Can a Lack of Extended-Spectrum β-Lactamase–Producing *Enterobacteriaceae* Rectal Carriage Help Avoid Carbapenem Prescription?*

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Extended-spectrum β-lactamase–producing *Enterobacteriaceae* (ESBL-E) are most commonly acquired in the ICU, and despite advancement in critical care, remain a major burden on patient outcome and healthcare costs (1). A substantial proportion of nosocomial infections, including ventilator-associated pneumonia (VAP), are preventable, hence illustrating the importance of nosocomial infection prevention and early detection.

Numerous efforts have been made to reduce ESBL-E carriage and infection rates, including contact isolation precautions, antibiotic restrictions, decolonization regimens, and selective digestive decontamination (2–4). In this issue of *Critical Care Medicine*, Remi et al (5) present a retrospective analysis of active surveillance screening for ESBL-E carriage in 587 French medical ICU patients with suspected VAP to determine its potential usefulness for predicting ESBL-E infection and better target antibiotic therapy. By examining the potential value of ESBL-E rectal screening samples at ICU admission and then weekly thereafter, they aimed to reduce unnecessary empiric carbapenem use in patients without colonization. Active surveillance screening and knowledge of prior intestinal colonization with ESBL-E demonstrated a high negative predictive value (99%), acceptable positive predictive value (42%), positive likelihood ratio of 19.8, and a negative likelihood ratio of 0.15.

Although the cohort of patients examined was large, the number of patients infected with ESBL-E was rather small ($n = 20$). Other limitations to its implications and generalizability include its retrospective, noninterventional, and single-center design. Although ESBL-E colonization, alone, may raise the risk of morbidity and mortality, the cohort with ESBL-E had higher Sequential Organ Failure Assessment scores, rate of comorbidities (kidney disease, heart failure, diabetes, cancer, and immunosuppression), ICU length of stay, and mechanical ventilation days compared with the group without ESBL-E, which may explain the significantly higher mortality in the ESBL-E colonized group (60% vs 38%; $p < 0.001$).

Although most studies on ESBL-E colonization are focused on ICU and high-risk populations (i.e., patients receiving immunosuppressive agents or chemotherapy), the prevalence of colonization can vary from 1% in a nonoutbreak setting (6) to 38% in an outbreak setting (7). Reliable identification of ESBL-E in clinical laboratories can be arduous, and thus, we often rely on risk factors alone when deciding on empiric anti–ESBL-E therapy. Common risk factors for ESBL-E colonization include the presence of comorbid conditions, prolonged medical ICU hospitalization, lengthy antibiotic exposure, colonization pressure, tracheostomy, arterial or bladder catheterization, prolonged intubation, abdominal surgery, broad-spectrum antibiotic use, and long-term care facility residence (8). Regional prevalence plays a significant role in ESBL-E acquisition, as institutions with a high ESBL prevalence are more likely to have colonization and infection in susceptible high-risk patients. As these risk factors are commonly encountered in ICU patients, it is no wonder why anti–ESBL-E antibiotics are commonly deployed from an intensivists' armamentarium.

In critically ill patients with infections, inappropriate empiric antimicrobial therapy is associated with increased mortality (9). Carbapenems are associated with better survival rates and improved bacterial clearance, and therefore, they are the treatment of choice for ESBL-producing organisms. Although some ESBL-producing organisms may be susceptible to aminoglycosides, these drugs have poor lung penetration and are not recommended for primary therapy of VAP. Colistin, although often susceptible, carries a high rate of adverse effects and intolerability. Cefepime, although not easily hydrolyzed by β-lactamases, has not been found to improve survival outcomes as seen with carbapenems. For these reasons, intensivists often prescribe carbapenems empirically when ESBL risk factors are present. However, risk factors alone are not enough and thus, several studies, like the one by Remi et al (5), have examined the effect of ESBL-E colonization on empiric carbapenem prescription (10). Identification of ESBL-E rectal carriage is even higher with selective preenrichment (26% vs 5%) (11). Furthermore, unless effectively treated, approximately 70% of patients who acquire ESBL-E colonization remain positive on subsequent screening and are more likely to develop ESBL-E infection (12–14).

Unfortunately, studies supporting the avoidance of carbapenems in patients without ESBL-E colonization are scarce. Therefore, critical care providers have limited resources capable of quickly ruling out ESBL infections when risk factors are present,

*See also p. 699.

Key Words: antibiotics; carbapenem; extended-spectrum β-lactamase; intensive care unit; rectal screening; ventilator-associated pneumonia

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and thus, they are forced to prescribe carbapenems. In turn, this affects healthcare costs and patient outcome, including the risk of carbapenem resistance. The novelty in this article is that it helps bolsters a provider's confidence to avoid empiric carbapenem prescription in patients who lack ESBL-E colonization.

Colonization with ESBL-E in the ICU is rapidly rising (14), and routine rectal surveillance may predict related infection, including VAP ecology. In a setting of low ESBL prevalence, the absence of detectable ESBL via weekly rectal surveillance cultures sufficiently lowers the probability of ESBL involvement in VAP, enabling us to safely avoid prescribing empirical carbapenem coverage. Although larger studies are still needed, the 96% specificity and 99% negative predictive values suggest that routine ESBL rectal surveillance may be effective in excluding ESBL-E disease and strengthening our antibiotic stewardship efforts.

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Biomarkers in Severe Sepsis and Septic Shock: Just Listen to the Heart?*

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Treatment strategies for severe sepsis and septic shock are summarized in bundles, and compliance with these guidelines has been repeatedly shown to be associated with marked reductions in mortality rates (1–3). Nonetheless, the individual variables and the corresponding target values used to guide therapy are controversially discussed. Therefore, there is a permanent quest for new biomarkers. However, expectations are high: the ideal biomarker should be generally available, cost effective, easy to measure, and interpret. In addition, it should reliably suggest when to start and when to stop therapy, distinguish between responders and nonresponders, and between survivors and nonsurvivors. In the case of sepsis such a biomarker is even harder to find because of the general definition, various manifestations, and severity levels of sepsis in different patient populations.

Because myocardial dysfunction is accepted to play a major role in severe sepsis and septic shock, it is conclusive to investigate myocardial biomarkers like natriuretic peptides and cardiac troponins in this setting. Natriuretic peptides are predominantly released because of distensions of the myocardial chambers, whereas cardiac troponins can be measured in the plasma following structural damage. Numerous studies demonstrated that increasing plasma levels of either N-terminal pro-brain natriuretic peptide (NT-pro-BNP) or cardiac troponin T are

*See also p. 707.

Key Words: albumin; high-sensitivity cardiac troponin T; N-terminal pro-brain natriuretic peptide; septic shock; severe sepsis

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Significance of Prior Digestive Colonization With Extended-Spectrum β-Lactamase–Producing *Enterobacteriaceae* in Patients With Ventilator-Associated Pneumonia*

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Objectives: Ventilator-associated pneumonia is frequent in ICUs. Extended-spectrum β-lactamase–producing *Enterobacteriaceae* are difficult-to-treat pathogens likely to cause ventilator-associated pneumonia. We sought to assess the interest of screening for extended-spectrum β-lactamase–producing *Enterobacteriaceae* rectal carriage as a way to predict their involvement in ventilator-associated pneumonia.

Design: A retrospective cohort study of patients with suspected ventilator-associated pneumonia in a medical ICU was conducted.

Patients: Every patient admitted between January 2006 and August 2013 was eligible if subjected to mechanical ventilation for more than 48 hours. Each patient with suspected ventilator-associated pneumonia was included in the cohort. Active surveillance culture for extended-spectrum β-lactamase–producing *Enterobacteriaceae* detection was routinely performed in all patients at admission and then weekly throughout the study period. Extended-spectrum β-lactamase colonization was defined by the isolation of at least one extended-spectrum β-lactamase–producing *Enterobacteriaceae* from rectal swab culture.

Interventions: None.

Measurements and Main Results: Among 587 patients with suspected ventilator-associated pneumonia, 40 (6.8%) were colonized with extended-spectrum β-lactamase–producing *Enterobacteriaceae* prior to the development of pneumonia. Over the study period, 20 patients (3.4%) had ventilator-associated pneumonia caused by extended-spectrum β-lactamase–producing *Enterobacteriaceae*; of whom, 17 were previously detected as being colonized with extended-spectrum β-lactamase–producing *Enterobacteriaceae*. Sensitivity and specificity of prior extended-spectrum β-lactamase–producing *Enterobacteriaceae* colonization as a predictor of extended-spectrum β-lactamase–producing *Enterobacteriaceae* involvement in ventilator-associated pneumonia were 85.0% and 95.7%, respectively. The positive and negative predictive values were 41.5% and 99.4%, respectively. The positive likelihood ratio was 19.8.

Conclusions: Screening for extended-spectrum β-lactamase–producing *Enterobacteriaceae* digestive colonization by weekly active surveillance cultures could reliably exclude the risk of the involvement of such pathogens in patients with ventilator-associated pneumonia in low-prevalence area. (*Crit Care Med* 2016; 44:699–706)

Key Words: enterobacteriacae; extended-spectrum β-lactamase; multidrug resistance; ventilator-associated pneumonia

Ventilator-associated pneumonia (VAP) is the most commonly acquired infection in ICUs and is responsible for prolonged length of stay and excess mortality (1). Inappropriate first-line antibiotic is likely to worsen VAP prognosis (2). Current guidelines recommend the prompt administration of broad-spectrum antimicrobial therapy if multidrug-resistant (MDR) bacterial species are suspected (3). Such suspicions are generally based on the time between ICU admission and VAP onset, prior exposure to antibiotics and knowledge of local resistance patterns. However, this strategy is rather haphazard and leads to the overuse of broad-spectrum drugs, including carbapenems. In addition, even short-term

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exposure to these antimicrobial agents could lead to the loss of their efficacy in a given patient (4). Carbapenems should be used cautiously in the current era of emerging carbapemase-producing Gram-negative bacilli (GNB). Hence, there is a growing need for more accurate diagnostic tools able to predict the risk of MDR isolation in patients with VAP.

Extended-spectrum β-lactamase–producing *Enterobacteriaceae* (ESBL-EB) are increasingly encountered in patients with hospital-acquired infections, including VAP, with additional mortality and cost (5–9).

At the same time, ESBL-EB digestive carriage is more and more common in patients admitted to ICUs and in the community as well (10). Various risk factors of ESBL-EB isolation in hospitalized patients have been identified (6, 7, 11, 12). Finally, it is known that in most cases, bacteria that cause VAP come from the digestive tract flora and colonize the airways thereafter (13, 14).

Therefore, we sought to assess the interest of active surveillance of digestive colonization with ESBL-EB in the ICU as a way to predict their involvement in VAP. Thus, a retrospective cohort study addressing this issue was conducted in one medical French ICU.

MATERIALS AND METHODS

Study Population

The database used in this study has already been described elsewhere (15, 16). Briefly, every patient admitted to our ICU between January 2006 and October 2013 was eligible if subjected to mechanical ventilation (MV) for more than 48 hours. Each patient with suspected VAP according to the physician's clinical judgment because of suggestive signs and symptoms (e.g., fever, sputum purulence, new infiltrate on chest x-ray, and need to increase F_{IO_2}) was included by one of the investigators (R.B., P.E.C., J.P.Q., A.T., or S.P.) throughout the study period. Only the first episode was considered for analysis. The "modified" Clinical Pulmonary Infection Score (CPIS) was then calculated (17, 18). In accordance with French law, no informed consent was required because all measurements were part of routine management, as confirmed by our local Ethics Committee.

Definitions

Active Surveillance Culture. Active surveillance cultures (ASCs) for ESBL-EB detection were routinely performed in all patients at admission to the ICU and weekly thereafter. ASCs relied on rectal swab collection. Each sample was transported to the microbiology laboratory and stored at room temperature until processing. Stool samples were plated on selective Drigalski agar medium supplemented with cefotaxime (4 mg/L) (one plate) and ceftazidime (4 mg/L) (one plate). Cultures were incubated for 48 hours at 37°C under aerobic conditions. A double-disc synergy test was performed for each colony type (19). Strains with a positive synergy test were identified using the API20E system (BioMérieux, Marcy-L'Etoile, France).

According to the rectal swab culture result obtained prior to VAP onset, the patient was classified as an ESBL-EB carrier or not.

Description and Management of VAP Episodes

The included patients with suspected VAP were classified according to the microorganism isolated (i.e., ESBL-EB$^+$ or ESBL-EB$^-$ VAP). Because quantitative cultures of tracheal aspirate were performed, the cutoff value of 10^6 colony forming units/mL was applied to differentiate between positive and negative results. Patients with negative cultures were also considered because the empirical therapy issue was addressed by our study. In addition, this does not rule out VAP diagnosis (20).

In addition, bacteria were considered MDR in the following cases: 1) *Pseudomonas aeruginosa* resistant to at least two antibiotics (or antibiotic class) among the following: carbapenems, antipseudomonal penicillins, ceftazidime, aminoglycosides, and fluoroquinolones; 2) *Enterobacteriaceae* if resistant to third-generation cephalosporins and fluoroquinolones and/or an aminoglycoside; and 3) *Staphylococcus aureus* if resistant to oxacillin. Patients with negative tracheal aspirate cultures were considered free of MDR bacteria.

Immunosuppression was defined as neutropenia (polymorphonuclear counts, less than 1,500/mm^3), any immunosuppressive treatment prior to ICU admission, including steroids if given for more than 1 month.

The guidelines for the antibiotic therapy management were based on the knowledge of local susceptibility patterns of the most frequently isolated bacteria and on the clinical judgment of the attending physician. In addition, local guidelines regarding VAP management were available. They relied on the fact that MDR bacteria involvement was closely related to MV duration prior to VAP (less or more than five-day MV) and previous exposure to broad-spectrum antibiotics as well. The use of carbapenems was generally driven by previous exposure to third-generation cephalosporins or quinolones. In contrast, because such a strategy had not been yet evaluated, ESBL-EB carriage detection was not clearly used as a trigger for the administration of carbapenems.

The first-line treatment (i.e., the one delivered within the first 24 hours following the clinical suspicion of VAP) was considered appropriate if the isolated pathogen(s) was (were) susceptible to at least one drug administered at the onset of VAP according to the corresponding susceptibility testing report. When no antibiotic was given within the first 24 hours of management, the treatment was considered inappropriate regardless of the subsequently isolated pathogen if any.

Data Collection

"Modified" CPIS values, demographic data, and usually reported risk factors of MDR bacteria were prospectively recorded on a standard form (i.e., time between VAP suspicion and ICU admission, previous hospitalization, exposure to antibiotics defined as the administration of at least one two-day course of antibiotics during the ICU stay prior to VAP suspicion, residence in a nursing home, and underlying chronic obstructive pulmonary disease). The clinical course of VAP was also assessed through Sequential Organ Failure Assessment (SOFA) scores on days 1 and 3, the duration of MV, and the number of ventilator-free days.

Of note, colonization with ESBL-EB was assessed retrospectively after the data had been collected.

Statistical Analysis

Values are expressed as mean (SD) unless otherwise stated. Proportions were compared using the chi-square test. Continuous variables were compared by the Student *t* test.

Sensitivity, specificity, predictive values, and likelihood ratios (LRs) were obtained by standard statistical methods. The positive LR was calculated as sensitivity divided by (1 – specificity). An LR of greater than one indicated to what extent one positive test result was associated with the presence of disease, whereas as an LR of less than one indicated whether a negative result was associated with its absence. Performance characteristics and area under the receiver operating characteristic curve (ROC) of ASC as a predictor of ESBL-EB VAP were calculated.

Because ESBL-EB carriage was found to be significantly associated with ICU survival, two regression logistic models were constructed in an attempt to adjust for potential confounders with respect to the Harrell rule. To this purpose, the following variables were entered into the model in addition to ESBL-EB carriage: SOFA score on day 1, first-line antibiotic appropriateness, diabetes mellitus, chronic cardiac disease (model A), or chronic renal failure (model B).

Patients with suspected VAP in whom *Enterobacteriaceae* were recovered from respiratory cultures might be different from others. As a result, analysis restricted to those patients was also conducted (**Table S1**, Supplemental Digital Content 1, http://links.lww.com/CCM/B513).

The Prism Software (GraphPad Software, San Diego, CA) was used for ROC curve construction, and the Statview software (Cary, NC) was used otherwise.

RESULTS

Patient Characteristics

A total of 6,007 patients were admitted to our medical ICU during the study period; of whom, 3,439 underwent MV (**Fig. 1**). Six hundred twelve episodes of VAP were clinically suspected. The 25 subjects with no ASC during their ICU were excluded, and the remaining 587 patients were analyzed. Thus, an ASC compliance rate greater than 90% was achieved in our ICU.

ESBL-EB digestive colonization prior to the VAP episode was found in 40 cases (6.8%). Among these, 22 (55.0%) were detected at ICU admission, whereas 18 (45.0%) were detected during the ICU stay, one to several weeks before VAP onset.

The baseline characteristics of the study population according to prior colonization are presented in **Table 1**. It is worth noting that ESBL-EB colonized patients were significantly more frequently men and were more likely to have underlying diseases, such as diabetes mellitus. However, the Simplified Acute Physiology Score II calculation did not show any difference between groups. In addition, no difference was found regarding various MDR carriage risk factors. Finally, acute respiratory distress was the most frequent admission diagnosis regardless of colonization.

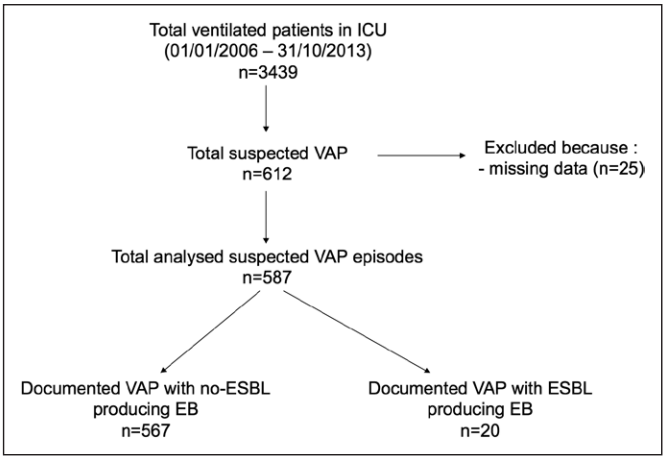

Figure 1. Flow chart of selection of study patients. EB = *Enterobacteriaceae*, ESBL = extended-spectrum β-lactamase, VAP = ventilator-associated pneumonia.

Description and Outcomes of Suspected VAP Episodes

The main features of the suspected VAP episodes are presented in **Table 2**. In our study, 403 cases (68.6%) were classified as late-onset VAP. Pneumonia occurred 15.3 (17.6) days after the start of MV, with no difference according to ESBL-EB colonization status. According to the SOFA score on day 1, VAP severity was greater in colonized patients than in their non-colonized counterparts. However, septic shock occurrence was similar in both groups.

Among the isolated pathogens, *Enterobacteriaceae* were more frequently found in colonized patients than in others, regardless of the antibiotics susceptibility pattern (52.5% vs 34.0%; $p = 0.02$). ESBL-EB were far more likely to be involved in patients with suspected VAP if digestive tract colonization with such species was detected previously (40.0% vs 0.7%; $p < 0.01$). Among ESBL-EB causing VAP, *Escherichia coli* and *Enterobacter cloacae* were the main species (40.0% and 35.0%, respectively).

In addition, MDR bacteria other than ESBL-EB were not more frequently isolated in colonized patients than in others (30.0% vs 26.1%, respectively; $p = 0.52$).

However, appropriate antibiotic was given to only half of the patients with prior ESBL-EB colonization when compared with 66.7% otherwise ($p = 0.03$).

ICU mortality was markedly higher in ESBL-EB colonized patients than in others (60.0% vs 37.8%, respectively; $p < 0.01$), except in the subset of patients with VAP caused by *Enterobacteriaceae* (**Table 3**; **Supplemental Table S4**, Supplemental Digital Content 4, http://links.lww.com/CCM/B516). It is worth noting that ESBL-EB carriers were markedly more severely ill. Indeed, ESBL-EB carriage was no more associated with a bad outcome after adjusting for potential confounders (Table 3).

Predictive Value of Screening for ESBL-EB Carriage

Overall ESBL-EB was considered a VAP causative agent in 20 (3.4%) of the 587 patients analyzed. The sensitivity, specificity, predictive values, and LRs of ESBL-EB ASC as a

TABLE 1. Baseline Characteristics of the Patients With Suspected Ventilator-Associated Pneumonia According to Previous Extended-Spectrum β-Lactamase–Producing *Enterobacteriaceae* Colonization

Variable	Overall (*n* = 587)	ESBL-EB Colonization Prior to Suspected VAP (*n* = 40)	No ESBL-EB Colonization Prior to Suspected VAP (*n* = 547)	*p*
Age (yr)	63.1 (14.7)	63.9 (13.0)	63.6 (14.8)	0.90
Simplified Acute Physiology Score II (points)	51.1 (15.3)	49.5 (16.2)	51.3 (15.3)	0.47
Gender, male, *n* (%)	401 (68.3)	34 (85.0)	367 (67.1)	0.02
Underlying disease(s), *n* (%)				
Chronic Obstructive Pulmonary Disease	99 (16.8)	3 (7.5)	96 (17.5)	0.10
Chronic renal failure	45 (7.6)	6 (15.0)	39 (7.1)	0.07
Chronic cardiac disease	234 (39.8)	21 (52.5)	213 (38.9)	0.09
Diabetes mellitus	117 (19.9)	14 (35.0)	103 (18.8)	0.01
Cirrhosis	32 (5.45)	2 (5.0)	30 (5.5)	0.90
Immunosuppression	31 (5.3)	4 (10.0)	27 (4.9)	0.17
Cancer	48 (8.2)	1 (2.5)	47 (8.6)	0.17
Nursing-home resident, *n* (%)	25 (4.2)	0 (0.0)	25 (4.6)	0.17
Hospitalization prior to ICU, *n* (%)	358 (61.0)	25 (62.5)	333 (60.9)	0.84
Antibiotic exposure in the ICU prior to suspected VAP episode	500 (85.2)	36 (90.0)	464 (84.8)	0.39
Main admission diagnosis, *n* (%)				
Respiratory distress	209 (35.6)	15 (37.5)	194 (35.5)	0.08
Extrapulmonary sepsis	155 (26.4)	17 (42.5)	138 (25.2)	
Neurologic failure	86 (14.6)	2 (5.0)	84 (15.4)	
Acute cardiac disease	105 (17.9)	5 (12.5)	100 (18.3)	
Miscellaneous	32 (5.4)	1 (2.5)	31 (5.7)	

ESBL-EB = extended-spectrum β-lactamase–producing *Enterobacteriaceae*, VAP = ventilator-associated pneumonia.

predictor of ESBL-EB VAP are summarized in **Table 4**. The overall performance of ESBL-EB ASC screening as assessed through the corresponding ROC curve construction was as follows: area under the ROC curve = 0.90 (0.81–0.99), 95% CI (**Fig. 2**). Indeed, sensitivity and specificity reached 85.0% (95% CI, 62.1–96.8) and 95.7% (95% CI, 93.7–97.2), respectively. In addition, the positive predictive value (PPV) was 41.4% (95% CI, 26.3–57.9), and the negative predictive value (NPV) was 99.4% (95% CI, 98.4–99.9). Of note, similar results were obtained when considering the subset of patients with suspected VAP in whom *Enterobacteriaceae* were recovered from respiratory cultures (**Supplemental Table S3**, Supplemental Digital Content 3, http://links.lww.com/CCM/B515).

Among the 20 patients with suspected ESBL-EB VAP, three patients (15%) did not have established ESBL-EB colonization prior to infection. However, a positive culture was obtained in two of them the following week.

The Impact of ESBL-EB Carriage on the Choice of First-Line Therapy

Carbapenems were more frequently chosen as the first-line therapy (32.5% vs 14.4%; $p < 0.01$) in patients with prior ESBL-EB digestive colonization than in those without (Table 2). When carbapenems were chosen, the rate of appropriate first-line antibiotic was enhanced, whenever the whole cohort or the only subset of patients with suspected VAP caused by *Enterobacteriaceae* was considered (**Supplemental Table S2**, Supplemental Digital Content 2, http://links.lww.com/CCM/B514).

However, 85 patients (15%) with suspected VAP not caused by ESBL-EB were also given carbapenems as the empirical therapy during the first 24 hours of management at least (Table 2).

DISCUSSION

VAP is the most frequently encountered ICU-acquired infection. Indeed, VAP prevalence reached 15 to 20 episodes per 1,000 ventilation days in our unit over the study period. In

addition, the rate of ESBL-EB is a growing concern in hospitalized patients. The appropriateness of empirical antimicrobial therapy is a critical issue in this setting, as is the need to limit exposure to carbapenems. However, the most recent American Thoracic Society guidelines published in 2005 aimed to reduce the rate of inappropriate empirical therapy in patients with VAP. These recommendations, however, could lead to an overestimation of the risk of MDR bacterial involvement and thus

TABLE 2. Suspected Ventilator-Associated Pneumonia Episode Description and Outcomes According to Extended-Spectrum β-Lactamase–Producing *Enterobacteriaceae* Colonization Before Suspected Ventilator-Associated Pneumonia

Variable	Overall (*n* = 587)	ESBL-EB Colonization Prior to Suspected VAP (*n* = 40)	No ESBL-EB Colonization Prior to Suspected VAP (*n* = 547)	*p*
VAP causative bacterial agents, *n* (%)				
Enterobacteriaceae	147 (35.3)	21 (52.5)	186 (34.0)	0.02
Pseudomonas aeruginosa	93 (15.8)	10 (25.0)	83 (15.2)	0.10
S. aureus	69 (11.7)	4 (10.0)	65 (11.9)	0.72
Other gram-negative	43 (7.3)	3 (7.5)	40 (7.3)	0.96
Other gram-positive	37 (6.3)	3 (7.5)	34 (6.2)	0.75
None	174 (29.6)	2 (5.0)	172 (31.4)	< 0.01
Polymicrobial	96 (16.4)	9 (22.5)	87 (15.9)	0.67
ESBL-EB causing VAP, *n* (%)	20 (3.4)	17 (42.5)	3 (0.5)	< 0.01
*Escherichia coli**	8 (40.0)	7 (43.7)	1 (25.0)	
*Enterobacter cloacae**	7 (35.0)	5 (31.2)	2 (50.0)	
*Klebsiella pneumoniae**	4 (20.0)	4 (25.0)	0 (00)	
*Haffnia alvei**	1 (5.0)	0 (0.0)	1 (25.0)	
VAP caused by MDR bacteria (overall), *n* (%)	175 (29.8)	28 (70.0)	147 (26.9)	< 0.01
VAP caused by MDR bacteria other than ESBL-EB, *n* (%)	155 (26.4)	12 (30.0)	143 (26.1)	0.52
Enterobacteriaceae†	48 (31.0)	2 (16.7)	46 (32.2)	
Pseudomonas aeruginosa†	32 (20.6)	2 (16.7)	30 (21.0)	
S. aureus†	17 (11.0)	3 (25.0)	14 (9.8)	
Polymicrobial†	48 (31.0)	3 (25.0)	45 (31.5)	
Other†	10 (6.4)	2 (16.7)	8 (5.6)	
Appropriate first-line ATB, *n* (%)	384 (65.5)	20 (50.0)	364 (66.7)	0.03
No ATB within the first 24 hr, *n* (%)	149 (25.3)	8 (20.0)	141 (25.8)	0.87
Carbapenem as first-line ATB, *n* (%)	92 (15.7)	13 (32.5)	79 (14.4)	< 0.01
Appropriate first-line ABT, *n* (%)‡	75 (81.5)	7 (53.8)	68 (85.9)	0.02
Time elapsed from MV onset, d	15.3 (17.6)	19.4 (24.2)	15.5 (17.3)	0.19
Time elapsed from ICU admission, d	15.9 (17.7)	21.4 (24.7)	16.0 (17.3)	0.07
CPIS D1 (points)	5.1 (1.7)	5.1 (2.1)	5.1 (1.7)	0.90
CPIS D3 (points)	6.4 (2)	6.7 (2.2)	6.4 (2.1)	0.40
Septic shock (N. [%])	183 (31.2)	13 (32.5)	170 (31.1)	0.85
SOFA score, day 1 (points)	8.6 (3)	9.5 (3.2)	8.5 (3.0)	0.05
SOFA score, day 3 (points)	8.2 (2.9)	8.9 (3.6)	8.2 (2.9)	0.17

(*Continued*)

TABLE 2. (*Continued*). Suspected Ventilator-Associated Pneumonia Episode Description and Outcomes According to Extended-Spectrum β-Lactamase–Producing *Enterobacteriaceae* Colonization Before Suspected Ventilator-Associated Pneumonia

Variable	Overall (*n* = 587)	ESBL-EB Colonization Prior to Suspected VAP (*n* = 40)	No ESBL-EB Colonization Prior to Suspected VAP (*n* = 547)	*p*
Outcomes, *n* (%)				
ICU length of stay, d	35.7 (30.6)	37.6 (37.9)	35.6 (30.1)	0.69
Mechanical ventilation duration, d	27.9 (25.3)	32.2 (32.1)	27.6 (24.7)	0.27
ICU mortality	231 (39.3)	24 (60.0)	207 (37.8)	< 0.01

ESBL-EB = extended-spectrum β-lactamase–producing *Enterobacteriaceae*, VAP = ventilator-associated pneumonia, MDR = multidrug resistance, ABT = antibiotic, CPIS = clinical pulmonary infection score, SOFA, Sequential Organ Failure Assessment.

*n (%) among EB-ESBL causing VAP.

†n (%) among MDR bacteria causing VAP other than ESBL-EB.

‡n (%) among patients who received carbapenem as first-line antibiotic.

trigger the overuse of broad-spectrum antibiotic regimens (3, 21). We hypothesized, therefore, that an ASC policy could be helpful in guiding first-line therapy.

We showed herein that by detecting prior ESBL-EB digestive colonization, it was possible to identify patients at risk of being infected with these pathogens if VAP was suspected thereafter. The specificity (95.7%) and the excellent NPV (99.4%) suggest that negative surveillance cultures can reliably exclude ESBL-EB involvement, at least in a low-prevalence area like our setting. Actually, one should admit that NPV would be probably quite lower if ESBL-EB were more frequently responsible for VAP. In addition, three of the 20 patients who developed ESBL-EB VAP had negative cultures prior to infection suspicion. Interestingly, ESBL-EB carriage was detected thereafter in two of them. Performing rectal swab twice a week could enhance the sensitivity of the screening. However, we should admit that given the quite low PPV (41.4%) in our cohort, screening for ESBL-EB digestive colonization could lead to an overestimation of the risk of such bacteria being involved in patients with suspected VAP.

TABLE 3. Independent Predictors of ICU Mortality of the Patients With Suspected Ventilator-Associated Pneumonia According to Two Logistic Regression Models (A and B)

Variable	OR	95% CI	*p*
Model A			
SOFA day 1	1.21	1.14–1.29	< 0.0001
Diabetes mellitus	1.11	0.71–1.74	0.646
Appropriate first-line ABT	0.66	0.46–0.96	0.031
Chronic cardiac disease	2.33	1.61–3.36	<0.0001
ESBL-EB colonization	1.93	0.96–3.90	0.067
Model B			
SOFA day 1	1.22	1.15–1.30	< 0.0001
Diabetes mellitus	1.30	0.83–2.02	0.248
Appropriate first-line ABT	0.69	0.48–0.99	0.045
Chronic renal failure	1.41	0.99–3.90	0.055
ESBL-EB colonization	1.96	0.96–3.90	0.067

OR = odds ratio, SOFA = Sequential Organ Failure Assessment, ABT = antibiotic, ESBL-EB = extended-spectrum β-lactamase–producing *Enterobacteriaceae*.

Some authors have studied the clinical impact of a twice-weekly surveillance culture that aimed to detect ESBL-EB rectal carriage (10). Interestingly, 82 patients (15.5%) were, thus, found to be colonized at ICU admission, a greater rate than in our cohort. Among the patients hospitalized more than 3 days, ESBL-EB colonization was acquired in 28 of them (13%). Interestingly, among the 90 patients with ESBL-EB colonization, only seven (7.7%) developed subsequent infection. All patients but one who developed an infection caused by ESBL-EB were a digestive carrier. However, most of the cases of ICU-acquired infections were bacteremia, and only one ESBL-EB–related VAP episode was recorded during the study period. Finally, to our knowledge, very few studies have evaluated the specific impact of weekly screening for digestive ESBL carriage on VAP ecology.

Different policies were evaluated in previous studies, generally reporting good concordance between surveillance culture results and the actual causative bacteria.

Several studies showed that despite low ESBL-EB colonization rates at ICU admission, 9% to 25% of colonized patients acquired ESBL-EB infection, thus emphasizing its good PPV (22, 23). Similar findings were published considering methicillin resistant *S. aureus* (MRSA) because some authors showed that weekly screening for prior upper airway colonization with MRSA yielded high specificity (92%) and a high NPV (96.7%) (24).

Altogether, these data suggest that screening for MDR carriage in ICU patients is likely to predict the involvement of such bacteria in subsequent infections, including VAP (25). It could, therefore, be used as an astute and efficient way to select patients in whom broad-spectrum antibiotic could be avoided

TABLE 4. Performance Characteristics of Extended-Spectrum β-Lactamase–Producing *Enterobacteriaceae* Active Surveillance Culture as a Predictor of Extended-Spectrum B-Lactamase–Producing *Enterobacteriaceae* Ventilator-Associated Pneumonia

	Sensitivity (%) [95% CI]	Specificity (%) [95% CI]	Positive Predictive Value (%) [95% CI]	Negative Predictive Value (%) [95% CI]	Positive LR [95% CI]	Negative LR [95% CI]
All ventilator-associated pneumonia	17/20 (85.0) [62.1–96.8]	543/567 (95.7) [93.7–97.3]	17/41 (41.5) [26.3–57.9]	543/546 (99.4) [98.4–99.9]	19.8 [9.8–35.4]	0.15 [0.0–0.4]

LR = likelihood ratio.

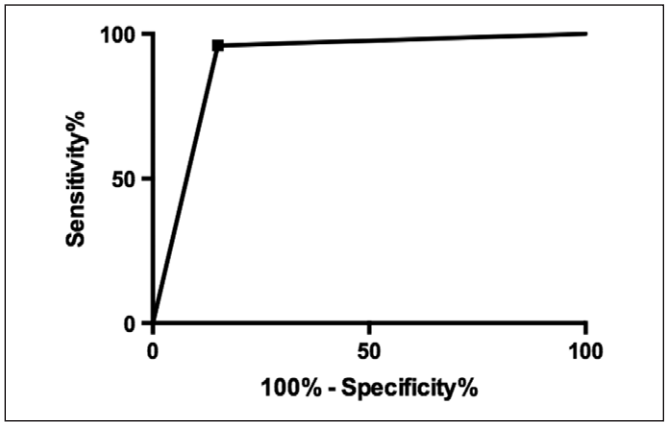

Figure 2. Receiver operating characteristic (ROC) curve for extended-spectrum β-lactamase–producing *Enterobacteriaceae* colonization to predict the presence of their involvement in patients with suspected ventilator-associated pneumonia in the ICU. The area under the ROC curve: 0.90 (95% CI, 0.81–0.99).

as the empirical therapy (26). The fact that in this study, other risk factors of MDR bacterial involvement were found in the same proportions regardless of ESBL-EB digestive colonization emphasizes this conclusion. However, we should acknowledge that among these factors, antibiotic exposure prior to ICU admission was not assessed (10).

However, one could argue that ESBL-EB, despite being a growing threat, are not the most frequently encountered MDR bacterial species, in Europe at least. In addition, rectal swab culture alone does not provide a comprehensive analysis of the whole colonizing bacterial flora likely to be involved in subsequent ICU-acquired infection, including VAP.

Some authors, thus, evaluated the accuracy of surveillance cultures of tracheal aspirates and urine samples along with once-weekly oral, nasal, and rectal samples (27). The sensitivity of an endotracheal surveillance culture alone in predicting the pathogens implicated in VAP was 69% but interestingly increased to 82% if it was combined with multiple site surveillance cultures. Similarly, the NPV for surveillance cultures increased from 80% to 87% if all sites were considered rather than tracheal aspirates alone. In addition, these findings suggest that such a policy could actually curtail the use of broad-spectrum antibiotic regimens. In line with these findings, another group showed that a twice-weekly tracheal aspirate culture was very helpful in selecting antibiotics in patients with suspected VAP (28). In the same way, others showed that weekly cultures of tracheal aspirates and rectal swabs that targeted the isolation of resistant Gram-negative microorganisms (i.e., not only ESBL-EB) accurately predicted the agents responsible for subsequent infection (29). Indeed, the causative bacterial species had been isolated previously from either respiratory or gastrointestinal tract surveillance cultures in 82% of VAP episodes. As a result, the rate of appropriate empirical treatment reached 91%.

However, one should admit that performing frequent surveillance cultures from multiple sites is laborious and costly. In addition, because predictive values are highly dependent on the prevalence of MDR bacteria, screening for only the most resistant species as described above (e.g., ESBL-EB and MRSA) should be applied only in ICUs with the highest rates of inappropriate first-line antibiotic therapy. Finally, none of these studies addressed the cost-effectiveness issue.

We, therefore, chose to apply a screening policy that corresponded to our local concerns. VAP was the main ICU-acquired infection and involved *Enterobacteriaceae* in up to 50% of cases, whereas MRSA was rarely isolated. In addition, rectal swab cultures are less time consuming than standard tracheal aspirate cultures, which should be repeated twice a week for a reliable prediction of the pathogen involved in late-onset VAP, that is, most of our cases (28, 30). Compelling evidence has emphasized the role of the gastrointestinal tract in the development of VAP. Indeed, the stomach could act as a reservoir of GNB likely to cause tracheobronchial colonization subsequent to regurgitation and swallowing disorders, leading thereby to repeated microaspirations within the airways (13, 31, 32). Finally, detecting ESBL-EB carriers allowed us to prevent the spread of these MDR bacteria, which occurred once before this screening policy was implemented in our ICU (33).

Nonetheless, our study has some limitations. First, our results reflect only the experience of a single centre and cannot be generalized to other ICUs with different microbial and resistance patterns or standards of care. In addition, VAP diagnosis relied on the calculation of the CPIS, which has been shown to probably overestimate the risk of pneumonia. However, it has been shown that antibiotics should be promptly started as soon as VAP is suspected, without waiting until culture results are available, especially in the most severely affected patients and provided that the therapy is reassessed thereafter. Regarding this point, it is worth noting that the SOFA scores were quite high in the study population, thus supporting the need for

the prompt administration of empirical therapy. Finally, our screening policy should be evaluated prospectively in another cohort before drawing firm conclusions regarding its predictive value.

As a conclusion, we showed herein that ESBL-EB rectal carriage could predict the subsequent isolation of such bacterial species within the airways of patients with suspected VAP in a low-prevalence area. The choice of first-line antibiotics could be thus more accurate.

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