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Short Communication

Use of non-carbapenem antibiotics to treat severe extended-spectrum β-lactamase-producing Enterobacteriaceae infections in intensive care unit patients

Charles-Edouard Luyt[a,b,*], Morgane Faure[c], Isabelle Bonnet[d,e], Sébastien Besset[a], Florent Huang[a], Helga Junot[f], Guillaume Hékimian[a], Matthieu Schmidt[a,b], Nicolas Bréchot[a,b], Alain Combes[a,b], Alexandra Aubry[d,e], Julien Mayaux[c], Jean Chastre[a]

[a] Service de Réanimation, Institut de Cardiologie, Groupe Hospitalier Pitié–Salpêtrière, Assistance Publique–Hôpitaux de Paris, Paris, France
[b] Sorbonne Universités, UPMC Université Paris 06, INSERM, UMRS_1166-ICAN Institute of Cardiometabolism and Nutrition, Paris, France
[c] Service de Pneumologie et Réanimation Médicale, Groupe Hospitalier Pitié–Salpêtrière, Assistance Publique–Hôpitaux de Paris, Paris, France
[d] Service de Bactériologie-Hygiène, Groupe Hospitalier Pitié–Salpêtrière, Assistance Publique–Hôpitaux de Paris, Paris, France
[e] Sorbonne Université, INSERM, U1135, Centre d'Immunologie et des Maladies Infectieuses, Cimi-Paris, équipe 13, F-75013, Paris, France
[f] Service de Pharmacie, Groupe Hospitalier Pitié–Salpêtrière, Assistance Publique–Hôpitaux de Paris, Paris, France

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ABSTRACT

Objectives: The aim of this study was to evaluate the use of non-carbapenem antibiotics to treat severe extended-spectrum β-lactamase-producing Enterobacteriaceae (ESBL-E) infections in intensive care unit (ICU) patients.
Methods: This retrospective observational study conducted in two ICUs compared the outcomes of patients with ESBL-E infections administered a carbapenem or a non-carbapenem antibiotic as their definitive treatment. The primary outcome was treatment failure within 30 days, a composite endpoint of ESBL-E infection recurrence and 30-day mortality. Secondary outcomes included 30-day and in-hospital mortality rates, ESBL-E infection recurrence and infection(s) due to other pathogen(s).
Results: Among 107 patients included in the study, 67 received a carbapenem and 40 received a non-carbapenem antibiotic as their definitive treatment. Clinical characteristics of the two groups were similar. Comparing patients given a non-carbapenem antibiotic with those administered a carbapenem, they had similar 30-day treatment failure (43% vs. 61%, respectively; $P = 0.06$) and ESBL-E infection recurrence rates (25% vs. 22%; $P = 0.8$), but the former had lower 30-day mortality (23% vs. 45%; $P = 0.02$) and in-hospital mortality rates (23% vs. 49%; $P = 0.005$). Secondary infection rates caused by other pathogen(s), including *Clostridium difficile*, were comparable. Outcomes were comparable regardless of whether or not patients received an empirical carbapenem.
Conclusion: For ICU patients with severe ESBL-E infections, treatment with a non-carbapenem antibiotic was not associated with poorer outcomes compared with a carbapenem antibiotic.

1. Introduction

Relatively recently, non-carbapenem antibiotics [i.e. β-lactam/β-lactamase inhibitors (BL/BLIs), cefepime and fluoroquinolones] have begun to be used to treat patients with extended-spectrum β-lactamase-producing Enterobacteriaceae (ESBL-E) infections [1]. Among possible non-carbapenem agents, piperacillin/tazobactam (TZP) is the most widely used [2,3], however data on cefepime [4,5] and fluoroquinolones [6,7] are also available. Although the results of observational studies were good, they were sometimes negative [8]. The more recent MERINO trial results advocated against the use of TZP to treat infections caused by third-generation cephalosporin-resistant *Escherichia coli* or *Klebsiella* spp. [9]. Two recent meta-analyses that did not include the MERINO trial concluded that BL/BLIs may be promising alternative antibiotics for definitive therapy in patients with ESBL-E infections [10,11].

However, most of these data, despite coming from large series [3,7], included small numbers of the most severely ill patients,

* Corresponding author. Present address: Service de Réanimation, ICAN, Groupe Hospitalier Pitié–Salpêtrière, 47–83 boulevard de l'Hôpital, 75651 Paris Cedex 13, France. Tel.: +33 1 42 16 38 24; fax: +33 1 42 16 38 17.
E-mail address: charles-edouard.luyt@aphp.fr (C.-E. Luyt).

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i.e. those hospitalised in the intensive care unit (ICU). Given the scarcity of ICU patient data and contradictory findings across studies, recent reviews raise concern, or at least recommend caution, when using non-carbapenem antibiotics to treat ESBL-E infections in ICU patients [12,13].

Therefore, this study was undertaken to evaluate the impact of administering non-carbapenem antibiotics to treat severe ESBL-E infections in ICU patients.

2. Materials and methods

All patients admitted to the two medical ICUs of Pitié–Salpêtrière Hospital (Paris, France) in 2016 and 2017 with severe ESBL-E infection (i.e. sepsis or septic shock requiring ICU admission or occurring during ICU stay) were retrospectively included in this study. Information on medical history as well as clinical and biological parameters at ICU admission and during ICU stay was collected retrospectively. The source of infection and antimicrobial treatment (dose and duration) were also recorded. Patients requiring prolonged antimicrobial treatment (i.e. for bone and joint infection, endocarditis) and those without severe infection (i.e. without sepsis [14]) were not included.

2.1. Definitions

Empirical therapy was defined as antibiotic(s) given between sampling and microbiological results. Empirical therapy was considered adequate when the patient received at least one antibiotic (including an aminoglycoside or fluoroquinolone) active against the responsible pathogen. Definitive treatment was defined as antibiotic(s) given after susceptibility test results were obtained.

According to their definitive antibiotic regimen, patients were categorised into one of the following two groups: carbapenem-definitive, when a carbapenem was definitively prescribed; and alternative-definitive, when a non-carbapenem antibiotic was definitively prescribed. Details regarding the non-carbapenem antibiotics and their respective dosing are available in the Supplementary material. Patients were considered immunocompromised when they fulfilled one of the following criteria: received prednisone $\geq$0.5 mg/kg for $>$1 month; had received a solid-organ transplantation; were taking an immunosuppressant (cyclosporine, mycophenolate mofetil, etc.); received a haematopoietic stem cell transplantation during the preceding year; had ongoing cancer or received cancer chemotherapy within 6 months; or had human immunodeficiency virus (HIV) with $\leq$200 CD4 cells/μL.

Sepsis and septic shock were defined according to the recent Sepsis-3 definitions [14].

2.2. Outcome measures

The primary outcome was treatment failure at 30 days, a composite endpoint of ESBL-E infection recurrence and 30-day mortality. Infection recurrence was defined as a new infectious episode due to ESBL-E (same strain as first episode or another strain) until Day 30.

Secondary outcome measures were mortality rates (30-day and in-hospital mortality), ESBL-E infection recurrence within 30 days, and infection with other pathogen(s) during the 30 days following the first infection onset, especially *Clostridium difficile*.

Patients receiving a carbapenem were compared with those receiving a non-carbapenem antimicrobial agent.

2.3. Statistical analyses

Data are expressed as the median (interquartile range) or mean $\pm$ standard deviation as appropriate. Between-group comparisons were analysed using Student's *t*-test, Mann–Whitney *U*-test or Kruskal–Wallis test for continuous variables and the χ^2 test for categorical variables. A Cox analysis was used to determine the univariable association of patients' clinical characteristics or ICU events and treatment failure. Thereafter, multivariable Cox regression models using backward stepwise variable elimination (with the variable exit threshold set at $P > 0.05$) compared factors that were significant ($P \leq 0.10$) in the univariable analyses and those previously reported to be strongly associated with treatment failure. Interactions were tested in the model; variables strongly associated with other(s) were not included in the multivariable model. For univariable and multivariable analyses, continuous variables were dichotomised according to their median values. To confirm the results obtained in the multivariable analysis, logistic regression models were again used with propensity score adjustments to balance independent risk factors for treatment failure between patient groups. Propensity scores were derived from predicted probabilities in logistic regression models of carbapenem compared with non-carbapenem treatment. The final model contained the following variables and strongly correlated with carbapenem treatment: age $>$57 years; Sequential Organ Failure Assessment (SOFA) score at infection onset $>$10; and infection due to *E. coli* (versus other Enterobacteriaceae). All analyses were performed using StatView 5.0 (SAS Institute, Cary, NC).

2.4. Ethical approval

In accordance with current French law, and as confirmed by the Ethics Committee of the Société de Réanimation de Langue Française, informed consent for demographic, physiological and hospital outcome data analyses was not obtained because this observational study did not modify existing diagnostic or therapeutic strategies. None the less, patients and/or relatives were informed about the anonymous data collection and were told that they could decline inclusion. This database is registered with the Commission Nationale l'Informatique et des Libertés (CNIL registration no. 1950673).

3. Results

During the study period, 118 patients developed an ESBL-E infection in the two participating ICUs. Eleven patients were excluded, including eight with infections without sepsis and three with postoperative mediastinitis requiring prolonged antibiotics (Supplementary Fig. S1).

The clinical characteristics of the patients are described in Table 1. Among the 107 patients, 70 received an empirical carbapenem and 37 received empirical non-carbapenem antibiotics. The empirical non-carbapenem antibiotics included TZP for 22 patients (59%), an antipseudomonal third-generation cephalosporin for 12 patients (32%) and a third-generation cephalosporin (cefotaxime or ceftriaxone) for 3 patients (8%). Of the 107 patients, 73 (68%) received a companion antibiotic, comprising 50/70 (71%) with an empirical carbapenem and 23/37 (62%) with an empirical non-carbapenem antibiotic ($P = 0.3$ for between-group comparison).

3.1. Definitive treatment

Among the 70 patients administered an empirical carbapenem, a carbapenem was pursued in 46 patients and was switched to another non-carbapenem antibiotic in 24 patients (Supplementary Fig. S1). Among the 37 patients administered an empirical non-carbapenem agent, it was switched to a carbapenem in 21 patients, whereas a non-carbapenem was instituted or continued for 16 patients.

Table 1
Patient characteristics and treatment details according to definitive antimicrobial treatment.[a]

Characteristic	Overall population ($N = 107$)	Carbapenem group[b] ($N = 67$)	Alternative group[c] ($N = 40$)
Age (years)	58 (52–64)	57 (51–62)	61 (53–68)
Male sex	74 (69)	48 (72)	26 (65)
Reason for ICU admission			
Cardiogenic shock	31 (29)	18 (27)	13 (33)
Septic shock	21 (20)	13 (19)	8 (20)
Acute respiratory failure	29 (27)	22 (33)	7 (18)
Postoperative respiratory failure	15 (14)	8 (12)	7 (18)
Cardiac arrest	5 (5)	3 (4)	2 (5)
Neurological	2 (2)	1 (1)	1 (3)
Miscellaneous	4 (4)	2 (3)	2 (5)
Immunocompromised	43 (40)	28 (42)	15 (38)
SAPS II score at admission	59 (43–75)	60 (43–72)	55 (46–79)
SOFA score at admission	11 (6–15)	11 (6–15)	12 (7–14)
Source of infection			
Pneumonia[d]	73 (68)	48 (72)	25 (63)
Blood	23 (21)	12 (18)	11 (28)
Urinary tract[e]	6 (6)	4 (6)	2 (5)
Cellulitis around ECMO cannula	4 (4)	2 (3)	2 (5)
Cholangitis	1 (1)	1 (1)	0
Nosocomial infection	99 (93)	64 (96)	35 (88)
At infection onset			
Organ/system failure[f]			
Cardiovascular	73 (68)	43 (64)	30 (75)
Respiratory	67 (63)	40 (60)	27 (68)
Renal	46 (43)	27 (40)	19 (48)
Central nervous	24 (22)	12 (18)	12 (30)
Hepatic	12 (11)	8 (12)	4 (10)
Coagulation	17 (16)	11 (16)	6 (15)
Clinical and biological presentation			
Temperature (°C)	37.4 (36.9–38.2)	37.5 (37–38.2)	37.3 (36.8–38.1)
WBC count ($\times 10^9$ cells/L)	13.2 (8.1–20.1)	12.6 (8.8–19.6)	13.8 (7.6–20.3)
Procalcitonin level (ng/mL)[g]	2.21 (0.69–7.28)	2.11 (0.6–7.94)	2.57 (1.30–5.97)
SOFA score	10 (7–14)	9 (6–14)	12 (8–15)
Septic shock	70 (65)	42 (63)	28 (70)
Sepsis	37 (35)	25 (37)	12 (30)
Interventions			
Mechanical ventilation	86 (80)	53 (79)	33 (83)
Renal replacement therapy	43 (40)	25 (37)	18 (45)
Catecholamine use	73 (68)	43 (64)	30 (75)
Treatment details			
Inappropriate initial antimicrobial treatment	11 (10)	7 (10)	4 (10)
Companion antibiotic[h]	73 (68)	43 (64)	30 (75)
Duration of antimicrobial treatment	8 (7–11)	8 (6–11)	9 (7–11)
Duration of carbapenem treatment[i]	5 (3–9)	7 (5–10)	2 (0–5)

ICU, intensive care unit; SAPS, Simplified Acute Physiology Score; SOFA, Sequential Organ Failure Assessment; ECMO, extracorporeal membrane oxygenation; WBC, white blood cell.
[a] Data are expressed as *n* (%) or median (interquartile range).
[b] Patients received a carbapenem as definitive treatment, regardless of empirical treatment.
[c] Patients received a non-carbapenem agent as definitive treatment, regardless of empirical treatment.
[d] Seven of whom had positive blood cultures (two in the alternative-definitive group and five in the carbapenem-definitive group).
[e] One in the carbapenem-definitive group had a positive blood culture.
[f] Organ/system failure was deemed present when the corresponding SOFA score was >2.
[g] Data were missing for 18 patients (13 in the carbapenem-definitive group and 5 in the alternative-definitive group).
[h] During the first 48 h of antimicrobial treatment (aminoglycosides for 72 patients and ciprofloxacin for 1 patient).
[i] $P < 0.0001$ for between-group comparison.

Finally, 67 patients comprised the carbapenem-definitive group and 40 patients comprised the alternative-definitive group. Definitive treatment for the 40 patients in the alternative-definitive group was TZP in 24 patients (60%), ceftazidime/avibactam in 7 patients (18%), temocillin in 3 patients (8%), cefepime in 2 patients (5%) and ciprofloxacin in 4 patients (10%). Among 67 patients in the carbapenem-definitive group, an alternative was deemed possible but was not given because the treating physician(s) estimated that a carbapenem would be better than the alternative in 18 patients (27%). Characteristics of the two groups as well as details on antimicrobial treatments are reported in Table 1, and the pathogens responsible for infection are reported in Supplementary Table S1. The two groups were comparable, except for the duration of therapy for carbapenems which was shorter than that of alternative antibiotics.

3.2. Outcomes according to treatment group

Outcomes according to the definitive treatment group are given in Table 2. Treatment failure rates were comparable between the groups. Fig. 1 shows the time to treatment failure for the two groups. Whilst ESBL-E infection recurrence rates and secondary non-ESBL-producing pathogen infection rates were similar between groups, the carbapenem-definitive group experienced significantly higher 30-day and in-hospital mortality. The SOFA scores from Day 1 (infection onset) to Day 14 were similar between groups (Supplementary Fig. S2). Apart from patients who died before the end of antimicrobial treatment, no patients had no response to therapy during the antimicrobial course.

Taking into account empirical and definitive treatments, the results were comparable: regardless of the treatment administered,

Table 2
Patient outcomes according to definitive antimicrobial treatment group.[a]

30-day outcome	Overall population ($N = 107$)	Carbapenem group[b] ($N = 67$)	Alternative group[c] ($N = 40$)	*P*-value
Primary outcome				
Treatment failure	58 (54)	41 (61)	17 (43)	0.06
Secondary outcomes				
Mortality	39 (36)	30 (45)	9 (23)	0.02
ESBL-E infection recurrence	25 (23)	15 (22)	10 (25)	0.8
Other secondary infection[d]	30 (28)	18 (27)	12 (30)	0.7
Clostridium difficile infection	2 (2)	2 (3)	0	0.9
In-hospital mortality	42 (39)	33 (49)	9 (23)	0.005

ESBL, extended-spectrum β-lactamase-producing Enterobacteriaceae.
[a] Data are expressed as *n* (%).
[b] Patients received carbapenem as definitive treatment, regardless of empirical treatment.
[c] Patients received a non-carbapenem agent as definitive treatment, regardless of empirical treatment.
[d] Infection due to a non-ESBL-producing pathogen occurring before Day 30.

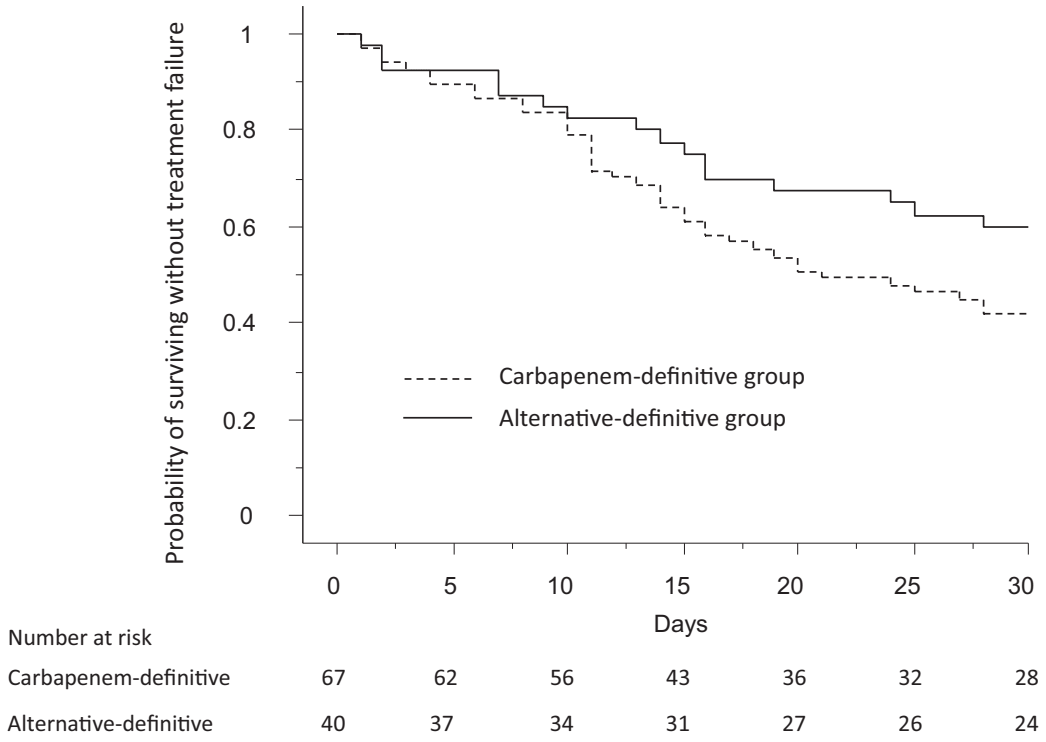

Fig. 1. Kaplan–Meier probability of survival without treatment failure according to the definitive antibiotic treatment group. $P = 0.09$, log-rank test for between-group comparison.

and outcomes were similar across groups (see Supplementary Table S6).

3.3. Multivariable analyses of factors associated with treatment failure

Factors associated with treatment failure identified by Cox univariable and multivariable analyses are reported in Supplementary Table S2. Whereas age >57 years, admission Simplified Acute Physiology Score (SAPS) II score >58 and baseline SOFA score >10 were positively associated with treatment failure, alternative-definitive administration and duration of treatment >8 days protected against treatment failure. Use of propensity score adjustments revealed no substantial differences compared with traditional multivariable analyses: the adjusted hazard ratio for treatment failure among patients treated with a non-carbapenem antimicrobial agent as their definitive treatment compared with a carbapenem agent was 0.5 (95% confidence interval 0.3–0.9).

4. Discussion

According to the results of this retrospective, multicentre cohort study, ICU patients with severe ESBL-E infection given non-carbapenem alternative-definitive treatment had treatment failure rates similar to those prescribed a carbapenem. Importantly, prescribing non-carbapenems to treat severe ESBL-E infections was not associated with higher infection recurrence or other infection rates (e.g. non-ESBL-producing pathogen, including *C. difficile*). Intriguingly, although non-carbapenem-treated patients appeared more ill, with higher SOFA scores and organ failure at infection onset than those given a carbapenem, their ICU- and in-hospital mortality rates were lower.

The efficacy of non-carbapenem agents to treat ESBL-E infections has been evaluated in many observational studies, yielded conflicting results. Most of them assessed BL/BLIs and showed that they were not associated with increased mortality compared with carbapenems [1–3,15,16]. However, other studies found dif-

ferent outcomes: in a large study of 213 patients, Tamma et al. reported that the 14-day and 30-day mortality rates of patients given BL/BLIs were higher than those administered a carbapenem (17% vs. 8% and 26% vs. 11%, respectively) [8]. Moreover, although that study included the largest number of ICU patients, no patients received BL/BLI extended-infusion therapy, which could have yielded poorer outcomes [17,18]. A recent randomised controlled trial compared TZP, cefepime and ertapenem for ESBL-producing *E. coli* urinary tract infections (UTIs) once susceptibility test results were available [19]. Assignment to receive cefepime was stopped after six patients were randomised because of the high treatment failure rate. Among the 66 patients randomised to receive TZP or ertapenem (33 per group), the clinical and microbiological success rates and 28-day mortality were similar. Recent MERINO trial results advocated against TZP use because, based on 378 patients with third-generation cephalosporin-resistant Enterobacteriaceae from nine countries, the 30-day mortality was higher for patients randomised to receive TZP compared with meropenem [23/187 (12.3%) vs. 7/191 (3.7%), respectively] [9]. Lastly, two recent meta-analyses concluded that BL/BLIs may be promising alternative antibiotics for definitive therapy in patients with ESBL-E infections [10,11]; however they did not include the results of the MERINO trial.

Using cefepime as a carbapenem-sparing agent to treat ESBL-E infection is more controversial [19,20]. A recent review summarised the main observational studies comparing cefepime or BL/BLIs to carbapenems to treat ESBL-E infections [12]; based on that analysis, the authors suggested that cefepime or BL/BLIs are potential alternatives for patients with mild-to-moderate 'low-inoculum' infections, but carbapenems should be prescribed preferentially, at least initially, for ICU patients, high bacterial load infections or elevated β-lactam minimum inhibitory concentrations (MICs) [12].

In those studies, the most severely ill patients, i.e. those with septic shock requiring ICU admission, were not or were inadequately studied. To the best of our knowledge, this particular population has not been the focus of previous studies. The patients described herein were severely ill ICU patients; 40% were immunocompromised, 65% were in septic shock when the infection started, and they were in poor general condition as assessed by their high SOFA scores at infection onset and the high 30-day and in-hospital mortality rates (36% and 39%, respectively). Notably, patients switched to a non-carbapenem (de-escalation group) were more severely ill (with a trend towards higher SOFA score and more frequently requirement for renal replacement therapy and catecholamines than others, especially patients receiving a carbapenem for their total treatment duration), but their outcomes were similar. However, because of the retrospective design of the current study, these findings should be interpreted with caution. Indeed, 18 patients received a carbapenem even though the infection-causing pathogen was susceptible to at least one non-carbapenem. Although we were unable to find any difference between these patients and those having received a non-carbapenem, it is possible that the treating physician(s) avoided de-escalation because they thought the patients were too severely ill (i.e. they had septic shock or several organ failure) to receive a non-carbapenem. Because experienced medical intuition and judgement may be better than scores, we cannot exclude that these patients were indeed more severely ill than those who received a non-carbapenem, which could have biased the results.

The difference between the current results and those of the MERINO trial [9] could be explained by the case mix and context: first, the study populations are different, with patients in the current study having severe infection and 65% having septic shock. Second, the infection origins and responsible pathogens differed markedly, as the MERINO trial enrolled a large proportion of patients with predominantly *E. coli* UTI. Third, the duration of TZP infusion in the MERINO trial (i.e. over 30 min) may not be optimal for severe infection [17,18]. Fourth, we cannot exclude that the strains responsible for infection in the MERINO trial were less susceptible than those from patients in the current study, which could explain, at least in part, our results. Lastly, most deaths in the TZP arm of the MERINO trial were due to underlying conditions (terminal cancer) rather than uncontrolled or relapsed infection, raising doubt on the external validity of the trial and its generalisation in other populations, especially in ICU patients [9].

Several limitations should be underlined. First, this retrospective, non-randomised study included a heterogeneous population with various antibiotic regimens (i.e. not only TZP but also cefepime, temocillin, ciprofloxacin, etc.), making it difficult to draw definitive conclusions as to the efficacy of a given drug because of the small number of patients available for comparison. However, this two-ICU study reflects the 'real life' setting with physicians choosing the best antibiotic according to the susceptibility test results. Second, 18 patients received a carbapenem even though the responsible bacterium was susceptible to at least one non-carbapenem. We cannot exclude that these patients were actually more ill than those who had received a non-carbapenem and that this choice could have biased the results. Third, because of Etest unavailability, we could not determine the TZP MICs for isolates from 14 patients, therefore their strains were classified as TZP-susceptible if the inhibition diameter exceeded by 3 mm the diameter recommended to consider a strain TZP-susceptible according to European and French guidelines (i.e. 23 mm instead of 20 mm, corresponding to a MIC of 8 mg/L). This strategy could have underestimated TZP susceptibility but it would only have disadvantaged patients who had received it. Lastly, despite the use of multivariable analyses to account for confounding factors, this was a retrospective cohort study and we cannot exclude that the study design might have biased the results.

5. Conclusions

Non-carbapenem administration to ICU patients with severe ESBL-E infections was not associated with poorer outcomes than carbapenem administration. These results warrant a new randomised controlled trial to test the non-inferiority of non-carbapenems in ICU patients. Importantly, clinicians should keep in mind that non-carbapenem MICs should be determined before being prescribed, with the following cut-offs for the use of a non-carbapenem agent: TZP, $\leq$8 mg/L; cefepime, $\leq$1 mg/L, temocillin, $\leq$8 mg/L; ceftazidime/avibactam, $\leq$8 mg/L; and ciprofloxacin when the strain is susceptible to nalidixic acid.

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Competing interests

C-EL has served as a consultant for Bayer Healthcare, Carmat and Thermo Fisher Brahms and has received lecture fees from MSD, Aerogen and bioMérieux; AA has received congress invitation from MSD. All other authors declare no competing interests.

Ethical approval

This study was approved by the Ethics Committee of the Société de Réanimation de Langue Française [registration no. CE SRLF 18-25].

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijantimicag.2019.02.001.

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