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Major article

Duration of colonization by extended-spectrum β-lactamase-producing *Enterobacteriaceae* after hospital discharge

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Background: The duration of gastrointestinal colonization with extended-spectrum β-lactamase-producing *Enterobacteriaceae* (ESBL-E) may play a major role in the spread of these organisms. We evaluated the time to, and factors associated with, ESBL-E clearance after hospital discharge.

Methods: We retrospectively reviewed prospective surveillance results obtained over 14 years in a 1,000-bed hospital. The surveillance collected demographic, hospital stay, microbiologic, and outcome data. An automatic alert system identified readmitted patients with prior ESBL-E carriage. ESBL-E clearance was defined as a negative rectal screening sample at readmission with no new positive clinical sample during the stay. Variables associated with ESBL-E clearance were identified using a Cox model.

Results: We included 1,884 patients with 2,734 admissions. Four hundred forty-eight patients with readmission screening formed the basis for the study. Of 448 patients with 1 to 16 readmissions, 180 (40%) were persistent carriers. The median time to ESBL-E clearance was 6.6 months. Variables independently associated with clearance was having the first positive culture in a screening sample only (adjusted hazard ratio, 1.31; 95% confidence interval, 1.02-1.69; $P = .04$) and period 2005-2010 (hazard ratio, 1.88; 95% confidence interval, 1.33-2.67; $P < .01$).

Conclusion: We found a long duration of ESBL-E carriage after hospital discharge. An automatic alert system was useful for identifying, screening, and isolating previous ESBL-E carriers.

Extended-spectrum β-lactamase-producing *Enterobacteriaceae* (ESBL-E) are now among the leading causes of hospital-acquired bacterial infections. Despite infection-control measures, most countries are experiencing a rise in the incidence of infections due to ESBL-E. In 2010, the proportion of invasive *Escherichia coli* resistant to third-generation cephalosporins was between 10% and 20% in 6 of 28 countries, and was >20% in 4 other countries. The proportion of *Klebsiella pneumoniae* resistant to cephalosporins between 10% and 20% in 9 of 28 and >20% in 11 of 28 countries.[1] The increasing proportions of ESBL-E translates into decreased effectiveness of antimicrobial drug therapy and higher risks of adverse patient outcomes.[2,3]

Most cases of ESBL-E infection are preceded by asymptomatic gastrointestinal tract colonization that may escape detection and constitute the starting point for dissemination of the organism in health care facilities.[4] Historically, hospitalized patients were the main reservoir of ESBL-E and the spread of these organisms was viewed as an epidemiologic problem only for health care facilities.[5] However, during the past decade, ESBL-E producing CTX-M enzymes have spread within the community.[6] These strains can persist in the gastrointestinal tract with an emergence and spread when antimicrobial therapy is used.[7] Hospital admission of patients carrying ESBL-E from the community could have important consequences and require special monitoring and infection control measures to prevent the spread of these organisms within a health care facility.

The duration of ESBL-E carriage in the gastrointestinal tract may constitute a critical factor in the epidemiology of ESBL-E in hospitals and the community. In addition, health care procedures during the hospital stay may affect ESBL-E clearance from the gastrointestinal tract. To our knowledge, the duration of ESBL-E carriage after hospital discharge has been assessed in only 2 published

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Conflicts of interest: None to report.

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studies of colonized patients, both of which had small numbers of patients.[8,9]

Our objective in this research was to assess the duration of, and factors associated with, clearance of gastrointestinal ESBL-E carriage in a population of readmitted patients identified as colonized or infected with ESBL-E at the time of a previous stay in our hospital.

METHODS

Setting

This study was performed at the Bichat-Claude Bernard Hospital, a 950-bed university hospital providing both primary and tertiary care with more than 35,000 stays longer than 24 hours per year. An institutional program to prevent the spread of multidrug resistant (MDR) bacteria was implemented in 1992. As part of this program, all patients diagnosed with ESBL-E colonization and/or infection are followed-up prospectively during their hospital stay.

Design and data collection

We retrospectively reviewed the data from a 14-year period of prospective surveillance (January 1, 1997, to December, 31, 2010), including age and sex, hospital-stay characteristics (ie, date and ward of admission, date of transfer within the hospital, and destination), microbiological data (ie, ESBL-producing species, origin of the colonization, sampling date, and site of colonization or infection), date of hospital discharge, and destination after discharge.[10,11] ESBL-E infection was defined according to standard criteria[12] and ESBL-E colonization was defined as the presence of ESBL-E in patients who failed to meet criteria for ESBL-E infection. The methodology used and the criteria collected for this active surveillance were uniform across the 14 years. In patients with ESBL-E colonization and/or infection (ie, patients testing positive for ESBL-E infection), contact precautions were used throughout the hospital stay.

The origin of ESBL-E colonization and/or infection was determined based on the time from admission to the first positive culture and if the positive result was from a screening or clinical sample. Criteria for defining imported cases were as follows: ESBL-E recovered in a rectal swab within 48 hours after admission, ESBL-E recovered in a clinical sample from an infected or colonized site within 72 hours after admission, or history of colonization and/or infection by an ESBL produced by the same species. Patients who did not meet these criteria were classified as having hospital-acquired ESBL-E colonization and/or infection.

Procedures at readmission

In addition to the above-mentioned in-hospital surveillance program, a readmission automatic alert system was started in 1997 to identify all readmitted patients having a history of colonization/infection recorded in the surveillance database.[10,11] The list of newly admitted patients recorded by the administrative admissions system is compared 3 times each day with the ESBL-E surveillance database. When a newly admitted patient is identified as having been colonized and/or infected with ESBL-E during a previous stay in our hospital, an automatic alert is sent to the infection control unit and to the admitting clinical ward. The infection control team provides prompt assistance to the ward staff for implementing contact-isolation precautions and obtaining a rectal swab to screen for ESBL-E. Preliminary data from our hospital suggested that ESBL-E carriage persisted at least 3 months after hospital discharge. In addition, this 3-month interval for readmission screening was chosen as consistent with the strategy used for methicillin-resistant *Staphylococcus aureus*.[11] Hence, contact-isolation precautions without readmission screening were implemented routinely for patients readmitted within 3 months after hospital discharge. However, in several high-risk units (mainly medical and surgical intensive care units), screening was performed routinely at admission then once a week.

Clearance of ESBL-E was defined as a negative rectal screening culture at readmission. In patients with persistent ESBL-E carriage, carriage duration was defined as the difference between the date of discharge after the first positive culture and the date of readmission with a positive screening culture.

Microbiological techniques

ESBL-E strains from screening and/or clinical specimens taken during the study period were investigated. Clinical specimens were isolated on conventional media used for infection diagnosis. Screening samples were cultured on selective media: Drigalski agar (Bio-Rad, Marnes-la-Coquette, France) supplemented with cefotaxime (0.5 mg/L) from 1997 to 2004, BLSE Agar (AES Chemunex, Ivry sur Seine, France) from 2005-2007, and ChromID ESBL Agar, (bioMérieux, Marcy-l'Etoile, France) from 2008-2010. *Enterobacteriaceae* species were identified using the API 20E ID system (bioMérieux, Marcy-l'Etoile, France). Susceptibility to antibiotics was tested using the disk diffusion method on Mueller-Hinton media (Biorad, Marne-la-Coquette, France) and interpreted as recommended by the French Society for Microbiology. All ESBL-producing strains detected using a positive double-disk synergy test were considered resistant to all extended-spectrum cephalosporins.[13] In AmpC producing *Enterobacteriaceae*, overproduction of intrinsic or plasmidic cephalosporinase AmpC was inhibited by studying susceptibility on cloxacillin agar as described.[14]

Statistical methods

The data are described as numbers (%) and as medians (25th-75th percentiles). Continuous variables were converted to dichotomous or categorical variables using the median value as the cutoff. A time period indicator was used to distinguish periods within the overall study period based on variations in ESBL-E incidence.

Time to clearance and probability of persistent carriage at readmission were assessed using Kaplan-Meier survival analyses. Patients without ESBL-E infection were censored at the time of the negative readmission screen. To identify variables associated with clearance, we compared continuous variables using univariate Cox analysis. Variables associated with $P < .20$ in the univariate analysis were entered into a multivariate Cox model. Hazard ratio compared the events corresponding to the listed variable against all others, correcting for clustering at the patient level. All tests were 2-tailed, and $P < .05$ was considered significant. Statistical analyses were performed using Stata release 10.0 (Stata Corp LP, College Station, TX).

RESULTS

Overall population with ESBL-E colonization/infection (n = 1,884)

ESBL-E was isolated from 1,884 patients with 2,734 admissions and 220 outpatient visits during the 14-year study period. Median age at the first positive-testing ESBL-E culture was 62.8 years (range, 49-75 years) and the male to female ratio was 1.21. Most patients (n = 1,381, 73.3%) were admitted only once during the study period. Two or more admissions occurred for 503 patients, who had 2 to 16 admissions per patient. Overall median hospital stay length was 16 days (range, 4-38 days) and admissions occurred

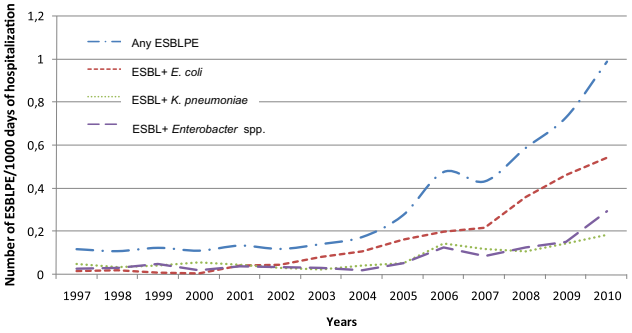

Fig 1. Incidence of any extended-spectrum beta-lactamase (ESBL)-producing *Enterobacteriaceae* and of ESBL-producing *Escherichia coli*, *Klebsiella pneumonia*, and *Enterobacter* spp. cultured from screening or clinical samples between January 1997 and December 2010 at the Bichat-Claude Bernard Hospital.

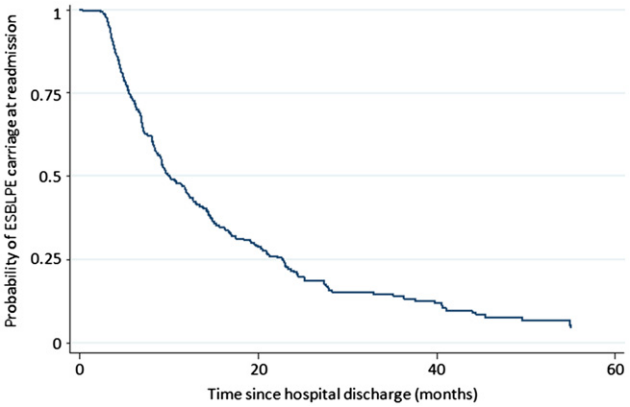

Fig 2. Kaplan-Meier estimate of time to clearance of extended-spectrum β-lactamase-producing *Enterobacteriaciea* (ESBLPE) in patients readmitted between January 1997 and December 2010 to the Bichat-Claude Bernard Hospital.

to 4 (range, 2-7) different wards per patient with a median of 7 days (range 2-18 days) per ward.

Among the 1,884 patients testing positive for ESBL-E infection, 951 (50.5%) met our definition for imported colonization/infection and 924 (49%) for hospital-acquired colonization/infection; in the remaining 9 (0.5%) patients, the origin of the colonization/infection was unclear. The overall incidence of imported plus acquired ESBL-E colonization/infection in clinical isolates increased from 0.11/1,000 patient-days in 1997 to 0.98/1,000 patient-days in 2010 (Fig 1). This increase was particularly marked between 2005 and 2010.

The distribution of the 2,102 ESBL-E isolates recovered from the 1,884 patients was as follows: *E coli* n = 1,093 (52%), *Enterobacter* species n = 438 (20.9%), *K pneumoniae* n = 423 (20.1%), and other *Enterobacteriaceae* n = 148 (7.0%). The incidence of *E coli* and *K pneumoniae*-producing ESBL in clinical samples increased from 0.02 and 0.05 in 1997 to 0.54 and 0.18/1,000 patient-days in 2010, respectively. This rise in the incidence of ESBL-E was associated with a change in the distribution of *Enterobacteriaceae* species producing ESBL. The ESBL-producing strains consisted chiefly of *K pneumonia* in 1997 (14 of 33 strains; 42.4%) and *E coli* in 2010 (150 of 274 strains, 54.7%). A single ESBL-E species was found in 1,695 (90%) patients, 2 species in 164 (8.7%) patients, 3 species in 21 (1.1%) patients, and 4 species in 4 (0.2%) patients. In 61 patients, the species changed over time, once in 50 patients, twice in 7 patients, and 3 times in 4 patients.

The overall antibiotic consumption in our hospital decreased from 726 to 612 defined daily doses per 1,000 patient-days between 2001 and 2010.

Findings at readmission (n = 448)

The automatic alert system identified 503 patients previously identified as positive for ESBL-E infection and readmitted after a median of 27 days (range, 10-67 days), including 448 patients readmitted after at least 3 months after hospital discharge. All of these 448 patients were screened at readmission and formed the study population. Of these 448 patients, 180 (40.2%) had specimens that tested positive for ESBL-E and 268 (59.8%) had specimens that tested negative for ESBL-E at readmission. The number of readmissions ranged from 1 (68.3%) to 10 (1.1%).

Of 268 patients with negative readmission screens, 149 (55.6%) had negative screens at the first readmission, 68 (25.4%) at the second readmission, and 51 (19.0%) at the third readmission and beyond. The Kaplan-Meier estimate of the median time to ESBL-E clearance was 6.6 months (range, 3.4-13.4 months) (Fig 2). The percentage of readmitted patients who were still ESBL-E carriers was 25.6% (115 of 448) after 1 year and 8.9% (40 of 449) after 2 years. The instantaneous risk of clearance increased from 0.05% to 0.24% per month during the first 2 years after hospital discharge and decreased slowly thereafter.

In the univariate Cox regression models, having the first positive culture on screening samples only and during 2005-2010 were associated with ESBL-E clearance. These variables remained significant in the multivariable model, namely having the first positive culture on screening samples only (adjusted hazard ratio, 1.31; 95% confidence interval, 1.02-1.69) and during 2005-2010 (adjusted hazard ratio, 1.88; 95% confidence interval, 1.33-2.67) (Table 1). The following factors were not significantly associated with ESBL-E clearance: species of *Enterobacteriaceae* and imported or acquired colonization/infection.

DISCUSSION

Of 448 patients previously known as colonized or infected with ESBL-E and readmitted and screened routinely, 40.2% were still colonized. Median time to ESBL-E clearance was 6.6 months (range, 3.4-13.4 months). We found no significant difference in the time to ESBL-E clearance across *Enterobacteriaceae* species. The variables significantly associated with ESBL-E clearance were having a positive culture in a screening sample only during the index admission and the first positive culture during 2005-2010 instead of 1997-2004.

Most of the available epidemiologic information about ESBL-E comes from patients who entered health care facilities with ESBL-E infection or were transferred between facilities.[15] However, the tight interconnections between the community and health care system must be taken into account to obtain an accurate picture of the spread of microorganisms. Little information has been obtained on gastrointestinal ESBL-E carriage after hospital discharge. The spread of ESBL-E colonization/infection is a major concern for health care systems worldwide. One reason for this rapid spread is the commensal nature of ESBL-E (most notably those producing CTX-M enzymes) in gut flora. Without screening, the presence of ESBL-E in the gastrointestinal tract remains undetected, unless an ESBL-E infection develops. In addition, in health care institutions the emergence, selection, and transmission of MDR bacteria is facilitated by comorbidities in the patient population, the use of invasive procedures and antimicrobials, and imperfect adherence to standard infection-control practices.[16] Thus, admitting a patient infected with ESBL-E to a hospital introduces the organism into an environment where there is a high risk of dissemination to nearby patients.

A long hospital stay length (>7 days) is known to be associated with a higher risk of readmission within 30 days after hospital

Table 1
Variables associated with clearance of extended-spectrum β-lactamase-producing *Enterobacteriaceae* (ESBLPE) identified using a Cox hazard proportional model

	n (%)			
	All (n = 448)	Cleared (n = 268)	Univariate HR (95% CI), *P*	Multivariable aHR (95% CI), *P*
Sex				
Female	228 (50.9)	137 (51.1)	1.00 (0.78-1.28), 0.96	
Male	220 (49.1)	131 (48.9)	Reference	
Age, y				
0-30	23 (5.1)	19 (7.1)	1.28 (0.79-2.07), 0.31	
31-45	57 (12.7)	36 (13.5)	1.03 (0.71-1.51), 0.86	
46-60	116 (25.9)	73 (27.2)	0.87 (0.75-1.15), 0.33	
>60	252 (56.3)	140 (52.2)	Reference	
ESBLPE species				
Klebsiella pneumoniae	68 (15.2)	43 (16.0)	0.85 (0.59-1.2), 0.48	
Enterobacter spp.	80 (17.8)	56 (20.9)	1.15 (0.84-1.59), 0.37	
Other species	83 (18.5)	38 (14.2)	0.84 (0.59-1.21), 0.38	
Escherichia coli	217 (48.4)	131 (48.9)	Reference	
Origin (n = 440)*				
Acquired	237 (53.1)	155 (58.0)	1.10 (0.86-1.41), 0.42	
Imported	209 (46.9)	112 (42.0)	Reference	
Time to positive culture after admission, d				
>4	200 (44.6)	132 (49.2)	1.11 (0.87-1.41), 0.39	
0-4	248 (55.4)	136 (50.8)	Reference	
Type of specimen at the first ESBLPE-positive culture				
Screening	187 (41.7)	130 (48.5)	1.50 (1.17-1.92), <0.01	1.31 (1.02-1.69), 0.04
Clinical	261 (58.3)	138 (51.5)	Reference	
In ICU at time of positive result				
Yes	96 (21.4)	65 (24.3)	1.07 (0.81-1.42), 0.64	
No	352 (78.6)	203 (75.7)	Reference	
Hospital stay length after first ESBLPE-positive culture, d				
>17	208 (46.4)	130 (48.5)	0.94 (0.74-1.19), 0.62	
0-17	240 (53.6)	138 (51.5)	Reference	
Ward at hospital discharge (n = 415)†				
Intensive care units	11 (2.6)	5 (1.9)	0.71 (0.26-1.90), 0.49	
Surgical wards	134 (32.3)	88 (34.1)	0.99 (0.76-1.29), 0.94	
Medical wards	270 (65.1)	165 (61.6)	Reference	
Year of first ESBLPE identification				
2005-2010	379 (84.6)	221 (82.5)	1.87 (1.34-2.61), <0.01	1.88 (1.33-2.67), <0.01
1997-2004	69 (15.4)	47 (17.5)	Reference	
Situation before readmission				
Home	324 (72.3)	191 (71.3)	1.07 (0.81-1.40), 0.62	
Other health care facility	124 (27.7)	77 (28.7)	Reference	

HR, hazard ratio comparing the events corresponding to the listed variable against all others correcting for clustering at the patient level; *CI*, confidence interval; *ICU*, intensive care unit.
*Origin unknown for 8 patients.
†Excluding outpatient visits.

discharge.[17] Median stay length in our patients with ESBL-E infection was 16 days, in line with the high readmission rate of 24.7% in patients included in the surveillance program. Among 503 patients identified as colonized or infected during the previous hospitalization, 251 (50%) still tested positive for ESBL-E infection at their first readmission. The population of patients at high risk for readmission can introduce ESBL-E into health care facilities. Therefore, an automatic alert system to identify MDR-positive patients at the time of readmission is critical to ensure that barrier precautions are instituted promptly.[10,11]

Few studies of the duration of ESBL-E colonization after hospital discharge have been published. The earliest study evaluated the stool of 24 patients during a 6-month period and estimated the duration of colonization at 98 days (range, 14-182 days).[8] The second study relied on an automatic alert system to identify readmitted patients for screening. Most of the 62 patients who tested positive for ESBL-E infection readmitted during a 6-month period were children. Median duration of colonization was evaluated at 132 days (range, 65-228 days).[9] Finally, a third study found a median time to clearance of 7.5 months (range 0-39 months) in 18 patients involved in a nosocomial outbreak of ESBL-E carriage.[18] In our study, median time to ESBL-E clearance was 6.6 months. In contrast to an earlier study,[8] routine screening was performed in our study only once in most (86.2%) patients, with a range of time to readmission after hospital discharge greatly varying from 1 day to 6.4 years. Regular screening of patients testing positive for ESBL-E infection at closer intervals would probably have shown faster clearance in some patients with a long duration before readmission. Thus, our study probably overestimated the median time to clearance.

Contrary to many earlier studies, our work started with an in-hospital event (ie, ESBL-E colonization/infection) then evaluated the affect on a community event (ie, time to clearance). This original approach allowed us to determine that having the first ESBL-E-positive culture on a screening sample only and between 2005 and 2010 were associated with more rapid clearance, we recently implemented an antimicrobial stewardship program that decreased global antimicrobial consumption in our hospital by 30%.[19] Restricting the use of antimicrobial therapy may decrease the burden of the resistant bacteria in the gut of treated patients. Thus, patients with ESBL-E colonization in recent years may have lower stool counts of ESBL-E and, consequently, may experience faster clearance. A more rapid clearance was associated with intestinal colonization only without colonization of infection at another site. ESBL-E colonization has been widely recognized as a risk factor for infection.[20] The transition from asymptomatic gastrointestinal tract colonization to infection is probably favored by an increase of fecal ESBL-E concentration, probably explaining a persistent carriage.

Unexpectedly, we found no significant difference in the time to ESBL-E clearance across *Enterobacteriaceae* species. *E coli* is the main *Enterobacteriaceae* in the commensal gut flora, with concentrations higher by 3-5 Log than those of other *Enterobacteriaceae* such as *Enterobacter* spp. or *K pneumoniae* in normal gut flora. We expected a longer time to clearance of *E coli* compared with other ESBL-producing *Enterobacteriaceae*. There is evidence of dissemination of ESBL-producing epidemic clones such as CTX-M 15 *E coli* O25;H4;ST131 in the community, which probably are better able to take part of the commensal flora.[21] However, none significant difference between species was found in our study.

Our study has several limitations. First, ESBL-E clearance was established based on a single negative rectal screening sample. Rectal and perirectal swabs have been demonstrated to be equivalent to fecal samples for detecting fecal colonization with resistant Gram-negative bacteria, provided they are adequately performed.[22] However, the sensitivity of the test may depend on the microbiological technique (with or without broth enrichment), the ESBL-E concentration in feces, and the amount of feces on the swab. For example, 26 of 268 (9.7%) patients with negative readmission screens had positive results of the third screens performed at subsequent readmissions. In addition, 9 (3.3%) patients had 4 consecutive samples with various alternations of positive and negative results, and 1 patient had 6 consecutive samples with alternating positive and negative results. These findings suggest false-negative results or the acquisition of a new strain after clearance.[23,24] Unfortunately, strains cultured during 2 consecutive hospital stays were considered unchanged if the species was the same, and molecular typing was not performed. Second, we had no information on antibiotics taken by the patients after hospital discharge. Most antibiotics probably increase the level of gut colonization and delay ESBL-E clearance. Third, the study population was composed only of readmitted patients. Patients requiring multiple admissions usually have characteristics that promote persistent ESBL-E carriage; that is, comorbidities and a need for invasive procedures or antibiotic treatments. Finally, our patients were not screened during the interval between admissions, which probably led us to overestimate the time to clearance. Moreover, readmission screening was performed only in patients readmitted >3 months after the end of their previous stay. This inclusion criterion may also have led to overestimation of the time to clearance.

In conclusion, we found a long duration of ESBL-E carriage after hospital discharge. These findings closely affect the clinical management of infections at the time of the readmission of colonized patients. Therefore, screening for ESBL-E and contact-isolation precautions at hospital readmission are advisable for all patients identified as testing positive for ESBL-E infection during an earlier hospital stay, whatever the time since the index admission. This recommendation holds true whatever the type of ESBL-producing *Enterobacteriaceae*, characteristics of the patients, and index hospital stays. These findings are probably transposable to carbapenemase-producing *Enterobacteriacae* in hospital settings.

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