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BRIEF REPORT

Predictive factors for extended-spectrum beta-lactamase producing *Enterobacteriaceae* causing infection among intensive care unit patients with prior colonization

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Abstract We investigated the predictive factors for extended-spectrum beta-lactamase producing *Enterobacteriaceae* (ESBL-PE) causing infections among intensive care unit patients with prior documented ESBL-PE colonization. Using multivariate analysis, referral from medical ward, nursing home or rehabilitation center [Odds ratio (OR), 2.5; 95 % confidence interval (CI), [1.3–5.0]; $p = 0.007$], previous fluoroquinolone treatment (OR, 3.4; CI, [1.1–10.5]; $p = 0.003$), extracorporeal membrane oxygenation (OR, 4.6; CI, [1.3–15.9]; $p = 0.02$), and absence of prior positive ESBL-PE rectal swab culture (OR, 5.0; CI, [1.6–10.0]; $p = 0.0009$) were risk factors for ESBL-PE infection. Easily identifiable factors may help with targeting carbapenem prescriptions.

Keywords Colonization · Infection · Extended spectrum beta-lactamase producing *Enterobacteriaceae* · Risk factors · Mortality

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Purpose

Extended-spectrum beta-lactamase producing *Enterobacteriaceae* (ESBL-PE) have spread both in hospitals and in the community [1]. Increased mortality in ESBL-PE bacteremia has been attributed to the delay in effective antibiotic administration [2]. Due to the dramatic increase in ESBL-PE carriage and requests for rapidly effective antibiotics, the extensive use of carbapenems as empirical antibiotics in critically ill patients with presumed or documented prior ESBL-PE colonization has become a major concern in the intensive care unit (ICU) [3], and is suggested to be responsible for the emergence of extensively drug-resistant bacteria [4]. Therefore, we sought to investigate the predictive factors for ESBL-PE involvement in the infectious episodes of patients with prior documented ESBL-PE colonization, to improve the empirical use of carbapenems.

Methods

Setting and patient inclusion criteria

Our institutional review board approved this study. All patients with at least one positive ESBL-PE culture, either from clinical or screening samples collected during their stay in our university hospital ICU from October 2005 to October 2011, were included.

Our ICU ESBL-PE screening policy included systematic nasal and rectal swabs, as well as tracheal aspirations in intubated patients on ICU admission and weekly thereafter. Swabs were seeded on a selective chromogenic medium (chromID® ESBL, bioMérieux, France) and ESBL-PE resistance pattern confirmed by the double disc synergy test

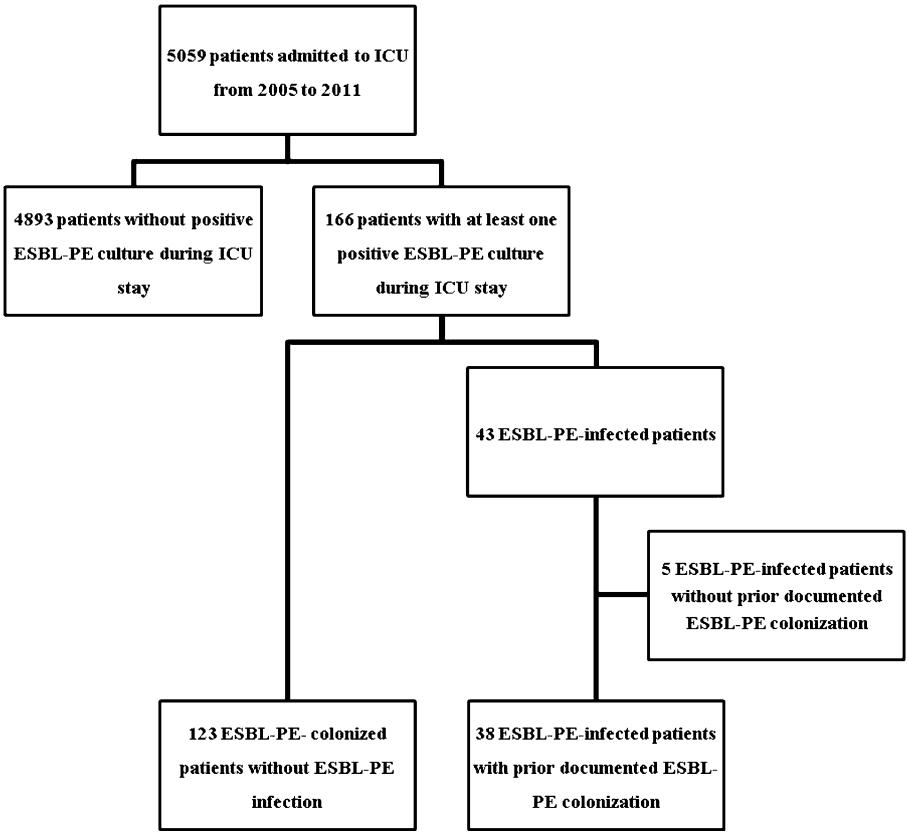

Fig. 1 Flow chart. *ESBL-PE* extended spectrum beta-lactamase producing *Enterobacteriaceae*

in accordance with French guidelines [5]. If the bacteriology laboratory considered the sampled material as insufficient, a swab was recollected. Neither the screening policy nor the ESBL-PE detection method changed during the study period. Contact isolation preventive procedures were prescribed on admission until screening results were available, and maintained until discharge if ESBL-PE was identified. Patients were managed according to standard treatment guidelines.

Patients were classified as "ESBL-PE-infected patients" and "ESBL-PE-colonized patients without infection." "ESBL-PE infected patients" were defined as the patients with prior ESBL-PE colonization who developed ESBL-PE infection fulfilling the accepted Centers for Disease Control and Prevention (CDC)/National Healthcare Safety Network (NHSN) criteria of healthcare-associated infections, both clinical and microbiological [6]. Regarding diagnosis of pneumonia, both bronchoalveolar lavage and tracheal aspirates were used to identify the involved bacteria. If the microbiological assessment was only based on tracheal aspirates, ESBL-PE pneumonia was considered as "probable," according to the recommendations [6]. If ESBL-PE carriage was diagnosed at the time of infection, patients were excluded. If a patient developed more than one ESBL-PE infection, only the first infection was recorded. "ESBL-PE colonized patients" were defined as the patients with positive ESBL-PE rectal or nasal swab cultures, or patients with a positive ESBL-PE culture from a clinical sample without clinical signs of infection.

Data collection

On ICU admission, the following data were collected: age, gender, location before ICU (healthcare facility vs. home), underlying diseases, other hospitalizations in the past 3-month period, prior antibiotics received during the past 3 months, the reason for ICU admission, McCabe score, Simplified Physiology Score II (SAPS II), and Sequential Organ Failure Assessment (SOFA) score. The presence of indwelling devices (on admission and during ICU stay), including chest tube, urinary and vascular catheters, and extracorporeal membrane oxygenation (ECMO), was recorded. Length of stay and outcome at ICU discharge were collected. Bacteriological data recorded on ICU admission and during ICU stay included ESBL-PE species involved in colonization or infection, antibiograms, and sampling sites.

Statistical analysis

Results are expressed as median (interquartile range) or percentages when appropriate. Univariate analysis was

performed using Mann–Whitney, *t* Student, and χ^2 tests, as appropriate. Significant variables at a 5 %-threshold in the univariate analysis were entered in a stepwise multivariate logistic regression model. Odds ratios (OR) and 95 %-confidence intervals (CI) were calculated. p value < 0.05 was considered as significant. Analysis was performed using SAS© version 9.2 software (SAS Institute Inc., USA).

Results

A total of 5,059 patients were admitted to the ICU from October 2005 to October 2011 (Fig. 1). Of these patients, 166 (3 %) had at least one ESBL-PE positive culture during their ICU stay. ESBL-PE incidence density was 1.7 per 1,000 hospitalization-days over the study period. Trends in ESBL-PE incidence densities from 2006 to 2011 are shown in Table 1. Five patients were excluded because they developed ESBL-PE infection without any prior documented ESBL-PE colonization. Finally, 161 ESBL-PE colonized patients (age: 59 years [47–77]) were included, of which 38 had developed ESBL-PE infection during ICU stay. Patients' characteristics are summarized in Table 2. ESBL-PE carriage was detected on ICU admission in 40 % and was ICU-acquired in 47 % of the cases. In the remaining 13 % of the cases, the absence of ESBL-PE screening within the first 24 h of admission did not allow a conclusion to be reached on the origin of the colonization. ESBL-PE colonized sites included rectum (61 %), urine (19 %), lung (10 %), and skin (8 %). ESBL-PE infections included probable pneumonia [$N = 20$, microbiologically documented by positive blood cultures ($N = 3$), bronchoalveolar lavage ($N = 15$), and tracheal aspirates ($N = 2$)], central line-related bloodstream infection ($N = 7$, including two infections attributed to the dialysis catheter and one to the ECMO cannula), urinary tract infection ($N = 5$), bloodstream infection of unknown primary origin ($N = 5$), and bone infection ($N = 1$). ECMO-treated patients developed the following ESBL-PE infection episodes: probable pneumonia ($N = 3$), bloodstream infection with either positive ($N = 1$) or negative ($N = 2$) culture of ECMO catheters, and bone infection in relation to necrosis of the cannulated lower limb ($N = 1$).

ESBL-PE infection was diagnosed on admission in 5/38 cases. The delays from ICU admission to ESBL-PE infection and from ESBL-PE colonization to ESBL-PE infection (when the infection did not occur on admission) were 10 days [5–14] and 7.5 days [4–16], respectively. ESBL-PE distribution was not significantly different between ESBL-PE-infected and ESBL-PE-colonized patients without infection (Table 1): *Klebsiella pneumoniae* (40 vs. 38 %), *Escherichia coli* (27 vs. 34 %), and *Enterobacter cloacae* (20 vs. 21 %). ESBL-PE resistance rates to fluoroquinolones (~81 %), aminoglycosides (~8 %), and tigecycline (~52 %) were comparable in both groups. Empiric antibiotics included carbapenems in only 5/38 cases (12 %), while carbapenems were further prescribed with a 2-day [1–3] delay in the other 33 patients. Mortality in ESBL-PE-colonized patients without infection and ESBL-PE infected patients did not significantly differ (32 vs. 34 %, respectively).

Using multivariate analysis, the onset of ESBL-PE infection in ICU patients with prior documented ESBL-PE colonization was significantly associated with ICU referral from a medical ward, nursing home or rehabilitation center [Odds ratio (OR), 2.5; 95 % confidence interval (CI) [1.3–5.0]; $p = 0.007$]; past fluoroquinolone treatment (OR, 3.4; CI, [1.1–10.5]; $p = 0.003$); extracorporeal membrane oxygenation (ECMO, OR, 4.6; CI, [1.3–15.9]; $p = 0.02$); and absence of prior positive ESBL-PE rectal swab culture (OR, 5.0; CI, [1.6–10.0]; $p = 0.0009$).

Discussion

Few studies have investigated risk factors for ESBLE-PE colonization/infection in the ICU [3]; however, to our knowledge, none has focused on the predictive factors for ESBLE-PE infection in ICU patients with prior ESBL-PE colonization.

ESBL-PE incidence density and mortality rates in our ICU were consistent with those observed in other French ICUs [7]. Since our ICU data were based on surveillance

Table 1 Trends from 2006 to 2011 in incidence densities of extended spectrum beta-lactamase producing *Enterobacteriaceae* in our hospital and intensive care unit (cases/1,000 hospitalization days)

	2006	2007	2008	2009	2010	2011
In our university hospital group[a] (based on diagnostic samples)	0.32	0.47	0.52	0.54	0.66	0.81
In our intensive care unit (based on diagnostic samples)	0.37	1.98	4.18	5.93	4.84	5.40
In our intensive care unit (based on surveillance + diagnostic samples)	1.30	3.40	7.20	8.20	9.90	11.30

[a] As published in Réseau BMR-Raisin [8]

Table 2 Clinical characteristics of extended spectrum beta-lactamase producing *Enterobacteriaceae*-infected versus only colonized patients

	ESBL-infected patients ($N = 38$)	ESBL-colonized patients ($N = 123$)	Odds ratio [95 % confidence interval]	p value
Demographics				
Gender (M/F, %)	68/32	55/45	0.6 [0.3–1.2]	0.2
Age (years)	56 [48–75]	61 [46–77]	1.0 [0.9–1.0]	0.7
Reason for ICU admission (%)				
Sepsis	3	5	2.9 [1.1–7.5]	**0.03**
Cardiac failure and arrest	16	7	2.4 [0.8–7.2]	0.1
Drug intoxication	21	20	1.1 [0.4–2.6]	0.9
Patients referred from medical ward, nursing home or rehabilitation center (%)	82	11	2.5 [1.3–5.0]	**0.007**
Past hospitalization (<3 months, %)	23	57	1.8 [0.9–3.7]	0.13
Underlying disease (%)				
Diabetes	18	24	0.7 [0.3–1.8]	0.5
Immunodeficiency	16	22	0.7 [0.3–1.8]	0.4
Chronic renal failure	18	8	2.6 [0.9–7.5]	0.07
McCabe score (1/2/3, %)	79/13/8	72/19/9	0.8 [0.2–3.1][a]	0.8
Prior antibiotics (<3 months, %)	97	84	7.2 [0.9–55.4]	0.06
Beta-lactams	89	76	2.6 [0.9–8.0]	0.06
Penicillins	71	56	1.9 [0.9–4.2]	0.09
Beta-lactamase inhibitors	66	46	2.2 [1.0–4.8]	0.1
Third generation cephalosporins	50	56	0.9 [0.4–1.6]	**0.03**
Carbapenems	8	10	0.8 [0.2–3.0]	0.5
Aminosides	39	20	2.6 [1.2–5.6]	0.7
Fluoroquinolones	24	8	3.5 [1.3–9.4]	**0.02**
Macrolides	29	14	2.5 [1.1–6.1]	**0.01**
Glycopeptides	11	8	1.3 [0.4–4.5]	0.7
Nitroimidazole	39	34	1.3 [0.6–2.7]	0.6
Severity scores on admission				
SAPS II	57 [39–71]	58 [45–73]	1.0 [0.9–1.0]	0.4
SOFA score	9 [5–12]	8 [6–11]	1.0 [0.9–1.1]	0.5
Devices before positive ESBL sample				
Tracheal intubation > 24 h	63	47	1.9 [0.9–4.1]	0.08
Urinary catheter > 24 h	68	53	1.9 [0.9–4.1]	0.09
Arterial catheter > 24 h	63	49	1.8 [0.9–3.8]	0.1
Venous catheter > 24 h	61	46	1.8 [0.9–3.9]	0.1
Dialysis catheter	32	14	2.9 [1.2–6.8]	**0.01**
Extracorporeal membrane oxygenation	18	6	3.7 [1.2–11.5]	**0.02**
ESBL colonization on admission (%)	60	43	0.5 [0.2–1.2]	0.1
ESBL acquisition in the ICU (%)	31	43		
Positive ESBL culture (%)				
Rectal swab	39	67	0.3 [0.2–0.7]	**0.003**
Skin swab	5	13	0.4 [0.1–1.7]	0.2
Tracheal aspiration	10	14	0.7 [0.2–2.3]	0.6
Urine	13	20	0.6 [0.2–1.7]	0.3
Catheter	13	22	0.5 [0.2–1.5]	0.2
ESBL bacteria (%)				
E. coli/*K. pneumonia*/*E. cloacae*	34/47/24	42/37/23	0.6 [0.2–1.4][b]	0.2
ICU length of stay (days)	22 [11–44]	12 [6–23]	1.0 [1.0–1.0]	**0.05**
Mortality rate (%)	32	34	1.1 [0.5–2.5]	0.8

Quantitative variables are expressed as median (interquartile range). Bolded values indicate statistical significance

ESBL-PE extended spectrum beta-lactamase producing *Enterobacteriaceae; ICU* intensive care unit; *SAPS II* simplified acute physiology score II; *SOFA* sequential organ failure assessment

[a] McCabe 1 versus McCabe 3

[b] *E. coli* versus *K. pneumoniae*

and clinical samples, incidence densities were significantly higher than those already published from our university hospital group (Table 1) [8]. Additionally, incidence densities significantly increased from 2006 to 2011, highlighting the real threat represented by ESBL-PE in ICU [1]. Interestingly, the mortality rate was not different between ESBL-PE-infected patients and ESBL-PE-colonized patients without infection, despite 13 reported bloodstream ESBL-PE infections and a 2-day delay in carbapenem prescription. However, mortality attributable to ESBL-PE infections remains difficult to determine due to confounding factors in the ICU.

Since no ESBL-PE typing was performed in our study, no causal relationship between colonization and infection could be definitively proven. Interestingly, the species (2/38 cases) as well as the antibiogram (an additional 5/38 cases) differed between the ESBL-PE involved in infection and the ESBL-PE involved in previous colonization. Since the median delay between colonization and infection was 10 days in our study, antibiotics may have selected additional resistant strains during this period of time.

Recently, predictive factors for ESBL *E. coli* infections were investigated in patients with prior rectal colonization [9]. Based on a multivariate analysis, previous use of beta-lactamase inhibitors as well as urinary catheterization was predictive of ESBL *E. coli* infection occurred among patients with prior colonization. However, this study included adults and children in various wards and was limited to patients with prior rectal ESBL *E.coli* colonization. In accordance with Goulenok's study [9], we found that well-known risk factors for hospital-acquired bacterial infections, such as previous use of selective pressure inducers (fluoroquinolones in our study vs. beta-lactamase inhibitors in Goulenok's study), and invasive procedures (ECMO implementation in our study vs. urine catheterization in Goulenok's study) represented major risk factors for the onset of ESBL-PE infection in patients with prior ESBL-PE colonization. Since urinary catheterization is present in almost all ICU patients, our study could not identify this parameter as a risk factor for ESBL-PE infection. Interestingly, exposure to fluoroquinolones resulting in long-term changes in the fecal flora [10] has been previously identified as a risk factor for ESBL-PE infection [1, 9]. Moreover, fluoroquinolone resistance in *Enterobacteriaceae* is associated with ESBL resistance patterns [11]. A patient's referral from home (vs. medical ward, nursing home and rehabilitation center) to the ICU is obviously associated with fewer underlying diseases, invasive procedures, and selective antibiotic pressure.

Surprisingly, absence of prior positive ESBL-PE rectal swab culture appeared to be a risk factor for ESBL-PE infection. Patients with the absence of prior positive ESBL-PE rectal swab culture represent a significant proportion of ESBL-PE-infected patients in real life. In Goulenok's study, 162/671 patients (20 %) had no documented rectal ESBL colonization before the onset of their ESBL *E. coli* infection episode [9]. In their prospective study with biweekly rectal screenings, Razazi et al. [3] identified one similar patient who developed an ESBL infection before any detectable rectal carriage. Additionally, in this study, 18 % of the ESBL-PE involved in the ICU-acquired infection were different from those isolated in rectal swabs based on species identification and/or antibiogram. Since the gut is the commensal site of *Enterobacteriaceae*, several hypotheses may explain the lack of prior positive ESBL-PE rectal swab culture before ESBL-PE infection: (1) a low digestive tract colonization under the limit of detection at the sampling time; (2) a direct ESBL-PE transmission by care-givers to a non-commensal site like urine or lungs in mechanically ventilated patients; and (3) ESBL-PE rectal acquisition between two weekly rectal swabs, since clinical samples were collected on the request of clinicians. One alternative explanation could be that, in ESBL-PE colonized patients, carbapenems were used more frequently or at earlier stages of treatment, thus resulting in an impaired microbiological diagnosis. However, our data did not support this hypothesis. Finally, the quality of sampling may also represent a possible detection bias, leading to false negative samples, while chromID ESBL, the ready-to-use chromogenic selective medium, was previously shown to be sensitive enough (88 % at 24 h and 94 % at 48 h [12]) for the rapid and presumptive identification of ESBL-producing *Enterobacteriaceae*. Interestingly, our data suggest that prior ESBL-PE detection in a non-commensal site is associated with an increased probability of infection.

Despite a dramatic increase in ESBL-PE infections [1], the likelihood of having an infectious episode caused by ESBL-PE in the presence of sepsis and known colonization with ESBL-PE appears low ($\sim$20 %), as previously estimated [3]. Physicians may consider reducing the consumption of broad-spectrum antimicrobials by using our easily identifiable predictive factors to improve the administration of empiric carbapenem therapy, recommended as first-line empiric therapy in previously known ESBL-PE-colonized patients. Additionally, infection control interventions [13] and less broad-spectrum antibiotics, including beta-lactamase inhibitors for treating ESBL-PE infections [14], although still controversial, represent promising solutions to reduce carbapenem prescriptions.

Our monocentric study has limitations. Despite repeated exhortation to improve caregivers' observance, screening on admission was missing in 12 % of our patients, as in similar studies [3]. Quality of sampling represents another possible bias, leading to false negative samples. Finally, like Goulenok et al. [9], we chose to exclude patients for

whom ESBL-PE infection and colonization were diagnosed simultaneously. These patients requiring empiric carbapenems may present particularities that could not be recognized using our predictive factors.

In conclusion, ESBL-PE infections rarely occur in ICU patients with prior ESBL-PE colonization. To limit the empiric use of carbapenems, intensivists may rely on easily recognizable predictive factors to improve carbapenem prescription in patients with prior ESBL-PE colonization who develop infection. However, these factors need validation in a larger prospective cohort.

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Conflict of interest All authors declare that there is no conflict of interest.

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