International Journal of Infectious Diseases 39 (2015) 62–67

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

Extended-spectrum beta-lactamase-producing *Enterobacteriaceae* (ESBL-PE) infections: are carbapenem alternatives achievable in daily practice?

B. Pilmis [a,b], T. Delory [c,1], M. Groh [d,1], E. Weiss [e], A. Emirian [f], H. Lecuyer [g], P. Lesprit [c], J.-R. Zahar [h,*]

[a] *Université Paris Descartes, Hôpital Necker Enfants Malades, Service de Maladies Infectieuses et Tropicales, Paris, France*
[b] *Groupe Hospitalier Paris Saint-Joseph, Equipe Mobile de Microbiologie Clinique, Paris, France*
[c] *Université Paris XII, Hôpital Henri Mondor, Unité de Contrôle Épidémiologique et Prévention de l'Infection, Créteil, France*
[d] *Université Paris Descartes, Hôpital Cochin, Service de Médecine Interne, Paris, France*
[e] *Université Paris Diderot, Hôpital Beaujon, Département d'Anesthésie-Réanimation, Clichy, France*
[f] *Université Paris XII, Hôpital Henri Mondor, Laboratoire de Bactériologie-Hygiène, Département de Virologie, Bactériologie-Hygiène, Parasitologie-Mycologie, Créteil, France*
[g] *Université Paris Descartes, Hôpital Necker Enfants Malades, Laboratoire de Microbiologie, Paris, France*
[h] *Université d'Angers, Unité de Prévention et de Lutte Contre les Infections Nosocomiales, CHU d'Angers, 4 rue Larrey, 49000 Angers, France*

ARTICLE INFO

Article history:
Received 10 May 2015
Received in revised form 27 July 2015
Accepted 22 August 2015

Corresponding Editor: Eskild Petersen, Aarhus, Denmark.

Keywords:
Extended-spectrum beta-lactamase
De-escalation
Carbapenem

SUMMARY

Objectives: To avoid the use of carbapenems, alternatives such as cephamycin, piperacillin–tazobactam, and others are suggested for the treatment of extended-spectrum beta-lactamase-producing *Enterobacteriaceae* (ESBL-PE) infections. The aim of this study was to evaluate the frequency and the feasibility of antimicrobial de-escalation for ESBL-PE-related infections.

Methods: A prospective observational, bi centric cohort study was conducted. All patients with ESBL-PE infections were included. De-escalation was systematically suggested if patients were clinically stable and the isolate was susceptible to possible alternatives.

Results: Seventy-nine patients were included: 36 (45.6%) were children, 27 (34.1%) were hospitalized in intensive care units, and 37 (47%) were immunocompromised. Urinary tract infections, pneumonia, and catheter-related bloodstream infections accounted for 45.6%, 19%, and 10%, respectively, of the cohort. *Escherichia coli*, *Klebsiella pneumoniae*, and *Enterobacter cloacae* were the three most frequent causative organisms isolated. On day 5, 47 (59.2%) of the patients were still receiving carbapenems. Antimicrobial resistance (44.7%), infection relapse (26.9%), and clinical instability (19.2%) were the most important reasons for not prescribing alternatives. *E. coli*-related infections appeared to be a protective factor against maintaining the carbapenem prescription (odds ratio 0.11, 95% confidence interval 0.041–0.324; $p = 0.0013$).

Conclusions: In clinical practice, less than 50% of patients with ESBL-PE-related infections were de-escalated after empirical treatment with carbapenems.

1. Introduction

Since the 1980s, extended-spectrum beta-lactamase (ESBL)-producing isolates have spread worldwide.[1,2] These isolates are often multidrug-resistant, and carbapenems are often regarded as a major antibacterial drug.[3,4] Massive prescription of these drugs has ecological consequences.[5] Indeed it increases the rise and spread of carbapenemase-producing *Enterobacteriaceae*[6] and the rate of subsequent multidrug-resistant bacteria-related infections.[3,4]

Several studies have tried to assess the safety and efficacy (mortality and length of hospital stay) of the use of non-carbapenem drugs for the treatment of ESBL-related infections.[7–10] Major studies have been non-randomized and have shown conflicting results.[8] In patients with susceptible ESBL-producing *Escherichia coli* bloodstream infections (BSI), Rodríguez-Baño et al.[7] showed

* Corresponding author. Tel.: +33 241354395; fax: +33 241354936.
E-mail address: JeanRalph.ZAHAR@chu-angers.fr (J.-R. Zahar).
[1] T. Delory and M. Groh contributed equally to this work.

http://dx.doi.org/10.1016/j.ijid.2015.08.011

that there was no difference in outcome between patients treated with carbapenems or beta-lactam/beta-lactam inhibitor (BLBLI) combinations (including piperacillin–tazobactam (PTZ) and amoxicillin–clavulanate (AAC)). However that cohort study was composed mainly of patients with bacteraemia originating from the urinary tract and did not take into account minimum inhibitory concentrations (MICs). Despite theoretical microbial susceptibility (as defined by the Clinical and Laboratory Standards Institute criteria), recent studies have reported suboptimal clinical and microbiological outcomes in patients treated with alternatives to carbapenems for infections with ESBL-producing strains.[11] In this setting, the use of cephalosporins (as compared to carbapenems) has also been associated with increased mortality, even when the MIC for *Enterobacteriaceae* remains within the susceptible range.[12,13] Conversely, the use of fluoroquinolones is also frequently restricted by antimicrobial co-resistance of ESBL strains.[4] Therefore, non-carbapenem alternatives may be used with caution in selected cases of infection with ESBL-producing strains, but clear guidelines are currently lacking.[14–16]

The primary aims of this observational prospective cohort study were to identify the rate of non-carbapenem alternative prescription and to evaluate the frequency and factors associated with the omission of de-escalation. The secondary aim was to identify daily practice factors associated with carbapenem prescription (either as empirical or as definitive therapy) in the setting of ESBL infections.

2. Materials and methods

2.1. Study design

This observational prospective study was performed in two French university hospitals (Hôpital Necker Enfants Malades, Paris, and Hôpital Henri Mondor, Créteil) from May 2012 to January 2013. Antimicrobial stewardship teams are well established in these hospitals, each composed of a pharmacist and a full-time infectious disease physician, assisted by one or two fellows.

At the time the antimicrobial stewardship team was alerted by the microbiologist, a first consultation (at day 0 or day +1) consisted of encouraging prescribers to adapt their treatment in accordance with local recommendations. A second visit was systematically performed when antimicrobial susceptibility tests were obtained. An advice and an evaluation were systematically delivered to improve and adapt antibiotic prescription. De-escalation was systematically proposed when clinical and microbiological data allowed it. Practitioners were free to follow or not these recommendations.

All consecutive patients (adults and children) treated for ESBL-producing *Enterobacteriaceae* (ESBL-PE) infections were included prospectively. Using a computer-generated alert system, the antimicrobial stewardship team conducted a systematic post-prescription review of all carbapenem prescriptions. All ESBL-PE documented infections were recorded daily by a microbiologist who notified the antimicrobial team. During the study period, a review of all antibiotic prescriptions initiated for ESBL-PE documented infections was also systematically performed. The team reviewed all prescriptions successively within the first 48 h, when antimicrobial susceptibility tests were available, and finally on day 5. Data collected at inclusion consisted of demographic characteristics (age, sex), comorbid conditions, Charlson's weighted index of morbidity, immunodeficiency, previously known ESBL rectal carriage for the last 6 months, and the clinical severity according to the Bone criteria.[17] Immunodeficiency was defined as neoplasia with recent chemotherapy (less than 30 days before infection), neutropenia (neutrophil count $<0.5 \times 10^9$ cells/l), treatment with glucocorticosteroids and/or other immunosuppressants within the last month, solid organ or bone marrow transplantation recipient, or AIDS (CD4 cell count <200/ml, or other evidence of AIDS as defined by the US Centers for Disease Control and Prevention (CDC)).[18]

The primary source of infection was determined according to the CDC criteria,[19] or otherwise defined as primary bacteraemia with no determined portal of entry.

Bacterial identification was performed in both hospitals with the commercially available Vitek 2 system or with the API 20 E, API 20NE strips (bioMérieux, Marcy l'Etoile, France). Microbiological ESBL diagnosis was carried out according to the European Committee on Antimicrobial Susceptibility Testing (EUCAST) breakpoints.[20] In vitro antimicrobial susceptibility testing was performed with the disk diffusion method or with the Vitek 2 system in accordance with the guidelines of the Antibiogram Committee of the French Microbiological Society.[21] Clinical outcome was recorded at hospital discharge.

Two non-mutually exclusive cohorts of patients (receiving either carbapenems or an alternative) were constructed and analyzed separately. The empirical therapy cohort (ETC) included patients during the first 24 h following positive microbiological results (day 0) and the definitive therapy cohort (DTC) included patients treated according to MIC results from day 5 until the end of antimicrobial therapy.

2.2. Alternatives to carbapenems

Third-generation cephalosporins (3GC), PTZ, and cephamycins were used as carbapenem alternatives, as per EUCAST recommendations. Thus, strains with a MIC <8 mg/l were considered susceptible to PTZ and strains with a MIC <1 mg/l were considered susceptible to 3GC.

2.3. Statistical analysis

2.3.1. Descriptive analysis

A descriptive analysis was performed using the median and interquartile range (IQR) or the mean and standard deviation (SD) for the quantitative variables, and the number and proportion for the qualitative variables.

2.3.2. Factors associated with the maintenance of carbapenems

Factors associated with the maintenance of carbapenem therapy were identified using both univariate and multivariate analysis, using a conditional logistic regression model. Analyses were stratified on the centre and hospitalization in a ward dedicated to paediatric care. Associations are reported as the odds ratio (OR) and 95% confidence interval (CI). Factors considered for the multivariate model were those with at least 10 events, without missing data, that were non-collinear with other factors (with a significance level $<10^5$), and associated with the status (maintenance or withdrawal of carbapenem therapy) on univariate analysis with a significance level (p-value) less than 0.20. Factors included in the final multivariate model were selected using a forward stepwise selection procedure based on the Akaike Information Criterion (AIC). The statistical analysis was performed by T.D. using R program version 3.02 (R Foundation for Statistical Computing, Vienna, Austria). This observational study is reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement.[22]

3. Results

During the study period, 79 ESBL-PE-related infections were included. Baseline characteristics of the patients are detailed in

Table 1. Most patients were male (65.8%). The median age was 35.4 (IQR 2.15–58.8) years and 36 (46%) patients were children (age <16 years). Fifty-three (67%) infections were nosocomially acquired, 37 (46.8%) were recorded in immunocompromised patients, and 54 (68.4%) patients were known to be previous ESBL rectal carriers.

3.1. Carbapenem prescription as empirical therapy

Antibiotic use is shown in Figure 1. Thirty-four (43.0%) patients were treated with carbapenems, while 45 patients received an alternative (BLBLI combination, $n = 20$; 3GC, $n = 18$; fluoroquinolones, $n = 2$; amikacin, $n = 5$).

Factors associated with carbapenem prescription (rather than an alternative drug) as empirical antibiotic therapy are detailed in Table 2. As compared to patients hospitalized in medical and surgical departments, intensive care unit (ICU) patients were treated more frequently with carbapenems (52.9% vs. 20% respectively; OR 4.5, 95% CI 1.7–12.1). Patients with nosocomial infections were also more frequently treated empirically with carbapenems (79.41% vs. 57.8%; OR 2.8, 95% CI 1.1–7.8). Last, previously known ESBL-PE rectal carriage was associated with increased carbapenem prescription (88.2% vs. 53.3%; OR 6.5, 95% CI 1.9–21.7). Among the 54 patients previously known to be ESBL-PE rectal carriers, 26 (48%) carriage strains were considered as resistant to PTZ. Five patients (17.9%) known by ward physicians to have strains resistant to PTZ were treated empirically with PTZ for ESBL-PE rectal carriage.

3.2. Carbapenem prescription as definitive therapy

As compared to other pathogens, *E. coli* ESBL infections were more frequently treated with an alternative to carbapenem (OR 0.11, 95% CI 0.041–0.324) (Table 3). On day 5, after obtaining the results of antimicrobial tests, 47 (59.5%) patients were treated with carbapenems. Among them, 26 (55.3%) were infected with strains that were susceptible to alternatives. For these patients, the main reasons for carbapenem maintenance were the following: a history of prior treatment failure and/or the recurrence of infection ($n = 7$, 26.9%), poor clinical outcome at day 3 of antimicrobial therapy ($n = 5$, 19.2%), underlying immunosuppression ($n = 4$, 15.4%), the source of infection ($n = 4$, 15.4%), and the clinical severity at onset of infection ($n = 3$, 11.5%) (Table 4).

Table 1
Demographic, clinical, and microbiological data for the 79 study patients

Data: type and parameter	No. (%) of patients
Demographic data	
Total patients	79 (100)
Male	52 (65.8)
Female	27 (34.1)
Adults	43 (54.4)
Children	36 (45.6)
Age, years, median (IQR)	35.4 (2.15–58.8)
Clinical data	
Underlying conditions	
Immunosuppressive therapy	26 (33)
Neutropenia	4 (5)
Diabetes mellitus	11 (14)
HIV infection	1 (1)
Ward	
Medical department	44 (55.7)
Surgical department	8 (10)
Intensive care unit	27 (34.18)
Charlson score, median (IQR)	3 (1–6)
Nosocomial infection/health care-associated	53 (67)
Community-acquired infection	26 (33)
Origin of infection	
Catheter	5 (6.3)
Lung	15 (19)
Urinary tract	42 (53.1)
Skin and soft tissue	4 (5)
Digestive	3 (10)
Bacteraemia	9 (11.4)
Eye	1 (1.2)
Microbiological data	
Escherichia coli (%)	34 (43)
Susceptible to alternatives	13 (16.4)
Klebsiella pneumoniae (%)	28 (35.4)
Susceptible to alternatives	9 (11.4)
Klebsiella oxytoca (%)	1 (1.3)
Enterobacter cloacae (%)	16 (20.3)
Susceptible to alternatives	4 (5)

IQR, interquartile range.

3.3. Carbapenem prescription among patients with strains susceptible to alternatives

Among the 54 previously known ESBL-PE rectal carrier patients, 26 (48%) had strains resistant to PTZ and 28 (52%) had strains susceptible to alternatives. No risk factor appeared to be associated with carbapenem prescription as empirical therapy in previously known ESBL-PE carriers. However, these results must be qualified because of the lack of power of the study.

Fifty-eight (73.4%) patients in the definitive therapy cohort (DTC) were infected with strains susceptible to alternatives (according to MIC testing), among whom 47 (81%) were treated with carbapenems as definitive therapy. De-escalation was applied in only 16 (34%) patients who were treated empirically with carbapenems and infected with PTZ-susceptible strains, without compromising in-hospital mortality.

4. Discussion

Data regarding the use of non-carbapenem antimicrobial therapy for ESBL-PE bacteraemia remain scarce.[23] Recent retrospective studies have reported that de-escalation of empirical antimicrobial therapy occurs in approximately 50% of patients with ESBL-producing *Enterobacteriaceae*-related sepsis,[24] but data are heterogeneous and large ranges of de-escalation incidences have been reported among studies. Indeed, until very recently there was no consensus definition for de-escalation.[25–28] Furthermore, in a recent article, Tamma et al.[29] reported an increased risk of death among patients receiving PTZ compared to patients receiving carbapenem therapy for ESBL-producing *Enterobacteriaceae*-related infections. In this retrospective study, antibiotic de-escalation was analyzed in 79 consecutive patients with ESBL-producing *Enterobacteriaceae* bacteraemia. De-escalation, as a global management of antibiotic therapy, occurred in 20% of cases. Several plausible reasons might explain why this rate of antimicrobial therapy de-escalation is lower than those reported in many studies.[23] First, all of the patients in the present study were infected with ESBL-producing *Enterobacteriaceae* strains, thus reducing the number of possible alternatives to carbapenems. Second, one-third of the patients were immunocompromised and two-thirds of the infections were nosocomially acquired, facts that did not encourage the treating physicians to de-escalate. However, although the study was not powered for clinical outcomes, de-escalation appeared to be safe in the present study cohort.

Factors associated with carbapenem maintenance were microbiological (i.e., lack of susceptibility to alternatives) in 21 cases (44.7%) and clinical in 26 cases (55.3%). Among the latter, a history of treatment failure, relapse of infection, clinical severity at onset of sepsis, underlying co-morbidities (e.g. immunosuppression), and polymicrobial infection were the most frequent. In the present cohort, there was a strong correlation between the type of pathogen and the physician's decision to de-escalate or not to de-escalate antibiotics. According to the multivariate analysis, *E. coli*-related infections appeared to be a protective factor against carbapenem prescription (OR 0.11, 95% CI 0.041–0.324; $p = 0.0013$)

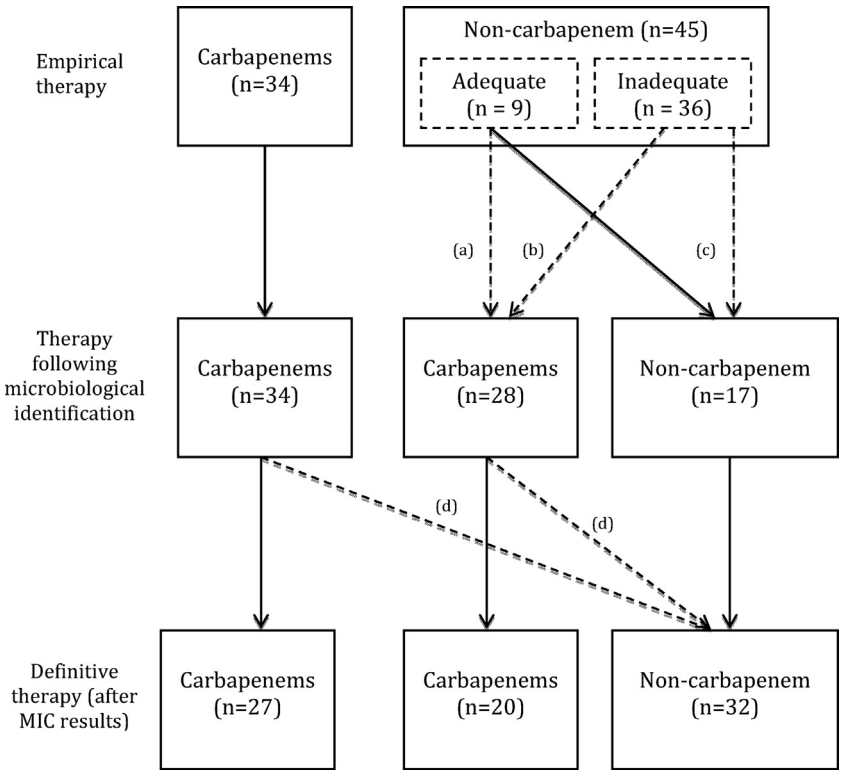

Figure 1. Antibiotic use for the treatment of ESBL-producing *Enterobacteriaceae*-related infections. Thirty-six patients continued to receive empirical treatment as the definitive therapy (continuous lines), including 27 patients receiving carbapenems and nine patients receiving non-carbapenem antibiotics (all PTZ). Antibiotics were changed for 43 patients (dashed lines): from adequate non-carbapenem antibiotics to carbapenems ($n = 2$) (a); from inadequate empirical therapy to carbapenem ($n = 26$) (b); from inadequate empirical therapy to adequate non-carbapenem therapy ($n = 10$). After MIC results were obtained, 15 patients were de-escalated (dashed line) from carbapenem therapy to adequate non-carbapenem therapy (d).

in comparison with infections related to other pathogens (e.g. *Klebsiella pneumoniae* and *Enterobacter cloacae*). An explanation for this could be that these pathogens are more frequently resistant to alternatives and that there are more data regarding the use of alternatives for *E. coli* than for other strains.

There could be multiple reasons behind the slow adoption of antibiotic de-escalation, including hesitancy to change an effective antibiotic regimen (especially for ICU patients) and poor understanding of how and when to de-escalate.[26] As demonstrated by Giantsou et al., de-escalation should be based on reliable microbiological samples[27] and rapid antibiogram testing.[30] Currently, the results of standard microbiological reports (i.e., based on full bacterial identification and on antimicrobial susceptibility tests) rarely reach the treating physician before 48–72 h after the sampling has been performed.[31] In this study, it was found that previously known ESBL-PE rectal carriage was associated with increased empirical carbapenem prescription. One

Table 2
Factors associated with carbapenem prescription as empirical antibiotic therapy in patients with ESBL-related *Enterobacteriaceae* bacteraemia

	ETC Carbapenems $n = 34$	ETC Non-carbapenems $n = 45$	OR (95% CI)	p-Value
Age, years, median (IQR)	46.7 (23–58.3)	24.7 (2.3–58.9)	-	0.878
Nosocomial infections (%)	27 (79.41)	26 (57.8)	2.8 (1.1–7.8)	0.043
Underlying condition				
Immunosuppressive treatment (%)	12 (35.3)	14 (3.1)	1.2 (0.4–3.1)	0.695
Neutropenia (ANC $<0.5 \times 10^9$/l) (%)	1 (2.9)	3 (6.67)	0.42 (0.04–4.2)	0.455
Diabetes mellitus (%)	7 (20.6)	4 (8.89)	2.7 (0.7–9.9)	0.137
HIV infection (%)	1 (2.9)	0 (0)	-	0.247
Hospitalization department				
Intensive care unit (%)	18 (52.9)	9 (20)	4.5 (1.7–12.1)	0.002
Not intensive care unit (%)	16 (47.1)	36 (80)	-	-
Charlson score, median (IQR)	4 (1–6.75)	2 (1–6)	-	0.197
Prior ESBL rectal carriage (%)	30 (88.23)	24 (53.3)	6.5 (1.9–21.7)	0.001
Source of infection				
Catheter (%)	3 (8.8)	5 (11.1)	0.77 (0.17–3.49)	0.739
Lung (%)	9 (26.5)	6 (13.3)	2.25 (0.7–7.7)	0.140
Urinary tract (%)	15 (44.1)	21 (46.7)	0.9 (0.36–2.2)	0.822
Skin and soft tissue (%)	2 (5.9)	1 (2.3)	2.7 (0.2–31.6)	0.415
Digestive (%)	2 (5.9)	6 (13.3)	0.4 (0.07–2.15)	0.277
Unknown (%)	3 (8.8)	6 (13.3)	0.6 (0.14–2.7)	0.532

ESBL, extended-spectrum beta-lactamase; ETC, empirical therapy cohort, univariate analysis; OR, odds ratio; CI, confidence interval; IQR, interquartile range; ANC, absolute neutrophil count.

Table 3
Factors associated with carbapenem maintenance when, following MIC results, alternative drugs were microbiologically suitable

	DTC Carbapenems $n=47$	DTC Non-carbapenems $n=32$	Univariate analysis		Multivariate analysis	
			OR (95% CI)	*p*-Value	OR (95% CI)	*p*-Value
Age, years, median (IQR)	40.9 (3.1–58.8)	24.7 (13–57.6)	1.02 (0.98–1.06)	0.253	1.08 (1–1.16)	0.027
Gender						
Male	30 (63.8)	22 (68.7)	0.96 (0.38–2.47)	0.94	-	-
Female	17 (36.2)	10 (31.3)	-	-		
Nosocomial infection (%)	32 (69.5)	21 (63.64)	1.52 (0.58–4.03)	0.39	-	-
Hospitalization department						
Intensive care unit (%)	18 (38.3)	9 (28.1)	1.96 (0.71–5.4)	0.191	-	-
Not intensive care unit (%)	29 (61.7)	23 (71.9)	-	-		
Charlson score, median (IQR)	3.5 (1–6)	2 (1–5)	1.08 (0.94–1.23)	0.266	-	-
Bone score, median (IQR)	1 (1–2)	1 (1–2)	1.74 (0.94–3.22)	0.079	3.04 (0.99–9.35)	0.052
Prior ESBL-PE rectal carriage	32 (68)	22 (68.7)	0.96 (0.357–2.58)	0.938	-	-
Origin of infection						
Urinary tract (%)	22 (46.8)	20 (62.5)	2.48 (0.88–7.01)	0.087	4.35 (0.71–26.7)	0.11
Non urinary tract infection (%)	25 (53.2)	12 (37.5)	-	-	-	-
Microorganisms						
Escherichia coli (%)	10 (21.3)	24 (75)	0.11 (0.041–0.324)	<0.001	0.04 (0.007–0.24)	<0.001
Non *Escherichia coli (%)*	37 (78.7)	8 (25)	-		-	
Initial clinical efficacy (%)	28 (59.5)	23 (71.9)	0.52 (0.189–1.46)	0.216	0.09 (0.01–0.59)	0.012
Initial monotherapy (%)	16 (34)	17 (53.1)	0.46 (0.18–1.17)	0.104	0.1 (0.016–0.62)	0.014

MIC, minimum inhibitory concentration; DTC, definitive therapy cohort, univariate analysis; OR, odds ratio; CI, confidence interval; IQR, interquartile range; ESBL-PE, extended-spectrum beta-lactamase-producing *Enterobacteriaceae*.

promising approach to reduce carbapenem consumption could be the routine use of MIC testing on ESBL rectal colonization strains with possible susceptibility (according to inhibition zone diameters) to carbapenem alternatives.

In spite of its multiple strengths, this study also has limitations: a small number of patients, factors specific to the institutions (and the fact that the study was bi centric), and limited study duration. The results suggest that a large multicentre prospective study of ESBL-producing *Enterobacteriaceae*-related infections should be conducted in order to better characterize the features associated with carbapenem prescription in daily practice, the rates of non-carbapenem alternative prescription, and the frequency of omission of de-escalation despite accurate antibiotic susceptibility testing. The results of ongoing randomized controlled studies comparing carbapenems to alternatives for the treatment of ESBL-producing *Enterobacteriaceae*-related infections are also eagerly awaited. Stronger evidence-based data will be required to convince physicians that, when performed in a standardized procedure, de-escalation is both safe and effective.

In conclusion, it was found that de-escalation after empirical treatment with carbapenems for ESBL-producing *Enterobacteriaceae*-related infections was performed for less than half of the patients. Reasons for not de-escalating included the absence of an antimicrobial alternative according to antibiotic susceptibility tests, and also clinical and/or microbiological considerations.

Ethical approval: Ethical approval was not required.

Table 4
Reasons for maintaining carbapenem as definitive therapy

Definitive therapy cohort of patients treated with carbapenems (%)	$n=47$
Non-susceptible to alternative (%)	21 (44.7)
Susceptible to alternative (%)	26 (55.3)
Severe sepsis/septic shock (%)	3 (11.5)
Co-morbidities (immunosuppression, etc.) (%)	4(15.4)
Administration facilities (subcutaneous administration) (%)	2 (7.8)
Poor clinical outcome (%)	5 (19.2)
Sepsis source (HCAP, etc.) (%)	4 (15.4)
Polymicrobial infection (%)	1 (3.8)
Relapse or recurrence of the infection (%)	7 (26.9)

HCAP, health care-associated pneumonia.

Conflict of interest: The authors declare that they have no competing interests.

References

1. Arpin C, Quentin C, Grobost F, Cambau E, Robert J, Dubois V, et al. Nationwide survey of extended-spectrum β-lactamase-producing *Enterobacteriaceae* in the French community setting. *J Antimicrob Chemother* 2009;**63**:1205–14. http://dx.doi.org/10.1093/jac/dkp108.
2. Meier S, Weber R, Zbinden R, Ruef C, Hasse B. Extended-spectrum β-lactamase-producing Gram-negative pathogens in community-acquired urinary tract infections: an increasing challenge for antimicrobial therapy. *Infection* 2011;**39**:333–40. http://dx.doi.org/10.1007/s15010-011-0132-6.
3. Hoban DJ, Nicolle LE, Hawser S, Bouchillon S, Badal R. Antimicrobial susceptibility of global inpatient urinary tract isolates of *Escherichia coli*: results from the Study for Monitoring Antimicrobial Resistance Trends (SMART) program: 2009-2010. *Diagn Microbiol Infect Dis* 2011;**70**:507–11. http://dx.doi.org/10.1016/j.diagmicrobio.2011.03.021.
4. Paterson DL, Mulazimoglu L, Casellas JM, Ko WC, Goossens H, Von Gottberg A, et al. Epidemiology of ciprofloxacin resistance and its relationship to extended-spectrum beta-lactamase production in *Klebsiella pneumoniae* isolates causing bacteremia. *Clin Infect Dis* 2000;**30**:473–8. http://dx.doi.org/10.1086/313719.
5. Pletz MW, Rau M, Bulitta J, De Roux A, Burkhardt O, Kruse G, et al. Ertapenem pharmacokinetics and impact on intestinal microflora, in comparison to those of ceftriaxone, after multiple dosing in male and female volunteers. *Antimicrob Agents Chemother* 2004;**48**:3765–72. http://dx.doi.org/10.1128/AAC.48.10.3765-3772.2004.
6. Cantón R, Akóva M, Carmeli Y, Giske CG, Glupczynski Y, Gniadkowski M, et al. Rapid evolution and spread of carbapenemases among *Enterobacteriaceae* in Europe. *Clin Microbiol Infect* 2012;**18**:413–31. http://dx.doi.org/10.1111/j.1469-0691.2012.03821.x.
7. Rodríguez-Baño J, Alcalá JC, Cisneros JM, Grill F, Oliver A, Horcajada JP, et al. Community infections caused by extended-spectrum beta-lactamase-producing *Escherichia coli*. *Arch Intern Med* 2008;**168**:1897–902. http://dx.doi.org/10.1001/archinte.168.17.1897.
8. Vardakas KZ, Tansarli GS, Rafailidis PI, Falagas ME. Carbapenems versus alternative antibiotics for the treatment of bacteraemia due to *Enterobacteriaceae* producing extended-spectrum β-lactamases: a systematic review and meta-analysis. *J Antimicrob Chemother* 2012;**67**:2793–803. http://dx.doi.org/10.1093/jac/dks301.
9. Retamar P, López-Cerero L, Muniain MA, Pascual Á, Rodríguez-Baño J, ESBL-REIPI/GEIH Group. Impact of the MIC of piperacillin–tazobactam on the outcome of patients with bacteremia due to extended-spectrum-β-lactamase-producing *Escherichia coli*. *Antimicrob Agents Chemother* 2013;**57**(7):3402–4. http://dx.doi.org/10.1128/AAC.00135-13.
10. Park SH, Choi SM, Chang YK, Lee DG, Cho SY, Lee HJ, et al. The efficacy of non-carbapenem antibiotics for the treatment of community-onset acute pyelonephritis due to extended-spectrum β-lactamase-producing *Escherichia coli*. *J Antimicrob Chemother* 2014;**69**(10):2848–56. http://dx.doi.org/10.1093/jac/dku215.

11. Lee NY, Lee CC, Huang WH, Tsui KC, Hsueh PR, Ko WC. Cefepime therapy for monomicrobial bacteremia caused by cefepime-susceptible extended-spectrum beta-lactamase-producing *Enterobacteriaceae*: MIC matters. *Clin Infect Dis* 2013;**56**:488–95. http://dx.doi.org/10.1093/cid/cis916.
12. Kim YK, Pai H, Lee HJ, Park SE, Choi EH, Kim J, et al. Bloodstream infections by extended-spectrum beta-lactamase-producing *Escherichia coli* and *Klebsiella pneumoniae* in children: epidemiology and clinical outcome. *Antimicrob Agents Chemother* 2002;**46**:1481–91.
13. Paterson DL. Recommendation for treatment of severe infections caused by *Enterobacteriaceae* producing extended-spectrum beta-lactamases (ESBLs). *Clin Microbiol Infect* 2000;**6**:460–3.
14. Mandell LA, Wunderink RG, Anzueto A, Bartlett JG, Campbell GD, Dean NC, et al. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. *Clin Infect Dis* 2007;**44**(Suppl 2):S27–72. http://dx.doi.org/10.1086/511159.
15. Solomkin JS, Mazuski JE, Bradley JS, Rodvold KA, Goldstein EJ, Baron EJ, et al. Diagnosis and management of complicated intra-abdominal infection in adults and children: guidelines by the Surgical Infection Society and the Infectious Diseases Society of America. *Surg Infect* 2010;**11**:79–109. http://dx.doi.org/10.1089/sur.2009.9930.
16. Gupta K, Hooton TM, Naber KG, Wullt B, Colgan R, Miller LG, et al. International clinical practice guidelines for the treatment of acute uncomplicated cystitis and pyelonephritis in women: a 2010 update by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases. *Clin Infect Dis* 2011;**52**:e103–20. http://dx.doi.org/10.1093/cid/ciq257.
17. Bone RC, Balk RA, Cerra FB, Dellinger RP, Fein AM, Knaus WA, et al. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine. 1992. Chest 2009; 136(5 Suppl) e28.
18. Centers for Disease Control, Prevention (CDC). Revised surveillance case definition for HIV infection—United States, 2014. *MMWR Recomm Rep* 2014;**63**(RR-03):1–10.
19. Stevenson KB, Khan Y, Dickman J, Gillenwater T, Kulich P, Myers C, et al. Administrative coding data, compared with CDC/NHSN criteria, are poor indicators of health care-associated infections. *Am J Infect Control* 2008;**36**:155–64. http://dx.doi.org/10.1016/j.ajic.2008.01.004.
20. European Committee on Antimicrobial Susceptibility Testing. Clinical breakpoints, version 01/01/2014. Available at: http://www.eucast.org (accessed March 31, 2014).
21. Soussy CJ, Carret G, Cavallo JD, Chardon H, Chidiac C, Choutet P, et al. [Antibiogram Committee of the French Microbiology Society. Report 2000-2001]. *Pathol Biol (Paris)* 2000;**48**:832–71.
22. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Lancet* 2007;**370**:1453–7. http://dx.doi.org/10.1016/S0140-6736(07)61602-X.
23. Delory T, De Pontfarcy A, Emirian A, About F, Berdougo B, Brun-Buisson C, et al. Impact of a program combining pre-authorization requirement and post-prescription review of carbapenems: an interrupted time-series analysis. *Eur J Clin Microbiol Infect Dis* 2013;**32**:1599–604. http://dx.doi.org/10.1007/s10096-013-1918-5.
24. Heenen S, Jacobs F, Vincent JL. Antibiotic strategies in severe nosocomial sepsis: why do we not de-escalate more often? *Crit Care Med* 2012;**40**:1404–9. http://dx.doi.org/10.1097/CCM.0b013e3182416ecf.
25. Niederman MS, Soulountsi V. De-escalation therapy: is it valuable for the management of ventilator-associated pneumonia? *Clin Chest Med* 2011;**32**:517–34. http://dx.doi.org/10.1016/j.ccm.2011.05.009.
26. Weiss E, Zahar JR, Lesprit P, Ruppe E, Leone M, Chastre J, et al. Elaboration of a consensual definition of de-escalation allowing a ranking of β-lactams. *Clin Microbiol Infect* 2015;**21**. http://dx.doi.org/10.1016/j.cmi.2015.03.013. 649.e1-649.e10.
27. Giantsou E, Liratzopoulos N, Efraimidou E, Panopoulou M, Alepopoulou E, Kartali-Ktenidou S, et al. De-escalation therapy rates are significantly higher by bronchoalveolar lavage than by tracheal aspirate. *Intensive Care Med* 2007;**33**:1533–40. http://dx.doi.org/10.1007/s00134-007-0619-x.
28. Leone M, Bourgoin A, Cambon S, Dubuc M, Albanèse J, Martin C. Empirical antimicrobial therapy of septic shock patients: adequacy and impact on the outcome. *Crit Care Med* 2003;**31**:462–7. http://dx.doi.org/10.1097/01.CCM.0000050298.59549.4A.
29. Tamma PD, Han JH, Rock C, Harris AD, Lautenbach E, Hsu AJ, et al. Carbapenem therapy is associated with improved survival compared with piperacillin–tazobactam for patients with extended-spectrum β-lactamase bacteremia. *Clin Infect Dis* 2015;**60**(9):1319–25. http://dx.doi.org/10.1093/cid/civ003.
30. Bouza E, Torres MV, Radice C, Cercenado E, de Diego R, Sánchez-Carrillo C, et al. Direct E-test (AB Biodisk) of respiratory samples improves antimicrobial use in ventilator-associated pneumonia. *Clin Infect Dis* 2007;**44**:382–7. http://dx.doi.org/10.1086/510587.
31. Garnacho-Montero J, Gutiérrez-Pizarraya A, Escoresca-Ortega A, Corcia-Palomo Y, Fernández-Delgado E, Herrera-Melero I, et al. De-escalation of empirical therapy is associated with lower mortality in patients with severe sepsis and septic shock. *Intensive Care Med* 2014;**40**:32–40. http://dx.doi.org/10.1007/s00134-013-3077-7.