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Clinical outcomes of carbapenem de-escalation regardless of microbiological results: A propensity score analysis

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ABSTRACT

Objective: The aim of this study was to evaluate the safety and efficacy of de-escalation in patients under treatment with carbapenems and its impact on clinical outcomes.
Methods: A prospective observational study was conducted for 1 year. Patients administered active carbapenems for at least 24 h were included. Primary outcomes were in-hospital mortality, mortality at 30 days after carbapenem prescription, and infection-related readmission within 30 days. De-escalation was defined as the substitution of carbapenem with narrower spectrum antimicrobial agents or its discontinuation during the first 96 h of treatment.
Results: The study included 1161 patients, and de-escalation was performed in 667 (57.5%) of these. In the de-escalation group, 54.9% of cultures were positive. After propensity score matching, 30-day mortality was lower (17.4% vs. 25.7%, $p = 0.036$), carbapenem treatment was 4 days shorter (4 vs. 8 days, $p < 0.001$), total antibiotic therapy duration was 2 days longer (12 vs. 10 days, $p = 0.003$), and length of hospital stay was 5 days shorter (8 vs. 13 days, $p = 0.008$) in the de-escalated versus non-de-escalated patients. In-hospital mortality and 30-day readmission rates did not differ significantly between these groups.
Conclusion: Carbapenem de-escalation is a safe strategy that does not compromise the clinical status of patients.

Introduction

Infectious diseases require the rapid administration of appropriate empirical treatment, and a delay of hours can worsen the prognosis (Pogue et al., 2015). Gram-negative bacilli cause almost half of all bacteremia cases in hospitals, mostly from a previous focus of infection (Livermore, 2012).

Carbapenems are broad-spectrum beta-lactam bactericidal antibiotics that act on cell wall synthesis, binding to penicillin binding protein (PBP) and inhibiting beta-lactamases with the broadest spectrum of activity. They remain the antibiotics of choice for the treatment of bacteria producing extended-spectrum beta-lactamase (ESBL) and AmpC beta-lactamases (Vardakas et al., 2012; Breilh et al., 2013). Carbapenems are often prescribed in the case of immunosuppression, intensive care unit (ICU) admission, recent hospitalization or antibiotherapy, colonization by ESBL-producing *Enterobacteriaceae*, and nosocomial infection, and they are also used as rescue therapy (Masterton, 2009; Pilmis et al., 2015).

Carbapenems have shown advantages over certain antibiotics in the treatment of bacteremia caused by ESBL-producing *Enterobacteriaceae* (Vardakas et al., 2012; Lee et al., 2013; Tamma et al., 2015), but their indiscriminate use and excessive lengths of treatment, among other factors, have favoured the emergence of carbapenem-resistant bacteria (Gupta et al., 2011; Doi and Paterson, 2015; Mladenovic-Antic et al., 2016). The emergence of multi-resistant bacteria has prompted policies to minimize inappropriate antibiotic administration and to reduce prescriptions, dosages, and the length of treatment (Lipsitch and Samore, 2002).

Antibiotic therapy optimization programmes are designed to control and treat multi-resistant microorganisms and reduce antibiotic-related adverse effects such as infection by *Clostridium difficile*. One approach to avoid the overuse and misuse

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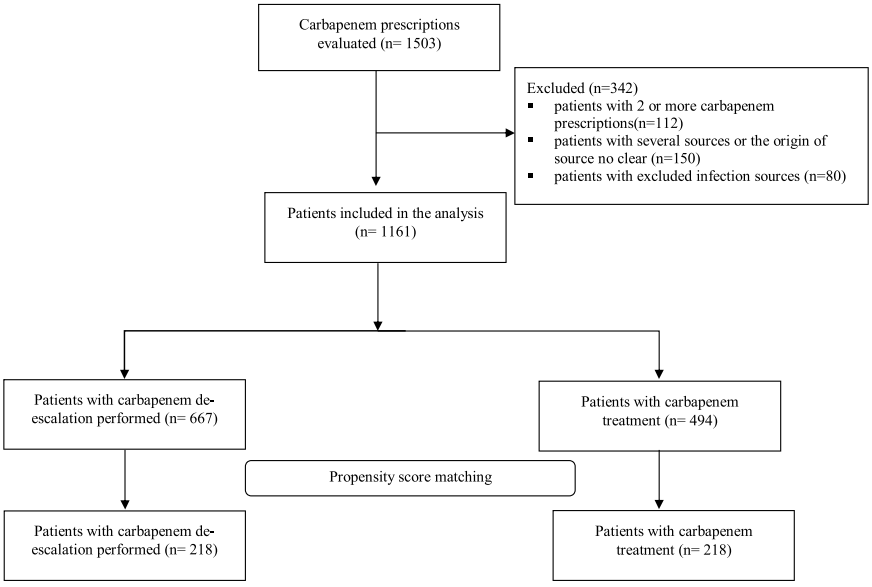

Figure 1. Flowchart of patient selection.

of broad-spectrum antibiotics and the emergence of resistance is de-escalation (Rodríguez-Baño et al., 2012b). De-escalation options include the following: adjustment of the antibiotic treatment according to the clinical response, microbiological culture results, and/or susceptibility of the isolated pathogen; discontinuation of the treatment; and/or the conversion of combined therapy to monotherapy (Masterton, 2011; Weiss et al., 2015).

The main objective of this study was to evaluate the safety and efficacy of de-escalation in patients under treatment with carbapenems and its impact on clinical outcomes, in order to implement interventions for the de-escalation of broad-spectrum antibiotics as part of the competencies of the Antimicrobial Stewardship Programme (ASP) team.

Table 1
Characteristics of patients in the study cohort.

	Total (*N* = 1161)
Age, years, median (IQR)	74 (59–83)
Sex, male, *n* (%)	694 (59.8)
Charlson index score, median (IQR)	5 (3–7)
Comorbidities, *n* (%)	
Cancer	238 (20.5)
Diabetes	344 (29.6)
Kidney disease	194 (16.7)
Liver disease	124 (10.7)
Cardiac disease	249 (21.4)
Lung disease	209 (18.0)
Admission in previous 30 days, *n* (%)	252 (21.7)
Antibiotic therapy in previous 30 days, *n* (%)	122 (10.5)
Department, *n* (%)	
Medical	626 (53.9)
Surgical	535 (46.1)
Source, *n* (%)	
Intra-abdominal	411 (35.4)
Respiratory	338 (29.1)
Urinary	269 (23.2)
Skin and soft tissue	143 (12.3)
Sepsis, *n* (%)	151 (13.0)
Nosocomial origin, *n* (%)	260 (22.4)
Invasive procedure, *n* (%)	476 (41.0)
ICU stay, *n* (%)	126 (10.9)
Urinary catheter, *n* (%)	496 (42.7)
Time to carbapenem prescription since admission, days, median (IQR)	0 (0–6)
Carbapenem, *n* (%)	
Ertapenem	384 (33.1)
Anti-pseudomonal	777 (66.9)
Monotherapy, *n* (%)	743 (64.0)
Culture request, *n* (%)	902 (77.7)
Positive culture	466 (51.7)
Negative culture	436 (48.3)
Bacteremia, *n* (%)	128 (11.0)
Appropriate therapy, *n* (%)	792 (68.2)
Incidence of *Clostridium difficile* infection, *n* (%)	17 (1.5)

IQR, interquartile range; ICU, intensive care unit.

Methods

Study design and population

This prospective observational study was conducted in an 1100-bed tertiary-level university hospital in southern Spain between August 1, 2013 and July 31, 2014. All patients hospitalized in the medical wards who started treatment with carbapenems at the time of admission or during their hospital stay for intra-abdominal, respiratory, urinary, skin, or soft tissue infections were included. All infectious syndromes included were diagnosed based on clinical, laboratory, and imaging data. Patients hospitalized in the oncology and haematology departments were excluded from the study due to the lack of conclusive evidence about short-course treatments and narrow-spectrum antibiotics in immunocompromised patients; in addition, the treatment of these patients is performed according to specific protocols and guidelines (Freifeld et al. 2011). Patients receiving multiple carbapenem treatments were only included once.

The ASP team was founded in 2010. At the time of the study, it included two infectious disease (ID) specialists, two pharmacists, one microbiologist, one critical care specialist, one paediatrician, and one epidemiologist.

Microbiological isolates were collected prospectively, and antimicrobial susceptibility was determined by disc diffusion method according to the contemporary breakpoints recommended by the Clinical and Laboratory Standards Institute (CLSI). Surveillance for *C. difficile* infection was performed during the patient's hospital stay and this infection was diagnosed by toxin A/B rapid immunoassay.

Data were gathered using the hospital electronic medical records and were treated in accordance with current data protection legislation (Law 15/1999, December 13). The study

Table 2.1
Enterobacteriaceae sensitivity (%).

AM–CL[1]	PIP-TZ[2]	CEF3G[3]	ERTA[4]	IMI[5]	CIPRO[6]	FOSFO[7]	AMG[8]	CEF[9]	TMP–SMX[10]
56.2	92.6	63.4	96	92.1	66.1	77.3	88.4	83.3	53.1

[1]Amoxicillin–clavulanate; [2]piperacillin–tazobactam; [3]third-generation cephalosporins; [4]ertapenem; [5]imipenem; [6]ciprofloxacin; [7]fosfomycin; [8]aminoglycosides; [9]cefepime; [10]trimethoprim–sulfamethoxazole.

was approved by the ethics committee of the hospital and complied with the principles of the Declaration of Helsinki and biomedical research legislation (Law 14/2007, July 3).

Variables and definitions

Data were gathered on age, sex, comorbidities, Charlson index, hospital department, sepsis, hospitalization during the previous 30 days, history of antimicrobial treatment, infection focus, nosocomial infection, use of invasive procedures, previous ICU admission for at least 48 h, bladder catheterization, carbapenem type, prescription type (first-choice or rescue; monotherapy or combined therapy), microbiological test requests and results, and the appropriate/inappropriate prescription of carbapenems.

The main outcome variables were in-hospital mortality, mortality at 30 days after carbapenem prescription, and infection-related re-admission within 30 days. Secondary outcome variables were the durations of carbapenem treatment, total antibiotic therapy, and hospital stay, and the onset of *C. difficile* infection during hospital stay.

De-escalation was defined as the substitution of the carbapenem with a narrower spectrum antimicrobial agent, following Kollef et al. (2006), or discontinuation of the carbapenem after ≤96 h of treatment. Carbapenem treatment was considered appropriate when prescribed for severely ill patients with risk factors for infection by ESBL-producing bacteria (Tumbarello et al., 2011; Johnson et al., 2013) or when active against the isolated microorganism. Regarding patients with ESBL-producing *Enterobacteriaceae*, de-escalation was applied in the same way according to antimicrobial susceptibility testing and the site of infection. The most commonly used antibiotics were amoxicillin–clavulanate, piperacillin–tazobactam, and fluoroquinolones. Two antibiotics were active against gram-negative bacteria. De-escalation was always ordered by the attending physician. For patients with negative cultures, de-escalation was performed based on the changes in the patient's clinical examination and laboratory test results and depending on the site of infection, microorganisms most frequently involved, and local susceptibility of these microorganisms. The Department of Microbiology reports local annual cumulative antimicrobial susceptibility testing data, which facilitates empirical prescribing and antimicrobial de-escalation.

Statistical analysis

In the descriptive analysis, the mean and standard deviation, or median and interquartile range were calculated for quantitative variables, and absolute and relative frequencies were calculated for qualitative variables. The Pearson Chi-square test or Fisher's exact test was used to analyze relationships among qualitative variables, and the non-parametric Mann–Whitney test was used to examine relationships between qualitative and quantitative variables with a non-normal distribution (assessed by Kolmogorov–Smirnov test).

The propensity score (PS) method, which yields the likelihood of a subject being in a particular group, was used to adjust for baseline differences between study groups. In order to calculate the probability of carbapenem de-escalation, a non-parsimonious logistic regression model was constructed considering the following variables: age, Charlson index, hospital department, infection focus, sepsis, hospitalization during the previous 30 days, nosocomial infection, invasive procedures, bladder catheterization, ICU admission for at least 48 h, carbapenem type, monotherapy, and culture result. The PS was entered into the multivariate analysis as a covariate and was then used for stratified analysis according to PS quartiles, and finally for matching patients by the nearest neighbour method to balance the groups and minimize bias. The goodness-of-fit of the logistic regression model was evaluated with the Hosmer–Lemeshow test, and a receiver operating characteristics (ROC) curve was constructed to determine the predictive capacity of the model. IBM SPSS Statistics version 19 and R version 3.3.1 software programs were used for the statistical analysis; $p < 0.05$ was considered significant in all tests.

Table 2.2
Pseudomonas aeruginosa sensitivity (%).

PIP–TZ[1]	MER[2]	IMI[3]	CIPRO[4]	FOSFO[5]	AMG[6]	Anti-Ps-CEF[7]
92.6	90.7	84.5	62.5	36.8	83.8	82.5

[1]Piperacillin–tazobactam; [2]meropenem; [3]imipenem; [4]ciprofloxacin; [5]fosfomycin; [6]aminoglycosides; [7]anti-pseudomonal cephalosporins.

Results

Study population

Out of a total of 1503 prescriptions identified during the study period, 342 were excluded (Figure 1). De-escalation was performed in 667 (57.5%) of the final sample of 1161 patients after a median treatment duration of 4 days. The remaining 494 patients (42.5%) continued with the same treatment.

Table 1 lists the clinical and epidemiological characteristics of the patients and data on their carbapenem prescription; 21.7% had been hospitalized during the previous 30 days and 10.5% had received antibiotherapy, 13.0% met sepsis criteria and 22.4% had a nosocomial infection, and 10.9% were in the ICU for at least 48 h during their hospital stay. Carbapenem treatment was considered appropriate in 68.2% of the patients according to their clinical status and/or the isolated microorganism.

Microbiological diagnostic tests were requested for 77.7% (902/1161) of the patients and the microorganism was isolated in 51.7% (466/902). Isolates were gram-negative bacilli (GNB) in 66.7% (311/466). Among GNB, 74.0% (230/311) were *Enterobacteriaceae*, 22.8% (71/311) *Pseudomonas aeruginosa*, and 6.8% other non-fermenting GNB. Among *Enterobacteriaceae*, 35.2% (81/230) were ESBL or AmpC-producing, affecting 6.98% of the study population. *Enterobacteriaceae* were susceptible to piperacillin–tazobactam in 92.6% of cases, cefepime in 83.3%, ertapenem in 96.0%, and imipenem in 92.1%. *P. aeruginosa* was susceptible to piperacillin–tazobactam in 92.6% of cases, meropenem in 90.7%, and imipenem in 84.5% (Tables 2.1 and 2.2). The frequency of infection by *C. difficile* was 1.5% among the patients in the cohort (Table 3).

De-escalation group

Bivariate analysis

The Charlson index was lower in the de-escalated group ($p = 0.031$), and a smaller percentage of this group (19.5%) were

Table 3
Characteristics of patients in the study cohort and the propensity matched cohort.

	Unmatched cohort			Matched cohort		
	Carbapenem de-escalation ($n = 667$)	Carbapenem no de-escalation ($n = 494$)	p-Value	Carbapenem de-escalation ($n = 218$)	Carbapenem no de-escalation ($n = 218$)	p-Value
Age, years, median (IQR)	74 (56–83)	75 (61–82)	0.235	77 (61–84)	75 (59–83)	0.645
Sex, male, *n* (%)	406 (60.9)	288 (58.3)	0.377	122 (48.8)	128 (51.2)	0.561
Age-adjusted Charlson index score, median (IQR)	5 (3–7)	5 (4–7)	0.031	5 (4–7)	5 (3–6)	0.341
Comorbidities, *n* (%)						
Cancer	121 (18.1)	117 (23.7)	0.021	38 (43.7)	49 (56.3)	0.187
Diabetes	197 (29.5)	147 (29.8)	0.935	67 (50.4)	66 (49.6)	0.917
Kidney disease	115 (17.2)	79 (16.0)	0.573	38 (57.6)	28 (42.4)	0.181
Liver disease	61 (9.1)	63 (12.8)	0.049	15 (39.5)	23 (60.5)	0.174
Cardiac disease	134 (20.1)	115 (23.3)	0.191	46 (47.7)	51 (52.6)	0.565
Lung disease	119 (17.8)	90 (18.2)	0.869	46 (52.9)	41 (47.1)	0.549
Admission in previous 30 days, *n* (%)	130 (19.5)	122 (24.7)	0.033	47 (21.6)	36 (16.5)	0.180
Antibiotic therapy in previous 30 days, *n* (%)	67 (10.0)	55 (11.1)	0.550	23 (63.9)	13 (36.1)	0.082
Department, *n* (%)						
Medical	347 (52.0)	279 (56.5)	0.132	130 (59.6)	124 (56.9)	0.560
Surgical	320 (48.0)	215 (43.5)		88 (40.4)	94 (43.1)	
Source, *n* (%)						
Intra-abdominal	215 (32.2)	196 (39.7)	0.001	75 (34.4)	87 (39.9)	0.160
Respiratory	184 (27.6)	154 (31.2)		73 (33.5)	68 (31.2)	
Urinary	175 (26.2)	94 (19.0)		56 (25.7)	41 (18.8)	
Skin and soft tissue	93 (13.9)	50 (10.1)		14 (6.4)	22 (10.1)	
Sepsis, *n* (%)	77 (11.5)	74 (15.0)	0.085	28 (12.8)	25 (11.5)	0.660
Nosocomial origin, *n* (%)	138 (20.7)	122 (24.7)	0.105	44 (20.2)	34 (15.6)	0.211
Invasive procedure, *n* (%)	263 (39.4)	213 (43.1)	0.207	79 (36.2)	80 (36.7)	0.921
ICU stay ≥48 h, *n* (%)	60 (9.0)	66 (13.4)	0.018	9 (4.1)	12 (5.5)	0.502
Urinary catheter, *n* (%)	273 (40.9)	223 (45.1)	0.151	88 (40.4)	88 (40.4)	1.000
Carbapenem, *n* (%)						
Ertapenem	247 (37.0)	137 (27.7)	0.001	75 (34.4)	75 (34.4)	1.000
Anti-pseudomonal	420 (63.0)	357 (72.3)		143 (65.6)	143 (65.6)	
Monotherapy, *n* (%)	448 (67.2)	295 (59.7)	0.009	142 (65.1)	140 (64.2)	0.841
Culture request, *n* (%)	510 (76.5)	392 (79.4)	0.242	169 (49.4)	173 (50.6)	0.641
Positive culture	280/510 (54.9)	186/392 (47.7)	0.026	82 (49.1)	85 (50.9)	0.910
Negative culture	230/510 (45.1)	206/392 (52.6)		87 (49.7)	88 (50.3)	
Bacteremia, *n* (%)	74 (11.1)	54 (10.9)	0.930	22 (10.1)	22 (10.1)	1.000
ESBL and AmpC producing *Enterobacteriaceae*,*n* (%)[a]	36/139 (25.9)	45/91 (49.5)	<0.001	10/40 (25.0)	20/41 (48.8)	0.027
Pseudomonas aeruginosa, *n* (%)[b]	43/186 (23.1)	28/125 (22.4)	0.882	14/49 (28.6)	15/56 (26.8)	0.838
Appropriate therapy, *n* (%)	441 (66.1)	351 (71.1)	0.074	137 (62.8)	143 (65.6)	0.549
Primary outcomes, *n* (%)						
In-hospital mortality	93 (13.9)	97 (19.6)	0.010	33 (15.1)	46 (21.1)	0.106
30-day mortality	109 (16.3)	124 (25.1)	<0.001	38 (17.4)	56 (25.7)	0.036
30-day re-admission	70 (10.5)	48 (9.7)	0.664	29 (13.3)	20 (9.2)	0.172
Secondary outcomes						
Duration of carbapenem therapy, days, median (IQR)	4 (3–6)	8 (6–11)	<0.001	4 (3–6)	8 (6–10)	<0.001
Hospital stay, days, median (IQR)	9 (5–18)	15 (9–26)	<0.001	8 (6–17)	13 (9–21)	0.008
Duration of antibiotic therapy, days, median (IQR)	12 (6–17)	10 (7–14)	0.213	12 (6–16)	10 (7–13)	0.003
Incidence of *Clostridium difficile* infection, *n* (%)	8 (1.2)	9 (1.8)	0.383	3 (1.4)	3 (1.4)	1.000

IQR, interquartile range; ICU, intensive care unit; ESBL, extended-spectrum beta-lactamase.
[a] Of the total *Enterobacteriaceae* isolated.
[b] Of the total of gram-negative pathogens.

hospitalized during the previous 30 days in comparison to the non-de-escalated group (19.5% vs. 24.7%, $p = 0.033$). The de-escalated group included a lower percentage of patients with cancer (18.1% vs. 23.7%, $p = 0.021$), liver disease (9.1% vs. 12.8%, $p = 0.049$), and/or ICU admission for at least 48 h (9.0% vs. 13.4%, $p = 0.018$), and also of patients with carbapenem monotherapy (67.2% vs. 59.7%, $p = 0.009$) in comparison to the non-de-escalated group. Carbapenems were more frequently prescribed within 1 day of admission in the non-de-escalated group ($p = 0.031$). De-escalation was performed in 25.9% (36/139) of patients with ESBL-producing *Enterobacteriaceae* versus 49.5% (45/91) of those without ($p < 0.01$), and in 54.9% of patients with positive cultures versus 45.1% of those without ($p = 0.026$). In terms of the variables related to the severity of the patients' conditions, no difference was found between the groups in the frequency of sepsis ($p = 0.085$), nosocomial infection ($p = 0.105$), or bacteremia ($p = 0.930$), or the isolation of *P. aeruginosa* ($p = 0.882$). The rate of appropriateness was 66.1% in the de-escalated group compared to 71.1% in the non-de-escalated group ($p = 0.074$) (Table 3).

De-escalated and non-de-escalated patients were matched according to PS values, obtaining 218 pairs. The two groups differed only in the percentage with ESBL-producing *Enterobacteriaceae* (25% vs. 48.8%, respectively, $p = 0.027$) (Table 3).

Primary outcome variables: in-hospital mortality, 30-day mortality, and readmissions

The in-hospital mortality rate was 13.9% for the de-escalated group versus 19.6% for the non-de-escalated group ($p = 0.010$) in

Table 4.1
Logistic regression analysis showing the association between different variables and in-hospital mortality.

	Univariate analysis		Adjusted analysis	
	OR (95% CI)	*p*-Value	OR (95% CI)	*p*-Value
Age	1.05 (1.04–1.07)	<0.001	1.03 (1.01–1.05)	<0.001
Sex				
Male	1.09 (0.79–1.50)	0.580		
Female	Reference			
Charlson index score	1.36 (1.27–1.45)	<0.001	1.20 (1.10–1.31)	<0.001
Department				
Medical	3.51 (2.44–5.05)	<0.001	1.94 (1.30–2.88)	0.001
Surgical	Reference			
Invasive procedure	0.44 (0.31–0.63)	<0.001		
Nosocomial origin	1.52 (1.07–2.16)	0.018		
ICU stay	1.23 (0.77–1.98)	0.389		
Urinary catheter	2.57 (1.87–3.54)	<0.001	1.48 (1.03–2.12)	0.032
Antibiotic therapy in previous 30 days	1.89 (1.21–2.93)	0.005		
Admission in previous 30 days	4.25 (3.05–5.91)	<0.001	2.86 (1.98–4.14)	<0.001
Duration of carbapenem therapy	0.99 (0.95–1.24)	0.456		
Time to carbapenem prescription since admission	1.02 (1.006–1.003)	0.005	1.02 (1.01–1.04)	0.007
Time to use of carbapenem as rescue	1.02 (0.97–1.07)	0.438		
Sepsis	4.80 (3.30–6.97)	0.001		
Carbapenem		0.068		
Ertapenem	Reference			
Anti-pseudomonal	1.38 (0.98–1.95)			
Carbapenem as first-line choice	0.62 (0.45–0.85)	0.003		
Carbapenem as rescue therapy	Reference			
Source				
Skin and soft tissue	Reference			
Intra-abdominal	0.71 (0.41–1.23)	0.220		
Respiratory	1.65 (0.98–2.78)	0.060		
Urinary	1.05 (0.59–1.83)	0.870		
Culture request	0.94 (0.65–1.37)	0.758		
Positive culture	0.83 (0.54–1.26)	0.370		
ESBL and AmpC producing *Enterobacteriaceae*	1.08 (0.59–1.98)	0.804		
Monotherapy	0.70 (0.51–0.96)	0.025		
Carbapenem de-escalation	0.66 (0.49–0.91)	0.010	0.75 (0.53–1.07)	0.112
Propensity score	0.013 (0.003–0.054)	<0.001	0.29 (0.06–1.46)	0.134

OR, odds ratio; CI, confidence interval; ICU, intensive care unit; ESBL, extended-spectrum beta-lactamase.

the bivariate analysis and was 15.1% versus 21.1%, respectively, in the PS-matched cohort ($p = 0.106$) (Table 3).

For patients with ESBL-producing *Enterobacteriaceae*, no significant differences were found between the de-escalated group and non-de-escalated group in the bivariate analysis ($p = 0.077$) or in the PS-matched cohort ($p = 0.682$) (**Supplementary Material**, Table S1).

In the adjusted multivariate analysis, the following variables were significantly associated with a likelihood of in-hospital mortality: age (odds ratio (OR) 1.03, 95% confidence interval (CI) 1.01–1.05, $p < 0.001$), Charlson index (OR 1.20, 95% CI 1.10–1.31, $p < 0.001$), hospitalization in the medical versus surgical department (OR 1.94, 95% CI 1.30–2.88, $p = 0.001$), bladder catheterization (OR 1.48, 95% CI 1.03–2.12, $p = 0.032$), and previous hospitalization (OR 2.86, 95% CI 1.98–4.14, $p < 0.001$) (Table 4.1).

The 30-day mortality rate was lower in the de-escalated versus non-de-escalated group in the bivariate analysis (16.3% vs. 25.1%, $p < 0.001$) and PS-matched cohort (17.4% vs. 25.7%, respectively, $p = 0.036$) (Table 3). Furthermore, for patients with ESBL-producing *Enterobacteriaceae* the 30-day mortality rate was lower in the de-escalated group (8.3% vs. 31.1%, $p = 0.014$) and PS-matched cohort (20.0% vs. 35.0%, $p = 0.675$) (**Supplementary Material**, Table S2).

In the adjusted multivariate analysis, the following variables were significantly associated with 30-day mortality: age (OR 1.03, 95% CI 1.02–1.05, $p < 0.001$), Charlson index (OR 1.20, 95% CI 1.10–1.31, $p < 0.001$), hospitalization in the medical versus surgical department (OR 2.47, 95% CI 1.68–3.63, $p < 0.001$), previous hospitalization (OR 2.81, 95% CI 1.97–4.01, $p < 0.001$), and longer hospital stay (OR 1.02, 95% CI 1.01–1.03, $p < 0.001$) (Table 4.2).

No statistically significant between-group difference was found in the percentage of patients readmitted within 30 days in either the bivariate analysis or PS-matched cohort ($p = 0.664$ and $p = 0.172$, respectively) (Table 3). No significant difference between the two groups was evident in patients with ESBL-producing *Enterobacteriaceae* in both analyses ($p = 0.618$ and $p = 0.657$, respectively) (**Supplementary Material**, Table S2).

When patients were stratified into quartiles according to PS values, in-hospital mortality and 30-day mortality were found to be significantly lower in de-escalated patients than in non-de-escalated patients in the third and fourth PS quartiles (Q3: $p = 0.019$ and $p = 0.006$; Q4: $p = 0.002$ and $p = 0.001$, respectively) (Table 5).

Secondary outcomes

In comparison to non-de-escalated patients, carbapenem treatment was 4 days shorter ($p < 0.001$) for de-escalated patients in the bivariate analysis and PS-matched cohort, while the hospital stay was 6 days shorter in the bivariate analysis ($p < 0.01$) and 5 days shorter in the PS-matched cohort ($p = 0.008$). No between-group difference in the duration of total antibiotic treatment was observed in the bivariate analysis, but it was 2 days longer for de-escalated patients in the PS-matched cohort ($p = 0.03$) (Table 3). No significant differences were found between groups and in both analyses in patients with combination therapy (**Supplementary Material**, Table S1).

For patients with ESBL-producing *Enterobacteriaceae*, carbapenem treatment was 6 days shorter ($p < 0.001$) in the de-escalated group in the bivariate analysis and PS matched cohort. No significant differences were found between the de-escalated and

Table 4.2
Logistic regression analysis showing the association between different variables and 30-day mortality.

	Univariate analysis		Adjusted analysis	
	OR (95% CI)	*p*-Value	OR (95% CI)	*p*-Value
Age	1.06 (1.04–1.07)	<0.001	1.03 (1.02–1.05)	<0.001
Sex				
Male	0.97 (0.73–1.30)	0.849		
Female	Reference			
Charlson index score	1.37 (1.29–1.47)	<0.001	1.20 (1.10–1.31)	<0.001
Department				
Medical	4.26 (3.02–5.99)	<0.001	2.47 (1.68–3.63)	<0.001
Surgical	Reference			
Invasive procedure	0.39 (0.28–0.55)	<0.001		
Nosocomial origin	1.38 (0.98–1.91)	0.058		
ICU stay	0.98 (0.62–1.56)	0.946		
Urinary catheter	2.42 (1.80–3.24)	<0.001		
Antibiotic therapy in previous 30 days	1.63 (1.07–2.49)	0.024		
Admission in previous 30 days	4.04 (2.96–5.52)	<0.001	2.81 (1.97–4.01)	<0.001
Duration of carbapenem therapy	0.99 (0.96–1.03)	0.799		
Hospital stay	1.01 (1.001–1.02)	<0.001	1.02 (1.01–1.03)	<0.001
Duration of antibiotic therapy	0.97 (0.95–0.99)	0.006	0.92 (0.89–0.95)	<0.001
Time to carbapenem prescription since admission	1.01 (1.00–1.03)	0.028		
Time to use of carbapenem as rescue	1.01 (0.97–1.06)	0.597		
Sepsis	4.65 (3.24–6.66)	<0.001		
Carbapenem				
Ertapenem	Reference	0.019		
Anti-pseudomonal	1.47 (1.06–2.02)			
Carbapenem as first-line choice	0.70 (0.52–0.94)	0.018	0.58 (0.40–0.84)	0.004
Carbapenem as rescue therapy	Reference			
Source				
Skin and soft tissue	Reference			
Intra-abdominal	0.73 (0.44–1.22)	0.231		
Respiratory	1.93 (1.18–3.15)	0.009		
Urinary	1.21 (0.72–2.05)	0.470		
Culture request	0.99 (0.71–1.41)	0.997		
Positive culture	1.00 (0.69–1.47)	0.976		
ESBL and AmpC producing *Enterobacteriaceae*	1.03 (0.59–1.81)	0.908		
Monotherapy	0.71 (0.53–0.95)	0.021		
Carbapenem de-escalation	0.58 (0.44–0.78)	<0.001	0.75 (0.54–1.05)	0.095
Propensity score	0.013 (0.004–0.048)	<0.001	0.24 (0.05–1.19)	0.081

OR, odds ratio; CI, confidence interval; ICU, intensive care unit; ESBL, extended-spectrum beta-lactamase.

Table 5
Stratified analysis by quartiles of the propensity score for primary outcomes.

Propensity score quartiles	In-hospital mortality (%)		30-day mortality (%)		30-day re-admission infection-related (%)	
	Carbapenem de-escalation *n* = 667	Carbapenem no de-escalation *n* = 494	Carbapenem de-escalation *n* = 667	Carbapenem no de-escalation *n* = 494	Carbapenem de-escalation *n* = 667	Carbapenem no de-escalation *n* = 494
1st quartile (0–0.50)	34/124 (27.4)	35/166 (21.1)	36/124 (29.0)	45/166 (27.1)	8/124 (6.5)	10/166 (6.0)
2nd quartile (0.50–0.58)	35/155 (22.6)	30/136 (22.1)	43/155 (27.7)	39/136 (28.7)	23/155 (14.8)	15/136 (11.0)
3rd quartile (0.58–0.66)	15/175 (8.6)[a]	21/115 (18.3)[a]	20/175 (11.4)[c]	27/115 (23.5)[c]	19/175 (10.9)	14/115 (12.2)
4th quartile (0.66–0.84)	9/213 (4.2)[b]	11/77 (14.3)[b]	10/213 (4.7)[d]	13/77 (16.9)[d]	20/213 (9.4)	9/77 (11.7)[e]
Total	93/667 (13.9)	97/494 (19.6)	109/667 (16.3)	124/494 (25.1)	70/667 (10.5)[f]	48/494 (9.7)[f]

[a] $p = 0.014$; [b] $p = 0.003$; [c] $p = 0.006$; [d] $p = 0.001$; [e] $p = 0.730$; [f] $p = 0.564$. The greater likelihood of de-escalation performance has lower in-hospital mortality and 30-day mortality rates.

non-de-escalated groups in terms of hospital stay and duration of antibiotic therapy (bivariate analysis: $p = 0.155$ vs. $p = 0.475$, respectively; PS-matched cohort: $p = 0.728$ vs. $p = 0.880$, respectively) (**Supplementary Material**, Table S2).

Discussion

The main finding of this study was that carbapenem de-escalation is a safe strategy that does not compromise the prognosis of severely ill hospitalized patients. There appeared to be no increase in 30-day mortality, 30-day re-admission rate, or length of hospital stay for these patients.

Carbapenems are highly potent antibiotics administered to severely ill patients at risk of infection by multi-resistant bacteria (Kollef et al., 2011). However, their utilization favours the emergence of resistant microorganisms, even when administered for less than 3 days (Armand-Lefèvre et al., 2013), including highly resistant bacteria such as *Acinetobacter baumannii* (Ng et al., 2014). In the present study, de-escalation achieved a significant reduction in carbapenem treatment duration of up to 4 days, similar to previously published findings (Alvarez-Lerma et al., 2006; Apisarnthanarak et al., 2013a; Lew et al., 2014). This reduction in exposure to broad-spectrum antibiotics such as carbapenems has been found to lead to a reduced emergence of microorganisms

resistant to these antibiotics during treatment (Anucha Apisarnthanarak, 2011; Routsi et al., 2013). However, the mean duration of total antibiotic therapy was 2 days longer for these patients than for the patients in the non-de-escalated group ($p = 0.03$), as reported previously (Carugati et al., 2015; De Bus et al., 2016). Nevertheless, it is more important to avoid 4 days of carbapenem than to prolong narrow-spectrum antibiotics for 2 days. De-escalation is a complementary strategy to avoid antibiotic overuse and it does not exclude the need to promote an overall reduction in antibiotic therapy.

The longer duration of antimicrobial therapy is difficult to explain. A possible explanation for these results might be that clinicians performed de-escalation without taking into account the previous days of antibiotic treatment with carbapenem. Another possible explanation is the existence of a mistrust in the narrower-spectrum antibiotics, thereby leading to an extended treatment duration and consequently to overtreatment of the patient. Furthermore, no differences were observed in terms of disease severity or in the readmission rate between the groups.

De-escalation was investigated in the period up until day 4 from the beginning of carbapenem use as empirical or rescue treatment. The duration from the time at which microbiological culture results were known to the performance of de-escalation was not measured. Normally, 48–72 h are considered from microbiological isolation and susceptibility results are available. The time taken varies between studies (Eachempati et al., 2009; Apisarnthanarak et al., 2013b; Lew et al., 2014; Viasus et al., 2017). It was decided to use an average of four until microbiological results and issue of the definitive susceptibility report. Nevertheless, if there is the opportunity to perform de-escalation later than this period and reduce exposure to carbapenems, this should be done, even though the impact will be lower.

Previous studies on de-escalation have included critical care patients with severe sepsis, mechanical ventilation-associated pneumonia, or community-acquired pneumonia, and most patients had an identified pathogen with a susceptibility profile (Alvarez-Lerma et al., 2006; Eachempati et al., 2009; Gonzalez et al., 2013; Garnacho-Montero et al., 2014; Carugati et al., 2015; Yamana et al., 2016; Viasus et al., 2017). In contrast, patients with and without a microbiological diagnosis were included in the present study; nevertheless, the de-escalation rate achieved (57.5%) was within the range described in previous studies (23–68%) (Alvarez-Lerma et al., 2006; De Waele et al., 2010; Apisarnthanarak et al., 2013a; Lew et al., 2014).

Despite the higher frequency of bacteremia in the de-escalated group (11.1%) than in the non-de-escalated group (10.9%), the 30-day mortality rate was lower in the former group in both the bivariate and PS analyses (16.3% vs. 25.1%, $p < 0.001$ and 17.4% vs. 25.7%, $p = 0.036$, respectively). Previous studies on bacteremic patients with community-acquired pneumonia (Carugati et al., 2015; Viasus et al., 2017) or *Enterobacteriaceae* (Lee et al., 2017) also observed lower in-hospital and 30-day mortality rates in de-escalated patients than in those who continued with broad-spectrum antibiotics. The shorter length of hospital stay in the de-escalated group in the present study is also in line with previous reports (Schlueter et al., 2010).

De-escalation is less frequently applied in more vulnerable patients with more comorbidities, more ICU stays, and a greater risk of infection from multidrug-resistant bacteria, especially ESBL-producing *Enterobacteriaceae*. There is a logical tendency to continue treatment in these patients using the antibiotic with the highest documented activity, as in the case of carbapenems. However, it is important to note that rates of sepsis, bacteremia, and nosocomial infection did not differ between the de-escalated and non-de-escalated patients in the present study, and more than one-quarter of the *Enterobacteriaceae* isolated in the de-escalated group were ESBL or AmpC-producing. These results corroborate the findings of previous studies on carbapenem-sparing regimens in infections produced by these bacteria (Rodríguez-Baño et al., 2012a).

In general, the low frequency of infections due to ESBL-producing *Enterobacteriaceae* in the study sample (6.89% of total) suggests that carbapenems were over-prescribed and that a higher de-escalation rate could have been achieved. A similar study on ESBL-producing *Enterobacteriaceae* found that 29% of *Escherichia coli* and 40% of *Klebsiella pneumoniae* infections involved ESBL-producing organisms; nevertheless, they performed de-escalation in 68% of cases (Lew et al., 2014).

Limitations of this single-centre study include the absence of hospital protocols for de-escalation and of standardized criteria for carbapenem prescriptions, which were the responsibility of the attending physicians. The strengths of the study are its prospective design and the large sample size, including patients with negative, positive, and no cultures. The outcomes obtained contribute further evidence on the safety of carbapenem de-escalation, at least in non-critical patients.

Finally, it is concluded that carbapenem de-escalation is a safe strategy in patients with severe infections hospitalized in medical or surgical departments. In addition, it does not worsen the clinical outcomes of the patients, lengthen their hospital stay, or increase the re-admission rate.

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Ethical approval

This research was approved by the Ethics Committee of the University Hospital Virgen de las Nieves, Granada (Spain).

Conflict of interest

All authors report no conflicts of interest.

Author contributions

SSD: study design, data collection, analysis of data, writing. PAP: study design, final approval of manuscript. JPL: critical revision, writing, final approval of manuscript. MER: analysis of data, critical revision. MACH: critical revision, final approval of manuscript. CHT: study design, critical revision, writing, final approval of manuscript.

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Appendix A. Supplementary data

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