MAJOR ARTICLE

A Multinational Survey of Risk Factors for Infection with Extended-Spectrum β-Lactamase–Producing Enterobacteriaceae in Nonhospitalized Patients

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Background. Infections caused by extended-spectrum β-lactamase (ESBL)–producing Enterobacteriaceae are increasing in frequency and are associated with high mortality rates. Circulation of CTX-M–type ESBLs in the community is of particular concern, because it may confound standard infection-control measures.

Methods. We analyzed the results of epidemiologic studies of infection caused by ESBL-producing Enterobacteriaceae in nonhospitalized patients from 6 centers in Europe, Asia, and North America. Risk factors for infection with an ESBL-producing organism were identified by univariate and multivariate analyses.

Results. A total of 983 patient-specific isolates were reviewed (890 [90.5%] of which were *Escherichia coli*, 68 [6.9%] of which were *Klebsiella* species, and 25 [2.5%] of which were *Proteus mirabilis*); 339 [34.5%] of the isolates produced ESBLs. CTX-M types were the most frequent ESBLs (accounting for 65%). Rates of co-resistance to ciprofloxacin among ESBL-producing isolates were high (>70%), but significant variation was seen among centers with respect to rates of resistance to gentamicin, amoxicillin-clavulanate, and trimethoprim-sulfamethoxazole. Similar risk factors for infection with an ESBL-producing organism were found in the different participating centers. Significant risk factors, identified by multivariate analysis, were recent antibiotic use, residence in a long-term care facility, recent hospitalization, age ⩾65 years, and male sex (area under the receiver-operator characteristic [ROC] curve, 0.80). However, 34% of ESBL-producing isolates (115 of 336 isolates) were obtained from patients with no recent health care contact; the area under the ROC curve for the multivariate model for this group of patients was only 0.70, which indicated poorer predictive value.

Conclusions. Community-acquired ESBL-producing Enterobacteriaceae are now prevalent worldwide, necessitating international collaboration. Novel approaches are required to adequately address issues such as empirical treatment for severe community-acquired infection and infection control.

Production of extended-spectrum β-lactamases (ESBLs) by gram-negative bacteria is an emerging health concern in hospitals and long-term care facilities worldwide. ESBLs confer resistance against all β-lactam antibiotics except carbapenems and cephamycins [1]. Furthermore, ESBL-encoding plasmids frequently bear resistance genes for additional antibiotic classes, such as sulfonamides, aminoglycosides, and fluoroquinolones [2, 3]. Treatment options for infections due to these multidrug-resistant organisms are therefore limited, and initial empirical therapy is often ineffective and associated with increased mortality [4–6]. Thus, early recognition of patients who are at risk for infection with ESBL-producing bacteria is necessary to guide empirical treatment and to apply preventive measures to limit the dissemination of infection.

In the past decade, there has been a dramatic increase

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in the prevalence of gram-negative bacteria that produce CTX-M–type β-lactamases, which have now replaced TEM and SHV variants as the most common type of ESBL [7]. At the same time, *Escherichia coli* has replaced *Klebsiella* species as the predominant species of ESBL-producing Enterobacteriaceae in much of the world. $bla_{\text{CTX-M}}$ genes originate from environmental bacteria but have migrated to highly transmissible plasmids, which have been linked with circulation of ESBLs in the community. *E. coli* with CTX-M–type ESBLs have been isolated from domestic animals, food products, sewage, and stool samples from healthy individuals [8, 9]; it is therefore not surprising that gram-negative bacteria that produce these ESBLs are increasingly implicated as causes of community-acquired infection [10]. The remarkable global spread of CTX-M β-lactamases has reached endemic proportions in South America, Canada, most European countries, Asia, and Australia [7]. A recent report highlighted their emergence in the United States [11].

Stratification of patients into risk groups according to the likelihood of their harboring drug-resistant bacteria is a common infection-control strategy. Well-accepted risk factors for infection due to drug-resistant bacteria include recent hospitalization, residence in a long-term or intermediate-term care facility, and recent antibiotic use [12]. More-variably reported risk factors include age, sex, use of gastric acid–modifying drugs, the number and type of comorbid conditions, and functional status. Such risk factors generally apply even where infections become manifest in the community. However, the emergence of community-acquired ESBL-producing bacteria—notably, CTX-M type β-lactamases—among patients who have had no recent contact with the health care system may confound strategies that are based on traditional risk factors. We have previously reported that nearly 20% of patients with infection due to ESBL-producing Enterobacteriaceae at the time of hospital admission in Israel had no identifiable risk factors [2]. The validity of these observations across a range of diverse geographic regions remains unknown. Therefore, we sought to establish an international collaboration that would allow sharing of epidemiologic data on ESBL-producing bacteria. We report here the results of a meta-synthesis of data on community-acquired ESBL infection from 6 centers in Europe, Asia, and North America.

METHODS

A literature search was conducted to identify published journal articles reporting epidemiologic studies of infection due to ESBL-producing bacteria among nonhospitalized patients. The Medline database was searched for the period 1990–2007 with the terms "extended-spectrum β-lactamase" and "ESBL" cross referenced with the terms "community," "non-hospitalized," and "outpatient." Studies were considered for inclusion if they were either laboratory-based or population-based surveys that sought to define risk factors for community-acquired infection due to ESBL-producing Enterobacteriaceae. Authors were invited to share their data in this multinational collaboration. Individual studies were included on the basis of the availability of data regarding risk factors for ESBL production. Authors who were eligible and willing to participate in this study were required to complete a structured questionnaire on each ESBL-positive case patient and ESBL-negative control subject in their database. Items in the questionnaire included demographic data (age at the time of study entry, sex, functional status, and residence in a long-term care facility) [13]; McCabe score [14]; comorbid conditions, the presence of indwelling urinary or vascular catheters, or nasogastric feeding; and any hospitalization, stay in an intensive care unit, mechanical ventilation, surgery, dialysis, or use of antibiotics within the 3 months prior to study entry. Antibiotic exposure was analyzed separately for each antibiotic class and for all antibiotic classes combined. A subanalysis of risk factors was performed for patients who were not hospitalized and had not resided in any long-term care facility within the previous 3 months.

For all isolates (ESBL producers and nonproducers), data were collected on susceptibilities to gentamicin, trimethoprim-sulfamethoxazole, amoxicillin-clavulanate, and ciprofloxacin. Data on the specific ESBL enzymes produced were collected when available, but they were not required for study participation.

Statistical analysis. Data on case patients and control subjects from all centers were examined separately for each center and for all centers in aggregate. All variables were examined by univariate analysis using the χ^2 or Fisher's exact test, as appropriate. Continuous variables were analyzed by Student's t test. Variables with $P < .2$ in univariate analysis were examined in the multivariate model using logistic regression. A final model was built including all variables for which $P < .05$. Variables that were not retained in the model by this procedure were then tested for confounding by adding them one at a time to the model and examining their effect on the β coefficients. Variables that caused substantial confounding (ie, change in β coefficient of >10%) were included in the final model. The area under the receiver-operator characteristic (ROC) curve was calculated for the predictive models. All statistical tests were 2-tailed. $P < .05$ was considered to be statistically significant. SPSS software, version 13.0 (SPSS), was used for statistical analyses.

RESULTS

We identified 191 publications through the literature search. Of these, 8 were either laboratory- or population-based surveys that included sufficient epidemiological data to meet our inclusion criteria [2, 3, 15–20]. Authors of 6 of these studies were

Table 1. Characteristics of Centers Participating in an Epidemiologic Survey of Infection with Extended-Spectrum β-Lactamase (ESBL)–Producing Enterobacteriaceae among Nonhospitalized Patients

Region	Population	Facility	Design	Exclusion	No. of ESBL-positive subjects/control subjects	Species	Source	Period	Study
Calgary, Canada	958,610	All medical facilities in Calgary region	Population-based survey	…	115/NA	*Escherichia coli*	Any	Jan 2000–Dec 2002	[20]
Turkey	NA	15 Medical centers	Population-based survey, case-control	Hospital stay within 1 month, LTCF	41/473	*E. coli*	Urine	Jan 2004–May 2004	[16]
Barcelona, Spain	~300,000	Urban hospital	Survey at hospital admission	Hospital stay within 1 month	19/NA	*E. coli*	Urine	Jan 2000–Jan 2001, Oct 2003–Dec 2003	[17]
Seville, Spain	~450,000	Urban hospital	Survey at hospital admission, case-control	Hospital stay within 1 month	49/98	*E. coli*	Blood (6), Urine (43)	Jan 2001–May 2002	[3]
France	NA	28 Private laboratories	Population-based survey	…	78/NA[a]	*Klebsiella* species, *E. coli*, *Proteus mirabilis*	Urine (76), Skin (2)	1999, 2004, 2006	[15, 36][b]
Tel Aviv, Israel	~700,000	Urban hospital	Survey at hospital admission, case-control	…	38/72	*Klebsiella* species, *E. coli*, *P. mirabilis*	Blood	Jan 2000–Dec 2003	[2]

NOTE. There were a total of 339 ESBL-positive subjects and 644 control subjects. LTCF, long-term care facility; NA, not applicable.

[a] A total of 23 non–*E. coli*, non-*Klebsiella* species, non-*Proteus* species isolates were removed from analysis.

[b] Includes data from an unpublished study conducted in 2006.

Table 2. Predictors of Infection with an Extended-Spectrum β-Lactamase–Producing Pathogen among Patients with Community-Acquired Infection

Variable	Univariate analysis		Multivariate analysis	
	Odds ratio (95% confidence interval)	*P*	Odds ratio (95% confidence interval)	*P*
All patients (n = 983)				
Functional dependence	3.7 (2.1–6.4)	<.001	…	
Male sex	2.18 (1.6–2.9)	<.001	2.5 (1.7–3.7)	<.001
Age ⩾65 years	3.7 (2.7–4.9)	<.001	2.4 (1.6–3.6)	<.001
Admission from LTCF	8.5 (4.3–16.8)	<.001	7.5 (3.5–16.3)	<.001
McCabe score >1	2.4 (1.4–4.0)	.001	…	
Recent hospitalization[a]	2.9 (2.0–4.2)	<.001	2.9 (1.9–4.4)	<.001
Pulmonary disease	2.4 (1.04–5.7)	.04	…	
Cardiovascular disease	1.3 (0.8–2.1)	.3	…	
Diabetes mellitus	1.7 (0.98–2.9)	.06	…	
Renal disease[b]	1.9 (1.0–3.8)	.05	…	
Cerebrovascular disease	2.3 (1.06–5.1)	.04	…	
Malignancy	1.2 (0.6–2.2)	.6	…	
Bladder catheter[a]	4.3 (2.8–6.7)	<.001	…	
Surgery[a]	1.1 (0.8–1.5)	.3	…	
Dialysis	4.0 (0.7–22.5)	.18	…	
Recent use of any antibiotic[a]	1.5 (1.1–2.0)	.02	1.8 (1.2–2.6)	.001
Recent use of a fluoroquinolone[a]	1.2 (0.8–1.7)	.2	…	
Recent use of a cephalosporin[a]	2.9 (1.8–4.9)	<.001	…	
Patients with no recent health care contact (n = 795)				
Male sex	1.7 (1.1–2.5)	.009	2.9 (1.8–4.7)	<.001
Age ⩾65 years	3.6 (2.5–5.1)	<.001	3.5 (2.5–5.6)	<.001
Recent use of any antibiotic[a]	1.6 (1.08–2.4)	.02	…	
Recent use of a cephalosporin[a]	3.7 (1.8–7.3)	<.001	3.6 (1.8–7.3)	<.001
Functional dependence	3.6 (1.5–8.7)	.004	…	
Bladder catheter[a]	3.3 (1.7–6.5)	.001	…	

NOTE. LTCF, long-term care facility.

[a] Exposure within 3 months prior to date of Enterobacteriaceae culture.

[b] Renal disease was defined as a serum creatinine level >3 mg/dL.

able to provide adequate data and consented to participate in the present analysis [2, 3, 10, 15–17].

Characteristics of the participating centers are outlined in table 1. They included 3 tertiary level hospitals (2 in Spain [Seville and Barcelona] and 1 in Israel [Tel Aviv]) and networks of medical facilities in studies from Canada (Calgary Health Region), France (28 private laboratories), and Turkey (15 geographically dispersed medical centers). All of the studies were conducted from 1999 through 2006; collection of isolates occurred during 1999, 2004, and 2006 in the study from France and during 2004 in the study from Turkey. The other 4 studies were performed during the period from 2000 through 2003.

Three studies were hospital-based surveys that evaluated patients at hospital admission [2, 3, 17], and 3 studies were population based [15, 16, 20, 36]. Three of the studies followed a case-control design [2, 3, 16]. In addition, there were differences among studies with respect to patient inclusion criteria, as well as with respect to the Enterobacteriaceae species and the infection sites surveyed (table 1).

A total of 983 patient-specific isolates were included in 6 studies: 890 (90.5%) of the isolates were *E. coli,* 68 (6.9%) were *Klebsiella* species, and 25 (2.5%) were *Proteus mirabilis.* Of these isolates, 339 (34.6%) were ESBL producers; *E. coli* was the most common ESBL-producing organism (297 [87.6%] of 339 ESBL-producing isolates). The proportion of ESBL-producing isolates was 33.5% for *E. coli* (298 of 890 isolates), 39.7% for *Klebsiella* species (27 of 68), and 60% for *P. mirabilis* (15 of 25).

Risk factors for infection due to an ESBL-producing Enterobacteriaceae, identified through univariate analysis, were functional dependence of any grade, bladder catheterization, McCabe score >1, male sex, age ⩾65 years, hospital admission from a long-term care facility, the presence of a comorbid condition (pulmonary disease, cerebrovascular disease, or renal function impairment), hospitalization within the preceding 3

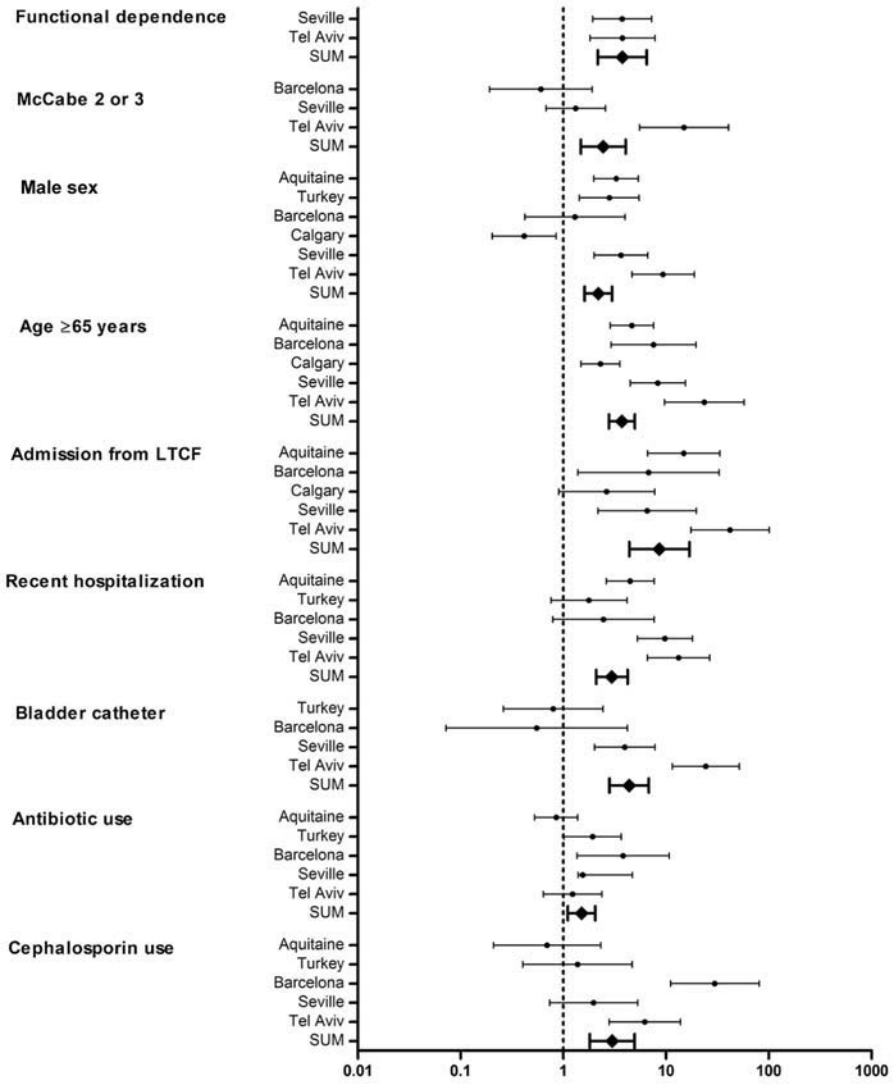

Figure 1. Risk factors for infection due to extended-spectrum β-lactamase—producing Enterobacteriaceae, by center. *Circle,* odds ratio for each center-variable pair; *diamonds,* pooled odds ratio for all centers analyzed for each variable; *LTCF,* long-term care facility; *whiskers,* 95% confidence interval.

months, use of any antibiotic agent, and use of a cephalosporin antibiotic (table 2 and figure 1). Similar risk factors were noted in all studies, with 2 exceptions: age ⩾65 was inversely correlated with ESBL production in the Turkish study [16], which was the only study to exclude long-term care facility residents, and female sex was associated with ESBL production in the Canadian study [20] (figure 1).

Multivariate analysis identified 5 variables as statistically significant predictors of infection due to an ESBL-producing Enterobacteriaceae: age ⩾65 years (odds ratio [OR], 2.4; 95% confidence interval [CI], 1.6–3.6), recent use of any antibiotic (OR, 1.8; 95% CI, 1.2–2.6), recent hospitalization (OR, 2.9; 95% CI, 1.9–4.4), residence in a long-term care facility (OR, 7.5; 95% CI, 3.5–16.3), and male sex (OR, 2.5; 95% CI, 1.7–3.7) (table 2). Use of this model to construct an ROC curve yielded an area under the ROC curve of 0.80 (figure 2).

A total of 795 (81%) of 983 patients had no recent (ie, within the previous 3 months) hospitalization or stay in a long-term care facility; 221 (28%) of these 795 patients had infection due to ESBL-producing organisms. These 221 patients were less likely, compared with patients with infection due to an ESBL-producing bacteria and recent health care contact, to be elderly (OR, 0.3; $P < .001$); to have a McCabe score of >1 (OR, 0.16; $P < .001$); to have an indwelling bladder catheter (OR, 0.26; $P = .001$); or to have cardiovascular disease (OR, 0.18; $P < .001$), renal impairment (OR, 0.26; $P = .02$), or malignancy (OR, 0.1; $P = .001$). The multivariate model for infection with an ESBL-producing organism among patients without recent

health care contact included age ⩾65 years, male sex, and recent use of a cephalosporin (table 2). However, the area under the ROC curve for this model was only 0.70, reflecting lower accuracy for the prediction of infection due to an ESBL producer, compared with a model fitted for a population that included patients with recent health care contact ($P = .003$ for comparison of the ROC curves) (figure 2).

β-Lactamase genes. Identification of the ESBL genes was performed for 269 isolates from 5 centers. The technique involved polymerase chain reaction (PCR) amplification with specific primers for bla_{TEM}, bla_{SHV}, and $bla_{CTX\text{-}M}$ and sequencing of the PCR product. CTX-M was by far the most common ESBL enzyme and was detected in 176 (65%) of the isolates (table 3). TEM, SHV, and OXA type ESBLs were found in 21%, 14%, and 1.4% of isolates, respectively. CTX-M β-lactamases were more frequent among *E. coli* than they were among non–*E. coli* isolates (OR, 4.8; $P < .001$), whereas TEM-type ESBLs were more frequent among *Klebsiella* species (OR, 5.7; $P = .002$).

Four centers located in Spain, France, and Israel characterized the $bla_{CTX\text{-}M}$ genes, and different CTX-M subtypes predominated in each of these countries. CTX-M-14 was detected in 27 (90%) of 30 CTX-M–positive isolates from Seville, Spain; CTX-M-toho2 accounted for 3 (50%) of 6 CTX-Ms in isolates from Barcelona, Spain. CTX-M-15 was the dominant CTX-M enzyme in isolates from France (27 [59%] of 46), followed by CTX-M-1 and CTX-M-14 (accounting for 7 and 6 isolates, respectively), whereas CTX-M-2 enzymes accounted for 6 (75%) of 8 CTX-M–positive isolates from Tel-Aviv, Israel (table 3).

Antibiotic susceptibility patterns. Co-resistance to non–β-lactam antimicrobials was examined in all 6 centers (table 4). The rates of susceptibility to ciprofloxacin among ESBL-producing Enterobacteriaceae were uniformly low in all regions (17.8%–28.7%), with the exception of Barcelona (12 [63%] of 19 isolates were susceptible to ciprofloxacin). Compared with isolates from all other regions, ESBL-producing isolates from Tel Aviv had higher rates of resistance to gentamicin (77.8%; $P < .001$), whereas lower rates of gentamicin resistance were observed among isolates from Calgary, Canada (20%; $P < .001$); France (43.2%; $P = .03$); and Barcelona, Spain (10.5%; $P = .04$). Rates of resistance to trimethoprim-sulfamethoxazole were higher among ESBL-producing isolates from Tel Aviv (75%; $P = .03$), Seville (77.6%; $P = .003$), and France (71.1%; $P = .012$) and were lower among isolates from Calgary (36.5%; $P < .001$). Isolates from Turkey were more likely to be resistant to amoxicillin-clavulanate than were isolates from other regions (73.2% vs 33.8%; $P < .001$). Compared with isolates that produce other ESBLs, those isolates that produce CTX-M–type β-lactamases were more likely to be resistant to ciprofloxacin (81.6% vs 52.2%; $P < .001$) but less likely to be resistant to trimethoprim-sulfamethoxazole (45.1% vs 81.3%; $P < .001$).

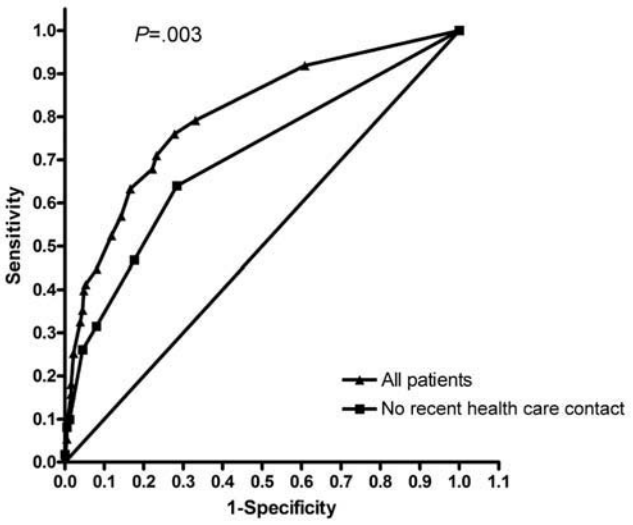

Figure 2. Diagnostic accuracy of multivariate predictive models for infection due to an extended-spectrum β-lactamase–producing Enterobacteriaceae. Receiver-operator characteristic (ROC) curves for the multivariate models are shown for 2 patient populations. For the entire study population (983 patients), the multivariate model included age ⩾65 years, male sex, recent hospitalization, residence in a long-term care facility, and recent antibiotic use; the area under the ROC curve for this model was 0.80 *(triangles).* For patients with no recent health care contact (795 patients), the multivariate model included age ⩾65 years, male sex, and recent cephalosporin use; the area under the ROC curve for this model was 0.70 *(squares).*

DISCUSSION

The worldwide dissemination of gram-negative bacteria that produce ESBLs—and specifically, CTX-M enzymes—has been described as an unfolding pandemic [7]. An epidemiological trend of this magnitude calls for international collaboration to identify and implement effective infection-control strategies. In the present study, we have analyzed data from 6 groups of researchers, representing 5 countries on 3 continents. Our results underscore the similarities in risk factors for ESBL infection among these diverse locations. In addition, some region-specific differences were noted.

Our study summarizes 339 patient-specific isolates of community-acquired ESBL-producing Enterobacteriaceae. The majority of these isolates (297; 87.6%) were *E. coli,* and most (286; 84.4%) were implicated in urinary tract infection. As expected, CTX-M enzymes were the most common ESBL type, present in 176 (65%) of isolates. However, the distribution of $bla_{CTX\text{-}M}$ genes differed among the participating centers. The findings reported here are consistent with the known geographic variations in the prevalence of $bla_{CTX\text{-}M}$ genes: $bla_{CTX\text{-}M\text{-}14}$ and $bla_{CTX\text{-}M\text{-}9}$ were reported to be endemic in Spain [21, 22];

Table 3. β-Lactamase Genes in Extended-Spectrum β-Lactamase–Producing Isolates Reported by 4 Centers

	No. (%) of isolates					
bla Gene	Calgary, Canada	Seville, Spain	Barcelona, Spain	France	Tel Aviv, Israel[a]	Total
CTX-M	86 (74.8)	30 (61.2)	6 (32)	46 (59)	8 (100)	176 (65)
CTX-M-1			1	7		8
CTX-M-2				2	6	8
CTX-M-3				1		1
CTX-M-9		2	2	2		6
CTX-M-25/26					1	1
CTX-M-27				1		1
CTX-M-14		27		6		33
CTX-M-15				27	1	28
CTX-M-28					1	1
CTX-M-toho-2			3			3
Undefined	86	1				87
TEM	12 (10.4)	2 (4.1)	15 (79)	28 (36)	0 (0)	57 (21)
SHV	12 (10.4)	17 (34.7)	4 (21)	4 (5)	1 (12.5)	38 (14)
OXA					4 (50)	4 (1)
Undefined	5 (4.3)					5 (2)
Total	115 (100)	49 (100)	19 (100)	78 (100)	8 (100)	269 (100)

[a] The *bla* genes were identified in 8 isolates that were deemed "true community-acquired" (ie, the patient had no recent contact with the health care system or antibiotic use) [2]. One of these isolates had 2 $bla_{\text{CTX-M}}$ genes.

$bla_{\text{CTX-M-2}}$ predominates in South America, Japan, and Israel [2]; and $bla_{\text{CTX-M-15}}$ is distributed worldwide and is dominant in most of Europe (except for Spain) and in North Africa, the Middle East, and Canada [7, 23, 24].

Results from numerous studies indicate that most ESBL-producing Enterobacteriaceae are resistant to multiple antibiotic classes [25, 26]. However, it is unclear whether the same pattern applies to community-acquired ESBL-producing isolates. In the present study, isolates from most regions displayed high rates of resistance to ciprofloxacin (>70%), which suggests that resistance to fluoroquinolones is near ubiquitous among community-acquired ESBL-producing bacteria. Resistance to other antibiotics, including gentamicin, trimethoprim-sulfamethoxazole, and amoxicillin-clavulanate, was more heterogenous. Geographic variation in resistance to these antibiotics may reflect differences in co-carried resistance genes, such as OXA enzymes, which are inhibitor-resistant penicillinases; geographic variation may also be affected by local practices of antibiotic use in humans and animal husbandry.

Risk factors for community-onset infection with ESBL-producing Enterobacteriaceae included indicators of contact with the health care system (recent hospitalization, residence in a long-term care facility, recent surgery, and bladder catheterization), recent use of antibacterial agents, poor functional performance, greater disease severity, and the presence of comorbidities. Five risk factors were independently predictive of ESBL positivity by multivariate analysis: male sex, age ⩾65 years, recent antibiotic use, recent hospitalization, and residence in a long-term care facility.

These risk factors generally were consistent across the different participating centers (figure 1). A notable exception was the association of ESBL production with female sex in the study from Canada [20]. More generally, different studies have shown conflicting associations between sex and infection due

Table 4. Susceptibility Rates of Extended-Spectrum β-Lactamase–Producing Enterobacteriaceae to Non–β-Lactam Antibacterial Agents

	No. (%) of susceptible isolates						
Antibacterial	Calgary, Canada[a] (*n* = 115)	Turkey[a] (*n* = 41)	Seville, Spain[a] (*n* = 49)	Barcelona, Spain[a] (*n* = 19)	France[b] (*n* = 74)	Tel Aviv, Israel[a] (*n* = 38)	Total
Gentamicin	92 (80)	27 (65.9)	34 (69.4)	17 (89)	42 (56.8)	8 (21.1)	223 (67.4)
Ciprofloxacin	33 (28.7)	11 (26.8)	11 (22.4)	12 (63)	17 (23)	9 (23.7)	81 (24)
Trimethoprim-sulfamethoxazole	73 (63.5)	19 (46.3)	11 (22.4)	6 (32)	22 (28.9)	9 (23.7)	134 (39.6)
Amoxicillin-clavulanate	71 (61.7)	11 (26.8)	27 (71.1)	16 (84)	…	…	129 (54.4)

[a] Determined using Clinical and Laboratory Standards Institute methodology [37].
[b] Determined using Societe Francais de Microbiologie methodology [38].

to ESBL-producing Enterobacteriaceae [27–30]. These discrepancies may reflect regional differences in sex-related antibiotic prescription practices (eg, antibiotic use for cystitis in women), as well as methodological issues, such as control group selection [31].

The multivariate model derived from our data had fairly good predictive accuracy for infection due to ESBL-producing organisms, as defined by an area under the ROC curve of 0.80. However, 81% of the study population (795 patients), including 221 (65%) of 339 patients infected with ESBL-producing bacteria, had no recent contact with the health care system. These patients comprised a healthier group than did patients with recent health care contact, as reflected by lower McCabe scores, fewer comorbidities, and a lower prevalence of bladder catheterization. The multivariate model derived for patients without recent health care contact yielded an area under the ROC curve of 0.70, suggesting that the ESBL risk in this group of patients is inadequately defined by prediction models that rely on health care–related risk factors. Moreover, given the ongoing diffusion of ESBLs into the wider population, the proportion of patients with ESBL-producing Enterobacteriaceae infection who have had no recent health care contact is likely to increase over time.

Because of the elevated mortality associated with infection due to ESBL-producing bacteria and the adverse consequences of delay in appropriate treatment [4], there is clearly a need to improve upon the limited predictive value of risk-factor based surveillance. To that end, several methods for rapid detection of ESBL-producing Enterobacteriaceae have been proposed. Molecular detection of CTX-M genes by real-time PCR and pyrosequencing has been reported [32] but is currently too costly and technically demanding for routine use. Simpler methods, such as a protocol for accelerated detection of ESBL-producing organisms in blood culture [33], a chromogenic Cica-β assay [34], and the use of selective chromogenic medium [35] have also been described and can significantly shorten the time to ESBL detection. Additional studies will be needed to define the role of such methods in clinical decision making.

Our study has limitations. As noted, there was considerable heterogeneity in study design and inclusion criteria among the participating studies (table 1), and isolates were not tested at a central laboratory. It might be argued that the inclusion of 3 hospital-based studies biased our investigation towards a sicker patient population. Furthermore, it is difficult to ascertain whether all isolates were associated with infection, particularly for population-based studies. However, restriction of risk factor analysis to data derived from population-based studies or case-control studies did not significantly alter the results (figure 1). A recently published case-control study of urinary tract infection caused by ESBL-producing *E. coli* among outpatients identified risk factors that were similar to those observed in our study: advanced age, recent hospitalization, antibiotic use, and invasive urinary tract procedures [30].

In summary, we characterized risk factors for community-acquired infection due to ESBL-producing Enterobacteriaceae in 6 centers in Europe, Asia, and North America. Overall, we found that, despite the heterogeneity of the included studies, similar risk factors were associated with ESBL status in the different participating centers. International collaboration among health care professionals and policy makers is required if we are to face the challenge of community-acquired ESBL-producing Enterobacteriaceae.

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