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ORIGINAL ARTICLE

Clinical and microbiological determinants of severe and fatal outcomes in patients infected with Enterobacteriaceae producing extended-spectrum β-lactamase

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Abstract Although extended-spectrum β-lactamase (ESBL)-producing Enterobacteriaceae have become a worldwide public health concern, little is known regarding the clinical course of colonized or infected individuals. Our objective was to characterize the determinants of fatal outcomes related to ESBL-producing microorganisms at a large hospital in Paris, France. In 2012–2013, all consecutive patients with clinical samples testing positive for ESBL-producing Enterobacteriaceae at Saint-Antoine Hospital were identified. Patient clinical data were obtained at hospital entry, while information on intensive care unit (ICU) admissions and death were prospectively collected. Risk-factors for fatal 1-year outcomes were assessed using logistic regression. In total, 643/4684 (13%) ESBL-positive samples were observed, corresponding to 516 episodes ($n = 206$, 40% treated) among 330 patients. Most episodes were nosocomial-related ($n = 347/516$, 67%) involving *Escherichia coli* ($n = 232/516$, 45%) or *Klebsiella pneumoniae* ($n = 164/516$, 32%). Empirical antibiotic therapy was adequate in 89/206 (43%) infections, while the median length of hospital stay was 30 days [interquartile range (IQR) = 11–55] and 39/201 (19%) were admitted to the ICU. Overall, 104/241 patients (43%) with available data died within 1 year. In the multivariable analysis, 1-year death was associated with age >80 years ($p = 0.01$), concomitant comorbidity ($p = 0.001$), nosocomial-acquired infection ($p = 0.002$), and being infected rather than colonized ($p < 0.001$). In this series of patients with identified samples of ESBL-producing Enterobacteriaceae, hospital burden was large and 1-year mortality rates high. Understanding which patients in this setting would benefit from broad-spectrum empirical antibiotic therapy should be further examined.

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Introduction

In the Enterobacteriaceae family of Gram-negative bacteria, extended-spectrum β-lactamase (ESBL)-producing microorganisms started to emerge during the 1980s and have developed into a worldwide public health concern. ESBL-encoding plasmids frequently bear genes conferring resistance to multiple antibiotics, such as aminoglycosides or fluoroquinolones [1]. For instance, recent studies ranging from community-onset to pyelonephritis-associated infections have observed much higher rates of resistance to trimethoprim–sulfamethoxazole, ciprofloxacin, and gentamicin in ESBL- compared to non ESBL-producing strains [2].

Consequently, the treatment of ESBL-producing microorganisms remains a challenge. Many of the currently recommended antibiotic agents used for empirical treatment are inadequate. Carbapenems, another class of β-lactam agents used to treat

multidrug-resistant strains, are an ideal therapeutic alternative; however, its widespread use could contribute to increased selection of carbapenemase-producing bacteria [1]. Considering recent estimates from the United States that at least 2 million people are infected with antibiotic-resistant microorganisms and 23,000 die as a result (Centers for Disease Control and Prevention, CDC), there is a strong need to characterize the types of currently circulating ESBL-producing Enterobacteriaceae in order to help identify the types of patients needing treatment and clarify more effective antibiotic combinations for empirical therapy.

Little is known regarding the genetic epidemiology and clinical consequences of these strains in France. Several studies have been conducted in this setting, but have been restricted to urine samples [3], bacteremia [4], or ESBL-producing *Escherichia coli* infections [5]. A more recent study across much of France evaluated 28-day mortality rates among carriers of and patients infected with ESBL-producing Enterobacteriaceae, with the limitation that only intensive care units (ICUs) were included [6]. We conducted a prospective, observational study at a university teaching hospital located in Paris, France, in order to determine the characteristics of circulating ESBL-producing Enterobacteriaceae and to evaluate which proportion of strains was susceptible to various antibiotics. We also sought to describe the determinants resulting in severe and fatal outcomes related to infection.

Patients and methods

Study design

We conducted a prospective study at Saint-Antoine Hospital, Paris, France from April 2012 to April 2013. Biological samples, with the exception of rectal swabs, from patients attending in- or outpatient clinics were processed at the Department of Microbiology. In this study, we included any samples testing positive for an ESBL-producing Enterobacteriaceae. Any samples from patients on palliative care were further excluded. It should be mentioned that multiple samples could have been taken during an episode and more than one episode could have occurred within the same patient.

Assessing clinical characteristics

Clinical characteristics were assessed at the start of each episode. An episode was classified as either "infection" if the patient's referent physician decided to treat with antibiotics or as "colonization" otherwise. The portal of entry was classified as lung, urinary tract, digestive tract, or unknown according to the referent physician. Acquisition of ESBL-producing Enterobacteriaceae was characterized as follows: community-acquired, if the first positive sample was detected ≤48 h of admission without any recent hospitalization; hospital-acquired, if the first positive sample was detected >48 h after admission; or healthcare-associated, if the first positive sample was detected ≤48 h after admission and the patient underwent hospitalization within 3 months prior.

Microbiological testing

The phenotypic and genotypic characteristics of all strains were determined at the same microbiology laboratory. Antibiotic susceptibility was tested using the diffusion method on Mueller–Hinton medium (Bio-Rad, Marne-la-Coquette, France) and the results were interpreted according to recommendations provided by the Comité de l'Antibiogramme de la Société Française de Microbiologie (CA-SFM) (http://www.sfm-microbiologie.org). ESBL were detected using the double disk diffusion method. The minimum inhibitory concentrations (MICs) of antimicrobial agents were determined using Etests (bioMérieux, Marcy l'Etoile, France) if necessary and were interpreted according to CA-SFM recommendations.

Genetic characterization was performed using multiplex polymerase chain reaction (PCR), from previously developed procedures, able to detect the most widely distributed genes encoding ESBL, plasmid-mediated AmpC β-lactamases, and class A, B, and D carbapenemases [7]. After amplification using specific primers, PCR products were purified using the ExoSap purification kit (Illustra, Exostar 1-step; D. Dutscher, Brumath, France) and bidirectional sequencing was performed using a BigDye Terminator 3.1 Cycle Sequencing Kit (Applied Biosystems, Foster City, CA). Each sequence was aligned using Applied Biosystems SeqScape software v2.7 and then compared with β-lactamase gene reference sequences using a multiple sequence alignment program (BLAST, GenBank database). If a patient harbored >1 isolate with the same phenotype, only one of these isolates was characterized with PCR.

Statistical analysis

Data were analyzed among isolates, episodes, or patients depending on the end-point. Unless otherwise stated, all comparisons were performed using the Kruskal–Wallis test for continuous variables and Pearson's χ^2 or Fisher's exact test for categorical variables. Statistical analysis was performed using STATA (v12.1, College Station, TX) and R (v3.2.0, Vienna, Austria), while significance was determined using a p-value < 0.05.

In a risk factor analysis, all-cause mortality was used as an end-point. For patients with multiple episodes, only the last episode was considered in the analysis. Odds ratios (ORS) and 95% confidence intervals (CIs) were determined using logistic regression. A multivariable model was constructed in which all covariables with a $p < 0.2$ in the univariable analysis were

placed in a full model, while removing any variables below this threshold in a backwards stepwise fashion.

Results

During the study period, 4684 samples were positive for Enterobacteriaceae, 643 (13%) of which were ESBL-producing strains. In total, these isolates were observed in 516 episodes occurring among 330 patients (Fig. 1). The patient characteristics at the first episode are provided in Table 1. Half of the patients were male, with a median age of 70 years [interquartile range (IQR) = 57–84]. Roughly two-thirds presented with at least one comorbidity. The minority of patients (20.0%) did not have at-risk exposure for ESBL carrier status (i.e., antibiotic therapy, previous hospitalization, or trip abroad) 3 months prior to their infection. Accordingly, 32 of 330 (9.7%) patients had neither any comorbidity nor at-risk exposure for carriage.

Bacterial characteristics of isolates

Of the 643 ESBL-producing isolates retrieved, 445 had distinctly identified phenotypes. In total, 200 were *E. coli* (44.9%), 123 *Klebsiella pneumoniae* (27.6%), 88 *Enterobacter* sp. (19.8%), and 20 *Citrobacter freundii* (4.5%). Based on antibiotic resistance testing, 44 strains were susceptible to amoxicillin clavulanate (9.9%), 220 to piperacillin–tazobactam (49.4%), 298 to cefoxitin (67.0%), 2 to cefotaxime (0.5%), 8 to cefepime (1.8%), 368 to amikacin (82.7%), 175 to gentamicin (39.3%), 116 to trimethoprim–sulfamethoxazole (26.1%), 84 to ciprofloxacin (18.9%), 379 to fosfomycine (85.6%), and 390 to tigecycline (92.0%). ESBL-producing genes were characterized in 309 strains, with 92.9% ($n = 287$) identified as CTX-M type (62.1% CTX-M-15, 11.7% CTX-M-14, 7.8% CTX-M-1, 3.2% CTX-M-27), 3.9% ($n = 12$) as TEM type (2.9% TEM-15, 1.3% TEM-20, 0.3% TEM-26), and 3.2% ($n = 10$) as SHV type (3.2% SHV-12). Except for one strain, all TEM- or SHV-producing strains were involved in nosocomial-acquired or healthcare-associated infections.

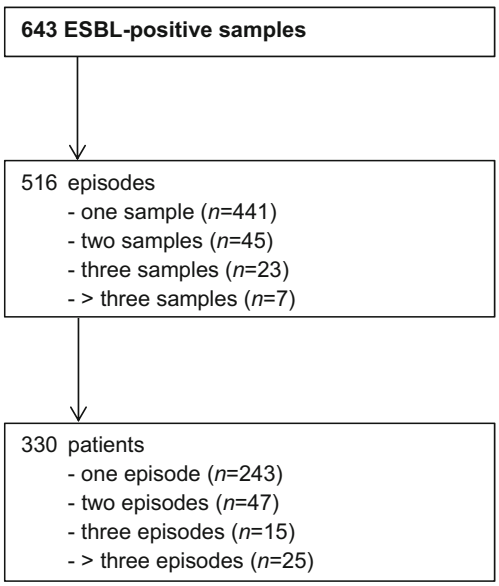

Fig. 1 Study flow chart

Clinical characteristics of episodes

Of the 516 episodes, 243 (47.1%) were from only one isolate, 90 (17.4%) were reinfections with strains sharing the same phenotypic characteristics, and 183 (35.5%) were de novo infections with a phenotypically different strain. The predominant source of infection was urinary tract (41.8%, $n = 86$), followed by digestive tract (28.6%, $n = 59$), pulmonary (12.1%, $n = 25$), and undefined (6.8%, $n = 14$). Bacteremia was involved in 11.8% of episodes. In the 206 (39.9%) infections with data on outcomes after antibiotic therapy, 89 (43.8%) were treated with adequate empirical antibiotic therapy. Fifty infections were identified in patients who had already been identified as ESBL-producing Enterobacteriaceae carriers. Of them, 37 (74.0%) were empirically treated with carbapenems or piperacillin-tazobactam. For the 114 patients with inadequate empirical treatment, 93 (81.6%) had optimal definitive treatment. Of note, no patient received cephalosporin as definitive treatment.

Infection and colonization episodes are compared in Table 2. A higher proportion of infections were healthcare-associated and a lower proportion nosocomial-acquired when compared to colonization ($p = 0.04$). A significantly higher prevalence of

Table 1 Description of patient characteristics

	$N = 330$
Male*	162 (49.1)
Age, years**	70 (57–84)
At least one comorbidity*	222 (67.3)
Solid malignancy	77 (23.3)
Hematological disorder	56 (17.0)
Immunosuppressive treatment	130 (39.4)
Hemodialysis	7 (2.1)
Diabetes	85 (25.8)
At-risk exposure*	264 (80.0)
Antibiotics within 3 months	203 (61.5)
Hospitalization within 3 months	222 (67.3)
Trip abroad within 3 months	34 (10.3)
Known colonization with ESBL-producing Enterobacteriaceae*	83 (25.2)

ESBL Extended-spectrum β-lactamase

*Number (%)

**Median (IQR)

Table 2 Description of episode characteristics

	Total	Episode*		*p*-Value**
	N = 516	Infection *n* = 206	Colonization *n* = 310	
Episode type				0.04
Nosocomial-acquired	347 (67.3)	126 (61.2)	221 (71.3)	
Healthcare-associated	93 (18.0)	47 (22.8)	46 (14.8)	
Community-acquired	76 (14.7)	33 (16.0)	43 (13.9)	
Suspected location of infection				*ntp*
Urine	–	86 (41.8)	–	
Lungs	–	25 (12.1)	–	
Digestive tract	–	59 (28.6)	–	
Skin	–	22 (10.7)	–	
Unknown		14 (6.8)		
Polybacterial	28 (5.4)	15 (7.3)	13 (4.2)	0.13
Bacteremia	–	52 (25.2%)	–	*ntp*
Species				
Escherichia coli	232 (45.0)	108 (52.4)	124 (40.0)	0.005
Klebsiella pneumoniae	164 (31.8)	55 (26.7)	109 (35.2)	0.04
Enterobacter cloacae	108 (20.9)	41 (19.9)	67 (21.6)	0.6
Citrobacter freundii	22 (4.3)	6 (2.9)	16 (5.2)	0.2
Klebsiella oxytoca	6 (1.2)	1 (0.3)	5 (2.4)	0.04
Enterobacter aerogenes	5 (1.0)	3 (1.5)	2 (0.7)	0.4
Morganella morganii	3 (0.6)	1 (0.3)	2 (0.7)	0.6
Salmonella sp.	1 (0.2)	1 (0.5)	0	0.4
Adequate empirical antibiotic treatment	–	89 (43.2)	–	*ntp*
Length of stay, days	28 (11–67)	30 (11–55)	27 (11–75)	0.7
Admission to intensive care unit (*N* = 201)	–	39 (19.4)	–	*ntp*
Death within 15 days (*N* = 145)†	–	24 (16.6)	–	*ntp*
Death within 12 months (*N* = 241)†	104 (43.2)	66 (59.5)	38 (29.2)	<0.001

The data in the table represent 516 episodes among 330 patients

*Number (%) for categorical variables and median (IQR) for continuous variables

**Significance between treatment groups determined using the Kruskal–Wallis test for continuous variables and Pearson's χ^2 test or Fisher's exact test for categorical variables

ntp No test performed

† Data taken at last episode within patient, only in patients with available outcome data

isolates containing *E. coli* ($p = 0.005$) was also noted in infections, whereas this was the opposite for *K. pneumoniae* ($p = 0.04$). No other significant differences between infections and colonization were noted with respect to proportion with polybacterial infections, *bla* gene distribution, or length of hospital stay (Table 2).

Clinical and bacterial determinants associated with severe and fatal outcomes

Of all infection episodes with available outcome data, 39/201 (19.4%) resulted in transfer to an ICU. The only factor associated with ICU admission was infection with an isolate other than *E. coli* ($p = 0.01$). No other factors, including at-risk exposure, concomitant comorbidity, immunosuppression, episode type, antibiotic evaluation, septicemia, or antibiotic resistance, were associated with ICU admission (data not shown).

In treated individuals with available data, 24/145 (16.6%) died within the first 15 days of follow-up. Patient characteristics are compared between those who did versus those who did not die within this time frame in Table 3. Death occurred more frequently in those admitted to the ICU versus those who were not ($p < 0.001$). The proportion of patients with comorbidities was no different between those who survived versus those who died after 15 days ($n = 91/121$, 75.2% vs. $n = 19/24$, 79.2%, respectively, $p = 0.7$). Empirical antibiotic therapy was effective for 45.8% deceased patients compared to 63.6% of those who remained alive ($p = 0.1$).

Table 3 Patient-level risk factors associated with fatal outcomes within 15 days (only in treated patients)

	Total	Vital status		*p*-Value†
		Death	Alive	
	N = 145	*n* = 24	*n* = 121	
Age*				0.2
17–40	9 (6.2)	1 (4.2)	8 (6.6)	
41–60	37 (25.5)	7 (29.2)	30 (24.8)	
61–80	59 (40.7)	6 (25.0)	53 (43.8)	
≥80	40 (27.6)	10 (41.7)	30 (24.8)	
Male*	78 (53.8)	17 (70.8)	61 (50.4)	0.07
At-risk exposure††*	131 (90.3)	24 (100)	107 (88.4)	0.13
Immunocompromised*	60 (41.4)	14 (58.3)	46 (38.0)	0.07
Systolic blood pressure** (*N* = 134)	116 (100–135)	108 (88–125)	118 (101–135)	0.14
Diastolic blood pressure** (*N* = 134)	67 (58–75)	60 (54–68)	70 (60–75)	0.06
Episode type*				0.04
Nosocomial-acquired	82 (56.6)	19 (79.2)	63 (52.1)	
Healthcare-associated	37 (25.5)	4 (16.7)	33 (27.3)	
Community-acquired	26 (17.9)	1 (4.2)	25 (20.7)	
Adequate empirical antibiotic treatment	88 (60.7)	11 (45.8)	77 (63.6)	0.10
Bacteremia*	39 (26.9)	6 (25.0)	33 (27.3)	0.9
Admitted to ICU* (*N* = 144)	28 (19.4)	11 (45.8)	17 (14.2)	0.001

*Number (%)

**Median (IQR)

† Significance between vital status groups determined using the Kruskal–Wallis test for continuous variables and Pearson's χ^2 test or Fisher's exact test for categorical variables

†† Defined as having at least one of the following: antibiotic treatment <3 months, hospitalization <3 months, or trip abroad <3 months

Of the overall study population with available data, 104/241 (43.2%) died within 12 months of their last episode. As shown in Table 4, mortality was associated with age >80 years ($p = 0.01$), concomitant comorbidity ($p = 0.001$), nosocomial-acquired infections (versus healthcare-associated or community-acquired, $p = 0.06$ or $p = 0.002$, respectively), and being infected rather than colonized ($p < 0.001$) in the multivariable analysis. There was no difference in mortality when comparing adequate versus inadequate empirical antibiotic therapy in the multivariable analysis (adjusted OR = 0.78, 95% CI = 0.33–1.83, $p = 0.6$). In a sensitivity analysis restricted to colonized patients, age >80 years ($p = 0.01$) and concomitant comorbidity ($p = 0.03$) remained significantly associated factors in the multivariable model. When restricting analysis to infected patients, concomitant comorbidity ($p = 0.02$) and nosocomial-acquired infection (vs. community-associated, $p = 0.002$) remained associated with mortality.

Discussion

In this study, ESBL-producing Enterobacteriaceae were identified in 13% of isolates. Similar data in France are currently sparse; nevertheless, this proportion could be considered comparable to other epidemiological investigations reporting 1–4% (in specifically urine samples [8, 9], and 6% carriage [10]), but somewhat lower compared to ICU settings (15–25%) [6]. The difference in prevalence of our study can be explained by the wide range of departments included, many of which the prevalence is unknown or has been poorly studied. Thus, our investigation yields further insight on the epidemiology and potential clinical impact of ESBL-producing isolates from a more diverse and encompassing group of patients.

The effect of ESBL-producing infections, particularly bacteremia, on increased clinical severity has already been well described in the literature [11, 12]. In our series of ESBL-positive isolates, ICU admission rates (20%) and median length of hospital stay (30 days) among infections were remarkably higher compared to overall hospital-wide estimates at 6 days (APHP data, 2015). Furthermore, despite the fact that most infection episodes involved urinary infection with expectedly low risk of severe clinical outcomes [13], 12% of treated patients died within 15 days. Part of these findings could be explained by the inclusion of all types of infections, and not only bacteremias, and that most of the isolates originated from units associated with high risk of

Table 4 Determinants of 1-year fatal outcomes during infection with extended-spectrum β-lactamase (ESBL)-producing Enterobacteriaceae

	Vital status*		Crude		Adjusted	
	Died, $n = 104$	Alive, $n = 137$	OR (95% CI)	p-Value	OR (95% CI)	p-Value
Age (years)						
<60	32 (30.8)	51 (37.2)	1.00		1.00	
60–80	44 (42.3)	58 (42.3)	1.21 (0.67–2.18)	0.5	1.28 (0.66–2.47)	0.5
>80	28 (26.9)	28 (20.4)	1.59 (0.80–3.16)	0.18	2.84 (1.28–6.40)	0.01
Male	44 (42.3)	72 (52.6)	0.66 (0.40–1.11)	0.12		
At-risk exposure[†]	97 (93.3)	106 (77.4)	4.05 (1.71–9.63)	0.002		
Concomitant comorbidity	88 (84.6)	89 (65.0)	2.97 (1.57–5.61)	0.001	3.29 (1.60–6.77)	0.001
Immunocompromised	61 (58.7)	57 (41.6)	1.99 (1.19–3.34)	0.009		
Admitted to ICU ($N = 107$)	15 (23.1)	6 (14.3)	1.80 (0.64–5.09)	0.3		
Episode type						
Nosocomial-acquired	76 (73.1)	78 (56.9)	1.00		1.00	
Healthcare-associated	19 (18.3)	28 (20.4)	0.70 (0.36–1.35)	0.3	0.49 (0.23–1.04)	0.06
Community-acquired	9 (8.7)	31 (22.6)	0.30 (0.13–0.67)	0.003	0.24 (0.10–0.60)	0.002
Episode						
Colonization	38 (36.5)	92 (68.2)	1.00		1.00	
Infection	66 (63.5)	45 (32.9)	1.88 (1.44–2.46)	<0.001	2.08 (1.55–2.80)	<0.001
E. coli infection	46 (44.2)	66 (48.2)	0.85 (0.51–1.42)	0.5		
Piperacillin–tazobactam resistance	18 (17.3)	24 (17.5)	0.99 (0.50–1.93)	0.9		

Including 241 patients at their last episode with available data. Male gender and septicemia were not included in the multivariable model because their associated p-values were below the pre-specified threshold ($p = 0.486$ and $p = 0.491$, respectively). At-risk exposure and immunocompromised status were not included in the multivariable model due to high collinearity with concomitant comorbidity ($p = 0.02$ and $p = 0.04$, respectively)

CI Confidence interval, *ICU* intensive care unit, *OR* odds ratio

*Number (%) for categorical variables and median (IQR) for continuous variables

[†] Any one of the following within 3 months prior to episode: antibiotic therapy, hospitalization, or trip abroad

morbidity and mortality, such as oncology and hematology. In addition, two-thirds of patients in this study had at least one comorbidity and most were above 65 years of age. Whether this unexpectedly high mortality rate is due entirely to comorbidities and the type of infection or to ESBL-producing infection itself is difficult to determine, considering that data on causes of death were not collected.

In a previous study, infection with ESBL-producing Enterobacteriaceae has been associated with increased risk of 28-day morbidity and mortality when compared to carriers or patients without carriage [6]. Assuming that infected or carrier status, respectively, could be determined by whether a patient was treated or not, we extend these observations to 1 year of follow-up and similarly demonstrate a more than two-fold increase in odds of death when comparing infected versus colonized individuals. Infection status would appear to be a strong and independent surrogate for "disease severity" as defined by mortality. Nevertheless, it should be noted that other indicators of morbidity, such as longer length of stay in the ICU, have been observed in both carriers and infected patients when compared to those without colonization [6].

One key finding of our study was that only 44% of those included had successful empirical treatment. This result is rather concerning, given previous data in which inadequate empirical treatment of ESBL-producing *E coli* was shown to increase overall mortality [12]. We were able to, likewise, observe a slightly higher, albeit non-significant, 15-day mortality rate in patients with inadequate versus adequate empirical therapy, yet no difference was observed when examining death rates at 1 year. Nonetheless, those with adequate compared to inadequate initial therapy did have a higher prevalence of comorbidities (82% vs. 72%, respectively), which likely masked any association between effective empirical treatment and mortality.

In addition, 74% of known carriers of ESBL-producing microorganisms received carbapenem or piperacillin–tazobactam, which are considered more effective treatment options for this group of patients [14], underscoring the inadequacy of current methods to establish appropriate treatment. Indeed, this shortcoming could be improved by more accurately identifying patients at risk of ESBL-producing Enterobacteriaceae infection. A score able to detect carriers from non-carriers upon hospitalization has been developed

by Tumbarello et al., yet the lack of external validation, low positive predictive value (44%), and inability to identify those needing treatment with carbapenems during infection limits its use [15]. There is another, more recently published algorithm based on specific demographic and risk factors that can relatively accurately identify patients with ESBL-producing microorganisms [16]. On the other hand, more rapid diagnostics identifying the presence of C3G-resistant Enterobacteriaceae would substantially improve the delivery of adequate initial therapy, but these tools are mostly in development.

Bearing in mind that 10% of the study population did not have any risk factors for ESBL-producing microorganisms, it could be hypothesized that their presence had been established via community sources. Community-acquired ESBL-producing Enterobacteriaceae have been identified to a large degree [17], while recent data from the Observatoire national de l'épidémiologie de la résistance aux antibiotiques (Onerba) has reported a steady annual increase in the incidence of community-acquired infection throughout France. As expected, 92.9% of ESBL enzymes were CTX-M type [17].

Taken together, these data call for more effective preventive measures, which could be abetted by the rapid detection of ESBL-producing bacteria, and their immediate control.

Notwithstanding the fact that our investigation contains one of the larger collections of ESBL-producing Enterobacteriaceae in France to date, certain limitations should be addressed. First, the generalizability of our results to any specific unit can be challenging considering the diversity of departments and patients included. Second, the study population had a high prevalence of comorbidities, making it difficult to determine whether these results apply to healthy individuals colonized or infected with ESBL-producing microorganisms.

In conclusion, we observed a noteworthy and high rate of mortality in patients infected with a wide range of ESBL-producing Enterobacteriaceae. This heightened risk extends particularly to older individuals and those with comorbidities and hospital-acquired infection. As individuals undergoing therapy were also at higher risk of mortality, likely reflecting infection, it would warrant evaluating if more adequate treatment aided by the rapid diagnosis of ESBL-producing microorganisms could help decrease mortality. Further studies should also examine whether the genetic or pathophysiological features of these bacteria are also associated with deleterious patient outcomes.

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Compliance with ethical standards

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Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent All patients have been informed of this observational study.

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