# Ventilator-associated pneumonia related to extended-spectrum beta-lactamase producing Enterobacterales during severe acute respiratory syndrome coronavirus 2 infection : risk factors and prognosis

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# Ventilator-associated pneumonia related to extended-spectrum beta-lactamase producing Enterobacterales during severe acute respiratory syndrome coronavirus 2 infection: risk factors and prognosis

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## Abstract

**Background** Patients infected with the severe acute respiratory syndrome coronavirus 2 (SARS-COV 2) and requiring mechanical ventilation suffer from a high incidence of ventilator associated pneumonia (VAP), mainly related to Enterobacterales. Data regarding extended-spectrum beta-lactamase producing Enterobacterales (ESBL-E) VAP are scarce. We aimed to investigate risk factors and outcomes of ESBL-E related VAP among critically ill coronavirus infectious disease-19 (COVID-19) patients who developed Enterobacterales related VAP.

**Patients and methods** We performed an ancillary analysis of a multicenter prospective international cohort study (COVID-ICU) that included 4929 COVID-19 critically ill patients. For the present analysis, only patients with complete data regarding resistance status of the first episode of Enterobacterales related VAP (ESBL-E and/or carbapenem-resistant Enterobacterales, CRE) and outcome were included.

**Results** We included 591 patients with Enterobacterales related VAP. The main causative species were *Enterobacter sp* (n = 224), *E. coli* (n = 111) and *K. pneumoniae* (n = 104). One hundred and fifteen patients (19%), developed a first ESBL-E related VAP, mostly related to *Enterobacter sp* (n = 40), *K. pneumoniae* (n = 36), and *E. coli* (n = 31). Eight patients (1%) developed CRE related VAP. In a multivariable analysis, African origin (North Africa or Sub-Saharan Africa) (OR 1.7 [1.07–2.71], $p = 0.02$), time between intubation and VAP (OR 1.06 [1.02–1.09], $p = 0.002$), $PaO_2/FiO_2$ ratio on the day of VAP (OR 0.997 [0.994–0.999], $p = 0.04$) and trimethoprim-sulfamethoxazole exposure (OR 3.77 [1.15–12.4], $p = 0.03$)

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were associated with ESBL-E related VAP. Weaning from mechanical ventilation and mortality did not significantly differ between ESBL-E and non ESBL-E VAP.

**Conclusion** ESBL-related VAP in COVID-19 critically-ill patients was not infrequent. Several risk factors were identified, among which some are modifiable and deserve further investigation. There was no impact of resistance of the first Enterobacterales related episode of VAP on outcome.

**Keywords** COVID-19, ARDS, Nosocomial pneumonia, Ventilator-associated pneumonia, ESBL

## Introduction

Antimicrobial resistance is a leading global health issue. Lower respiratory tract infections alone accounted for more than 400,000 attributable deaths and 1.5 million associated deaths in 2019, worldwide [1]. Among critically ill patients, ventilator associated pneumonia is frequent. The incidence of ventilator-associated pneumonia (VAP) in COVID-19 patients ranges from 30 to 84% [2–4]. Potential explanations for the high incidence of VAP in COVID-19 patients include prolonged invasive mechanical ventilation, the high incidence of acute respiratory distress syndrome (ARDS), lung microbiota alteration, COVID-19-related specific lesions, neuromuscular blocking and administration of treatments which depress the immune system. Additionally, COVID-19 patients were often treated empirically by broad-spectrum antibacterial therapy at ICU admission [5]. The main microbial species involved in VAP were Enterobacterales [3, 4]. Recent studies have reported an increase in the frequency of healthcare-associated infections and antibiotic resistance during the COVID-19 pandemic [6]. VAP-attributable mortality was higher for patients with COVID-19 than non COVID-19, with more than 9% of the overall mortality related to VAP [7].

Data regarding the outcome of VAP related to Enterobacterales according to resistance in a homogeneous group of mechanically ventilated COVID-19 patients are scare. We conducted this study to assess risk factors and prognosis of extended-spectrum beta-lactamase producing Enterobacterales (ESBL-E) related VAP in patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pneumonia and who developed a first episode of enterobacterales-related VAP.

## Methods, study design and patients

We performed an ancillary analysis of the COVID-ICU study. COVID-ICU was a multi-center, observational, prospective cohort study conducted in 149 ICUs from 138 centers, across three countries (France, Switzerland, and Belgium) which has been previously been described [8]. Ethical committees in Switzerland (BASEC # 2020-00704), France (French intensive care Society CE-SRLF 20-23) and Belgium (2020-294) approved this study and all patients or relatives were informed that their data were included in the COVID-ICU cohort. In case of refusal, the data were withheld accordingly. This manuscript follows the STROBE statement for reporting cohort studies.

### Study population and data collection

All consecutive patients over 16 years of age admitted to participating ICUs between February 25, 2020, and May 4, 2020, with laboratory-confirmed SARS-CoV-2 infection were included. Patients who had been invasively ventilated for more than 24 h before transfer to one of the participating centers were excluded. Details of the data collected daily over the first 14 days from admission and then on Days 28, 45, 60, and 90 have been described elsewhere [8] and are briefly summarized below. We recorded baseline demographics [age, sex, body mass index (BMI), active smoking, treated hypertension, diabetes], long-term corticosteroids, immunodeficiency, Clinical Frailty Scale, and clinical information and ICU severity scores [Simplified Acute Physiology Score (SAPS) II and Sequential Organ Failure Assessment (SOFA)]. The study investigators recorded time-updated information, respiratory support, arterial blood gas, standard laboratory parameters, use of adjuvant therapies for ARDS, microbiological results of respiratory samples and antibiotics use. Patient vital status (with the exact date of death) was collected by study investigators 90 days after ICU admission, with a phone call to patients or their relatives if they were discharged from hospital before Day 90. Data describing the participating centers, including the number of ICU physicians, nurses, and number of beds, were also collected.

### VAP definition

VAP diagnosis was based on: (1) clinical and radiological suspicion based on criteria established by the European Center of Disease Control [9]; (2) confirmed by at least one positive quantitative microbiological sample defined when culture recovered $\geq 10^6$ CFU/mL for tracheal aspirate, $\geq 10^4$ CFU/mL for broncho-alveolar lavage (BAL), and $\geq 10^3$ CFU/mL for distal protected specimen brush or aspirate [9]; and (3) leading the attending physician to initiate antimicrobial therapy. In addition, pneumonia must have occurred at least 48 h after mechanical

ventilation onset. For each positive respiratory sample culture, investigators could identify the micro-organism responsible of the infection within a restricted list: Enterobacterales, *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, *Streptococcus pneumonia*, Group A or B *Streptococcus, Enteroccoccus spp*., methicillin-susceptible *Staphylococcus aureus*, methicillin resistant *Staphylococcus aureus*, *Haemophilus infuenzae*, anaerobes or other. Therefore, "other" denotes all micro-organisms not present in the preceding list and were not specified. Since respiratory cultures may identify multiple microorganisms, investigators could identify several micro-organisms within a single respiratory sample.

For this report, we restricted our analysis to patients who presented VAP related to *Enterobacterales* in whom resistance status (including ESBL-E and CRE) were known. Additional data were requested from participating centers, including involved species and coinfection with other micro-organisms. Only the first episode of VAP was considered. ESBL-E phenotype were determined by disk diffusion. Double-disk diffusion testing of clinical specimens detected production of ESBL by a synergistic effect between clavulanic acid/amoxicillin or clavulanic acid/ticarcillin and cefotaxime, ceftazidime, aztreonam or cefepime.

### Statistical analysis

Categorical variables were expressed as number (percentage) and continuous variables as median and interquartile range [IQR]. When appropriate, chi square and Fisher's exact tests were used to compare categorical variables. The Mann–Whitney U test and the Wilcoxon test were used to compare continuous variables when applicable. To identify patients' characteristics associated with ESBL-E VAP, we used multivariable logistic regression. Non-redundant variables selected by bivariate analysis ($p < 0.10$) or considered clinically relevant were entered into a logistic regression model. Multiple imputations were used to replace missing values using chained equations method and five imputations. Overall survival curves were estimated using the Kaplan–Meier method and a Cox model to assess the effect of Enterobacterales on overall survival. Results were expressed as hazard ratio and 95% confidence interval. We used a Fine and Gray model (cumulative incidence function of the Gray model) to properly estimate the effect of Enterobacterales related VAP on weaning, while considering death as a competing event using cmprsk package developed by Gray in R software (http://biowww.dfci.harvard.edu/~gray/cmprsk_2.1-4.tar.gz). Results were expressed as subdistribution hasard ratio associated to its 95% confidence interval. Two-sided *p*-values < 0.05 were considered significant.

## Results

Among the 4929 patients included in the COVID-ICU database, 1087 had VAP with Enterobacterales or "other" microorganism in the database. After additional data requested from participating centers, 494 patients were excluded because respiratory sample found no microorganism (n = 154), no Enterobacterales but another microorganism (n = 177), or no response of the center (n = 165). 591 had all data available on Enterobacterales related VAP and were included in the current analysis (see flow chart Fig. 1). Characteristics of patients and their clinical and biological data at ICU admission are available in Tables 1 and 2. Median age was 63 [55–69] years. Four hundred and sixty-eight (79%) patients were male. Two hundred and thirty-eight (42%) patients were obese (BMI ≥ 30 kg/m$^2$). The most frequent comorbidities were hypertension (298/586, 51%) and diabetes (156/588, 27.5%). There were 46/588 (8%) immunocompromised patients. Median SAPS II and SOFA scores at ICU admission were 37 [28–49] and 5 [3–8], respectively.

### ESBL-E VAP

Among the 591 patients with a first episode of VAP related to Enterobacterales, the main species were *Enterobacter sp* (n = 224), *E. coli* (n = 111) and *K. pneumoniae* (n = 104). One hundred and ninety (32%) patients had polymicrobial VAP involving the following species: several Enterobacterales without other species (n = 64, 11%), *Staphyloccocus aureus* (n = 31, 5%), *Streptococcus sp.* (n = 20, 3%), *Haemophilus influenzae* (n = 12, 2%), *P. aeruginosa* (n = 42, 7%), or other non-fermenting gram negative bacteria (n = 17; 3%). One hundred and fifteen patients (19%), developed a first episode of VAP with ESBL-E, mostly caused by *Enterobacter sp* (n = 40), *K. pneumoniae* (n = 36), and *E. coli* (n = 31). Eight patients (1%) developed CRE related VAP. All but one CRE VAP were also ESBL-E and were therefore analyzed within the ESBL-E VAP group. There was no significant association between ICU characteristics and ESBL-E VAP, except for a higher number of ICU beds in the ESBL-E group (Additional file 1: Table E1). Risk factors for developing ESBL-E VAP were tested by univariate analysis (Tables 1, 2). African origin (North Africa or Sub-Saharan Africa), time from intubation, immunodeficiency, lower oxygenation, and higher positive end expiratory pressure level, were associated with ESBL-E VAP. Concerning antibiotic exposure, risk factors for ESBL-E VAP included exposure to fluoroquinolone, trimethoprim-sulfamethoxazole or glycopeptid. By multivariable analysis (Table 3), African origin (OR 1.7 [1.07–2.71], $p = 0.02$), time between intubation and VAP (OR 1.06 [1.02–1.09], $p = 0.002$), $PaO_2/FiO_2$ ratio on the day of VAP (OR 0.997 [0.994–0.999], $p = 0.04$) and Trimethoprim-sulfamethoxazole exposure

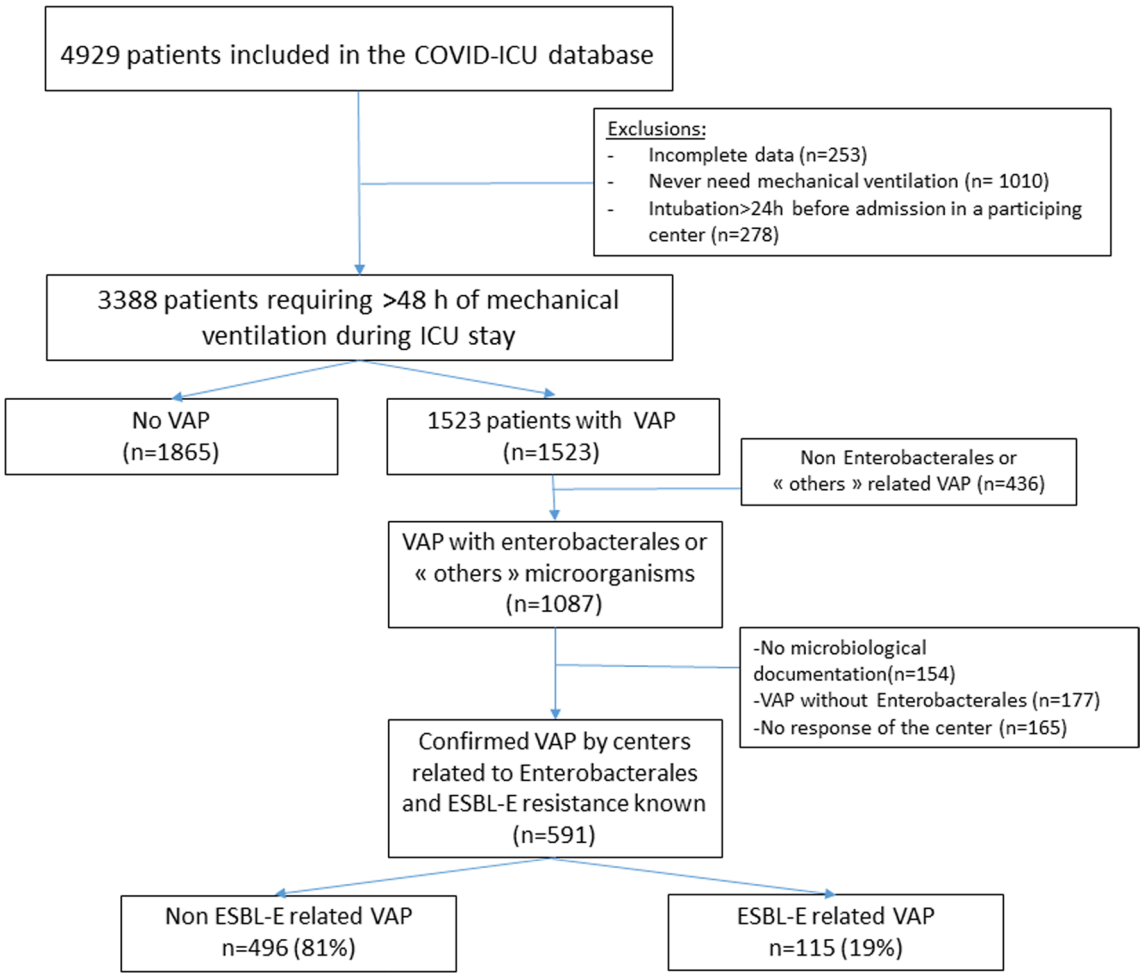


**Fig. 1** Flow chart of the study

(OR 3.77 [1.15–12.4], $p=0.03$), were associated with ESBL-E VAP. Risk factors did not differ after excluding the eight patients with CRE VAP, excepted for $PaO_2/FiO_2$ ratio on the day of VAP which felt short of statistical significance [OR = 0.99 (0.99–1.00), $p=0.07$) (Additional file 1: Table E2). During the 24 h following VAP onset, patients with ESBL-E VAP received more frequently carbapenem [26/115 (23%) vs 49/476 (10%), $p<0,001$] and less frequently penicillins [27/115(23%) vs 164/476 (34%), p = 0.02], as compared to their counterparts (Additional file 1: Table E3).

### Outcome

The number of VAP episodes after the first episode was lower in patients with VAP due to ESBL-E or CRE as compared to patients with non-ESBL-E VAP (1 [0–1] vs 1 [0–2], p = 0.04). ESBL-E VAP was not associated with a worse outcome as compared to non-ESBL-E VAP. Weaning from mechanical ventilation (Fig. 2), as well as mortality at ICU discharge, in hospital, at 28 days and at 90 days (Additional file 1: Table E4, Fig. 3) did not differ between ESBL-E and non ESBL-E VAP. Mortality was not influenced by species, chromosomally-encoded AmpC-producing Enterobacterales, or polymicrobial VAP (Additional file 1: Table E5). Results on mortality were similar after excluding the eight patients with CRE VAP (HR 0.94 [0.62–1.41], $p=0.75$), after excluding polymicrobial VAP with *Staphylococcus aureus* or *Pseudomonas aeruginosa* (HR 0.91 [0.61–1.36], $p=0.64$), after excluding polymicrobial VAP with other species than Enterobacterales (HR 0.94 [0.62–1.41], $p=0.75$), in 220 patients sampled with BAL or protected distal sample (HR 1.07 [0.62–1.86], $p=0.81$), or after adjusting for the use of corticosteroids in the first week (HR 0.89 [0.61–1.3], $p=0.54$).

## Discussion

The main findings of this prospective multicenter study of patients with a first episode of Enterobacterales related VAP, during the first COVID wave are: (i) 19% of VAPs

**Table 1** Demographic, clinical, biological and ventilatory support characteristics of patients with VAP according to the occurrence of ESBL-E VAP

| | Number with missing data | No ESBL-E VAP (n = 476) | ESBL-E VAP (n = 115) | *P* value |
|---|---|---|---|---|
| Age, years | 0 | 63 [56–70] | 63 [53–68] | 0.22 |
| Male gender | 3 | 375 (79%) | 93 (81%) | 0.71 |
| Body mass index, kg/m$^2$ | 30 | 29 [25–33] | 29 [25–33] | 0.65 |
| Ethnic origin | 111 | | | 0.03 |
| Caucasian | | 218 (57%) | 43 (43%) | |
| African | | 111 (29%) | 42 (42%) | |
| Other | | 52 (14%) | 14 (14%) | |
| Clinical frailty scale | 53 | 2 [2–3] | 2 [2–3] | 0.66 |
| *Comorbidities* | | | | |
| No comorbidities | 2 | 81 (17%) | 16 (14%) | 0.41 |
| Alcohol consumption | 15 | 22 (5%) | 5 (5%) | 0.92 |
| Tabaco consumption | 14 | 19 (4%) | 4 (4%) | 0.99 |
| Chronic respiratory disease | 5 | 103 (22%) | 28 (25%) | 0.49 |
| Cardiovascular co-morbidities | 8 | 306 (65%) | 70 (61%) | 0.53 |
| Treated hypertension | 5 | 241 (51%) | 57 (50%) | 0.84 |
| Coronary artery disease | 4 | 52 (11%) | 9 (8%) | 0.33 |
| Chronic heart failure | 8 | 15 (3%) | 4 (4%) | 0.77 |
| Known Diabetes | 3 | 127 (27%) | 29 (25%) | 0.77 |
| Chronic renal failure | 3 | 40 (8%) | 16 (14%) | 0.07 |
| Cirrhosis | 3 | 3 (1%) | 0 (0%) | 0.99 |
| Immunodeficiency | 3 | 31 (7%) | 15 (13%) | 0.02 |
| Hematological malignancies | 3 | 13 (3%) | 3 (3%) | 0.99 |
| Active solid tumor | 3 | 5 (1%) | 0 (0%) | 0.59 |
| Solid organ transplant | 3 | 9 (2%) | 6 (5%) | 0.04 |
| Human Immunodeficiency Virus | 3 | 6 (1%) | 2 (2%) | 0.66 |
| *Home treatment* | | | | |
| Immunosuppressive therapy[a] | 101 | 17 (4%) | 11 (11%) | 0.009 |
| Long-term corticosteroids | 102 | 16 (4%) | 8 (8%) | 0.09 |
| Treatment with NSAID before ICU admission | 91 | 34 (9%) | 7 (7%) | 0.63 |
| In another country during 3 weeks before ICU admission | 89 | 15 (4%) | 4 (4%) | 0.99 |
| Living place: home | 3 | 454 (96%) | 114 (99%) | 0.15 |
| *At ICU admission* | | | | |
| SAPS II score | 27 | 37 [29–51] | 41 [32–49] | 0.25 |
| SOFA score at ICU admission | 72 | 6 [3–9] | 7 [4–9] | 0.13 |
| *Patient origin* | | | | |
| Emergency room Direct admission from home/emergency medical ambulance | 1 | 300 (63%) | 67 (58%) | |
| Medical wards | 1 | 130 (27%) | 38 (33%) | |
| Other ICU or Operating theatre | 1 | 45 (9%) | 10 (9%) | |
| Concomitant bacterial pneumonia | 11 | 47 (10%) | 9 (8%) | 0.49 |
| Invasive mechanical ventilation | 3 | 369 (78%) | 89 (77%) | 0.89 |
| Biology[c] | | | | |
| White blood count, $\times 10^6$/L | 44 | 8600 [6200–11700] | 9000 [5300–9800] | 0.50 |
| C-reactive protein, mg/L | 274 | 160 [110–248] | 169 [113–267] | 0.46 |
| Procalcitonine, ng/mL | 386 | 0.46 [0.23–1.37] | 0.64 [0.38–2.48] | 0.08 |
| During the first 48 h following ICU admission | | | | |
| Prone position | 42 | 215 (48%) | 60 (57%) | 0.11 |
| Neuromuscular blockade | 42 | 385 (86%) | 96 (91%) | 0.19 |

**Table 1** (continued)

| | Number with missing data | No ESBL-E VAP (n = 476) | ESBL-E VAP (n = 115) | *P* value |
|---|---|---|---|---|
| ECMO | 2 | 24 (5%) | 3 (3%) | 0.33 |
| Dialysis | 2 | 33 (7%) | 14 (12%) | 0.06 |
| Antibiotics | 1 | 435 (92%) | 109 (95%) | 0.25 |
| CT scan | 51 | 113 (26%) | 25 (25%) | 0.89 |
| Corticosteroids | 3 | 81 (17%) | 17 (15%) | 0.61 |
| Corticosteroids the first week | 0 | 126 (27%) | 31 (27%) | 0.98 |
| On the day of VAP | | | | |
| Time between admission and VAP | 0 | 10 [7–15] | 12 [9–21] | 0.001 |
| Time between intubation and VAP | 0 | 8 [5–12] | 10 [7–18] | 0.003 |
| SOFA score | 194 | 9 [7–11] | 10 [7–13] | 0.15 |
| Non respiratory SOFA | 194 | 7 [7, 8] | 7 [4–9] | 0.21 |
| Catecholamine | 94 | 153 (37%) | 34 (39%) | 0.76 |
| $PaO_2/FiO_2$ | 110 | 150 [115–220] | 138 [103–184] | 0.02 |
| PEEP | 107 | 11 [8–13] | 12 [10–14] | 0.03 |
| Neuromuscular blockade | 93 | 193(47%) | 47 (53%) | 0.28 |
| Prone position | 92 | 105 (26%) | 28 (32%) | 0.23 |
| ECMO | 85 | 28 (7%) | 8 (9%) | 0.43 |
| Dialysis | 80 | 51 (12%) | 15 (17%) | 0.24 |
| Antibiotics | 81 | 237 (56%) | 56 (62%) | 0.30 |

Categorical variables are expressed as n (%) and continuous variables as median [interquartile range]

[a] Except corticosteroids.; NSAID: non-steroidal anti-inflammatory drug; SAPS II Simplified Acute Physiology Score II, SOFA: Sequential Organ Failure Assessment; ECMO extracorporeal membrane oxygenation; VAP ventilator associated pneumonia

**Table 2** Antibiotics in ICU before VAP related enterobacterales according to ESBL-E

| Variables | No ESBL-E VAP (n = 476) | ESBL-E VAP (n = 115) | *P* value |
|---|---|---|---|
| Ab in ICU before VAP | 443 (93%) | 112 (97%) | 0.086 |
| Penicillins | 207 (44%) | 49 (43%) | 0.86 |
| Cephalosporin | 340 (71%) | 90 (78%) | 0.14 |
| Fluoroquinolone | 6 (1%) | 6 (5%) | 0.02 |
| Carbapenem | 23 (5%) | 9 (8%) | 0.20 |
| Aminoglycoside | 42 (9%) | 13 (11%) | 0.41 |
| Co-trimoxazole | 7 (1%) | 8 (7%) | 0.001 |
| Glycopeptides | 12 (3%) | 8 (7%) | 0.02 |
| Linezolid | 30 (6%) | 6 (5%) | 0.66 |
| Macrolides | 278 (58%) | 67 (58%) | 0.98 |

**Table 3** Multivariable analysis of risk factors of ESBL-E related VAP

| Variables | OR | 95% CI | *p*-value |
|---|---|---|---|
| SAPS II at ICU admission | 1.00 | 0.98–1.01 | 0.90 |
| African origin | **1.70** | **1.07–2.71** | **0.02** |
| Chronic renal failure | 1.31 | 0.61–2.78 | 0.48 |
| Immunodeficiency | 1.38 | 0.62–3.09 | 0.42 |
| Time between intubation and VAP | **1.06** | **1.02–1.09** | **0.002** |
| Non respiratory SOFA* | 1.05 | 0.92–1.20 | 0.48 |
| $PaO_2/FiO_2$* | **0.997** | **0.994–0.999** | **0.04** |
| ECMO* | 0.69 | 0.29–1.64 | 0.41 |
| Antibiotics in ICU before VAP | 2.23 | 0.63–7.90 | 0.21 |
| Fluoroquinolone before VAP | 2.59 | 0.71–9.43 | 0.14 |
| Co-trimoxazole | **3.77** | **1.15–12.4** | **0.03** |
| Glycopeptides | 1.65 | 0.58–4.67 | 0.35 |

Bold value indicates $p < 0.05$

African origin denotes North Africa or Sub-Saharan Africa origin; SAPS II Simplified Acute Physiology Score II, SOFA: Sequential Organ Failure Assessment; ECMO extracorporeal membrane oxygenation; VAP ventilator associated pneumonia, ICU intensive care unit *on the day of VAP

were related to ESBL-E; (ii) African origin, duration of mechanical ventilation, PaO2/FiO2 ratio the day of VAP and trimethoprim-sulfamethoxazole exposure were associated with ESBL-E VAP; (iii) ESBL-E VAP was not associated with a worse outcomes, including mortality, as compared to other Enterobacterales VAP.

Resistance patterns of Enterobacterales related VAP were heterogeneous across studies in COVID-19 patients. Our finding of 19% ESBL-E among Enterobacterales VAP is in accordance with findings from Vacheron et al., describing a frequency of ESBL-E VAP in COVID-19 or non-COVID-19 patients of about 13% in France [10]. Prevalence of ESBL-E ICU acquired infection were

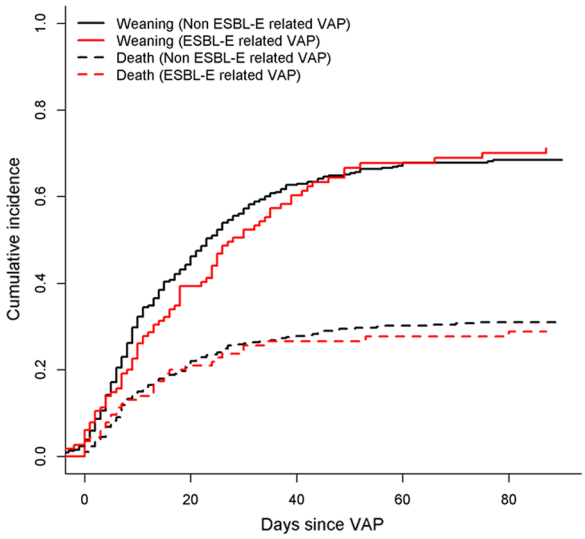


**Fig. 2** Cumulative probability of weaning in ESBL-E related VAP (red) and non ESBL-E related VAP (black) patients. For analysis purpose, time from intubation to weaning (continuous line) to death (dotted line) were handled as competing risks

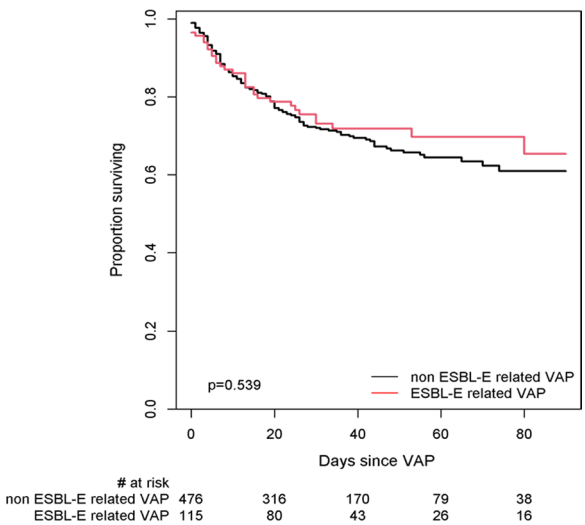


**Fig. 3** Ninety-day survival in patients with ESBL-E related VAP and non ESBL-E related VAP

reported as heterogeneous in France [11]. Most patients in our study were recruited in regions with higher ESBL-E prevalence (58% of the patients were recruited in the Paris or Greater Paris area).

ESBL-E infection is usually associated with previous colonization and invasive procedures [12]. Thus, it was not surprising that time between intubation and VAP was one of the main risk factor of ESBL-E VAP, as previously shown [13]. A previous study also showed that the prevalence of ESBL increased during the second or third episode of VAP [2]. In our study, microbiological details were only available for the first episode of VAP [2]. In our cohort, most patients received antibiotics before VAP occurrence and the use of trimethoprim/sulfamethoxazole before VAP onset was independently associated with ESBL-E VAP. Exposure to trimethoprim/sulfamethoxazole was associated with ESBL-E organisms in previous reports [13–16]. The third risk factor identified by multivariable analysis was an African origin. This is in accordance with a previous French study reporting that a country of birth outside of Europe was a risk factor for ESBL-E infection [17]. In the USA, an African American origin was reported as a risk factor for ESBL-E infection [14, 18]. The role of a patient's origin may be driven by diet, food habits and/or travel abroad over the previous years [19]. We could only assess travels over a 3 week period preceding ICU admission. A lower $PaO_2/FiO_2$ ratio on the day of VAP was also a risk factor for ESBL-E VAP identified in this cohort. These results are in accordance with previous studies showing that ARDS was a risk factor for multidrug resistant bacteria VAP [20].

VAP was associated with significantly increased 28-day mortality in SARS-CoV-2 patients [21]. VAP-attributable mortality was higher for patients with COVID-19, with more than 9% of the overall mortality related to VAP [7]. Current evidence of the clinical burden of infections caused by ESBL-producing bacteria is highly heterogeneous and based mainly on unadjusted estimates derived from retrospective studies [22]. Lambert et al. showed that the risk of death associated with antimicrobial resistance (i.e., additional risk of death to that of the infection) was 1.2 (1.1–1.4) for pneumonia but this effect was mainly driven by *S. aureus* and *P. aeruginosa* [23]. We herein did not find different outcomes between ESBL-E and non ESBL-E VAP. Additionally, a sensitivity analysis in patients infected only with Enterobacterales excluded the hypothesis that co-infecting microorganisms could have influenced the results. Several studies with fewer ESBL-E episodes also showed no difference in outcome between ESBL-E and non ESBL-E VAP [24, 25]. Our study with a homogeneous population of COVID-19 patients strengthens these findings. Multi-drug resistant related VAP was associated with increased mortality when empiric antibiotherapy was inadequate [26, 27]. Information on early adequate regimen was unavailable but could be similar between ESBL-E and non ESBL VAP, explaining the absence of difference in outcome in this study. Given the poor accuracy of chest radiograph to detect new infiltrates, the diagnosis of VAP in patients with ARDS is challenging [28]. In a restrictive antibiotic policy, physician may have started antibiotic therapy after culture results. We cannot formally exclude that patients

developed ventilator associated tracheobronchitis and not VAP, but the number of patients requiring catecholamine (more than 1/3) was higher than reported in recent VAP cohorts [29]. In addition, mortality was similar in ESBL-E and non ESBL-E VAP among patients with distal quantitative samples. Lastly, mortality in COVID-19 critically was mainly altered by age, comorbidities, corticosteroids and organ failure [30, 31].

Strengths of our study include the large number of patients assessed and data recorded prospectively, and the absence of case-mix with only COVID-19 patients. We acknowledge several limitations to our study. First, all patients were included during the first epidemic wave of SARS-CoV-2 affecting Europe in the spring of 2020, a unique period when ICUs were overwhelmed. It cannot be excluded that antibiotic stewardship in COVID-19 patients with less antibiotic administration at ICU admission may change ESBL-E prevalence. Moreover, the acquisition of immunity following subsequent epidemic waves or vaccination, and/or the emergence of new SARS-CoV-2 variants, may change some of our results. Second, although this study was conducted in 149 ICUs from 138 centers, across three countries, our results were obtained from a west European population, a region of the world with relatively low prevalence of ESBL-E colonization or infection.

## Conclusions

In this prospective multicenter study of patients with a first episode of VAP related to Enterobacterales, almost a fifth were ESBL-E. African origin, duration of mechanical ventilation, a lower $PaO_2/FiO_2$ ratio and trimethoprim-sulfamethoxazole exposure were associated with ESBL-E VAP. ESBL-E VAP was not associated with a worse outcome as compared to other Enterobacterales-related VAP.

## Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13054-024-04906-2.

**Additional file 1. Table E1.** Centers informations; **Table E2.** Multivariable analysis of risk factors of ESBL-E related VAP after exclusion of the 8 patients with CRE related VAP; **Table E3.** Antibiotics administered in the 24 hours following VAP according to ESBL-E; **Table E4.** Outcome according to the occurrence of ESBL-E VAP; **Table E5.** Risk factors for death in patients with VAP related to enterobacterales according to species.

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**Author contributions**
KR, AMD designed the study, interpreted the data and wrote the manuscript. KR and ACN performed statistical analysis. All authors made significant intellectual concept. All authors read and approved the final manuscript.

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**Availability of data and materials**
The data sets generated during the current study are available from the corresponding author on reasonable request.

## Declarations

**Ethics approval and consent to participate**
Human research ethics committee approval for the study was the ethical committee of the French Intensive Care Society (CE-SRLF 20-23) following our local regulations.

**Competing interests**
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