MAJOR ARTICLE

Influx of Extended-Spectrum β-Lactamase–Producing Enterobacteriaceae into the Hospital

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(See the editorial commentary by Rodriguez-Baño and Paterson on pages 935–7)

Background. The prevalence of infections caused by extended-spectrum β-lactamase (ESBL)–producing Enterobacteriaceae is increasing worldwide. The influx of these bacteria into hospitals has major implications for infection-control and empirical treatment strategies.

Methods. Isolates from 2 patient cohorts—patients with gram-negative bacteremia within 2 days after admission and patients screened for fecal colonization at admission—were assessed for ESBL production. ESBL phenotype was confirmed according to Clinical and Laboratory Standards Institute guidelines. Predictors of ESBL phenotype were examined by univariate and multivariate analyses.

Results. Of 80 Enterobacteriaceae isolates from blood samples obtained at admission to the hospital, 13.7% produced ESBL. Thirty-eight patients with ESBL-positive isolates and 72 with ESBL-negative isolates were included in a case-control study. Predictors of ESBL production were male sex and nursing home residence (area under receiver operator characteristic curve, 0.7). Of 241 persons screened at admission, 26 (10.8%) had fecal carriage of ESBL-producing Enterobacteriaceae. Predictors of fecal carriage were poor functional status, antibiotic use, chronic renal insufficiency, liver disease, and use of histamine$_2$ blockers (area under receiver operator characteristic curve, 0.8). Four (15.4%) of the 26 individuals with fecal carriage had subsequent bacteremia with ceftazidime-resistant Enterobacteriaceae, compared with 1 (0.5%) noncarrier (odds ratio, 38.9; $P < .001$). Of 80 ESBL-producing Enterobacteriaceae isolates obtained at admission, 65 were health care associated, and 15 were community acquired. The 15 community-acquired ESBL-producing Enterobacteriaceae belonged to diverse clones. The most prevalent ESBL gene among these isolates was CTX-M-2 (found in 53.3% of the isolates).

Conclusions. We report high rates of bacteremia and colonization with ESBL-producing Enterobacteriaceae at admission to our institution, which may undermine infection-control measures and complicate the selection of empirical treatment.

Extended-spectrum β-lactamase (ESBL)–producing Enterobacteriaceae are increasingly prevalent nosocomial pathogens in intensive care units [1–3], general medicine wards, and long-term care facilities [4–6]. In our institution, there is a high prevalence of ESBL-producing Enterobacteriaceae among clinical isolates: 35% of all *Klebsiella* species, 12% of *Escherichia coli*, and 35% of *Proteus mirabilis* produce ESBL [7]. Among isolates of Enterobacteriaceae from blood at our institution, 24% produce ESBL [8]. These organisms are multidrug-resistant and pose a serious public health threat, in that only a limited number of antimicrobial agents can be reliably used against them [1, 9, 10].

Recent studies suggest that ESBL-producing Enterobacteriaceae should not be considered to be exclusively nosocomial pathogens. ESBL-producing organisms have been reported to cause urinary tract infections [11–13] and bacteremia [12–14] in nonhospitalized persons. In a recent study from Spain, ESBL-producing organisms were isolated from the stool samples of 3.7%–5.5% of nonhospitalized patients [15]. The role that these community-acquired ESBL-producing organisms may play in the epidemiology of ESBL in hospitals is currently unknown. Unrecognized influx of ESBL-producing organisms into hospitals may hinder infection-control measures. Furthermore, empirical antibiotic treatment of community-acquired infections

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Table 1. List of oligonucleotides used for PCR amplification.

bla Gene	Primer sequence	Product length, kb	Reference
TEM full	F: KACAATAACCCTGRTAAATGC; R: AGTATATATGAGTAAACTTGG	0.94	[23]
SHV full	F: TTTATCGGCCYTCACTCAAGG; R: GCTGCGGGCCGGATAACG	0.93	[23]
CTX-M group			
CTX-M-deg	F: CGYTTTSCIATGTGCAG; R: ACCGCRATATCRTTGGT	0.55	[23]
CTX-M-9	F: GTGACAAAGAGAGTGCAACGG; R: ATGATTCTCGCCGCTGAAGCC	0.86	[24]
CTX-M-10	F: GCAGCACCAGTAAAGTCATGG; R: GCGATATCGTTGGTGGTACC	0.53	[25]
FEC-1	F: CGATAACGTGGCGATGAATAAGC; R: GTTGAGCTGGGTGAAGTAAGTGA	0.41	Present study
CTX-M-25 full	F: CACACGAATTGAATGTTCAG; R: TCACTCCACATGGTGAGT	0.92	[26]
OXA group			
OXA-1	F: ACACAATACATATCAACTTCGC; R: AGTGTGTTTAGAATGGTGATC	0.81	[27]
OXA-2	F: TTCAAGCCAAAGGCACGATAG; R: TCCGAGTTGACTGCCGGGTTG	0.7	[28]
OXA-10	F: CGTGCTTTGTAAAAGTAGCAG; R: CATGATTTTGGTGGGAATGG	0.65	[29]

NOTE. CTX-M-deg, degenerated primers; I, inosin; K, G or T; R, A or G; Y, C or T.

may become inadequate if ESBL-producing organisms are highly prevalent in the community. The present study was conducted to quantify and characterize the influx of ESBL-producing Enterobacteriaceae into the hospital.

MATERIALS AND METHODS

Three studies were conducted at the Tel Aviv Medical Center, a 1100-bed tertiary hospital; these included a prospective study to evaluate the prevalence of the ESBL phenotype in organisms causing bloodstream infections at the time of hospital admission, a case-control study of bloodstream infections at admission to assess for predictors of the ESBL phenotype, and screening to assess the prevalence and predictors of fecal carriage of ESBL-producing Enterobacteriaceae at the time of admission. Strains were classified as nosocomial, health care–associated, or community-acquired according to the scheme proposed by Friedman et al. [16]. The study protocol was approved by the ethics committee of the Tel Aviv Medical Center.

Non-nosocomial bacteremia. Gram-negative bacilli cultured from blood samples submitted to the clinical microbiology laboratory at our institution from June 2003 through December 2003 were examined prospectively, as previously reported [8]. Data were cross-checked with the hospital admissions database to single out cultures of blood samples obtained within 2 days after admission. Organisms identified as *E. coli, Klebsiella* species, or *P. mirabilis* were assessed for ESBL production by the double-disk diffusion assay according to Clinical and Laboratory Standards Institute guidelines [17].

Case-control study. Adults hospitalized from January 2000 through December 2003 with at least 1 blood culture positive for *E. coli, Klebsiella* species, or *P. mirabilis* from a sample obtained within 2 calendar days of admission were included. Case patients were those with ESBL-producing isolates, and control subjects were patients with non–ESBL-producing isolates. Control subjects were randomly enrolled at a ratio of 2 :1. Case patients and control subjects were compared regarding demographic variables, comorbidities, exposure to the health care system, and antibiotic exposure before blood was cultured.

Fecal carriage at admission to the hospital. Screening was performed for a sample of patients admitted to a medical ward from December 2002 through September 2003. Demographic and clinical data were collected by interviewing patients and reviewing medical documentation.

Stool samples collected at the time of admission were inoculated into brain-heart infusion broth (Hy-Labs), incubated at 35°C overnight, and then streaked onto MacConkey agar plates containing ceftriaxone (1 μg/mL) and amphotericin B (2 μg/mL). Oxidase-negative isolates were further identified, using the Vitek-2 ID-GNB card (bioMérieux) and kept at −70°C for further analysis. Isolates identified by double-disk

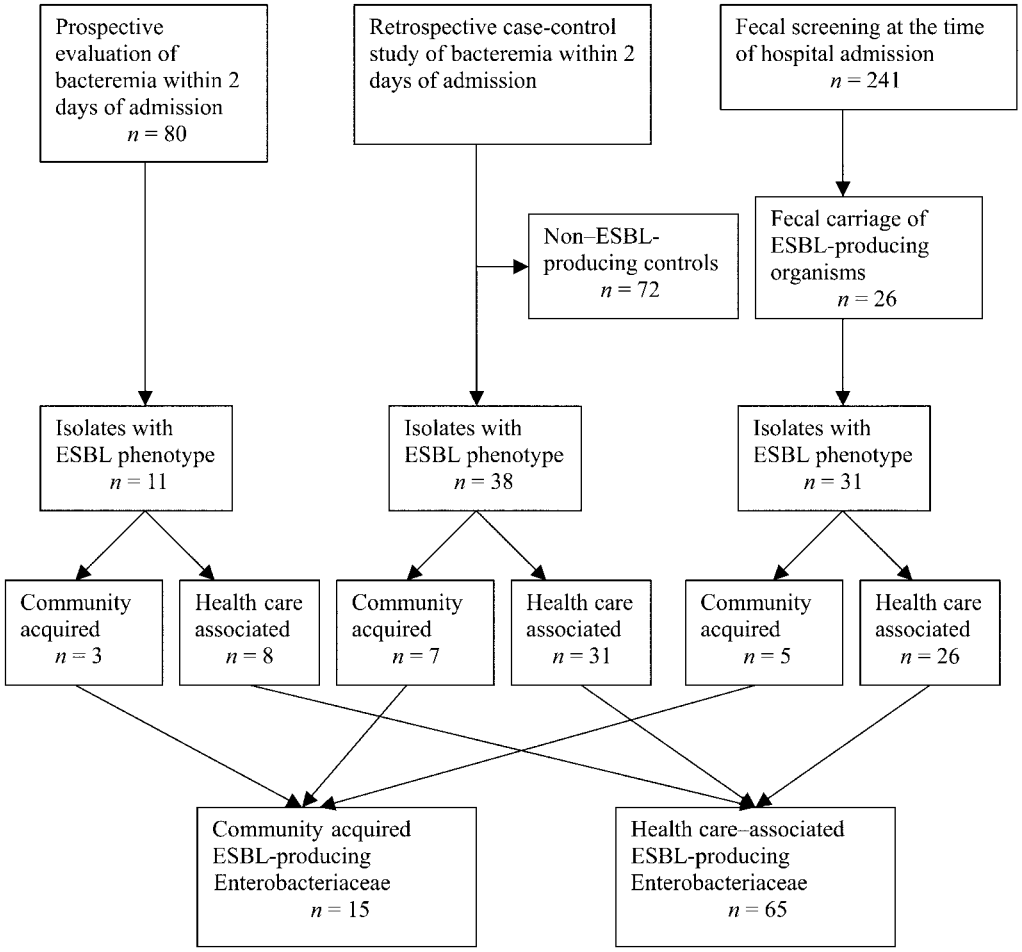

Figure 1. Overview of patient cohorts in a study of extended-spectrum β-lactamase (ESBL)–producing organisms at hospital admission

diffusion as ESBL-producing *E. coli, Klebsiella* species, and *P. mirabilis* were included in this study.

Bacterial isolates other than *E. coli, Klebsiella* species, and *P. mirabilis* were tested for the ESBL phenotype as described above, and if results were positive, the isolates were further evaluated by isoelectric focusing as described elsewhere [18], according to the method of Mathew et al. [19], using an LKB Multiphor II Electrophoresis System apparatus (Amersham Pharmacia Biotech). β-Lactamases with known isoelectric points were used as controls, and activity was revealed with nitrocefin.

Bacterial cultures obtained during hospital stay. To estimate the clinical consequences of fecal carriage of ESBL-producing Enterobacteriaceae, we searched the laboratory database for clinical specimens obtained from patients with fecal carriage up to 3 months after hospital admission. Resistance to ceftazidime (MIC >16 μg/mL) in *E. coli, Klebsiella* species, and *P. mirabilis* isolates was used as a marker for the ESBL-producing phenotype. Patients for whom culture of the initial stool sample yielded negative results for an ESBL-producing organism served as a control group.

Genetic characterization of community-acquired ESBL-producing strains. Community-acquired strains from all 3 cohorts were further characterized for their genetic relatedness and ESBL genes.

Genetic typing by PFGE. DNA was prepared and cleaved as described elsewhere [20, 21], using a CHEF-DR III apparatus (Bio-Rad). PFGE DNA patterns were compared between community-acquired strains and nosocomial strains of ESBL-producing organisms from the same species [22].

Detection of ESBL genes by PCR. Primers used for the PCR assays are listed in table 1. PCR reactions were performed with Hot-StarTaq DNA polymerase (Qiagen) according to the manufacturer's instructions. The resulting PCR products were analyzed in 1% agarose gels and were further sequenced using the PCR primers.

Cloning and sequencing of the PCR products. PCR products obtained with primers CTX-M-25-full and CTX-M-2 were cloned using pGEM-T (Promega) and sequenced using SP6 and T7 promoter primers. Sequences were analyzed with an ABI Prism 3100 Genetic Analyzer (PE Biosystems). The nu-

Table 2. Univariate and multivariate predictors of extended-spectrum β-lactamase production by *Enterobacteriaceae* causing bacteremia in patients newly admitted to the hospital.

Covariate	Case patients (n = 38)	Control subjects (n = 72)	OR (95% CI)	P
Demographics				
Age, median years (interquartile range)	75.5 (70–82)	79 (69–85.5)	…	.37
Male sex	25 (66)	32 (44)	2.4 (1.1–5.4)	.04
Dependent functional state	21 (55)	31 (43)	1.6 (0.7–3.6)	.24
Rapidly fatal underlying disease[a]	8 (21)	9 (13)	1.9 (0.6–5.3)	.27
Comorbidity				
Cerebrovascular disease	0	5 (7)	…	.16
Diabetes mellitus	8 (21)	27 (38)	0.4 (0.2–1.1)	.09
Cardiovascular disease	27 (71)	56 (78)	0.7 (0.3–1.7)	.48
Liver disease	7 (18)	8 (11)	1.8 (0.6–5.4)	.38
Lung disease	4 (11)	7 (10)	1.1 (0.3–4.0)	1.00
Malignancy	13 (34)	23 (32)	1.1 (0.5–2.5)	.83
Renal disease	11 (29)	19 (27)	1.1 (0.5–2.7)	.82
Solid organ transplantation	0	2 (3)	…	.54
Recent events[b]				
Current use of antibiotics	9 (24)	5 (7)	4.2 (1.3–13.5)	.02
Bladder catheterization	27 (71)	41 (57)	1.9 (0.8–4.3)	.16
Central venous catheterization	7 (18)	8 (11)	1.8 (0.6–5.4)	.38
Contact with health care system				
Admitted from long-term care facility	16 (42)	10 (14)	4.5 (1.78–11.4)	.001
Hospitalized <3 months before admission	23 (61)	35 (49)	1.6 (0.7–3.6)	.32
Multivariate analysis				
Male sex	…	…	2.57 (1.08–6.12)	.03
Admitted from long-term care facility	…	…	4.76 (1.82–12.4)	.001

NOTE. Data are no. (%) of patients, unless otherwise indicated.

[a] Defined according to the McCabe-Jackson score [30].

[b] Within <3 months before admission to the hospital.

cleotide acid and the deduced protein sequences were analyzed and compared using BLAST software (available at http://www.ncbi.nlm.nih.gov/BLAST/).

Statistical analysis. Statistics were analyzed with Stata software, version 7 (Stata). All variables were examined by univariate analysis using the χ^2 test or Fisher's exact test, as appropriate. Continuous variables were analyzed by Student's t test. Variables with $P < .2$ in univariate analysis were included in the multivariate model. Predictors were examined using logistic regression. A final model was built including all the variables with $P \leqslant .05$. 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 effects on the β coefficients. Variables that caused substantial confounding (change in β coefficient of >10%) were included in the final model. Effect modification between variables was evaluated by testing appropriate interaction terms for statistical significance. Colinearity was examined by replacing variables with each other and examining the effect on the model. The area under the receiver operator characteristic (ROC) curve was calculated for the predictive models. All statistical tests were 2-tailed. $P \leqslant .05$ was considered to be statistically significant.

RESULTS

Non-nosocomial bacteremia. Eighty episodes of bacteremia were studied (50 due to *E. coli,* 20 due to *Klebsiella* species, and 10 due to *P. mirabilis*). Eleven isolates (13.7%) possessed the ESBL phenotype; 3 were community-acquired strains (all of which were *E. coli*), and 8 were health care–associated strains (1 *E. coli,* 5 *Klebsiella* species, and 2 *P. mirabilis*) (figure 1). The proportion of ESBL-positive isolates was 8% for *E. coli* (4 isolates), 25% for *Klebsiella* species (5 isolates), and 20% for *P. mirabilis* (2 isolates).

Case-control study. The case-control study included 110 patients: 38 case patients with ESBL-positive isolates (15 *E. coli,* 17 *Klebsiella* species, and 6 *P. mirabilis*) and 72 randomly selected control patients with non–ESBL-producing isolates (21 *E. coli,* 41 *Klebsiella* species, and 10 *P. mirabilis*). Of the 38 patients with ESBL-producing blood isolates, 7 (18.4%) had

Table 3. Univariate and multivariate predictors of fecal carriage of extended-spectrum β-lactamase (ESBL)–producing Enterobacteriaceae at admission to the hospital.

Covariate	ESBL-negative subjects (n = 215)	ESBL-positive subjects (n = 26)	OR (95% CI)	P
Demographic characteristics				
Male sex	108 (50.2)	18 (69.2)	2.2 (0.9–5.3)	.07
Age, median years (interquartile range)	75.5 (66–82)	79.5 (68.5–89)	…	.14
Dependent functional state	34 (15.8)	12 (46.2)	4.5 (1.9–10.7)	<.001
Rapidly fatal underlying disease[a]	36 (16.7)	5 (19.2)	1.2 (0.4–3.3)	.7
Comorbidity				
Diabetes mellitus	71 (33.0)	8 (30.8)	0.9 (0.3–2.1)	.8
Ischemic heart disease	91 (42.3)	12 (46.2)	1.1 (0.5–2.6)	.7
Congestive heart failure	45 (20.9)	7 (26.9)	1.4 (0.5–3.5)	.4
Chronic lung disease	41 (19.1)	3 (11.5)	0.5 (0.15–1.9)	.3
Liver disease	4 (1.9)	2 (7.7)	4.3 (0.7–25.2)	.07
Cerebrovascular disease	40 (18.6)	4 (15.4)	0.7 (0.2–2.4)	.6
Neoplastic disease	41 (19.1)	5 (19.2)	1.0 (0.3–2.8)	.9
Decubitus ulcer	5 (2.3)	4 (15.4)	7.6 (1.9–30.5)	.001
Chronic renal insufficiency	31 (14.4)	10 (38.5)	3.7 (1.5–8.9)	.002
Recent events[b]				
Bladder catheterization	18 (8.4)	6 (23.1)	3.2 (1.1–9.2)	.018
Central venous catheterization	8 (3.7)	1 (3.8)	1.0 (0.1–8.6)	.9
Surgery	18 (8.4)	4 (15.4)	1.9 (0.6–6.4)	.2
Gastrointestinal endoscopic examination	11 (5.1)	5 (19.2)		
Dialysis	3 (1.4)	3 (11.5)	9.2 (1.7–48.3)	.002
Contact with health care system				
Admission from a long-term care facility	21 (9.8)	9 (34.6)	4.8 (1.9–12.3)	<.001
Hospitalized <3 months before admission	80 (37.2)	16 (61.5)	2.7 (1.1–6.2)	.017
⩾1 week in hospital in 3 months before admission	39 (18.1)	7 (26.9)	1.6 (0.6–4.2)	.2
Medications				
Antibiotics				
Current	30 (14.0)	10 (38.5)	3.8 (1.6–9.2)	.002
Up to 3 months before admission	71 (33.0)	13 (50.0)	2.0 (0.8–4.6)	.08
Proton pump inhibitors	54 (25.1)	5 (19.2)	0.7 (0.2–1.9)	.5
$Histamine_2$ receptor antagonists	35 (16.3)	10 (38.5)	3.2 (1.3–7.6)	.006
Multivariate analysis				
Poor functional status	34 (15.8)	12 (46.2)	4.2 (1.6–10.9)	.004
Current antibiotic use	30 (14.0)	10 (38.5)	3.4 (1.3–9.0)	.015
Chronic renal insufficiency	31 (14.4)	10 (38.5)	2.8 (1.1–7.3)	.03
Liver disease	4 (1.9)	2 (7.7)	11.1 (1.4–87.1)	.02
$Histamine_2$ receptor antagonists	35 (16.3)	10 (38.5)	2.8 (1.1–7.4)	.03

NOTE. Data are no. (%), unless otherwise indicated.

[a] Defined according to the McCabe-Jackson score [30].

[b] Within <3 months before admission to the hospital.

community-acquired bacteremia, and 31 had health care–associated bacteremia (figure 1). Mean age, functional status, McCabe score, and the number and types of comorbid conditions were similar for case patients and control subjects. Univariate predictors of ESBL-positive bacteremia were admission from a long-term care facility, current use of antibiotics, and male sex (table 2).

On multivariate analysis, male sex (OR, 2.57; 95% CI, 1.08–6.12; $P = .03$) and admission from a long-term care facility (OR, 4.76; 95% CI, 1.82–12.40; $P = .001$) remained significant predictors of bacteremia associated with an ESBL-producing organism (table 2). Area under the ROC curve for the multivariate model was 0.7, indicating moderate prediction.

Fecal carriage at admission to the hospital. A total of 241 patients were screened for fecal carriage of ESBL-producing organisms at admission to a medical ward. The median age

Table 4. Antibiotic-resistance patterns of extended-spectrum β-lactamase–producing Enterobacteriaceae obtained within 2 days after hospital admission.

Antibiotic	No. (%) of isolates with resistance to drug		
	Community-acquired strains (n = 15)	Health care–associated strains (n = 65)	All (n = 80)
Gentamicin	8 (53)	41 (63)	49 (61)
Amikacin	0	1 (2)	1 (1)
Trimethoprim-sulfamethoxazole	12 (80)	39 (60)	51 (64)
Ciprofloxacin	9 (60)	42 (65)	51 (64)
Piperacillin-tazobactam	4 (27)	15 (23)	19 (24)
Imipenem	1 (7)[a]	2 (3)	3 (4)

NOTE. There were no significant differences in the proportion of isolates resistant to any antimicrobial agent between community-acquired strains and health care–associated strains.

[a] One community-acquired strain was resistant to carbapenems and susceptible only to amikacin and piperacillin-tazobactam.

was 76 years (interquartile range, 66–82 years); 52% were male. Two hundred and eleven patients (87.6%) were admitted from home, and 30 (12.4%) were admitted from a long-term care facility. Ninety-four patients (39.0%) were hospitalized, and 83 patients (34.4%) received antibiotic treatment in the 3 months before their current admission.

Twenty-six patients (10.8%) were identified as having fecal carriage of 31 ESBL-positive isolates (figure 1). ESBL-producing isolates from stool included *E. coli* (17 isolates), *P. mirabilis* (6), *Klebsiella* species (5), *Providencia* species (2), and *Enterobacter* species (1). On univariate analysis, fecal carriage of ESBL-producing organisms was significantly associated with admission from a long-term care facility, recent hospitalization (within the previous 3 months), a dependent functional state, presence of decubitus ulcer(s), presence of an indwelling bladder catheter, chronic renal insufficiency, hemodialysis, use of histamine$_2$ (H_2) receptor antagonists, and current antibiotic use. There was a tendency for carriage of ESBL-producing organisms to be associated with male sex (OR, 2.2; $P = .07$) (table 3).

Although antibiotic use at the time of admission was significantly associated with carriage of ESBL-producing Enterobacteriaceae, earlier antibiotic use (i.e., within 3 months before hospital admission) was not (table 3). Specifically, current use of a penicillin or a cephalosporin (30.8% of patients with fecal carriage vs. 10.2% of patients without; OR, 3.9; 95% CI, 1.5–10.0; $P = .003$) and trimethoprim-sulfamethoxazole (7.7% vs. 0.5%; OR, 17.8; 95% CI, 1.6–204.0; $P = .002$) was associated with carriage of ESBL-producing Enterobacteriaceae.

On multivariate analysis, 5 variables were significantly associated with fecal carriage of ESBL-producing organisms; these included dependent functional state (OR, 4.2; $P = .004$), current use of antibiotics (OR, 3.4; $P = .015$), chronic renal insufficiency (OR, 2.8; $P = .03$), liver disease (OR, 11.1; $P = .02$), and use of a H_2 receptor antagonist (OR, 2.8; $P = .03$). Six (60%) of 10 patients with >2 predictors had carriage of ESBL-producing organisms at admission, compared with 9 (28.1%) of 32 patients with 2 predictors and 11 (5.5%) of 199 patients with 0 or 1 predictor (OR, 15.8; $P < .0001$, for comparison of patients with >2 and ≤2 predictors). The area under the ROC curve for this model was 0.81, indicating good prediction.

Clinical isolates obtained during hospital stay. Of the 26 patients found to have fecal carriage of ESBL-producing Enterobacteriaceae at admission, 4 (15.4%) had subsequent bacteremia with a ceftazidime-resistant isolate of the same species up to 3 months after admission, compared with 1 (0.5%) of those patients without carriage (OR, 38.9; $P < .001$). Bacteremia associated with ESBL-producing isolates occurred 7, 10, 38, and 73 days after hospital admission. Seven ceftazidime-resistant Enterobacteriaceae from any source were isolated from 5 (19.2%) of those patients who had fecal carriage at admission; all isolates belonged to the same species as the isolate from the stool sample found on screening. In comparison, 16 drug-resistant Enterobacteriaceae were isolated from 12 (5.6%) of the patients who had negative results of stool screening at admission ($P = .02$).

Antibiotic susceptibility patterns. ESBL-producing isolates obtained within 2 days after hospital admission were mostly multidrug-resistant (table 4). The proportions of isolates resistant to gentamicin, trimethoprim-sulfamethoxazole, ciprofloxacin, and piperacillin-tazobactam were 61%, 64%, 64%, and 24%, respectively. Similar rates of coresistance to antimicrobial agents were seen in community-acquired and health care–associated strains.

Community-acquired ESBL-producing Enterobacteriaceae. Of a total of 80 ESBL-producing isolates obtained from all 3 cohorts, 65 were health care-associated and 15 were community-acquired (figure 1). The 15 community-acquired isolates included 8 *E. coli,* 4 *Klebsiella pneumoniae,* and 3 *P. mirabilis*; 5 were isolated from stool samples, and 10 were isolated from

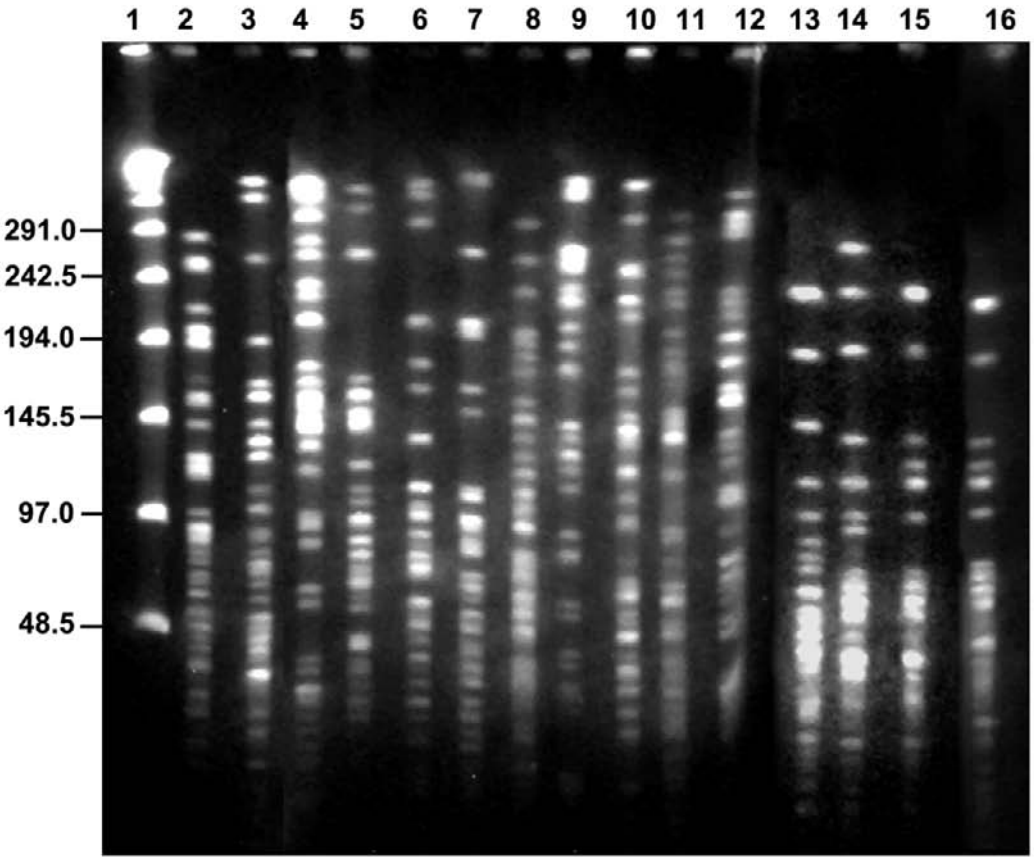

Figure 2. PFGE profiles of community-acquired extended-spectrum β-lactamase (ESBL)–producing clones. DNA was restricted with 20 U of *Spe*I endonuclease for *Escherichia coli* and *Klebsiella pneumoniae* isolates and with *Sma*I (New England Biolabs) for *Proteus mirabilis* isolates. *Lane 1,* λ DNA ladder molecular weight marker; *lanes 2–8, E. coli* isolates belonging to diverse genetic clones; *lanes 9–12, K. pneumoniae* isolates belonging to diverse genetic clones; *lanes 13–15, P. mirabilis* isolates, 1 unique clone and 2 genetically related clones, which are identical to the predominant *P. mirabilis* ESBL-producing clone in our institution *(lane 16).*

blood samples. These 15 isolates were further studied for genetic relatedness, and their ESBL enzymes were characterized.

Genetic relatedness. PFGE did not demonstrate clonality among *E. coli* or *K. pneumoniae* isolates. A single *E. coli* isolate had a PFGE pattern identical to that of a nosocomial ESBL-producing *E. coli* clone recognized at our hospital, whereas all other *E. coli* and *K. pneumoniae* isolates were genetically unrelated to each other and to nosocomial strains. Two of the 3 community-acquired ESBL-producing *P. mirabilis* strains belonged to the same clone, which is also abundant among nosocomial ESBL-producing strains of *P. mirabilis* at our hospital (figure 2).

ESBL genes. The most common ESBL genes carried by community-acquired ESBL-producing organisms were members of the CTX-M group, which were identified in 11 isolates (73.3%); 8 of these 11 enzymes were CTX-M-2. Three isolates (20%) had ESBL genes belonging to the SHV group. We were unable to identify the ESBL genes carried by 2 isolates with an ESBL-producing phenotype (table 5).

DISCUSSION

ESBL-producing Enterobacteriaceae are emerging worldwide and present a major challenge to clinicians, public health professionals, and hospital infection-control teams. Recent reports on the occurrence of ESBL-producing Enterobacteriaceae in nonhospitalized persons [11, 12, 14, 15, 31] imply that important reservoirs of these pathogens exist outside of hospitals. Failure to consider the emergence of drug-resistant organisms in the community could undermine infection-control efforts in hospitals and render empirical antibiotic therapy inadequate. However, the influx of ESBL-producing organisms into hospitals is poorly understood. In the present study, we assessed the prevalence and clinical predictors of bacteremia and fecal carriage involving ESBL-producing Enterobacteriaceae in newly admitted patients, the association of fecal carriage with later invasive infection, and genetic characteristics of community-acquired ESBL-producing strains.

We found a high prevalence (13.7%) of the ESBL phenotype

Table 5. Extended-spectrum β-lactamases (ESBLs) produced by 15 community-acquired Enterobacteriaceae.

Sample type, isolate	Bacteria	CTX-M type	SHV type
Stool			
1	*Escherichia coli*	None	SHV-5
2	*E. coli*	CTX-M-2	SHV-5
3	*Proteus mirabilis*	CTX-M-2	None
4	*E. coli*	None	None
5	*E. coli*	CTX-M-16-like	None
Blood			
6	*E. coli*	CTX-M-2	None
7	*P. mirabilis*	CTX-M-2	None
8	*Klebsiella pneumoniae*	CTX-M-39[a]	None
9	*K. pneumoniae*	CTX-M-28-like	None
10	*K. pneumoniae*	CTX-M-2	None
11	*K. pneumoniae*	CTX-M-2	None
12	*P. mirabilis*	CTX-M-2	None
13	*E. coli*	CTX-M-2	None
14	*E. coli*	None	SHV-12[b]
15	*E. coli*	None	None

NOTE. There were no isolates with TEM- or OXA-type ESBLs. Isolates 9, 10, and 11 carried the *bla*SHV1 gene. Isolates 4 and 15 possessed the ESBL phenotype, but PCR reactions with specific ESBL *bla* primers (table 1) did not reveal products.

[a] A new ESBL enzyme reported previously from our hospital [26].

[b] Alternative designation: SHV 2a.

among patients recently admitted to our institution who had bacteremia due to Enterobacteriaceae. Admission from a long-term care facility and male sex were predictors of bacteremia due to an ESBL-producing organism. However, the area under the ROC curve of 0.7 indicates only moderate prediction by the model. This finding may be explained by the heterogeneity of patients with bacteremia caused by ESBL-producing organisms at the time of hospital admission, a group that includes both community-acquired and health care–associated infections. Thus, prediction schemes that rely mostly on assessment of previous contact with the health care system are bound to be imperfect. In a separate cohort of unselected patients screened for fecal colonization at the time of hospital admission, 10.8% were carriers of ESBL-producing Enterobacteriaceae. Patients were mostly elderly individuals, reflecting the population admitted to a medical service. Poor functional status, current antibiotic use, chronic renal or liver disease, and use of H_2 receptor antagonists predicted fecal carriage of ESBL-producing organisms. The multivariate model allowed better prediction of fecal carriage of ESBL-producing organisms in newly admitted patients and could help direct infection-control measures, such as selective screening of persons at risk and implementation of barrier precautions for those with confirmed carriage [32, 33]. This model should be further examined in larger populations from several institutions to refine and validate its performance.

The predictors of ESBL bacteremia and colonization identified by our multivariate models include factors associated with environmental exposure to ESBL-producing organisms, such as residence in a long-term care facility and recent hospitalization, and factors that increase the susceptibility of the gastrointestinal tract to bacterial colonization, such as use of H_2 receptor antagonists and antibiotics. Long-term care facilities have repeatedly been shown to be reservoirs of ESBL-producing Enterobacteriaceae [4, 6, 34]. Interinstitutional transfer of patients allows for dissemination of these organisms, facilitating outbreaks among both hospitalized patients and nursing home residents. Poor functional status is associated with contact with the health care system and residence in long-term care facilities. However, among patients screened at admission, a debilitated state was more strongly associated with carriage of ESBL-producing organisms than was residence in a long-term care facility. This finding may indicate that bedridden patients represent a subpopulation at special risk for carriage of ESBL-producing organisms within or outside of long-term care facilities. Functional decline is increasingly recognized as a major risk factor for infection among residents of long-term care facilities [4, 6, 35, 36]. It is notable that 5 of the 12 bedridden ESBL carriers were admitted from home. Bedridden patients residing at home are cared for by home care providers, who may serve as vectors for disseminating infectious agents from hospitals into the community and among patients [37]. It may be practical to regard such patients as living in a "hospital at home" [38].

Carriers of ESBL-producing organisms at admission were at high risk for subsequent infection with ceftazidime-resistant Enterobacteriaceae, most notably bloodstream infection, which occurred in 15.4% of patients with fecal carriage (OR, 38.9 vs. patients without fecal carriage). Bacteremia caused by ESBL-producing Enterobacteriaceae has been shown to be associated with inappropriate initial antibiotic treatment and mortality [39–43]. Thus, detection of fecal carriage of ESBL-producing organisms at admission may have important implications for the management of subsequent infectious episodes.

ESBL-producing Enterobacteriaceae obtained within 2 days after hospital admission were often multidrug-resistant, and similar resistance patterns were seen in community-acquired and health care–associated isolates. These high levels of antimicrobial coresistance are comparable with those recently reported in ESBL-producing isolates from our hospital, most of which were nosocomial [10].

CTX-M–type β-lactamases were the predominant ESBLs found in 15 community-acquired strains. CTX-M ESBLs were previously shown to be the most prevalent ESBLs among nosocomial Enterobacteriaceae at our institution [26, 44, 45].

PFGE revealed 3 isolates (1 *E. coli* and 2 *P. mirabilis*) that were related to nosocomial clones found at our institution, whereas all other community-acquired ESBL producers belonged to diverse clones (figure 2). This pattern may indicate ESBL spread via plasmids from nosocomial strains of Enterobacteriaceae to community strains. It has been noted that CTX-M–encoding plasmids are often easily transmissible by conjugation in vitro, explaining their effective dissemination [46].

An alternative source for community-acquired ESBLs may be environmental bacteria (e.g., *Kluyvera* species) that are known to contain chromosomal CTX-M genes [46]. Genetic transfer of ESBLs from environmental bacteria may explain the occurrence of ESBLs in subjects with no prior health care contact and the widespread emergence of these ESBLs among community strains in England [47], Spain [12], and Greece [48] in nonoutbreak circumstances. The emergence of ESBLs in the community may be aided by the use of antibiotics in agriculture, whereas hospitals and other health care facilities may act as amplifiers for ESBL genes introduced into them from community reservoirs.

In conclusion, fecal carriage of ESBL-producing Enterobacteriaceae and bacteremia due to these organisms are frequent occurrences among patients admitted to our institution. Fecal carriage of ESBL-producing organisms confers an increased risk for subsequent invasive infection with the same organism. Prediction tools that aid in identifying patients at risk for fecal carriage may be useful in preventing institutional spread of these pathogens and need to be further refined and validated.

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