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Non-Carbapenem Antibiotics to Treat Severe Extended-Spectrum-β-Lactamase-Producing *Enterobacteriaceae* Infections in Intensive Care Unit Patients

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Running Tittle: Carbapenem alternatives for ICU patients

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ABSTRACT

Purpose. To evaluate the use of non-carbapenem antibiotics to treat severe extended-spectrum β-lactamase–producing *Enterobacteriaceae* infections in intensive care unit (ICU) patients.

Methods. This retrospective observational study conducted in 2 ICUs compared outcomes of patients with extended-spectrum β-lactamase–producing *Enterobacteriaceae* 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 extended-spectrum β-lactamase–producing *Enterobacteriaceae*-infection recurrence and day-30 mortality. Secondary outcomes included day-30 and in-hospital mortality rates, extended-spectrum beta-lactamase–producing *Enterobacteriaceae*-infection recurrence, and infection(s) due to other pathogen(s).

***Results*:** Among the 107 patients included, 67 received a carbapenem and 40 a non-carbapenem antibiotic as their definitive treatment. Clinical characteristics of the 2 groups were similar. Comparing patients given a non-carbapenem antibiotic to those administered carbapenem, respectively, the former had similar day-30 treatment-failure (43% vs. 60%, P =0.06) and extended-spectrum β-lactamase–producing *Enterobacteriaceae*-infection–recurrence rates (25% vs. 22%, P = 0.8), but lower day-30 (23% vs. 45%, P = 0.02) and in-hospital (23% vs. 49%, P = 0.002) mortality rates. Secondary infection rates caused by other pathogen(s), including *Clostridium difficile*, were comparable. Outcomes were comparable regardless of whether or not patients received empirical carbapenem.

Conclusions. For ICU patients with severe extended-spectrum β-lactamase–producing *Enterobacteriaceae* infections, treatment with a non-carbapenem antibiotic was not associated with poorer outcome, compared to a carbapenem.

Keywords. Extended-spectrum-β-lactamase-producing *Enterobacteriaceae*; carbapenem-sparing agent; antimicrobial stewardship.

ABBREVIATION LIST

βL-βLIs: β-lactam–β-lactamase inhibitors

ESBL: extended-spectrum β-lactamase

ICU: intensive care unit

MIC: minimum inhibitory concentration

SAPS: Simplified Acute Physiology Score

SOFA: Sequential Organ-Failure Assessment

1. Introduction

Relatively recently, the use of non-carbapenem antibiotics (namely, β-lactam–β-lactamase inhibitors (βL-βLIs), cefepime or fluoroquinolones) has emerged to treat patients with extended-spectrum β-lactamase (ESBL)–producing *Enterobacteriaceae* infections [1]. Among possible non-carbapenem agents, piperacillin–tazobactam is the most widely used [2,3], but data on cefepime [4,5] or fluoroquinolones [6,7] also exist. Although observational study results were good, they were sometimes negative [8]. The more recent Merino trial results advocated against piperacillin–tazobactam to treat infections caused by 3rd-generation cephalosporin-resistant *Escherichia coli* or *Klebsiella* spp. [9]. Two recent meta-analyses that did not include the Merino trial concluded that βL-βLIs may be promising alternative antibiotics for definitive therapy in patients with ESBL–producing *Enterobacteriaceae* infections [10,11].

However, most of those data, despite coming from large series [3,7], included small numbers of the most severely ill patients, ie those hospitalized in intensive care units (ICUs). Given the scarcity of ICU-patient data and contradictory findings across studies, recent reviews raised concern, or at least recommended caution, when using non-carbapenem antibiotics to treat ESBL–producing *Enterobacteriaceae* infections in ICU patients [12,13].

Therefore, we undertook this study to evaluate the impact of administering non-carbapenem antibiotics to treat severe ESBL–producing *Enterobacteriaceae* infections in ICU patients.

2. Materials and Methods

All patients admitted to our institution's 2 medical ICUs in 2016 and 2017, and who had severe ESBL–producing *Enterobacteriaceae* infections (ie, sepsis or septic shock requiring ICU

admission or occurring during ICU stay) were included retrospectively. Information on medical history, clinical and biologic parameters at ICU admission and during ICU stay was collected retrospectively. Source of infection, antimicrobial treatment (dose and duration) were also recorded. Patients requiring prolonged antimicrobial treatment (ie, bone-and-joint infection, endocarditis) and those without severe infection (ie, without sepsis [14]) were not included.

2.1. Definitions

Empirical therapy was defined as the antibiotics given between sampling and microbiological results. It was considered adequate when the patient received at least 1 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 categorized into one of the 2 following groups: carbapenem-definitive, when a carbapenem was definitively prescribed, and alternative-definitive group, when a non-carbapenem antibiotic was definitively prescribed. Details regarding the non-carbapenem antibiotics and their respective dosing are available in the online supplement. Patients were considered immunocompromised when they fulfilled one of the following criteria: received prednisone ≥0.5 mg/kg for >1 month; had received a solid-organ transplant; were taking an immunosuppressant (cyclosporine, mycophenolate mofetil…); received a hematopoietic stem-cell transplant during the preceding year; had ongoing cancer or received cancer chemotherapy within 6 months; or had human immunodeficiency virus with ≤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 infection recurrence and day-30 mortality. Infection recurrence was defined as a new infectious episode due to ESBL-producing *Enterobacteriaceae* (same strain as first episode or another one) until day 30.

Secondary outcome measures were mortality rates (day-30 and in-hospital mortality), ESBL-producing *Enterobacteriaceae*-infection recurrence within 30 days, infection with other pathogen(s) during the 30 days following the first infection onset, especially *Clostridium difficile*. Patients having received a carbapenem were compared to those having received a non-carbapenem agent.

2.3. Statistical Analyses

Data are expressed as medians (IQR) or means (± standard deviation (SD)), as appropriate. Between-group comparisons were analyzed with Student's *t*-test, Mann–Whitney *U*-test or Kruskal–Wallis test for continuous variables, and 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 the 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 dichotomized according to their median values. To confirm the results obtained in the multivariable analysis, we again used the logistic-regression models 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 yrs, SOFA score at infection onset >10, and infection due to E. coli (vs. other Enterobacteriaceae). All analyses were performed on Statview 5.0 (SAS Institute, Cary, NC, USA).

2.4. Ethics

In accordance with current French law, and as confirmed by the Ethics Committee of the Société de Réanimation de Langue Française (registration number CE SRLF 18-25), informed consent for demographic, physiologic and hospital-outcome data analyses was not obtained because this observational study did not modify existing diagnostic or therapeutic strategies. Nonetheless, patients and/or relatives were informed about the anonymous data collection and 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-producing *Enterobacteriaceae* infection in the 2 participating ICUs. Eleven patients were excluded: 8 with infections without sepsis and 3 with postoperative mediastinitis requiring prolonged antibiotics (Figure E1).

Patients' clinical characteristics are described in Table 1. Among the 107 patients, 70 received empirical carbapenem and 37 received empirical non-carbapenem antibiotics. The latter

included piperacillin–tazobactam for 22 (59%), an anti-pseudomonal 3rd-generation cephalosporin for 12 (32%) and a 3rd-generation cephalosporin (cefotaxime or ceftriaxone) for 3 (8%); 73 (68%) patients received a companion antibiotic with empirical carbapenem for 50 (71%) or a non-carbapenem for 23 (62%) (P = .3 for between-group comparison).

3.1. Definitive treatment

Among the 70 patients administered empirical carbapenem, it was pursued for 46, and switched to another antibiotic for 24 (Figure E1). Among the 37 patients administered empirical non-carbapenem agent, it was switched to a carbapenem for 21, while a non-carbapenem was instituted or continued for 16.

Finally, 67 patients comprised the carbapenem-definitive group and 40 the alternative-definitive group. Definitive treatment for the 40 patients of the alternative-definitive group were piperacillin-tazobactam for 24 (60%), ceftazidime-avibactam for 7 (18%), temocillin for 3 (7%), cefepime for 2 (5%) and ciprofloxacin for 4 (10%). In 18 (27%) patients of the carbapenem-definitive group, an alternative was deemed possible but not given because treating physicians estimated that carbapenem would be better than the alternative. Characteristics of the 2 groups and details on antimicrobial treatments are reported in Table 1 and pathogens responsible for infection in-Table E1 (online supplement) Groups were comparable except for the carbapenem duration, which was shorter than that of the 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 groups. Figure 1 reports the time-to-treatment failure for the 2

groups. While ESBL-producing *Enterobacteriaceae*-infection recurrence rates and secondary non-ESBL–infection rates were similar between groups, the carbapenem-definitive group experienced significantly higher 30-day and in-hospital mortality. The Sequential Organ-Failure Assessment (SOFA) scores from day 1 (infection onset) to day 14 were similar between groups (Figure E2, online supplement). Except patients who died before the end of antimicrobial treatment, no patients had no response to therapy during antimicrobial course.

When taking into account empirical and definitive treatments, results were comparable: regardless of the treatment administered, outcomes were similar across groups (see online supplement).

3.3. Multivariable Analyses of Treatment-Failure–Associated Factors

Factors associated with treatment failure identified by Cox univariable and multivariable analyses are reported in Table E2. Whereas age >58 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. The 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 agent as their definitive treatment as compared with a carbapenem agent was 0.4 (95% confidence interval, 0.2–0.8).

4. Discussion

According to the results of this retrospective, multicenter cohort study, ICU patients with severe ESBL-producing *Enterobacteriaceae* infection given non-carbapenem alternative-definitive

treatment had treatment-failure rates similar to those prescribed carbapenem. Importantly, prescribing non-carbapenems to treat severe ESBL-producing *Enterobacteriaceae* infections was not associated with higher infection-recurrence or other-infection rates (eg, non-ESBL-producing pathogen, including *C. difficile*). Intriguingly, although non-carbapenem–treated patients seemed sicker with higher SOFA score and organ failures at infection onset than those given carbapenem, their ICU- and in-hospital–mortality rates were lower.

The efficacy of non-carbapenem agents to treat ESBL-producing *Enterobacteriaceae* was evaluated in many observational studies that yielded conflicting results. Most of them assessed βL-βLIs and showed that they were not associated with increased mortality, compared to carbapenem [1–3,15,16]. However, other studies found different outcomes: in a large study on 213 patients, Tamma et al reported that the 14-day and 30-day mortality rates of patients given βL-βLIs were higher than those administered carbapenem (respectively: 17 vs 8% and 26 vs 11%) [8]. Moreover, although that study included the largest number of ICU patients, no patients received βL-βLI extended-infusion therapy, which could have yielded poorer outcomes [17,18]. A recent randomized–controlled trial compared piperacillin–tazobactam, cefepime and ertapenem for ESBL-producing *Escherichia coli* urinary tract infections once susceptibility-test results were available [19]. Assignment to receive cefepime was stopped after 6 patients were randomized because of the high treatment-failure rate. Among the 66 patients randomized to receive piperacillin–tazobactam or ertapenem (33 per group), the clinical and microbiological success rates and 28-day mortality were similar. Recent Merino-trial results advocated against piperacillin–tazobactam use because, based on 378 patients with 3rd-generation cephalosporin-resistant *Enterobacteriaceae* from 9 countries, 30-day mortality was higher for patients randomized to receive that combination than meropenem (23/187 (12.3%) vs 7/191 (3.7%),

respectively) [9]. Last, two recent meta-analyses concluded that βL-βLIs may be promising alternative antibiotics for definitive therapy in patients with ESBL–producing *Enterobacteriaceae* infections; however they did not include the results of the Merino trial [10,11].

Using cefepime as a carbapenem-sparing agent to treat ESBL-producing *Enterobacteriaceae* infection is more controversial [19][20]. A recent review summarized the main observational studies that compared cefepime or βL-βLIs to carbapenem to treat ESBL-producing *Enterobacteriaceae* infections [12]; based on that analysis, the authors suggested that cefepime or βL-βLIs 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 MICs [12].

In those studies, the most severely ill patients, ie, those with septic shock requiring ICU admission, were not or 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 (deescalation group) were sicker (with a trend towards higher SOFA score, more frequently required renal replacement therapy and catecholamines than others, especially patients receiving carbapenem for their total treatment duration), but their outcomes were similar. However, because of our study's retrospective design, these findings should be interpreted cautiously. Indeed, 18 patients received 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 physicians avoided deescalation because they thought the patients were too severe (i.e. they had septic shock or several organ failure) to receive a non-carbapenem. Because experienced medical intuition and judgment may be better than scores, we cannot exclude that these patients were indeed sicker than those who received a non-carbapenem, which could have biased the results.

The difference between our results and those of the Merino trial [9] could be explained by the case mix and context: first, the study populations are different, with our patients having severe infection, 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* urinary tract infections. Third, the duration of piperacillin–tazobactam infusion in the Merino trial (ie over 30 minutes) may not be optimal for severe infection [17,18]. Fourth, we cannot exclude that the strains responsible for the Merino-trial infections were less susceptible than those of our patients, which could explain, at least in part, our results. Last, most death in the piperacillin-tazobactam 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 generalization in other populations, especially in ICU patients [9].

Several limitations should be underlined. First, this retrospective, non-randomized study included a heterogeneous population with various antibiotic regimens (ie, not only piperacillin–tazobactam but also cefepime, temocillin, ciprofloxacin …), 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 2-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 sicker 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 piperacillin–tazobactam MICs for 14 patients' isolates, so their strains were classified as piperacillin–tazobactam-susceptible if the inhibition diameter exceeded by 3 mm the diameter recommended to consider a strain piperacillin–tazobactam susceptible according to European and French guidelines (ie, 23 mm instead of 20 mm, corresponding to a MIC of 8 mg). This strategy could have underestimated piperacillin–tazobactam 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 our results.

5. Conclusions

Non-carbapenem administration to ICU patients with severe ESBL-producing *Enterobacteriaceae* infections was not associated with poorer outcomes than for carbapenem recipients. These results deserve a new randomized–controlled trial to test the non-inferiority of 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 non carbapenem agent: piperacillin–tazobactam ≤8 mg/L; cefepime ≤1 mg/L, temocillin ≤8 mg/L, ceftazidime–avibactam ≤8 mg/L, and ciprofloxacin when the strain is susceptible to nalidixic acid.

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Contribution to authorship. CEL is the guarantor of the paper, and takes full responsibility for the integrity of the work as a whole. CEL, IB, AA, JM and JC designed the study, performed the analyses and drafted the manuscript. All authors reviewed and approved the final protocol, obtained the data, read and approved the final manuscript.

Conflicts of interest. C.-E. L. has served as consultant for Bayer Healthcare, Carmat, ThermoFischer Brahms and received lecture fees from MSD, Aerogen and Biomérieux. A.A. has received congress invitation from MSD. The other authors have no conflicts of interest to declare in relationship with this manuscript.

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***Ethical approval*:** This study has been approved by the Ethics Committee of the Société de Réanimation de Langue Française (registration number CE SRLF 18-25).

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Table 1. **Patients' Characteristics and Treatment Details According to their Definitive Antimicrobial Treatment**

Characteristic	Overall population N = 107	Carbapenem group[a] N = 67	Alternative group[b] N = 40
Age, years	58 (52–64)	57 (51–62)	61 (53–68)
Male sex	74 (69)	47 (70)	27 (68)
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)
Neurologic	2 (2)	1 (1)	1 (3)
Miscellaneous	4 (4)	2 (3)	2 (5)
Immunocompromised	43 (40)	28 (42)	15 (38)
Admission SAPS II score	59 (43–75)	60 (43–72)	55 (46–79)
Admission SOFA score	11 (6–15)	11 (6–15)	12 (7–14)
Source of infection			
Pneumonia[c]	73 (68)	48 (72)	25 (63)
Blood	23 (21)	12 (18)	11 (28)
Urinary tract[d]	6 (6)	4 (6)	2 (5)
Cellulitis around ECMO cannula	4 (4)	2 (3)	2 (5)
Angiocholitis	1 (1)	1 (1)	0

Nosocomial infection	99 (93)	64 (96)	35 (88)
At infection onset			
Organ/system failure[e]			
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 biologic presentation			
Temperature, °C	37.4 (36.9–38.2)	37.5 (37–38.2)	37.3 (36.8–38.1)
WBC count, G/L	13.2 (8.1–20.1)	12.6 (8.8–19.6)	13.8 (7.6–20.3)
Procalcitonin level, ng/mL[f]	2.21 (0.69–7.2)	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	88 (82)	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	12 (11)	7 (10)	5 (13)
Companion antibiotic[g]	73 (68)	43 (64)	30 (75)

Duration of antimicrobial treatment	8 (7–11)	8 (6–11)	9 (7–11)
Duration of carbapenem treatment[h]	5 (3–9)	7 (5–10)	2 (0–5)

Data are expressed as n (%) or median (interquartile range).

Abbreviations: ICU, intensive care unit; SAPS, Simplified Acute Physiology Score; SOFA, Sequential Organ-Failure Assessment; ECMO, extracorporeal membrane oxygenation; WBC, white blood cells.

[a]Patients received carbapenem as their definitive treatment, regardless of empirical treatment.

[b]Patients received a non-carbapenem agent as their definitive treatment, regardless of empirical therapy.

[c]Seven of whom had positive blood cultures: 2 in the alternative-definitive group, 5 in the carbapenem-definitive group.

[d]One in the carbapenem-definitive group had a positive blood culture.

[e]Organ/system failure was deemed present when the corresponding SOFA score was >2.

[f]Data are missing for 18 patients: 13 in the carbapenem-definitive group and 5 in the alternative-definitive group.

[g]During the first 48 hours of antimicrobial treatment: aminoglycosides for 71 patients, ciprofloxacin for 1 patient

[h]$P < 0.0001$ for between-group comparison.

Table 2. Patients' Outcomes According to their Definitive Antimicrobial-Treatment Group

Day-30 outcome	Overall population N=107	Carbapenem group[a] N = 67	Alternative group[b] N = 40	*P* value
Primary				
Treatment failure	58 (54)	41 (61)	17 (43)	0.06
Secondary				
Mortality	39 (36)	30 (45)	9 (23)	0.02
ESBL-infection recurrence	25 (23)	15 (22)	10 (25)	0.8
Other secondary infection[c]	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

Data are expressed as n (%).

Abbreviation: ESBL, extended-spectrum beta lactamase.

[a]Patients received carbapenem as their definitive treatment, regardless of their empirical regimen.

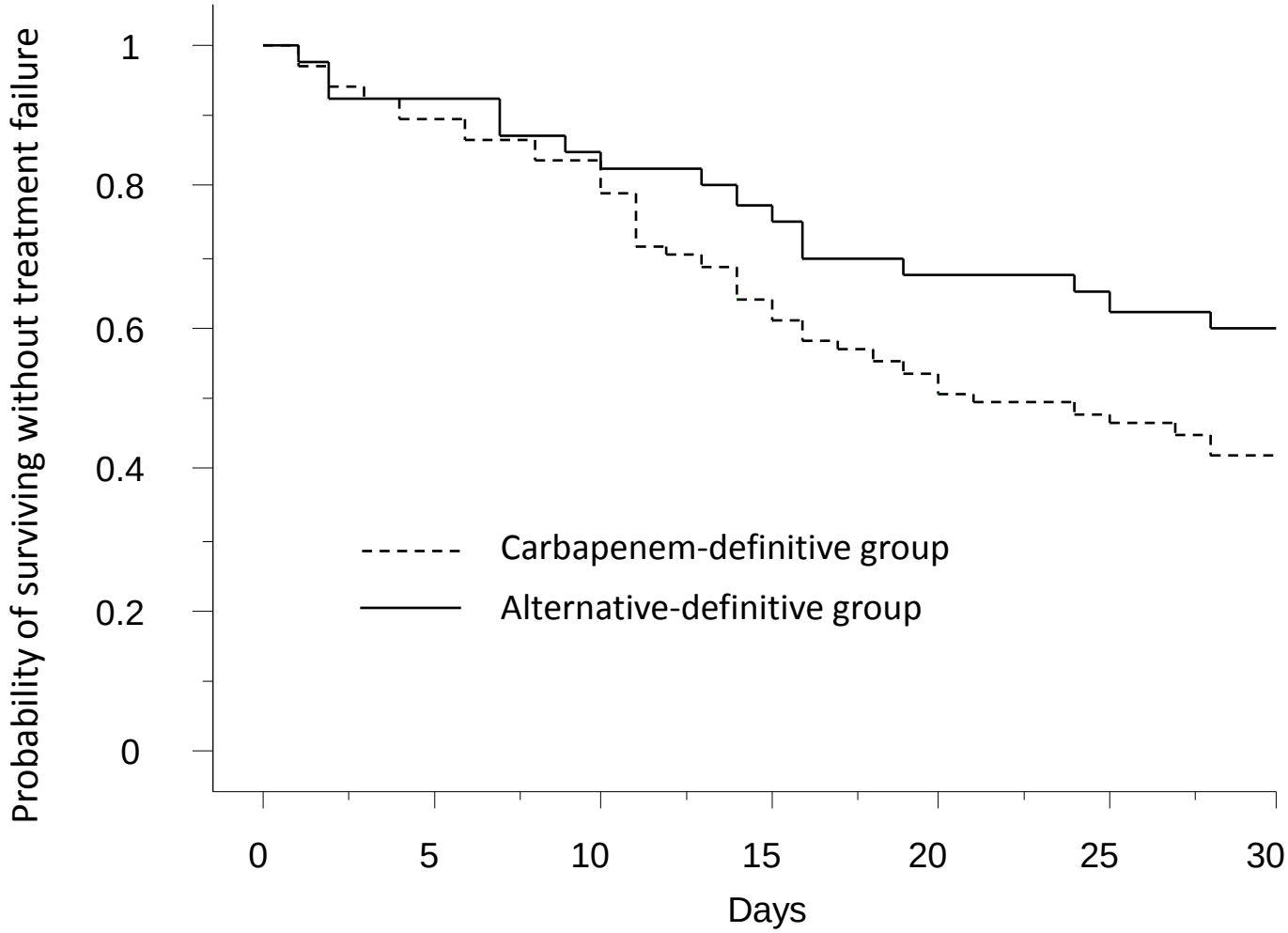
[b]Patients received a non-carbapenem agent as their definitive treatment, regardless of their empirical regimen.

[c]Infection due to a non-ESBL pathogen occurring before day 30.

Figure legends

Figure 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.

Figure 1



Number at risk							
Carbapenem-definitive	67	62	56	43	36	32	28
Alternative-definitive	40	37	34	31	27	26	24

Non-Carbapenem Antibiotics to Treat Severe Extended-Spectrum-β-Lactamase-Producing *Enterobacteriaceae* Infections in Intensive Care Unit Patients

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ONLINE SUPPLEMENTAL DATA

METHODS

Our hospital implemented an institutional policy in 2015 to spare carbapenems and promote the use of non-carbapenem antibiotics to treat ESBL-producing *Enterobacteriaceae* infections. Physicians, particularly ICU physicians, were asked to use non-carbapenem antibiotics to treat ESBL-producing *Enterobacteriaceae* infections, whenever possible, ie when infection-causing pathogens were susceptible to such carbapenem-sparing agents. The following non-carbapenems could be prescribed when their minimum inhibitory concentrations (MICs) allowed: piperacillin–tazobactam ≤8 mg/L; cefepime ≤1 mg/L, temocillin ≤8 mg/L and ceftazidime–avibactam ≤8 mg/L. Fluoroquinolone MICs were not determined and their use (always ciprofloxacin) was allowed when strains were susceptible to nalidixic acid in the disk-diffusion assay, according to the French Society for Microbiology Antibiogram Committee's (CA-SFM) recommendations.

Treatment of ESBL-producing Enterobacteriaceae infections

Patients received one of the following antibiotic regimens: meropenem: 2 g infused over 2 hours, 3 times a day (tid); piperacillin–tazobactam: 4.5 g infused over 4 hours, 4 times a day (qid); cefepime: 2 g infused over 4 hours, tid; temocillin: 2 g over 1 hour, tid; ciprofloxacin: 400 mg infused over 1 hour, tid; ceftazidime–avibactam: 2.5 g infused over 2 hours, tid; ceftolozane–tazobactam: 1.5 g infused over 1 hour, tid. All antibiotic doses were adjusted to renal function.

Microbiology Methods

The Pitié–Salpêtrière Microbiology Laboratory processed all biologic samples according to standard operating procedures. Isolate susceptibilities to antibiotics were determined with the disk-diffusion method, as recommended by the CA-SFM. Piperacillin–tazobactam, cefepime,

temocillin, ceftazidime–avibactam MICs were determined with Etests on Mueller–Hinton agar according to the manufacturer's instructions. Etest MIC values were rounded up to the nearest 2-fold dilution.

Because piperacillin–tazobactam Etests were temporarily unavailable in France during part of the study period, ESBL strain-susceptibility to piperacillin–tazobactam for 14 patients was based on the inhibition diameter, assuming that a diameter >23 mm corresponds to a MIC ≤8 mg/L.

Subgroup analysis according to initial and definitive treatment

According to their empirical and definitive antibiotic regimens, patients were categorized in 1 of the 4 following groups: carbapenem, only carbapenem throughout treatment duration; alternative, carbapenem alternative throughout the treatment duration; de-escalation-group patients received empirical carbapenem, then treatment was deescalated to a non-carbapenem agent once pathogen susceptibility was known; and escalation-group patients had received empirical non-carbapenem agent that was escalated to a carbapenem once pathogen susceptibility was known.

RESULTS

Subgroup analysis according to initial and definitive treatment

ICU admission and baseline characteristics of these 4 groups are given in Table E3, pathogens responsible for infections in Table E4 and antimicrobial-treatment details (appropriateness, treatment duration) in Table E5. The groups were comparable with the following exceptions: escalation- and alternative-group patients had significantly more frequent inadequate antimicrobial treatment, while no carbapenem and deescalation groups had inappropriate empirical antimicrobial treatment (P <0.0001 for among-group comparisons). Carbapenem-

administration durations also differed between groups, while the total antimicrobial-treatment durations were similar among groups.

Outcomes according to treatment group

Outcomes according to the 4 treatment groups are given in Table E6. Treatment-failure rates (ESBL-producing *Enterobacteriaceae*-infection relapse or day-30 mortality) were similar among groups, as were secondary outcomes (ESBL-producing *Enterobacteriaceae*-infection relapse by day 30, 30-day mortality and in-hospital mortality). The SOFA scores from day 1 (infection onset) to day 14 were similar among groups (Figure E3). Figure E3 shows the time to treatment failure for all 4 groups.

Table E1. Pathogens Responsible for Infection According to the Definitive Antimicrobial-Treatment Group

Pathogen	Overall population[a] N = 107	Carbapenem group[a,b] N = 67	Alternative group[a,c] N = 40
Klebsiella pneumoniae	52 (29)	35 (52)	16 (40)
Escherichia coli	23 (21)	9 (13)	14 (35)
Enterobacter spp	34 (32)	23 (34)	11 (28)
Klebsiella oxytoca	2 (2)	2 (3)	0
Serratia marcescens	1 (1)	1 (1)	0

Data are expressed as n (%).

[a]Sum of pathogens is superior to the number of patients because some patients were infected with 2 different microorganisms.

[b]Patients received carbapenem as their definitive treatment, regardless of their empirical regimen.

[c]Patients received a non-carbapenem agent as their definitive treatment, regardless of their empirical regimen.

Table E2. Univariable and Multivariable Cox Analyses of Factors Associated with Treatment Failure

Factor	Univariable analysis HR (95% CI)	Multivariable analysis HR (95% CI)
Age >57 years	1.3 (0.8–2.1)	
Male sex	1.3 (0.7–2.4)	
Immunocompromised	0.8 (0.5–1.4)	
Admission SAPS II score >58	2.8 (1.6–4.8)	2.6 (1.5–4.6)
SOFA score at infection onset >10	1.9 (1.1–3.3)	2.1 (1.2–3.6)
Septic shock	1.8 (1.01–3.1)	
Infection due to Escherichia coli	0.6 (0.3–1.3)	
Mechanical ventilation at infection onset	1.9 (1.1–3.5)	
Renal replacement therapy at infection onset	1.6 (0.9–2.7)	
Inappropriate initial antimicrobial treatment	1.1 (0.5–2.5)	
Companion antibiotic during the first 48 hours	1.1 (0.6–1.9)	
Duration of antimicrobial treatment >8 days	0.8 (0.5–1.3)	0.6 (0.3–0.9)
Non-carbapenem agent		
Empirical therapy	0.9 (0.5–1.6)	
Definitive therapy	0.6 (0.4–1.1)	0.5 (0.3–0.9)

Abbreviations: HR, hazard ratio; CI, confidence interval; SAPS, Simplified Acute Physiology Score; SOFA, Sequential Organ-Failure Assessment.

Table E3. Patients' Admission and Baseline Characteristics According to Treatment Group

Characteristic	Overall population N = 107	Carbapenem group[a] N = 46	Alternative group[b] N = 16	Deescalation group[c] N = 24	Escalation group[d] N = 21
Age, years	58 [52–64]	56 [51–62]	65 [58–72]	59 [48–65]	57 [54–64]
Male sex	74 (69)	30 (65)	13 (81)	13 (54)	18 (86)
Reason for ICU admission					
Cardiogenic shock	31 (29)	12 (26)	6 (38)	7 (29)	6 (29)
Septic shock	21 (20)	12 (26)	4 (25)	4 (17)	1 (5)
Acute respiratory failure	29 (27)	15 (33)	4 (25)	3 (13)	7 (33)
Postoperative respiratory failure	15 (14)	3 (7)	1 (6)	6 (25)	5 (24)
Cardiac arrest	5 (5)	2 (4)	1 (6)	1 (4)	1 (5)
Neurologic	2 (2)	1 (2)	0	1 (4)	0
Miscellaneous	4 (4)	1 (2)	0	2 (8)	1 (5)
Immunocompromised	43 (40)	18 (39)	4 (25)	11 (46)	10 (48)
Admission SAPS II score	59 [43–75]	61 [43–72]	59 [41–80]	57 [48–79]	57 [44–73]
Admission SOFA score	11 [6–15]	9 [6–13]	13 [7–14]	12 [8–16]	14 [7–16]
Source of infection					
Pneumonia[e]	73 (68)	30 (65)	11 (69)	14 (58)	18 (86)
Blood	23 (21)	9 (20)	2 (13)	9 (38)	3 (14)
Urinary tract[f]	6 (6)	4 (9)	1 (6)	1 (4)	0

Cellulitis around ECMO cannula	4 (4)	2 (4)	2 (13)	0	0
Angiocholitis	1 (1)	1 (2)	0	0	0
Nosocomial infection	99 (93)	45 (98)	13(81)	22 (92)	19 (90)
At infection onset					
Organ/system failure[g]					
Cardiovascular	73 (68)	26 (57)	11 (69)	19 (79)	17 (81)
Respiratory	67 (63)	28 (61)	9 (56)	18 (75)	12 (57)
Renal	46 (43)	15 (33)	6 (38)	13 (54)	12 (57)
Central nervous	24 (22)	9 (20)	4 (25)	8 (33)	3 (14)
Hepatic	12 (11)	6 (13)	1 (6)	3 (13)	2 (10)
Coagulation	17 (16)	10 (22)	1 (6)	5 (21)	1 (5)
Clinical and biological presentation					
Temperature, °C	37.4 [36.9–38.2]	37.7 [37–38.3]	37.1 [36.8–37.5]	37.4 [36.7–38.4]	37.5 [36.9–37.8]
WBC count, G/L	13.2 [8.1–20.1]	12.5 [8.6–17.9]	14.2 [10.5–20.3]	13.8 [6.9–21]	15.6 [8.6–24]
Procalcitonin level, ng/mL[h]	2.21 [0.69–7.28]	1.50 [0.65–7.94]	2 [1.16–2.59]	3.1 [1.58–24.6]	2.76 [0.52–7.24]
SOFA score	10 [7–14]	9 [6–13]	11 [7–13]	13 [9–16]	10 [8–14]
Septic shock	70 (65)	29 (63)	12 (75)	16 (67)	13 (62)
Interventions					
Mechanical ventilation	88 (82)	36 (78)	12 (75)	20 (83)	19 (90)
Renal replacement therapy	43 (40)	14 (30)	5 (31)	13 (54)	11 (52)
Catecholamine use	73 (68)	26 (57)	11 (69)	19 (79)	17 (81)

Data are expressed as n (%) or median [IQR].

Abbreviations: ICU, intensive care unit; SAPS, simplified acute physiology score; SOFA, sequential organ failure assessment; ECMO,

extracorporeal membrane oxygenation; WBC, white blood cells.

[a]Patients received exclusively carbapenem throughout the treatment duration.

[b]Patients received a carbapenem alternative throughout the treatment duration.

[c]Patients received an empirical carbapenem, which was deescalated to a carbapenem-sparing agent once pathogen susceptibility was known.

[d]Patients received an empirical non-carbapenem, which was escalated to carbapenem once pathogen susceptibility was known.

[e]Seven of whom had positive blood cultures: 2 in the deescalation group, 5 in the carbapenem group.

[f]One carbapenem-group patient had a positive blood culture.

[g] Organ/system failure was deemed present when the corresponding SOFA score was >2.

[h]Procalcitonin values were missing for 18 patients: 8 carbapenem group, 4 alternative group, 1 deescalation group and 5 escalation group.

Table E4. Pathogens Responsible for Infection According to Treatment Group

Pathogen	Overall population[a] N = 107	Carbapenem[b] N = 46	Alternative[c] N = 16	Deescalation[a,d] N = 24	Escalation[a,e] N = 21
Klebsiella pneumoniae	52 (49)	26 (57)	5 (31)	11 (46)	10 (48)
Escherichia coli	23 (21)	7 (15)	6 (38)	8 (33)	2 (10)
Enterobacter spp	34 (32)	14 (30)	5 (31)	6 (25)	9 (43)
Klebsiella oxytoca	2 (2)	2 (4)	0	0	0
Serratia marcescens	1 (1)	0	0	0	1 (5)

Data are expressed as n (%).

[a]Sum of pathogens is superior to the number of patients because some patients had infections with 2 different microorganisms.

[b]Patients received exclusively carbapenem throughout the treatment duration.

[c]Patients received a carbapenem alternative throughout the treatment duration.

[d]Patients received an empirical carbapenem, which was de-escalated to a carbapenem-sparing agent once pathogen susceptibility was known.

[e]Patients received an empirical non-carbapenem agent, which was escalated to carbapenem once pathogen susceptibility was known.

Table E5. Antimicrobial-Treatment Characteristics According to Treatment Group

Characteristic	Overall population N = 107	Carbapenem group[a] N = 46	Alternative group[b] N = 16	Deescalation group[c] N = 24	Escalation group[d] N = 21
Inappropriate initial antimicrobial treatment[e]	12 (11)	0	4 (25)	0	7 (33)
Companion antibiotic[f]	72 (67)	30 (65)	10 (63)	20 (83)	13 (62)
Duration of antimicrobial treatment	8 [7–11]	8 [5–11]	8 [5–9]	10 [7–13]	9 [7–12]
Duration of carbapenem treatment[e]	5 [3–9]	8 [5–11]	0	4 [2–5]	7 [5–9]

Data are expressed as n (%) or median [IQR].

[a]Patients received only carbapenem throughout the treatment duration.

[b]Patients received a carbapenem alternative throughout the treatment duration.

[c]Patients received an empirical carbapenem, which was deescalated to a carbapenem-sparing agent once pathogen susceptibility was known.

[d]Patients received an empirical non-carbapenem antibiotic, which was escalated to carbapenem once pathogen susceptibility was known.

[e]$P < 0.0001$ for among-group comparisons.

[f]During the first 48 hours of antimicrobial treatment: aminoglycosides for 71 patients, ciprofloxacin for 1.

Table E6. Outcomes According to Treatment Group

Day-30 outcome	Overall population N = 107	Carbapenem group[a] N = 46	Alternative group[b] N = 16	Deescalation group[c] N = 24	Escalation group[d] N = 21
Primary					
Treatment failure	58 (54)	29 (63)	7 (44)	10 (42)	12 (57)
Secondary					
Mortality	39 (36)	22 (48)	5 (31)	4 (17)	8 (38)
ESBL-producing *Enterobacteriaceae*-infection relapse	25 (23)	8 (17)	3 (19)	7 (29)	7 (33)
Other secondary infection[e, f]	30 (28)	9 (20)	1 (6)	11 (46)	9 (43)
Clostridium difficile infection	2 (2)	1 (2)	0	0	1 (5)
In-hospital mortality[f]	42 (39)	24 (52)	5 (31)	4 (17)	9 (43)

Data are expressed as n (%).

[a]Patients received exclusively carbapenem throughout the treatment duration.

[b]Patients received a carbapenem alternative throughout the treatment duration.

[c]Patients received an empirical carbapenem, which was deescalated to a carbapenem-sparing agent once pathogen susceptibility was known.

[d]Patients received an empirical non-carbapenem antibiotic, which was escalated to carbapenem once pathogen susceptibility was known.

[e]Infection due to a non-ESBL pathogen occurred before day 30.

[f]$P < 0.05$ for among-group comparisons.

Figure E1. Flow chart of the study. ESBL, extended-spectrum beta-lactamase

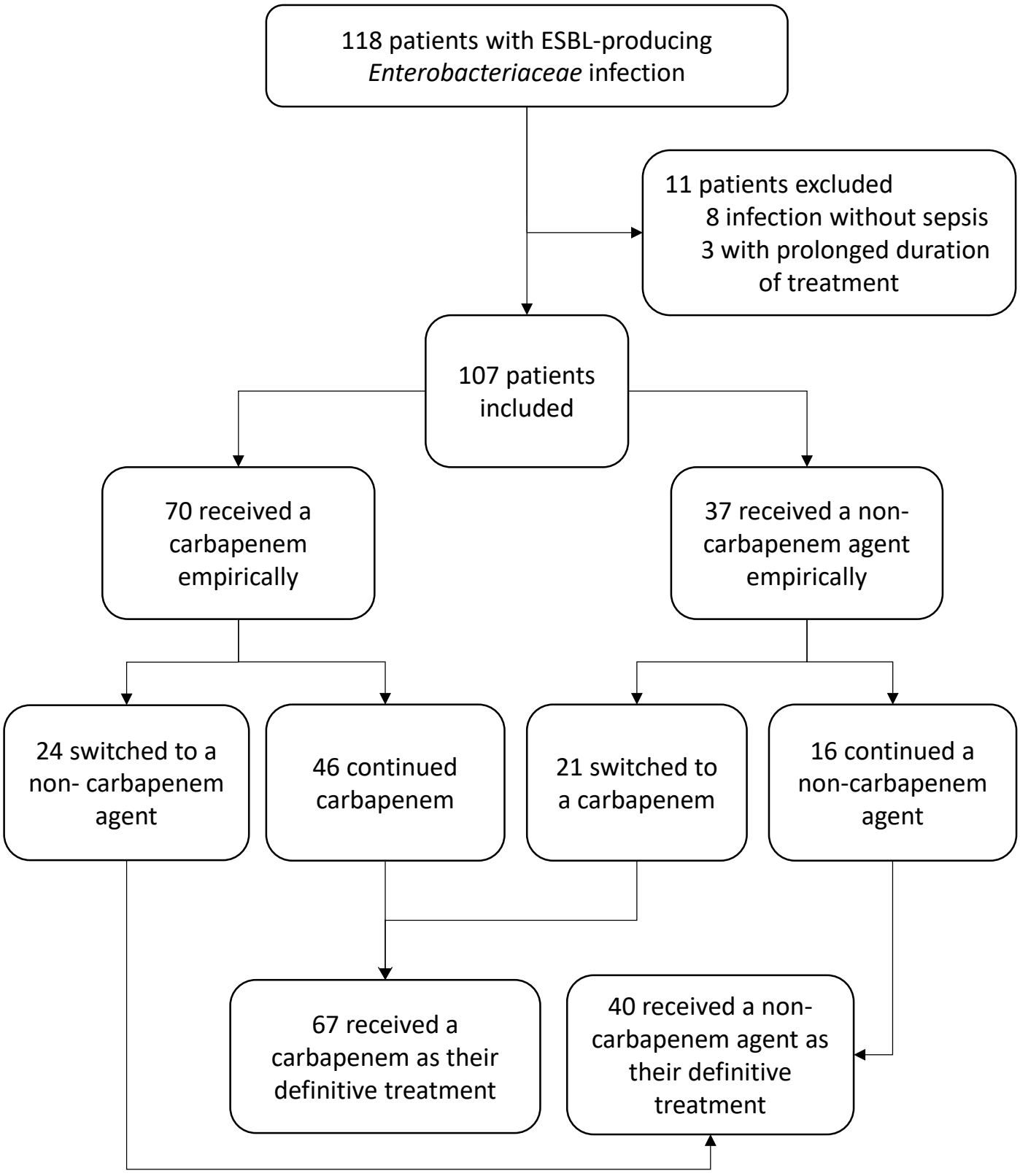


Figure E2. Sequential Organ-Failure Assessment (SOFA) score from day 1 to day 14 in patients according to their definitive antibiotic-treatment group. Results are expressed as mean ± SD.

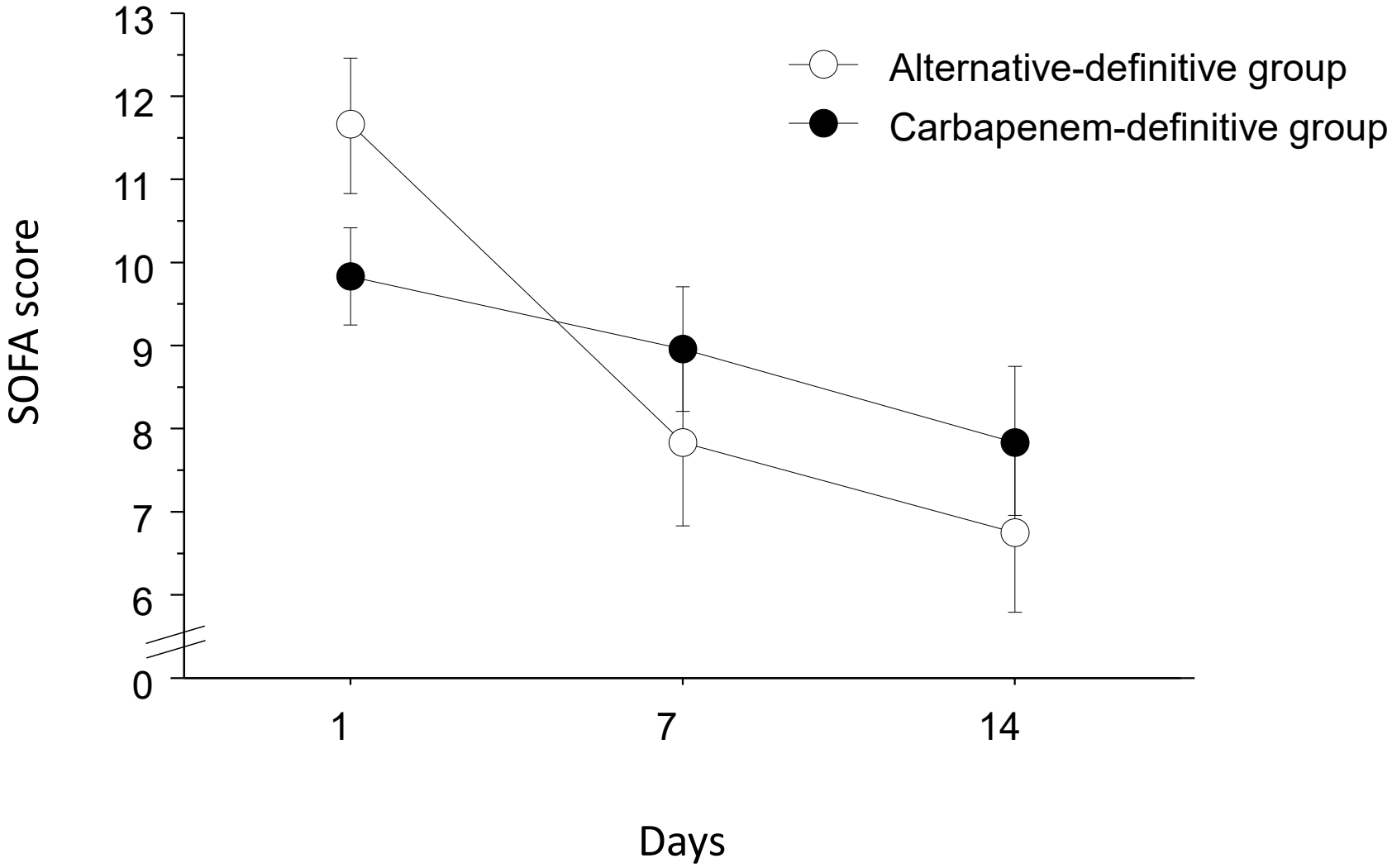


Figure E3. Means ± SD Sequential Organ-Failure Assessment (SOFA) score from day 1 (D1) to D14 in patients according to their treatment group: carbapenem (black circles); alternative (white circles); deescalation (hatched circles) and escalation (dotted circles).

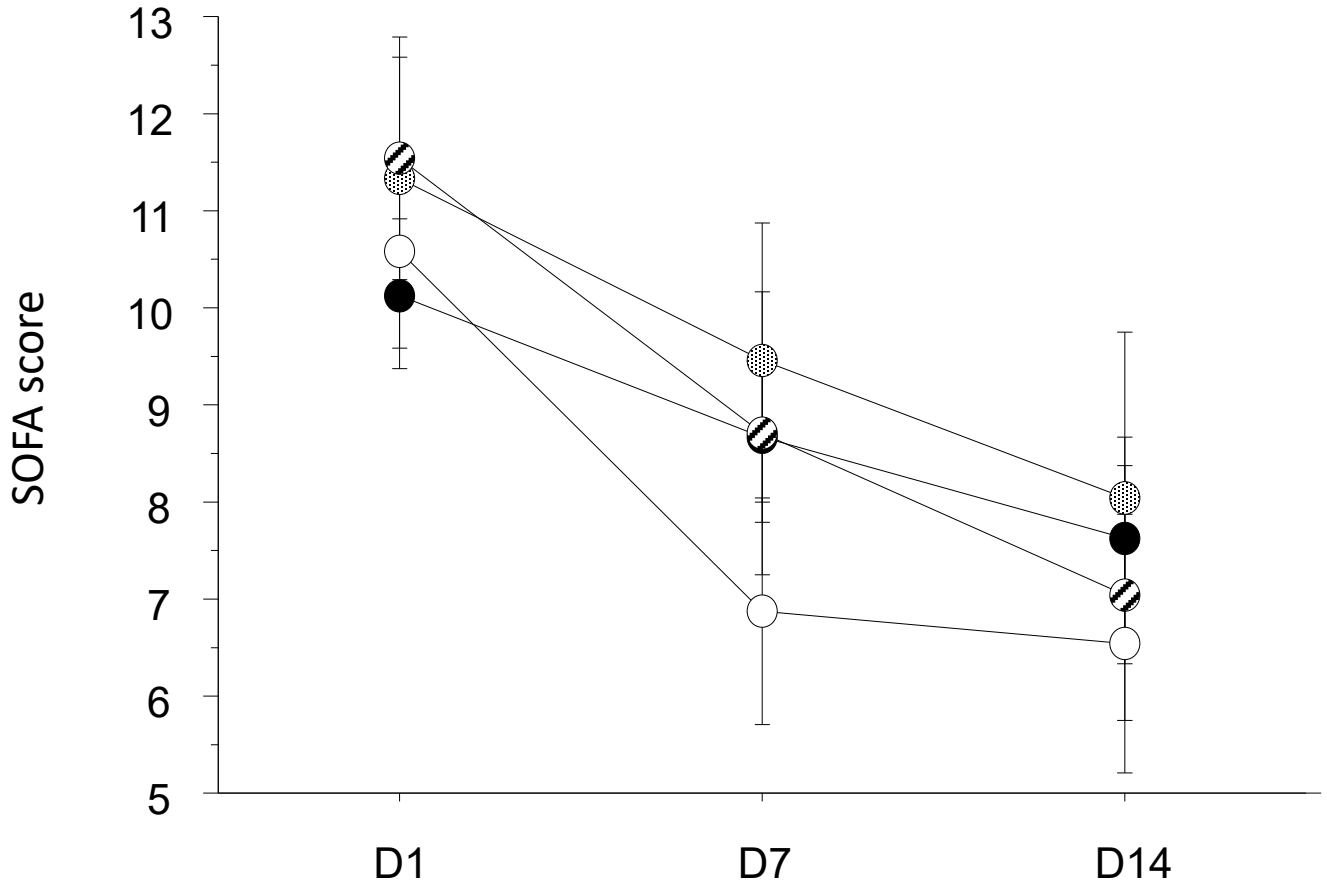


Figure E4. Kaplan–Meier probability of treatment failure according to treatment group (P = .3; log-rank test).

