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Epidemiology and Clinical Features of Infections Caused by Extended-Spectrum Beta-Lactamase-Producing *Escherichia coli* in Nonhospitalized Patients

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Infections due to extended-spectrum beta-lactamase (ESBL)-producing *Escherichia coli* (ESBLEC) in nonhospitalized patients seem to be emerging in different countries. Their incidence, epidemiology, and clinical impact in the community have not been studied. We describe the epidemiology and clinical features of infections caused by ESBLEC in nonhospitalized patients in Spain and the results of a case-control study performed to investigate the risk factors associated with the acquisition of these organisms. The clonal relatedness of the organisms was assessed by repetitive extragenic palindromic sequence PCR. The ESBLs and the genes encoding the ESBLs were initially characterized by isoelectric focusing and PCR, respectively. Forty-nine patients (76% with urinary tract infections, 22% with asymptomatic bacteriuria, and 2% with acute cholangitis) were included. Six patients were bacteremic. Diabetes mellitus (odds ratio, 5.5; 95% confidence interval, 1.6 to 18.7), previous fluoroquinolone use (odds ratio, 7.6; 95% confidence interval, 1.9 to 30.1), recurrent urinary tract infections (odds ratio, 4.5; 95% confidence interval, 1.3 to 15.1), a previous hospital admission (odds ratio, 18.2; 95% confidence interval, 5.3 to 61.1), and older age in male patients (odds ratio per year, 1.03; 95% confidence interval, 1.03 to 1.05) were identified as risk factors by multivariate analysis. The ESBLEC isolates were not clonally related. The ESBLs were characterized as members of the CTX-M-9 group, the SHV group, and the TEM group in 64, 18, and 18% of the isolates, respectively. ESBLEC is an emergent cause of urinary tract infections in nonhospitalized patients. There was no evidence of horizontal transmission of ESBLEC strains. Avoidance of fluoroquinolone use in high-risk patients should be considered whenever possible in order to avoid the selection of these organisms.

Extended-spectrum beta-lactamase (ESBL)-producing members of the family *Enterobacteriaceae* are resistant to penicillins, narrow- and extended-spectrum cephalosporins, and aztreonam (4). ESBL-producing organisms are also frequently resistant to aminoglycosides, trimethoprim-sulfamethoxazole, and quinolones.

Until recently, most infections caused by ESBL-producing *Escherichia coli* (ESBLEC) or *Klebsiella pneumoniae* had mostly been described as nosocomially acquired (4) or nursing home related (32). However, some recent data suggest that infections due to ESBL-producing organisms might be an emergent problem in outpatients in different countries (1, 8, 9, 11, 14, 15), but detailed epidemiological data were not collected in most of those studies. Moreover, the clinical relevance and the epidemiology of these infections outside nursing homes have not been studied.

In a recent nationwide study of ESBL-producing organisms in Spain, 93% of ESBL-producing *K. pneumoniae* strains were isolated from inpatients, while 51% of ESBL-producing *E. coli* (ESBLEC) strains were isolated from outpatients (13) Consequently, we conducted the study described in this report, in which we describe and analyze the clinical features and the epidemiology of infections due to ESBLEC in nonhospitalized patients.

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MATERIALS AND METHODS

Study population and design. The Microbiology Laboratory of the Hospital Universitario Virgen Macarena in Seville, Spain, receives samples from the hospital, the outpatient clinic, a nearby chronic-care hospital, and the primary care services of an area with 450,000 inhabitants in the south of Spain.

The base population of the case-control study consisted of outpatients from our area from whom a clinical sample had been sent to our laboratory for culture and in whom a community-acquired infection was suspected. The sample could have been obtained in a primary care office, the outpatient clinic, or the emergency department. A case patient was defined as a person who had not been admitted to a hospital during the previous month and from whom an ESBLEC strain had been isolated from a clinical sample. For patients with recurrent infections, only isolates from the first episodes were included. The case patients were enrolled by collecting epidemiological data for all patients infected with ESBLEC detected during the study period (January 2001 to May 2002). During the study period, all patients in whom ESBLEC was detected were included except those who had been admitted to a hospital for 48 h or more when the sample was collected (10) and those who had been admitted to a hospital during the previous month. For each case patient, two controls were randomly chosen (by a computerized method) from among the patients from whom a sample had been processed for culture during the same week. The same exclusion criteria used for the case patients applied to the controls.

The following data were collected: demographic data, underlying diseases, the severity of the underlying diseases according to the McCabe classification (19) and the Charlson index (6), whether the patient had a history of recurrent urinary tract infections (UTIs), whether the patient had used antibiotics in the previous

TABLE 1. Nucleotide sequences of the oligonucleotides used for PCR amplification

Primer	Nucleotide sequence (5′ to 3′)	Position	Product size (bp)	Reference
bla_{TEM}	1. 5′-ATG AGT ATT CAA CAT TTC CG-3′ 2. 5′-CTG ACA GTT ACC ATT GCT TA-3′	208 1075	1,075	30
bla_{SHV}	1. 5′-GGG TTA TTC TTA TTT GTC GC-3′ 2. 5′-TTA GCG TTG CCA GTG CTC-3′	58 988	930	24
$bla_{CTX\text{-}M9}$	1. 5′-GTG ACA AAG AGA GTG CAA CGG-3′ 2. 5′-ATG ATT CTC GCC GCT GAA GCC-3′	4 860	856	30
$bla_{CTX\text{-}M10}$	1. 5′-CCG CGC TAC ACT TTG TGG-3′ 2. 5′-TTA CAA ACC GTT GGT GAC G-3′	86 858	962	7, 29

2 months, whether the patient had received more than two cycles of antimicrobial therapy in the previous year, whether the patient had been admitted to a hospital or had had surgery in the last 12 months, whether the patient was a resident in a nursing home, whether the patient had urinary catheters, and the empirical treatment received. A structured questionnaire was used to collect the data. One of the investigators (M. D. Navarro) filled out the questionnaires by using data from the medical charts and interviewing the primary care doctors and the patients or their closest relatives. Case patients and controls were excluded if data were unavailable. The use of antimicrobial agents was determined in several ways: in short, the patient was asked whether he or she remembered having used antimicrobial agents or receiving therapy for any specific infection and whether he or she remembered having received specific antimicrobials. Patients (case patients and controls) and doctors were not informed about the purpose of the study until the end of the interview. The infections were classified according to the clinical and laboratory data. Patients with positive urine cultures (pure culture of a single microorganism with a colony count $>10^5$ CFU/ml) and clinical signs related to the urinary tract were considered to have UTIs unless proven otherwise. Asymptomatic patients with positive urine cultures were considered to have asymptomatic bacteriuria. Patients with more than two episodes of UTIs over a period of 6 months were considered to have recurrent UTIs. Antimicrobial treatment was considered appropriate when at least one antibiotic to which the organism was susceptible or intermediately susceptible in vitro was administered.

The study protocol was approved by the local ethics committee. Due to the observational character of the study, written informed consent was not required.

Microbiological methods. (i) Bacterial strains. Preliminary identification of the isolates and determination of their susceptibilities to antimicrobial agents were determined with the VITEK 2 system (bioMérieux, Hazelwood, Mo.). The final identity was determined with API 20E strips (bioMérieux). The isolates were screened for ESBL production by the disk diffusion method with Mueller-Hinton agar plates (Oxoid) with disks containing 30 μg of cefotaxime and ceftazidime with or without 10 μg of clavulanic acid (Oxoid, Basingstoke, United Kingdom), as recommended by the NCCLS (21). ESBL production was confirmed by the microdilution method, as described by the NCCLS. A ≥3 twofold dilution decrease in the MIC of either ceftazidime (GlaxoSmithKline, Greenford, Middlesex, United Kingdom) or cefotaxime (Sigma Laboratories, Madrid, Spain) tested in combination with clavulanic acid (GlaxoSmithKline) versus the MIC of each agent when it was tested alone was considered indicative of ESBL production, according to the NCCLS guidelines (21).

(ii) Antimicrobial agent susceptibility assays. The in vitro activities of ceftazidime, cefotaxime, cefoxitin (Sigma), amoxicillin (Sigma) plus clavulanate, imipenem (Merck Sharpe & Dohme, West Point, Pa.), ciprofloxacin (Sigma), gentamicin (Sigma), amikacin (Sigma), and trimethoprim-sulfamethoxazole (Galloso Laboratories, Madrid, Spain) were determined by a microdilution assay according to the NCCLS guidelines (20). *E. coli* ATCC 25922, *E. coli* ATCC 35218, *Pseudomonas aeruginosa* ATCC 27853, and *K. pneumoniae* ATCC 700603 were used as control strains.

(iii) Molecular typing. The clonal relationships among the strains were determined by repetitive extragenic palindromic sequence PCR (REP-PCR) with primers REP-1 (5′-IIIGCGCCGICATCAGGC-3′) and REP-2 (5′-ACGTCTT ATCAGGCCTAC-3′) (31). DNA extraction was performed by boiling a colony suspension at 100°C for 10 min. The supernatant from this suspension (24.5 μl) was used as the template for the PCR. All reactions were performed in a 50-μl volume with 2.0 U of *Taq* DNA polymerase (Invitrogen, Barcelona, Spain). The cycling conditions were as follows: denaturation at 94°C for 3 min, followed by 30 amplification cycles (94°C for 1 min, 40°C for 1 min, 65°C for 8 min) and a final extension cycle (65°C for 8 min). The DNA band patterns were evaluated by electrophoresis with 1.5% agarose gels. Two strains were considered clonally related when they had both the same numbers and the same locations of DNA bands.

(iv) Beta-lactamase characterization. Isoelectric focusing (IEF) and PCR were used for preliminary characterization of the beta-lactamases and beta-lactamase genes present in *E. coli* isolates, respectively. IEF (PhastGel IEF 3-9; Pharmacia, Barcelona, Spain) was performed to identify the numbers and isoelectric points (pIs) of the beta-lactamases present (5, 18). Bacterial strains expressing known beta-lactamases were included as controls. The IEF ranges were correlated to those of TEM, SHV, or CTX-M beta-lactamases (G. Jacoby and K. Bush, Amino acid sequences for TEM, SHV, and OXA extended-spectrum and inhibitor resistant beta-lactamases [http://www.lahey.org/studies/webt.htm]).

PCR was used to determine whether bla_{TEM}, bla_{SHV}, and $bla_{CTX\text{-}M}$ were present in each organism, as described previously (7, 22). Oligonucleotide primers were designed to amplify the genes encoding the most common subgroups within the family of ESBLs and are shown in Table 1. All reactions were performed in a 25-μl volume with 2.0 U of FastStart polymerase (Roche Diagnostics, Mannheim, Germany). Cycling parameters included 4 min of denaturation at 95°C, followed by 35 cycles of denaturation (95°C for 30 s), annealing (58°C for 30 s for TEM and SHV, 62°C for 30 s for CTX-M-9, 60°C for 30 s for CTX-M-10), and extension (72°C for 1 min), ending with a final extension period of 72°C for 7 min. Control organisms included *E. coli* strains containing the $bla_{TEM\text{-}1}$, $bla_{TEM\text{-}3}$, $bla_{SHV\text{-}1}$, $bla_{SHV\text{-}5}$, $bla_{CTX\text{-}M\text{-}9}$, or $bla_{CTX\text{-}M\text{-}10}$ gene. *E. coli* J53 Rif^r (negative control) was used as a negative control.

Statistical analysis. Continuous variables were compared by the Mann-Whitney U test. Qualitative variables were compared by the chi-square test or Fisher's exact test, as appropriate; odds ratios and 95% confidence intervals were calculated. Logistic regression analysis was performed to determine the variables and interactions that were significantly associated with the risk of infection with ESBLEC. Variables were selected in a stepwise backward process, in which the least significant variable was excluded at each step. The data were analyzed by using the SPSS software package.

RESULTS

During the study period, ESBLEC strains were isolated from 124 patients. Seventy-five patients had been admitted for 48 h or more when the sample had been obtained and were excluded. Thus, 49 case patients were included in the study. There was no apparent clustering of the case patients in terms of their geographical distribution. The distribution of the case patients throughout the study period is shown in Fig. 1. No patient had to be excluded because of a lack of data.

ESBLEC strains were isolated from cultures of urine from 45 patients and cultures of blood from 6 patients (for 2 patients, ESBLEC strains were isolated from cultures of both urine and blood). During the study period, ESBLEC strains were 1.4 and 15.1% of all *E. coli* strains isolated from cultures of urine and blood from outpatients, respectively.

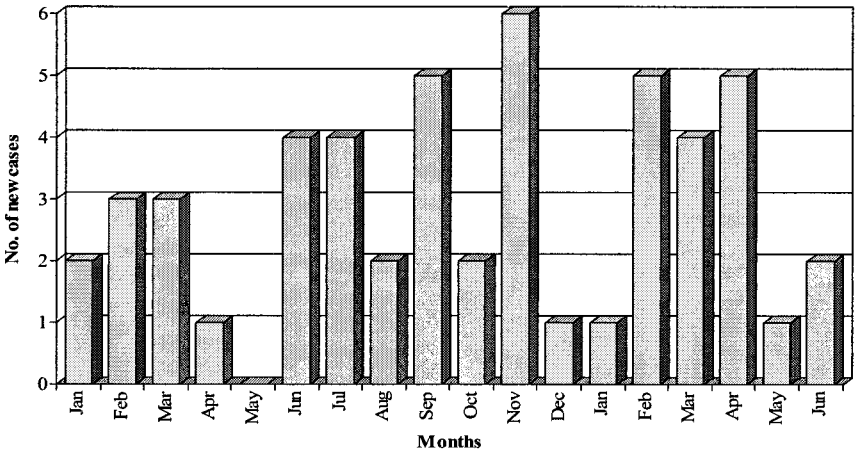

FIG. 1. Distribution of case patients during the study period (January 2001 to June 2002). Jan, January; Feb, February; Mar, March, Apr, April; Jun, June; Jul, July; Aug, August; Sep, September; Oct, October; Nov, November; Dec, December.

The median age of the case patients was 70 years (age range, 15 to 92 years). Fifty-seven percent of the case patients were female. Ten (21%) case patients were in the emergency department of the hospital when the sample was obtained, 7 (14%) were being attended to in the outpatient clinic, and 32 (65%) were in a primary care service. Twenty-seven patients (55%) had been admitted to a hospital during the preceding year. Only five patients (10%) were nursing home residents (all of them had also been hospitalized during the previous year). Other features of the case patients are shown in Table 2.

Thirty-seven patients (76%) were considered to have UTIs, 11 (22%) had asymptomatic bacteriuria, and 1 (2%) had acute cholangitis. Twenty-eight patients received empirical treatment, and this was considered appropriate, according to the in vitro susceptibility testing data, for only 10 patients (amoxicillin-clavulanic acid in 8 patients and ciprofloxacin in 2 patients). The inappropriately indicated empirical antimicrobial agents were ciprofloxacin (10 patients), levofloxacin (1 patient), cefuroxime (4 patients), cefotaxime (2 patients), and amoxicillin-clavulanic acid (1 patient). The UTIs relapsed after antimicrobial treatment in five patients (13% of patients with UTIs).

Six patients (12%; five patients with UTIs and one patient with cholangitis) had secondary bacteremia and needed to be hospitalized. All six bacteremic patients received empirical intravenous treatment (three with amoxicillin-clavulanic acid, two with cefotaxime, and one with levofloxacin), but the treatment was appropriate in only two of them, according to the results of in vitro susceptibility testing (amoxicillin-clavulanic acid in both patients). The fever rapidly subsided in these two patients. In the other four patients, the fever persisted until the treatment was changed (to imipenem in three patients and to piperacillin-tazobactam in one patient). All six patients were finally cured.

Microbiological studies. The clonal relatedness of 55 isolates (four patients were infected with 2 isolates and one patient was infected with 3 isolates) was studied by REP-PCR. The range of the number of bands was 10 to 20. All strains isolated from the same patient were indistinguishable. Forty-nine different profiles were obtained by REP-PCR. Data on the susceptibilities of the 49 clonally unrelated isolates to the antimicrobial agents tested are shown in Table 3. Thirty-one of the 49 isolates (64%) produced the CTX-M-9 ESBL. For three of these strains it was not possible to amplify a CTX-M-related gene, although both the pIs and phenotypic resistance (high-level resistance to cefotaxime and low-level resistance to ceftazidime) suggested the presence of a CTX-type ESBL. No CTX-M-10 ESBL was detected. TEM and SHV ESBLs were

TABLE 2. Features of 49 patients infected with community-acquired ESBLEC

Feature	No. (%) of patients
Female sex	28 (57)
McCabe classification of underlying disease	
Nonfatal underlying disease	35 (71)
Ultimately fatal underlying disease	14 (29)
Rapidly fatal underlying disease	0
Diabetes mellitus	20 (41)
Chronic respiratory disease	5 (10)
Chronic liver disease	1 (2)
Neoplasia	6 (12)
Recurrent UTIs	28 (57)
Permanent urinary catheter	11 (22)
Surgery (in preceding year)	4 (8)
Immunosuppressive drugs	0
Exposure to antimicrobial agents	
Previous antimicrobial treatment (in last 2 mo)	33 (67)
More than two cycles of antimicrobial treatment (in preceding year)	31 (63)
Aminopenicillins	4 (8)
Oral cephalosporins	5 (10)
Fluoroquinolones	20 (41)
Aminoglycosides	2 (4)
Trimethoprim-sulfamethoxazole	4 (8)

TABLE 3. Susceptibility data for 49 ESBLEC strains to different antimicrobial agents

Antimicrobial agent	MIC (mg/liter)[a]			% of strains susceptible
	50%	90%	Range	
Amoxicillin-clavulanic acid	16/8	32/16	2/1–256/128	48
Ciprofloxacin	8	64	<0.06–64	22
Gentamicin	0.5	64	<0.06–128	74
Amikacin	1	8	0.125–128	96
Imipenem	0.03	0.06	<0.015–0.125	100
Cefotaxime	128	512	2–>512	
Ceftazidime	16	128	<0.125–256	
Cefoxitin	4	32	1–128	84
Trimethoprim-sulfamethozaxole	≥32/608	≥32/608	<1/19–≥32/608	29

[a] 50% and 90%, MICs at which 50 and 90% of isolates are inhibited, respectively.

both detected in nine clones each (18%). No epidemiological relation was found among case patients infected with isolates sharing the same type of ESBL. Among the 27 patients with previous hospitalizations, CTX, TEM, and SHV ESBLs were found in 18 (67%), 6 (22%), and 3 (11%) patients, respectively. Among the five nursing home patients, four were infected with a CTX-producing clone and one was infected with an SHV-producing clone.

Case-control study. The results of univariate comparisons of the case patients and the controls are shown in Table 4. The multivariate analysis selected diabetes mellitus, the use of fluoroquinolones in the previous 2 months, recurrent UTIs, admission to a hospital during the preceding year, and older age in males as independent factors associated with an increased risk of isolation of ESBLEC. Eighty-two percent of the case patients had two or more of these risk factors. When only case patients infected with a CTX-producing clone were considered, the risk factors identified by multivariate analysis were older age, a higher Charlson index, and previous fluoroquinolone use. The results obtained with both multivariate models are shown in Table 5.

DISCUSSION

Infections due to ESBL-producing *K. pneumoniae* and ESBLEC in nursing home residents are well-known problems (32). However, even though some recent data suggest that infections due to ESBLEC in nonhospitalized patients might be emerging (1, 8, 9, 11, 14, 15), the epidemiology of these infections outside nursing homes had not been studied. Our study confirms the emergence of ESBLEC as a cause of infection in outpatients outside nursing homes.

E. coli is the most frequent cause of community-acquired UTIs and is frequently found to be responsible for intra-abdominal and soft tissue infections. Thus, resistance to commonly used antimicrobials in *E. coli* represents a problem for

TABLE 4. Crude analysis of potential risk factors for community-acquired ESBLEC infection

Variable	Case patients (n = 49)	Controls (n = 98)	OR (95% CI)[a]	P value
Age (yr [mean, SD])	65, 24	35, 24		<0.001
Male sex (% of patients)	43	19	3.1 (1.4–6.6)	0.003
Charlson index (mean)	1.82	1.52		<0.001
% of patients with:				
Diabetes mellitus	41	6	10.5 (3.8–28.8)	<0.001
Chronic pulmonary disease	18	5	4.1 (1.3–13.2)	0.01
Liver disease	2	2	1.0 (0.0–11.3)	1.0
Neoplasia	12	1	13.5 (1.5–115.8)	0.009
Recurrent urinary tract infections	57	19	5.5 (2.6–11.8)	<0.001
Permanent urinary catheter	22	0		<0.001
Previous antimicrobial treatment	67	9	20.3 (8.2–50.6)	<0.001
More than two cycles of antimicrobial treatment	63	8	19.3 (7.6–48.9)	<0.001
% of patients treated with:				
Aminopenicillins	8	2	4.2 (0.7–24.1)	0.07
Oral cephalosporins	10	1	11.2 (1.2–97.1)	0.01
Fluoroquinolones	41	5	12.8 (4.4–37.2)	<0.001
Trimethoprim-sulfamethoxazole	8	1	8.6 (0.9–79.3)	0.04
% of patients with:				
Hospital admission during last year	55	1	15.9 (6.1–41.3)	<0.001
Nursing home residency	10	0		0.004

[a] OR, odds ratio; CI, confidence interval.

TABLE 5. Multivariate analysis of factors associated with increased risk of community-acquired infection due to ESBLEC

Patient group and variable[a]	β coefficient	OR (95% CI)[b]	*P* value
All case patients			
Diabetes mellitus	1.7	5.5 (1.6–18.7)	0.006
Fluoroquinolone use	2.0	7.6 (1.9–30.1)	0.003
Recurrent urinary tract infections	1.5	4.5 (1.3–15.1)	0.01
Admission during last year	2.9	18.2 (5.3–61.6)	<0.0001
Age (yr) and sex	0.03	1.03 (1.01–1.05)	0.001
Age (yr)	0.003	1.0 (0.9–1.03)	0.7
Gender	0.2	1.2 (0.5–29.3)	0.8
Case patients infected with CTX-M-9-producing clone			
Fluoroquinolone use	1.6	5.2 (1.4–19.3)	0.01
Age (yr)	0.03	1.03 (1.01–1.06)	0.004
Charlson index	0.5	1.6 (1.1–2.5)	0.01

[a] Age and Charlson index are continuous variables. All other variables except sex are dichotomous and are codified as 0 (absence), or 1 (presence of the feature); sex is codified as 0 (female) or 1 (male).
[b] OR, odds ratio; CI, confidence interval.

the treatment of these infections. As expected, ESBLEC mainly caused UTIs in our study. Few oral antimicrobials that are active against these organisms are available: all of the organisms were resistant to ampicillin and cephalosporins, and many of them were resistant to ciprofloxacin and/or trimethoprim-sulfamethoxazole. Amoxicillin-clavulanic acid was the most active oral agent among those tested in our study, but it was active against only half the isolates.

The fact that ESBLEC was the cause of bacteremia in some of our patients is even more worrying. Some antimicrobial agents commonly recommended for the treatment of community-acquired urinary tract or intra-abdominal sepsis (extended-spectrum cephalosporins, fluoroquinolones) are probably not useful against ESBLEC (24, 26). Four of the six bacteremic patients in our series received inadequate empirical treatment, and sepsis was not controlled until the treatment was changed. Treatment with a combination of a beta-lactamase–beta-lactamase inhibitor was successful in three of the patients, but these combinations are not usually recommended, as a high mortality rate has been found in some nonrandomized studies (23, 28). Thus, a carbapenem is usually recommended as the drug of choice for the treatment of severe infections due to ESBL-producing organisms (26). However, the emergence of carbapenem-resistant organisms may be a concern.

In our study, several risk factors for infections due to ESBLEC in nonhospitalized patients were identified: previous admission to a hospital, diabetes mellitus, recurrent UTI, fluoroquinolone use during the previous 2 months, and older age in male patients. Fifty-five percent of the patients had been admitted to a hospital during the previous year. The horizontal transmission of ESBLEC during the previous hospital stay is improbable, since we found no clonal relationship among the strains obtained from those patients and those obtained from patients with nosocomially acquired ESBLEC (data not shown). A previous hospital admission might also be an indirect marker of other predisposing factors (underlying diseases, antimicrobial use). Nevertheless, almost half of the case patients had not been hospitalized during the past year, nor had they been in nursing homes, so their infections can be considered truly community acquired. Clonal dissemination of uropathogenic trimethoprim-sulfamethoxazole-resistant *E. coli* in the community has been described previously (16), but we found no clonal relatedness among the ESBLEC isolates in our study. However, as ESBLs are usually encoded on plasmids, we cannot discard the possibility of plasmid transmission between strains (32). Further studies are being conducted to elucidate this possibility.

Many ESBL types are geographically distributed (4). It is remarkable that 64% of the community-acquired strains produced a CTX-M-9-like ESBL. This ESBL, along with CTX-M-10 and CTX-M-14, have previously been described in Spain (2, 7) but have never been as prevalent in these types of strains. The sequencing of the genes that encode the ESBLs is in progress. It is also important to point out that a significant percentage of the ESBLEC isolates in our study produced TEM or SHV. Most of these enzymes have been related either to nosocomial infections or to nursing home-related infections (3).

In our study previous fluoroquinolone use was a risk factor both for the acquisition of ESBLEC and for the specific acquisition of a CTX-producing ESBLEC. Previous ciprofloxacin and/or trimethoprim-sulfamethoxazole treatment was also a risk factor for colonization with ESBL-producing organisms in nursing home patients (32). These antimicrobials may select for ESBLEC in previously colonized patients, since ESBL production and resistance to these antimicrobials are linked. The plasmids encoding ESBLs also frequently encode the genetic determinants of trimethoprim-sulfamethoxazole resistance; the association between ESBL production and quinolone resistance is more complex (17, 25). The prevalence of ESBLEC colonization in the community is not known.

Our study has some limitations. Our case patients probably represent only the most visible part of the population harboring these organisms. Systematic prospective surveillance for the detection of colonized patients is desirable for studying nosocomially acquired antimicrobial agent-resistant organisms (27), but is not possible in the community setting. However, we believe that our results might provide useful information for clinical purposes. We did not choose as controls patients infected with non-ESBL-producing *E. coli*, as such a design overestimates the implications of previous antimicrobial use (12, 27). Recall bias is always possible in these kinds of studies. We

tried to avoid recall bias in several ways: by not informing the patients or primary care doctors of the purpose of the study until the end of the interview and by using a detailed questionnaire on previous antimicrobial use.

The results of our study may have two main practical consequences. First, interventions directed at decreasing the use of fluoroquinolones for the treatment of UTIs in patients with other risk factors (diabetes mellitus, recurrent UTIs, admission to a hospital during the preceding year) should be attempted in our area. Second, studies designed to predict the risk of sepsis due to ESBLEC in the individual patient should be developed to identify those patients who should receive empirical treatment with an agent with activity against these organisms. In the meantime, in areas where infections due to ESBLEC are occurring, it might be prudent to consider therapy with activity against these organisms in the empirical treatment of high-risk patients with severe community-acquired urinary tract sepsis.

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