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ORIGINAL

Infection-related ventilator-associated complications in ICU patients colonised with extended-spectrum β-lactamase-producing Enterobacteriaceae

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Abstract

Purpose: To investigate the clinical significance of infection-related ventilator-associated complications (IVAC) and their impact on carbapenem consumption in mechanically ventilated (MV) patients colonised with extended-spectrum β-lactamase-producing Enterobacteriaceae (ESBLE).

Methods: Inception cohort study from the French prospective multicenter OUTCOMEREA database (17 ICUs, 1997–2015) including all ESBLE carriers (systematic rectal swabbing at admission then weekly and/or urinary or superficial surgical site colonisation) with MV duration > 48 h and ≥ 1 episode of IVAC after carriage documentation. All ICU-acquired infections were microbiologically documented.

Results: The 318 enrolled ESBLE carriers (median age 68 years; males 67%; medical admission 68%; imported carriage 53%) experienced a total of 576 IVAC comprising 361 episodes (63%) without documented infection, 124 (21%) related to infections other than ventilator-associated pneumonia (VAP), 73 (13%) related to non-ESBLE VAP and 18 (3%) related to ESBLE VAP. Overall, ESBLE infections accounted for only 43 episodes (7%). Carbapenem exposure within the preceding 3 days was the sole independent predictor of ESBLE infection as the causative event of IVAC, with a protective effect (adjusted odds ratio 0.2, 95% confidence interval 0.05–0.6; $P < 0.01$). Carbapenems were initiated in 9% of IVAC without infection, 15% of IVAC related to non-VAP infections, 42% of IVAC related to non-ESBLE VAP, and 56% of IVAC related to ESBLE VAP (ESBLE VAP versus non-ESBLE VAP: $P = 0.43$).

Conclusions: IVAC in ESBLE carriers mostly reflect noninfectious events but act as a strong driver of empirical carbapenem consumption. ESBLE infections are scarce yet hard to predict, strengthening the need for novel diagnostic approaches and carbapenem-sparing alternatives.

Keywords: Extended-spectrum beta-lactamase, Mechanical ventilation, Ventilator-associated pneumonia, Carbapenem, Outcome

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Introduction

The prevalence of colonisation with extended-spectrum β-lactamase-producing Enterobacteriaceae (ESBLE) has reached critical levels in patients admitted to the intensive care unit (ICU) owing to the successful spread of these pathogens in both healthcare settings and community-based populations [1, 2]. Carriage being the main prerequisite for ICU-acquired ESBLE infections [3], current guidelines advocate considering the colonisation status to heighten the likelihood of adequate empirical coverage in patients with suspected nosocomial sepsis [4]. Yet, this approach results in an excess consumption of carbapenems that could hasten the dissemination of carbapenem-resistant Gram-negative bacteria in the hospital environment [5–8], making the prediction of ESBLE infections a pivotal component of carbapenem-sparing initiatives in identified carriers. This appears especially relevant for patients under mechanical ventilation (MV), with ventilator-associated pneumonia (VAP) accounting for most of suspected and confirmed ICU-acquired infections in this population [9, 10].

A novel algorithm for reporting ventilator-associated events was issued by the Centers for Disease Control and Prevention (CDC) in 2013 [11]. This includes (1) ventilator-associated conditions (VAC)—an episode of worsening oxygenation defined by an increase in required levels of positive-end expiratory pressure (PEEP) and/or FiO_2 for at least two calendar days following a period of stability or improvement, (2) infection-related ventilator-associated complications (IVAC)—that is, a subset of VAC with systemic inflammatory response elements suggestive of a new infection and triggering either the initiation of an antimicrobial regimen or the broadening of spectrum in patients already receiving antibiotics, and (3) VAP, which are defined according to this new classification as IVAC with clinical and/or microbiological arguments for pneumonia, regardless of chest radiograph patterns.

Our group and others have previously shown that IVAC are common in MV patients and may be associated with pulmonary or non-pulmonary infections as well as a large panel of sepsis-mimicking conditions not resulting from an infectious event [12–14]. However, the epidemiology and clinical significance of IVAC have not been specifically investigated in MV patients colonised with ESBLE. In this inception cohort study, we sought to appraise the causes of IVAC—with a focus on VAP and other ICU-acquired infections due to ESBLE—and their impact on carbapenem exposure in a multicentre population of critically ill ESBLE carriers.

The results of this work were partly presented at the 2017 annual conference of the European Society of Intensive Care Medicine (Vienna, Austria, 23–27 September 2017, abstract 0944) [15].

Take-home messages

IVAC in mechanically ventilated ESBLE carriers mostly reflect non-infectious events but act as a strong driver of empirical carbapenem consumption.

The lack of reliable predictor of ESBLE infections emphasises the need for novel diagnostic approaches and carbapenem-sparing therapeutic alternatives.

Patients and methods

Patient data source: the OUTCOMEREA prospective database

This observational study was conducted using a multicentre longitudinal database fuelled since November 1996 by 17 ICUs contributing to the OUTCOMEREA network. The methodology implemented for data collection and quality control has been described elsewhere [5]. Briefly, a minimum of 50 patients older than 16 years and with an ICU stay of more than 24 h are included every year by each participating ICU, which may enter into the database either all admitted patients or only a subset of them following a fixed algorithm that ensures random recruitment (e.g. all admissions in predefined rooms in a given ICU) (Table S1 in the Electronic Supplementary Material, ESM). Data are collected at admission (demographical characteristics, chronic diseases, admission features, baseline severity indexes, admission diagnosis and admission type), then exhaustively recorded on a daily basis throughout the ICU stay [clinical and biological parameters, assessment of organ functions, requirement for MV with levels of PEEP and FiO_2, invasive procedures other than MV, fluid challenges, in-hospital transport, iatrogenic events, carriage of multidrug-resistant pathogens, ICU-acquired infections, antibiotic exposure, length of stay (LOS), final diagnoses of the ICU stay, decision to withhold or withdraw life-sustaining therapies, and vital status at ICU and hospital discharge]. These data are prospectively entered into the database by ICU staff through an anonymised electronic case report form using the Vigirea, Rhea and e-Rhea software (OutcomeRea, Rosny-sous-Bois, France). The database protocol was submitted to the Institutional Review Board of the Clermont-Ferrand University hospital (Clermont-Ferrand, France), who waived the need for informed consent (IRB no. 5891). The OUTCOMEREA database has been registered at the Commission Nationale de l'Informatique et des Libertés (registration no. 8999262), in compliance with French law on electronic data sources.

Study population and definitions

Patients admitted between May 1997 and December 2015 were considered for enrolment in the study cohort. We included all ESBLE carriers receiving invasive MV for more than 2 days and with no ESBLE VAP before and at least one episode of IVAC after the documentation of colonisation. Intestinal carriage of ESBLE was universally screened in all participating units by rectal swabbing at ICU admission and weekly afterwards. ESBLE carriage was defined as a positive rectal swab, a positive urine culture without evidence of urinary tract infection or a positive superficial sample from a surgical wound. Of note, colonisation of the lower respiratory tract or the normal skin by multidrug-resistant pathogens—including ESBLE—is not routinely monitored in ICUs contributing to the OUTCOMEREA database. ESBLE carriage was deemed imported in patients with a first positive sample within 48 h following admission and acquired in the ICU in cases of negative admission samples. Patients were considered colonised from the first positive carriage sample to ICU discharge or death.

VAP was diagnosed using standard criteria [16], i.e. new or persistent pulmonary infiltrates on chest X-ray combined with purulent tracheal secretions and/or fever or hypothermia (body temperature greater ≥ 38.5 or ≤ 36.5 °C, respectively) and/or leukocytosis or leukopenia (white blood cells count $\geq 10 \times 10.9$ or $\leq 4 \times 10.9$/L, respectively). A definite diagnosis of VAP required microbiological confirmation by quantitative culture from a protected brush [≥ 10.3 colony-forming unit (CFU)/mL], plugged telescopic catheter (≥ 10.3 CFU/mL), bronchoalveolar lavage fluid (≥ 10.4 CFU/mL), or endotracheal aspirate (≥ 10.5 CFU/mL). Other ICU-acquired infections were diagnosed using standard criteria, with microbiological documentation for all cases.

IVAC episodes were retrospectively ascertained by applying the CDC's definition (see ESM) [11]. We reviewed each episode to identify those associated with VAP, other ICU-acquired infections and non-infectious events within 2 calendar days (i.e. from 8:00 a.m. to 8:00 a.m. the following day) before and after the onset of worsening oxygenation, except for transports and fluid challenges which were only screened within the 2 preceding days. When two non-VAP-associated IVAC occurred within 4 days or less, we only retained the first episode for analyses. Also, IVAC episodes occurring within 8 days after a VAP-associated IVAC were discarded. Lastly, in patients with more than five IVAC, only the first five IVAC were considered to exclude very late episodes in patients with extremely long MV duration. Selected episodes were pooled in four mutually exclusive groups according to causative events, namely IVAC without documented infection (including those only attributable to one or more non-infectious sepsis-mimicking events and those with no identifiable source of infection), non-VAP ICU-acquired infections (involving ESBLE and/or other pathogens), non-ESBLE VAP (with or without a concomitant non-VAP ESBLE infection), and ESBLE VAP.

Statistical analyses

Data are expressed as median [interquartile range (IQR)] for continuous variables and number (%) for categorical variables. Patient characteristics were compared using the Kruskal–Wallis test for continuous variables and the Fisher exact test or χ^2 test for categorical variables, as appropriate. Exposure to each antimicrobial class before and after IVAC episodes was compared across the four IVAC groups using the Cochran–Mantel–Haenzel exact test for categorical variables and Cochran–Mantel–Haenzel or Wilcoxon non-parametric tests for continuous variables, with stratification on episode ranks. For these comparisons, β-lactams were pooled according to the classification of Weiss et al. [17].

Factors associated with the identification of an ESBLE infection (VAP or other than VAP) as the causative event of IVAC were first investigated by univariate logistic regression analyses using a marginal model, with each episode being handled independently (generalised estimating equations accounting for unknown covariance structure between distinct episodes in a given patient). Variables yielding P values < 0.20 were then entered into a multiple logistic regression model for the measurement of odds ratios (OR) and 95% confidence intervals (CI), with a diagnosis of IVAC related to an ESBLE infection as the primary outcome. The same procedure was applied to identify factors associated with a diagnosis of ESBLE VAP as the causative event in VAP-related episodes of IVAC. The Akaike information criterion was used in both models to avoid over-fitting. Missing values were handled by single imputation.

All statistical analyses were carried out with SAS v.9.4 (SAS Institute, Cary, NC, USA). P values < 0.05 were considered significant.

Results

Study cohort

We included 318 ESBLE carriers in the study [median age, 67.8 (58.4–76.5) years; males, 66.7%; medical admission, 67.9%] (Fig. 1; Table 1). ESBLE carriage was imported in 169 patients (53.1%) and acquired in the ICU after a median ICU LOS of 11 [7–17] days in the remaining 149 patients (46.9%). *Escherichia coli* ($n = 118$, 37.1%), *Klebsiella pneumoniae* ($n = 70$, 22%) and *Enterobacter* spp. ($n = 43$, 13.5%) accounted for most of the carriage isolates of ESBLE.

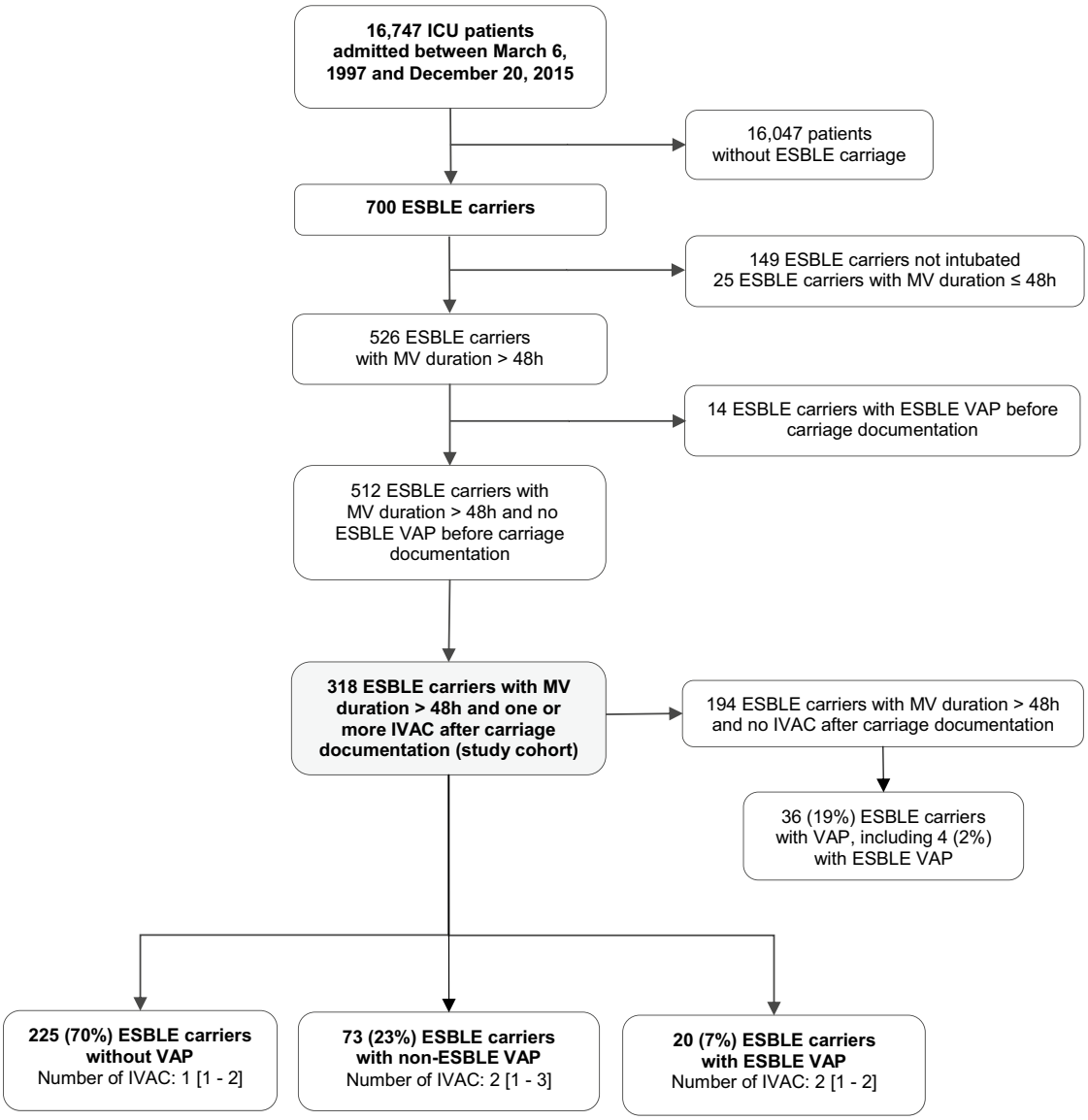

Fig. 1 Study flow-chart. Numbers of IVAC per patient categories are indicated as median [interquartile range]. *ICU* intensive care unit, *ESBLE* extended-spectrum β-lactamase-producing Enterobacteriaceae, *MV* mechanical ventilation, *IVAC* infection-related ventilator-associated complication, *VAP* ventilator-associated pneumonia

Description of IVAC episodes

A total of 576 episodes of IVAC were analysed. Among them, 361 episodes (62.7%) were not attributable to a documented ICU-acquired infection, 124 (21.5%) were related to one or more non-VAP ICU-acquired infections, 73 (12.7%) were related to a non-ESBLE VAP, and only 18 (3.1%) were related to an ESBLE VAP (Fig. 2; Table S2 in the ESM). Two or more underlying events were identified in 121 episodes (21%) (Table S2). Overall, only 43 episodes of IVAC (7.5%) were associated with one or more ICU-acquired ESBLE infections (VAP and/or infections other than VAP). Non-VAP ESBLE infections were catheter-related infections with or without bloodstream infection ($n=18$), non-catheter-related bloodstream infections ($n=12$) and surgical site infections ($n=18$).

The distribution of IVAC causes—including ESBLE infections—was neither significantly influenced by episode ranking nor by the number of days spent in the ICU since admission or carriage documentation (Table S2). Likewise, the causes of IVAC were similar between patients with imported and ICU-acquired carriage, as

Table 1 Characteristics of the 318 mechanically ventilated ESBLE carriers included in the study

Variable	Patients
Age, years	67.8 [58.4–76.5]
Sexe, male	212 (66.7)
Body mass index, kg/m^2	25.6 [21.8–28.8]
Chronic diseases	
Respiratory	57 (17.9)
Cardiac	44 (13.8)
Hepatic	14 (4.4)
Renal	23 (7.2)
Immunosuppression	62 (19.5)
Diabetes mellitus	66 (20.7)
MacCabe score	
0	164 (51.6)
1	116 (36.5)
2	38 (11.9)
Type of ICU stay	
Surgical, scheduled	27 (8.5)
Surgical, unscheduled	75 (23.6)
Medical	216 (67.9)
Type of ICU admission	
Direct (from the ED)	126 (39.6)
Transfer (from wards)	192 (60.4)
Hospital LOS before ICU admission, days	2 [1–13]
Reason for ICU admission	
Acute respiratory failure	79 (24.8)
Shock	112 (35.2)
Coma	43 (13.5)
Acute renal failure	12 (3.8)
Multi-organ failure	20 (6.3)
Miscellaneous	52 (16.4)
SOFA score at ICU admission	7 [4–10]
SAPS II at ICU admission	51 [40–64]
Type of ESBLE carriage	
Imported	169 (53.1)
Patients admitted from the ED	71 (22.3)
Patients transferred from wards	98 (30.8)
Acquired in the ICU	149 (46.9)
ICU LOS before carriage acquisition, days	11 [7–17]
Characteristics at the time of ESBLE colonisation[a]	
SOFA score	7 [4–10]
SAPS II	45 [34–55]
Invasive MV[b]	314 (98.7)
Vasopressors	184 (57.9)
Arterial line catheter	133 (41.8)
Central venous catheter	216 (67.9)
Renal replacement therapy	49 (15.4)
Urinary catheter	294 (92.4)
Proton-pump inhibitor	204 (64.1)
Enteral nutrition	181 (56.9)
Parenteral nutrition	91 (28.6)
Decision to withhold or withdraw life support	17 (5.3)
Prior CDAD	11 (3.4)
MRSA carriage	32 (10.1)
MDRPA carriage	11 (3.5)
AHE carriage	13 (4.1)
VAP after ESBLE colonisation	
None	225 (70.7)
Non-ESBLE VAP	73 (23.0)
ESBLE VAP	20 (6.3)
Outcome	
MV duration, days	19 [12–33]
ICU LOS, days	25 [14–42]
Hospital LOS after ICU discharge, days	35 [22–61]
Hospital LOS, overall, days	46.5 [26–75]
In-ICU death at day 28	58 (18.2)
In-ICU death, overall	105 (33.0)
In-hospital death, overall	134 (42.1)

Patient data are expressed as number (%) or median [interquartile range]

ESBLE extended-spectrum β-lactamase-producing Enterobacteriaceae, *ICU* intensive care unit, *ED* emergency department, *LOS* length of stay, *SOFA* sequential organ failure assessment, *SAPS II* simplified acute physiology score II, *MV* mechanical ventilation, *CDAD Clostridium difficile*-associated diarrhoea, *MRSA* methicillin-resistant *Staphylococcus aureus*, *MDRPA* multidrug-resistant *Pseudomonas aeruginosa*, *AHE* AmpC-hyperproducing Enterobacteriaceae, *VAP* ventilator-associated pneumonia

[a] Defined as the ICU day with the first carriage sample positive for ESBLE (see "Patients and methods" for details)

[b] Four patients were intubated after the documentation of ESBLE carriage

between those colonised with ESBL-producing *E. coli* and other ESBLE species (Tables S3 and S4, respectively).

Predictors of ESBLE infection as the causative event of IVAC

The characteristics of IVAC episodes related to an ESBLE infection (pooled, $n=43$) are compared to those of other episodes ($n=533$) in Table S5, with corresponding univariate OR. In the multivariable logistic regression model, the sole independent predictor of ESBLE infection was an exposure to carbapenems within the 3 days preceding the occurrence of IVAC, which exerted a protective effect (OR 0.2, 95% CI 0.05–0.6, $P<0.01$) (Table 2). This 3-day cut-off correlated with the significant variations that we observed in the frequency of carbapenem pre-exposure across the four IVAC sub-groups on the day preceding the occurrence of IVAC (that is, Day 1) but also from Day 3 to Day 2 before IVAC (Table 3). It is noteworthy that a recent exposure to non-anti-pseudomonal third-generation cephalosporins was not an independent predictor of ESBLE infection (Table S6).

A total of 120 VAP were diagnosed in 93 patients, including 24 ESBLE VAP (20%) in 20 patients (Table S7). In the subset of VAP-related IVAC, no independent

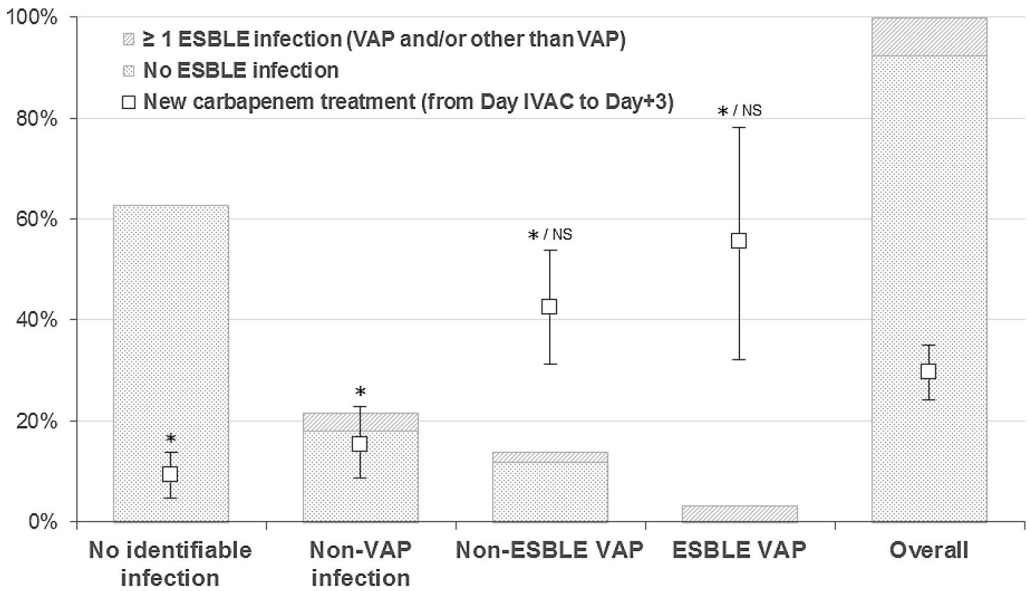

Fig. 2 Causes of IVAC, proportion of episodes attributable to one or more ICU-acquired ESBLE infections and initiation of carbapenem therapy in mechanically ventilated ESBLE carriers. *IVAC* infection-related ventilator-associated complication, *ICU* intensive care unit, *ESBLE* extended-spectrum β-lactamase-producing Enterobacteriaceae, *VAP* ventilator-associated pneumonia, *NS* non-significant. The rates of new carbapenem treatments are indicated as measured values and 95% confidence intervals. *$P < 0.001$ for overall comparison between the four causal groups (no significant difference between non-ESBLE VAP and ESBLE VAP, $P = 0.43$)

Table 2 Factors associated with an ESBLE infection as the causative event of IVAC: multivariable logistic regression model

Variable	Adjusted OR [95% CI]	*P* value
MacCabe score		0.13
0	1 (Ref)	
1	1.7 [0.81–3.72]	
2	3.4 [1.24–9.07]	
SAPS II at ICU admission, per point increase	1 [0.98–1.03]	0.55
Glasgow coma scale ≤ 9 at Day 1 before IVAC	0.2 [0.05–1.12]	0.07
ICU LOS before IVAC		0.20
< 13 days	1 (Ref)	
13–25 days	0.5 [0.22–1.09]	
> 25 days	0.6 [0.26–1.21]	
Aminoglycoside exposure from Day 3 to IVAC Day	0.4 [0.12–1.51]	0.11
Ureido-/carboxy-penicillin and/or 3GC exposure from Day 3 to IVAC Day	1.6 [0.75–3.36]	0.25
Carbapenem exposure from Day 3 to IVAC Day	0.2 [0.05–0.6]	< 0.01

Variables entered in the multivariable model (first step) were MacCabe score, hospital LOS before ICU admission, SASPS II and SOFA score at ICU admission, one or more previous IVAC before the considered episode, ICU LOS before IVAC, hepatic and neurological SOFA scores on the day preceding IVAC, and exposure to ureidopenicillins, carboxypenicillins, third-generation cephalosporins, carbapenems, aminoglycosides and metronidazole before IVAC (see Table S5 for the full results of univariate analyses)

ESBLE extended-spectrum β-lactamase-producing Enterobacteriaceae, *IVAC* infection-related ventilator-associated complication, *OR* odds ratio, *CI* confidence interval, *SAPS II* simplified acute physiological score II, *ICU* intensive care unit, *3GC* third-generation cephalosporins, *LOS* length of stay

Table 3 Associations between IVAC and carbapenem exposure according to causative events in mechanically ventilated ESBLE carriers

Variable	Causes of IVAC				*P* value[c,d]
	No documented infection (*n* = 361)	Non-VAP infections[a] (*n* = 124)	Non-ESBLE VAP[b] (*n* = 73)	ESBLE VAP (*n* = 18)	
Day 14 to Day 7 before IVAC					
Treated patient	185 (51.2)	50 (40.3)	31 (42.5)	6 (33.3)	0.08/0.69
Duration, days	1 [0–5]	0 [0–4]	0 [0–5]	0 [0–2]	0.17/0.89
Day 6 to Day 4 before IVAC					
Treated patients	148 (41)	40 (32.3)	24 (32.9)	5 (27.8)	0.19/0.81
Duration, days	0 [0–3]	0 [0–2]	0 [0–2]	0 [0–1]	0.11/0.74
Day 3 to Day 2 before IVAC					
Treated patients	124 (34.3)	32 (25.8)	17 (23.3)	1 (5.6)	0.01/0/10
Duration, days	0 [0–2]	0 [0–1]	0 [0–0]	0 [0–0]	< 0.01/0.09
Day 1 before IVAC					
Treated patients	103 (28.5)	25 (20.2)	15 (20.5)	0	0.01/0.03
IVAC Day to Day + 3					
Treatment discontinuation	9 (2.5)	1 (0.8)	1 (1.4)	0	< 0.01/1.00
Treatment continuation	94 (26)	22 (17.7)	12 (16.4)	0	0.01/0.11
New treatment	34 (9.4)	19 (15.3)	31 (42.5)	10 (55.6)	< 0.01/0.43
Duration, days	0 [0–2]	0 [0–2]	1 [0–3]	1.5 [0–3]	< 0.01/0.93
IVAC Day to Day + 7					
Treated patients	125 (34.6)	50 (40.3)	46 (63)	14 (77.8)	< 0.01/0.42
Duration, days	0 [0–2]	0 [0–3]	2 [0–5]	3.5 [1–6]	< 0.01/0.30
IVAC Day to Day + 14					
Treated patients	130 (36)	53 (42.7)	47 (64.4)	14 (77.8)	< 0.01/0.51
Duration, days	0 [0–3]	0 [0–4]	2 [0–7]	6 [1–9]	< 0.01/0.16

Data are expressed as number (%) or median [interquartile range]

IVAC infection-related ventilator-associated complication, *ESBLE* extended-spectrum β-lactamase-producing Enterobacteriaceae, *VAP* ventilator-associated pneumonia

[a] Including 20 non-VAP ESBLE infections

[b] Including five episodes with a concomitant non-VAP ESBLE infection

[c] Global comparison

[d] ESBLE-VAP versus non-ESBLE VAP comparison

predictor of ESBLE VAP could be identified by multivariable logistic regression analysis (Tables S8 and S9).

Correlation between IVAC and antimicrobial exposure

Overall, a new carbapenem-based antimicrobial regimen was started in 94 episodes of IVAC (29.6%) (Table 3). Of note, the empirical use of carbapenems was as frequent in episodes related to an ESBLE VAP as in those resulting from a non-ESBLE VAP (42.5 vs. 55.6%, respectively, $P = 0.43$). By contrast, an antipseudomonal β-lactam other than a carbapenem (i.e. either cefepime, ceftazidime, aztreonam, ticarcillin-clavulanate or piperacillin-tazobactam) was initiated in only 32 episodes of IVAC (5.5%) (Table S10).

Outcomes

The proportion of patients who died during the episode (overall 18%) and the median subsequent duration of MV [overall, 3 (6–10) days] were higher in VAP-related IVAC than in those with other causes but were similar for IVAC due ESBLE VAP and those due to non-ESBLE VAP (Table S11). Overall in-ICU and in-hospital mortality rates were 33 and 42.1%, respectively (Table 1).

Discussion

In this multicentre cohort of mechanically ventilated ESBLE carriers, a restricted proportion of IVAC (7.5%) resulted from an ICU-acquired ESBLE infection, with

VAP accounting for only 3.1% of episodes. No independent predictor of such infections could be identified except the protective effect of a recent or concurrent carbapenem exposure. Strikingly, the empirical initiation of a carbapenem-based regimen was common in IVAC not involving ESBLE.

The prevalence of colonisation with ESBLE is rising steadily in critically ill patients owing to a continuous influx from both community and healthcare ecosystems, with carriage rates at admission currently above 10% in most of ICUs [18–20]. This results in an increase in colonisation pressure that may favour subsequent cross-transmission and acquisition during the ICU stay [18, 21–23]. Hence, managing an ESBLE carrier with a suspicion of nosocomial infection has become a daily challenge for many intensivists worldwide. ESBLE infections are associated with a high likelihood of inadequate empirical coverage that translates into lower survival rates and extended hospital stays when compared to patients infected with broad-spectrum cephalosporins-susceptible Enterobacteriaceae [5, 24–26]. Yet, while negative surveillance samples have a high negative predictive value for ICU-acquired ESBLE infections, the incidence of such infections appears relatively weak in documented carriers (that is, from 10 to 25%), including in those receiving MV [5, 7, 20, 27, 29]. In this work, we attempted an original approach by investigating the clinical significance of IVAC rather than focussing on documented infections in this population. Albeit the accuracy of IVAC as a screening step for VAP remains controversial [16, 28], its definition that combines worsening oxygenation and systemic signs suggestive of a new infection depicts a pragmatic and frequent situation in intubated patients. Our findings indicate that, similarly to what has been reported in the general population of MV patients [12, 13], the occurrence of IVAC in ESBLE carriers correlates with a wide range of healthcare-associated infections as well as non-infectious events, and exerts a cause-dependent prognostic impact, VAP-related IVAC being associated with a worst outcome in terms of subsequent MV duration and short-term mortality than other episodes. More importantly, IVAC secondary to an ESBLE infection were scarce, while most VAP-related episodes implicated pathogens other than ESBLE. These data shed light on the complexity of rationalising the empirical use of carbapenems in ventilated ESBLE carriers when a condition compatible with VAP arises.

Predicting ESBLE infections is pivotal for the fine-tuning of initial therapy in known carriers. The few single-centre studies that addressed this issue yielded conflicting results, notably on the prognostic weight of ESBLE species or prior antimicrobial use [7, 29]. In the present cohort, a carbapenem exposure during the 3 preceding days was the sole feature independently associated with an ESBLE infection as the underlying event of IVAC, with an expected protective effect. We failed to demonstrate any significant association with other potential relevant predictors such as episode rank, invasive procedures, recent exposure to non-carbapenem antimicrobials [particularly β-lactam/β-lactamase inhibitor (BL–BLI) combinations and fluoroquinolones], colonisation with ESBL-producing *E. coli* versus other ESBLE or imported versus ICU-acquired carriage. Likewise, no independent relationship could be identified when tracking risk factors for ESBLE VAP in the subset of VAP-related IVAC. Thus, no reliable algorithm could be proposed to exclude an ESBLE infection and help restraining the empirical use of carbapenems when IVAC occurs in a documented carrier not recently exposed to this antimicrobial class.

Carbapenems remain the first-line regimen when a severe ESBLE infection is suspected [1, 4, 8]. Here, we observed that these agents were routinely introduced during IVAC not related to an ESBLE infection, especially non-ESBLE VAP. This excessive empirical consumption could lead to deleterious ecological side effects and promote the dissemination of carbapenem-resistant Gram-negative pathogens, at the carrier level as at the hospital scale [6, 7, 30]. Various antimicrobial stewardship initiatives may contribute to reduce the use of these antibiotics. Rapid diagnostic tools, such as direct susceptibility testing or point-of-care molecular assays on clinical samples, stand as promising strategies to narrow the empirical spectrum or allow earlier de-escalation in colonised patients [31–33]. Also, a link between the faecal relative abundance of ESBLE and the hazard of subsequent infection has been described in non-ICU patients and warrants further investigations in the specific context of critical illness [34]. In addition, efforts have recently been made to assess the safety of certain BL–BLI combinations as carbapenem-sparing alternatives for both the empirical and definite therapy of ESBLE infections [35]. Evidence has notably emerged to support a role for piperacillin-tazobactam provided that pharmacokinetic parameters are optimised with high-dose regimen and continuous or extended infusion [36, 37]. However, in our work, a recent piperacillin-tazobactam exposure did not protect carriers from ESBLE infections, including VAP. Convincing data are still lacking to appraise the yield of this combination for the initial therapy of severe ESBLE pneumonia [38]. Along this line, new BL–BLI combinations such as ceftolozane-tazobactam and ceftazidime-avibactam have been mainly evaluated in the treatment of complicated UTI or intra-abdominal infections but currently emerge as potential options for the treatment of hospital-acquired pneumonia due to ESBLE, including VAP [39, 40].

Strengths of this study include its multicentre design that minimises the potential influence of local outbreaks on our results, the large number of included patients, the exploitation of prospectively collected data and the use of accurate statistical methods to address its endpoints. Our work also has limitations that deserve to be underlined. First, we did not address the ecological impact of carbapenem misuse in IVAC unrelated to ESBLE infections. Second, the empirical regimens initiated during IVAC were not compared to those of a matched cohort of MV patients not colonised with ESBLE. Third, we did not investigate the potential impact of lower airways colonisation with ESBLE on the causes of IVAC since respiratory surveillance cultures were not routinely performed in participating ICUs. Fourth, all ICU-acquired infections were microbiologically documented, with strict application of validated culture thresholds for the diagnosis of VAP. Hence, we cannot firmly exclude that certain IVAC related to ICU-acquired infections were misclassified as not resulting from an infectious event in patients already receiving appropriate antimicrobial therapy when microbiological samples were collected, thereby over-estimating the protective effect of carbapenem pre-exposure regarding ESBLE infections. Lastly, it remains to be confirmed whether our results may be extrapolated to other critical care environments with distinct colonisation patterns, policies for empirical antimicrobial use and proportion of surgical patients.

In conclusion, the occurrence of IVAC in ESBLE carriers acts as a strong driver of empirical carbapenem use although most of episodes reflect events not resulting from a documented infection and are unrelated to the colonisation status. ESBLE infections appear scarce yet hardly predictable using standard clinical criteria. This study emphasises the global need for novel diagnostic approaches and the validation of carbapenem-sparing empirical regimen in this patient population.

Electronic supplementary material

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Conflict of interest

All authors declare that they have no conflict of interest relative to the present study.

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