65 years	6/94 (6)				
Charlson index					
>2	10/42 (24)	2.7 (1.3–5.5)	.004	…	
≤2	21/240 (9)				
Acquisition					
Strict community	17/152 (11)	0.8 (0.4–1.5)	.9	…	
Health care–associated	14/130 (11)				
Source of bacteremia					
Urinary tract	13/174 (7)	0.4 (0.2–0.8)	.01	0.3 (0.1–0.8)	.001
Other	18/108 (16)				
Pitt score					
>1	20/82 (24)	4.5 (2.2–9.0)	<.001	5.3 (2.3–12.2)	<.001
≤1	11/200 (5)				
Severe sepsis or septic shock					
Yes	13/63 (21)	2.5 (1.4–5.0)	.005	…	
No	18/219 (8)				
Empirical treatment					
Inappropriate	17/77 (22)	3.3 (1.6–6.2)	<.001	3.0 (1.3–12.2)	.007
Appropriate	14/205 (7)				
ESBL producer					
Yes	16/95 (17)	2.1 (1.0–4.1)	.02	…	
No	15/187 (8)				

Note. One patient with community-onset bloodstream infection due to non–extended-spectrum β-lactamase (ESBL)–producing *E. coli* was excluded because of lack of data. CI, confidence interval; OR, odds ratio; RR, relative risk.

use of the REP-PCR method and confirmed by use of pulsed-field gel electrophoresis. These included 2 SHV-12–producing isolates from a hospital in Barcelona, 3 CTX-M-14–producing isolates from a hospital in Madrid, and 2 CTX-M-15–producing isolates from the same hospital in Barcelona.

DISCUSSION

Our data show that ESBLEC is a significant cause of COBSI due to *E. coli*. Although the frequency of occurrence (~7% of all cases of COBSI caused by *E. coli* in the participating centers) may not seem alarmingly high, it was reached only 4–5 years after the emergence of the pathogen in Spain [20] and outlines the fact that COBSI may be caused by multidrug-resistant organisms. The predominance of CTX-M enzymes and clonally unrelated isolates coincided with the features of the community isolates circulating in Spain during the study period [21]. To the best of our knowledge, this is the first multicenter study to investigate the risk factors, molecular epidemiology, and clinical features of ESBLEC isolates as a cause of COBSI. Previous studies included a majority of nosocomial episodes and were performed in individual centers [11, 12, 22–25], or included diverse Enterobacteriaceae [7].

The appropriate design for investigating risk factors for infections due to antibiotic-resistant organisms is a challenge that depends on the particular research question. To investigate risk factors for resistance among patients with infections due to a specific microorganism, the control group should be chosen from among patients with the susceptible bacteria. However, such a design may overestimate the importance of previous antimicrobial use because patients who had received antimicrobials would probably be underrepresented in the control

population [26]. This can be avoided by choosing the control patients from among all patients at risk, although some of the identified risk factors might then be nonspecifically associated with the risk of developing an infection caused by the susceptible organism [26]. To overcome these limitations, a double case-control design (whereby, for groups of case patients, patients with a resistant and susceptible organism are compared with one control group made up of patients at risk) was proposed [27]. However, because the patient group in our study of BSI due to non-ESBL–producing *E. coli* was very large, this approach was not feasible, and we used instead a case-control-control design that had proved useful in previous studies [28, 29]. This involved matching case patients and control patients on the basis of hospital and time period but purposely not for variables such as age, sex, or severity of underlying condition, which might themselves have been risk factors [10]. Because sex, age, cirrhosis of the liver, and obstructive disease of the urinary tract were risk factors only in the sepsis population, these variables would probably be nonspecifically associated with bacteremia due to *E. coli.* Health care association (particularly long-term care residency), urinary catheter use, and previous antimicrobial use (particularly fluoroquinolones) were risk factors in both populations, indicating that they are truly associated with ESBLEC. Chronic obstructive pulmonary disease (which may be a surrogate marker for other variables) and previous cephalosporin use were risk factors only for the COBSI due to *E. coli* population and thus should be considered risk factors only for patients with bacteremia due to *E. coli.* It is noteworthy that, in both studies, a high percentage of cases were exposed to no risk factors at all or to just one. Because rectal colonization with virulent strains of ESBLEC is increasing among healthy individuals [30, 31], it can be hypothesized that these infections may increasingly occur among patients with no specific risk factors [10, 28].

The sources of COBSI due to ESBLEC were those expected for *E. coli,* with urinary tract infections predominating, followed by intra-abdominal infections (particularly biliary tract infections). Mortality was significantly higher for patients with COBSI due to ESBLEC than for patients with non-ESBL-producing *E. coli* [25]. However, our results suggest that the increased mortality is not related to ESBL production but to the fact that empirical therapy was more frequently inappropriate among patients with COBSI due to ESBLEC. The importance of appropriate empirical therapy for patients with sepsis has been previously demonstrated [32]. Thus, the outcome of patients with COBSI due to ESBLEC may be improved if appropriate empirical coverage is promptly used.

In our series, mortality was lower among patients treated with carbapenems than among those treated with cephalosporins or fluoroquinolones. Caution is needed in interpreting these results, because our study was not randomized, although

Table 5. Susceptibility to Different Antimicrobial Agents of 95 Isolates of Extended-Spectrum β-Lactamase (ESBL)–Producing *Escherichia coli* Obtained from Blood Samples

Antimicrobial agent	No. (%) of susceptible isolates
Ceftriaxone	5 (5)[a]
Ceftazidime	63 (66)[a]
Cefepime	35 (37)[a]
Amoxicillin-clavulanate	59 (62)
Piperacillin-tazobactam	88 (93)
Ticarcillin-clavulanate	15 (16)
Imipenem	95 (100)
Meropenem	95 (100)
Ertapenem	95 (100)
Ciprofloxacin	34 (36)
Amikacin	81 (85)
Gentamycin	81 (85)
Tobramycin	76 (80)
Tigecycline	95 (100)
Trimetoprim-sulfamethoxazole	35 (37)

[a] Using Enterobacteriaceae break points (all ESBL-producing isolates should be interpreted as resistant according to Clinical and Laboratory Standards Institute recommendations).

they do coincide with previous observations made concerning nosocomial BSI caused by other ESBL-producing Enterobacteriaceae [7]. The efficacy of β-lactam/β-lactam combinations in BSIs caused by ESBL-producing Enterobacteriaceae is controversial [7], but our data suggest that it may be better than previously thought; high doses were used in our study, probably increasing the probability of attaining the appropriate pharmacokinetic and pharmacodynamic target (adequate time above the minimum inhibitory concentration) [33]. However, resistance to these compounds in ESBLEC is frequent in some areas [34], which ruled them out as empirical options (although they might be useful in definite therapy for patients who had susceptible isolates). With regard to cephalosporins, the potential efficacy of those less affected by each specific ESBL is controversial [24, 33]. However, due to the diverse ESBLs produced, as shown in Table 5, none are sufficiently safe to be used empirically.

Our data confirm that carbapenems, including ertapenem, remain active against ESBLEC and are the most reliable agents against ESBL producers [7]. Because carbapenem resistance is also increasing among gram-negative bacteria worldwide, clinicians face a dilemma: the need to use carbapenems when ESBL-producing *E. coli* is a concern against the need to avoid their overuse. In this context, we would suggest the empirical use of carbapenems only for patients with community-onset urinary tract infection or intra-abdominal sepsis with any risk factor for ESBL-producing *E. coli,* and for those presenting with

severe sepsis or septic shock. Tigecycline has shown in vitro activity against these isolates and might be an alternative for non–urinary tract infections, but clinical experience with this compound is still limited [35].

Our study has limitations that need to be borne in mind. We believe that the results are applicable to areas in which most community-onset infections caused by ESBL-producing *E. coli* are caused by clonally unrelated isolates producing various ESBLs [8–13], but caution is necessary when extrapolating these results to areas in which clonally related isolates producing CTX-M-15 are predominant, because the latter are frequently resistant to β-lactam/β-lactam inhibitors [34, 36]. The investigation of risk factors and outcomes using a cohort design would have enabled predictive rules to be developed, but this did not prove feasible because of the high number of patients with community-onset sepsis or bacteremia due to *E. coli.* In the outcome analysis, the number of events (ie, deaths) was low, which limited the power of the multivariate analysis.

In conclusion, ESBL-producing *E. coli* is a pathogen that is increasingly found in the community and that may drive significant changes in the empirical use of antibiotics for certain infections. Although clinicians need to be aware of the situation, international public health control measures are needed to prevent the further spread of this pathogen.

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