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BRIEF REPORT

De-escalation of antimicrobial therapy for bacteraemia due to difficult-to-treat Gram-negative bacilli

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Abstract
Purpose To examine the status and clinical outcome of de-escalating antimicrobial therapy for bacteraemia due to hospital-acquired, Gram-negative bacilli that are difficult to treat.
Methods Among 1,610 patients presenting with positive blood cultures collected at our medical centre over a 6-year period, 133 were infected with *Serratia*, *Pseudomonas*, *Acinetobacter*, *Citrobacter* or *Enterobacter* sp. (SPACES). We examined the appropriateness of an empiric initial administration of antimicrobials based on in vitro sensitivity, and the success and outcomes of a pathogen-directed de-escalation of therapy. The treatment was considered to be successfully de-escalated when the antimicrobial spectrum was narrowed according to a spectrum ranking or when ≥2 antimicrobials prescribed initially were lowered to one agent. Outcome measures included persistent, recurrent and metastatic infections, infection-related deaths and cost of antimicrobials.
Results The treatment was initially appropriate in 79 of 133 patients (59 %), of whom 49 (62 %) were candidates for and 28 (57 %) underwent treatment de-escalation. No treatment failure was observed among these 28 patients, while 2 of 11 patients (18 %) whose treatment was not de-escalated died ($p = 0.13$). The median cost of antimicrobials was €250/patient lower in the de-escalated than in the non-de-escalated group ($p < 0.001$).
Conclusions Antimicrobial therapy for bacteraemia due to hard-to-treat SPACES was de-escalated in 57 % of candidates, based on the in vitro sensitivity, with no deaths and significantly lower costs of antimicrobial therapy.

Keywords Antimicrobial de-escalation · Empiric antimicrobial therapy · Bacteraemia · Drug resistance · Gram-negative bacilli

This study was performed at the University Medical Centre of Kyoto University Prefectural School of Medicine.

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Introduction

The initial administration of an effective antimicrobial agent pending the results of bacteriologic cultures is a major determinant of the survival of patients presenting with bacteraemia [1–5]. While the initial coverage must be broad enough to optimise its effectiveness, a de-escalation of the regimen is strongly recommended once the results of the cultures are known [6].

In an earlier study, we confirmed the safety and efficacy of narrowing the antimicrobial spectrum by de-escalating the pathogen-targeted drug regimen. However, our study

had not included hospital-acquired, potentially treatment-resistant, Gram-negative pathogens [5, 7, 8]. *Pseudomonas* and *Acinetobacter* are notorious glucose non-fermenting Gram-negative bacteria. Bacteraemia caused by these pathogens is associated with inordinately high mortality and morbidity due to their resistance to antimicrobial therapy [9–11]. The production of AmpC beta-lactamase by *Serratia*, *Citrobacter* and *Enterobacter* is of particularly great concern [12]. The de-escalation of treatment of these pathogens is especially important, as their antimicrobial resistance is often the source of excessively broad initial coverage. We, therefore, designed this study to examine the effectiveness and safety of de-escalating antimicrobial therapy in patients presenting with bacteraemia due to *Serratia*, *Pseudomonas*, *Acinetobacter*, *Citrobacter* or *Enterobacter* sp. (SPACES).

Patients and methods

This study was conducted in the Kyoto Prefectural School of Medicine and University Medical Centre, with the approval (# E-213) of its institutional ethics committee, which waived the need for informed consent from the patients. Our hospital is an 893-bed, urban, teaching institution, which includes a 12-bed intensive care unit. All data were collected retrospectively from a database kept by a hospital-based infection control team and by a review of medical records.

Between January 2006 and December 2011, the clinical laboratory of the Kyoto Prefectural University Medical Centre identified 1,610 patients with positive blood cultures. The duration of our study was chosen to optimise the chances of collecting a meaningful sample and to eliminate a bias due to time-dependent variations. Among these 1,610 patients, 1,362 had confirmed bacteraemia, based on (a) the number of bottles containing positive cultures, (b) clinical manifestations of systemic inflammation or haemodynamic dysfunction, and (c) the application of antimicrobial therapy. We limited our sample to patients infected by SPACES, an important family of Gram-negative pathogens often resistant to antimicrobials. Patients (a) <18 years of age (Fig. 1), (b) presenting with bacteraemia due to multiple pathogens, or (c) transferred to another hospital during the treatment period were excluded from this analysis. In addition, neither (a) patients with sustained neutropaenia nor (b) patients in whom antimicrobial resistance precluded a narrowing of the antibiotic spectrum were candidates for de-escalation. Furthermore, we considered that the appropriateness of treatment of a recovered pathogen had not been verified when (a) a patient was transferred to another facility before the initiation of antimicrobial therapy or (b) antimicrobial therapy had been initiated against another clinically suspected infection, which had not been confirmed by microbiological tests.

The initial empiric therapy, administered within 24 h after the first collection of blood cultures, was classified as *appropriate* if it was active against the causative pathogen, based on the in vitro testing of sensitivity, regardless of doses. The organisms' sensitivity was tested, using a broth dilution method, as described by the Clinical and Laboratory Standards Institute (CLSI) [13]. Recipients of an initially appropriate, broad-spectrum or combined empiric regimen who survived >3 days after collection of the blood culture, and whose white blood cell counts were $\geq$1,000/mm^3, were considered as candidates for de-escalation after return of the results of the bacteriologic cultures.

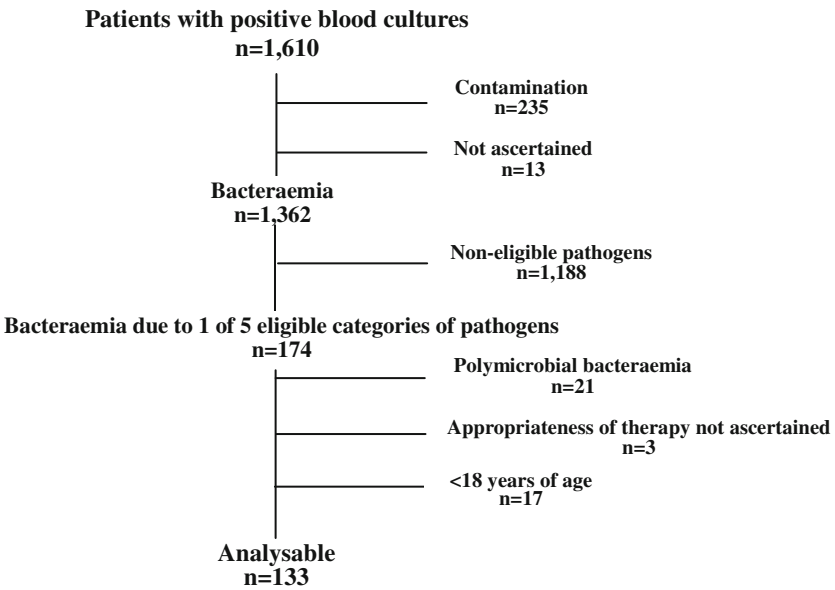

Fig. 1 Screening, exclusion and selection of patients for the analysis

The treatment was de-escalated as soon as the antibiotic susceptibility was known, usually within 48–72 h after collection of the blood cultures. It was considered to be de-escalated when the antimicrobial spectrum was narrowed or when ≥2 antimicrobials prescribed initially against Gram-negative pathogens were reduced to a single agent. The spectrum of antimicrobials was ranked on the basis of the study by Kollef et al. [14], as follows: carbapenems (broadest spectrum), fourth-generation cephalosporins, piperacillin/tazobactam, quinolone, antipseudomonal third-generation cephalosporins, and others. For example, a change of treatment from meropenem (carbapenem) to ceftazidime (third generation, antipseudomonal cephalosporin) was considered to be a successful de-escalation.

The decisions to obtain blood cultures and initiate antimicrobial therapy were left to the physician(s) in charge of the patient's care, in optional and occasional consultation with infection control specialists and in the absence of a formal antimicrobial stewardship programme or institutional protocol for the management of patients presenting with bacteraemia. Furthermore, the pharmacists neither participated in nor influenced any aspect of this study, and our formulary underwent no major change during the study period. The patients were followed by the hospital-based infection control team until the discontinuation of antimicrobial therapy for bacteraemia or until their death. No patient was treated with a continuous infusion of antimicrobial.

Data collection and classification

The demographic and clinical data collected included age, sex, body weight, acute physiology and chronic health evaluation (APACHE) II score, McCabe class [15] at the time of blood culture collection, origin of bacteraemia and the patient's surgical history. For the calculation of the APACHE II scores, we estimated PaO_2 and F_IO_2 values from the SpO_2 and oxygen flow administered via nasal cannulas or face masks, and assumed a normal pH when the arterial blood gas analysis was missing. The overall duration of antimicrobial therapy for bacteraemia was recorded. However, there was no formal criterion used to discontinue or shorten the duration of antimicrobial treatment. The causes of early termination of antibiotic therapy were not specifically determined. All-cause and infection-related mortality was measured at 28 days after collection of the initial blood culture. Death was classified as infection-related upon consensus reached between the caregivers in charge of the patient and the infection control specialists. A positive follow-up blood culture containing the same pathogen *during* antimicrobial treatment as the original pathogen was classified as *persistent*, and was not counted as a new infection. Bacteraemia due to the same microbiologically documented pathogen, developing *after* the discontinuation of treatment, was classified as *recurrent*. An infectious lesion by the same pathogen other than the initial focus, detected during or after treatment, was classified as *metastatic*. Infection-related deaths and persistent, recurrent or metastatic infections were classified as *treatment failures*.

The costs of empiric and pathogen-directed treatments were recorded. We calculated the individual costs of antimicrobials using the official drug price list from the year 2011 published by the Ministry of Health, Labour and Welfare of Japan.

Statistical analysis

Continuous data, expressed as medians (ranges), were compared using the Mann–Whitney *U*-test. Categorical data, expressed as counts and percentages, were compared using the Chi-square test or the G-test for multiple comparisons of categorical values. Duration and costs of therapy are expressed in median numbers and interquartile range (IQR). Odds ratio (OR) and 95 % confidence intervals (CIs) were calculated. A p-value <0.05 was considered to be statistically significant.

Results

Selected characteristics of the study sample

Selected demographic and clinical characteristics of the 133 patients retained for this analysis are shown in Table 1. The abdomen, the most frequent source of bacteraemia, was identified in 30 patients (23 %). Patients with bacteraemia of pulmonary origin suffered the highest mortality (37 %). *Pseudomonas aeruginosa*, the most frequent bacteraemic pathogen, was recovered in 59 patients (44 %). The antibiogram recorded in our institution during the study period is shown in Table 2.

Appropriateness of initial antimicrobial therapy and outcomes

The initial, empiric antimicrobial regimens administered and their respective appropriateness are shown in Table 3. The initial, empiric therapy was appropriate in 79 (59 %) and inappropriate in 54 (41 %) patients. Treatment failures were observed in 9 of 79 (11 %) appropriately versus 15 of 54 (28 %) inappropriately treated patients (OR = 0.33; 95 % CI 0.13–0.83; $p = 0.01$; Fig. 2). Carbapenems, the most frequently used class of antimicrobials, were prescribed to 23 patients (17 %), though the treatment choices varied widely. Empiric antimicrobial void of

Table 1 Selected characteristics of the study sample

		% appropriate	*p*-value	% mortality	*p*-value
Median age, years (IQR)	64 (59–73)				
Men	94 (71)				
Median APACHE II score (IQR)	13 (10–17)				
Non-fatal McCabe classification	79 (59)				
Neutropaenia	17 (13)				
Deaths at 28 days of follow-up					
All-cause	21 (16)				
Infection-related	16 (12)				
Median duration of antimicrobials (IQR)	9 (6–14)				
Pathogens resistant to multiple drugs	39 (29)				
Source of bacteraemia					
Central venous catheter	14 (11)	64	0.75	10	0.02
Urinary tract	27 (20)	56		4	
Abdomen	30 (23)	60		10	
Lung	19 (14)	58		37	
Skin and soft tissue	8 (6)	40		13	
Others	1 (<1)	100		0	
Undetermined	34 (26)	63		12	
Pathogen species					
Serratia	20 (15)	60	0.41	5	0.20
Pseudomonas	59 (44)	54		17	
Acinetobacter	21 (16)	52		5	
Citrobacter	5 (4)	60		0	
Enterobacter	28 (21)	75		14	

Unless specified otherwise, values are numbers (%) of observations

Table 2 Hospital antibiogram

	% susceptible							
	n	PIPC	CTX	AZT	CAZ	CFPM	IPM/CS	AMK	CPFX
Pseudomonas aeruginosa	3,540	87	NA	72	89	86	81	99	83
Acinetobacter calcoaceticus–baumannii complex	556	82	NA	NA	96	95	97	99	93
Enterobacter cloacae	1,026	69	68	91	69	93	96	98	85
Serratia marcescens	576	84	89	91	91	93	96	98	85
Citrobacter freundii complex	234	43	57	60	55	93	100	99	87

Hospital-wide data for all organisms isolated from 2006 through 2010; values are percentages of pathogens susceptible to each antimicrobial in vitro

PIPC piperacillin, *CTX* cefotaxime, *AZT* aztreonam, *CAZ* ceftazidime, *CFPM* cefepime, *IPM/CS* imipenem/cilastatin, *AMK* amikacin, *CPFX* ciprofloxacin, *NA* not applicable

antipseudomonal activity were prescribed to 28 patients (21 %), of whom 4 (14 %) received an appropriate regimen.

De-escalation and post-de-escalation outcomes

Among 79 recipients of appropriate antimicrobial therapy, 49 (62 %) were candidates for de-escalation. Among these 49 candidates, treatment was (a) de-escalated in 28 (57 %), (b) unchanged and discontinued within <7 days in 10 (20 %), and (c) continued unchanged or escalated in 11 (22 %) patients (non-de-escalated group). Among the 28 patients who underwent de-escalation, three were de-escalated from combined therapy to a single antimicrobial. In the remaining 25 patients, 14 were de-escalated from carbapenems to a narrower-spectrum antimicrobial, including cephalosporins in 11, piperacillin in one, quinolones in one and aztreonam in one, and three were de-escalated from a fourth-generation cephalosporin, two from piperacillin/tazobactam, two from quinolones and

Table 3 Initial empiric antimicrobial regimens

Regimen	Administered	Appropriate*
Monotherapy		
Penicillins (ampicillin, ampicillin/sulbactam)	3 (2)	0
Antipseudomonal penicillins (piperacillin, piperacillin/tazobactam)	3 (2)	3 (100)
Cephalosporin generations		
First (cefazolin)	4 (3)	0 (0)
Second (cefotiam, cefmetazole, flomoxef)	11 (8)	1 (9)
Third (cefotaxime, ceftriaxone)	8 (6)	3 (37)
Third antipseudomonal (ceftazidime, cefoperazone/sulbactam)	19 (14)	15 (79)
Fourth (cefepime, cefozopran, cefpirome)	19(14)	16 (84)
Carbapenems (meropenem, imipenem/cilastatin, panipenem/betamipron, biapenem, doripenem)	23 (17)	21 (91)
Quinolones (ciprofloxacin, levofloxacin)	8 (7)	7 (87)
Aminoglycosides (gentamicin, amikacin)	2 (2)	2 (100)
Glycopeptides (teicoplanin)	1 (1)	0 (0)
Clindamycin	1 (1)	0 (0)
Total	102 (77)	68 (67)
Combined		
β-lactams		
+ aminoglycosides	5 (3)	3 (60)
+ quinolones	1 (1)	1 (100)
+ glycopeptides	8 (6)	4 (50)
+ antifungals (fluconazole, micafungin)	2 (2)	1 (100)
+ glycopeptides + aminoglycosides	1 (1)	1 (100)
+ others	3 (2)	1 (33)
Total	20 (15)	11 (55)
No antimicrobial	11 (8)	0 (0)
Total	133 (100)	79 (59)

Values are numbers (%) of patients

* Numbers (%) of each empirically chosen antimicrobial that were appropriate

four from third-generation antipseudomonal cephalosporins to narrower-spectrum antimicrobials. No treatment failure was observed among the 28 patients whose treatment was de-escalated, whereas two patients (18 %) died among the 11 patients ($p = 0.13$) whose treatment was not de-escalated (Fig. 2). The median (IQR) duration of antimicrobial therapy was similar, being 12 (8−14) days in the de-escalated and 11 (8−17) days in the non-de-escalated groups. The median (IQR) cost of treatment was 26 (15−45) × 10^3 JPY in the de-escalated group, compared with 51 (19−75) × 10^3 JPY in the non-de-escalated group, or approximately €260 (150−450) versus €510 (190−750) ($p < 0.001$).

Discussion

Main study findings

Our analysis revealed that, in the presence of bacteraemia due to the difficult-to-treat Gram-negative bacilli known as SPACES: (1) the initial empiric choice of antimicrobial was appropriate in nearly 60 % of patients and was a critical determinant of treatment success, (2) among all patients who were candidates, therapy was de-escalated in 57 %, and (3) de-escalation of therapy, based on the in vitro susceptibility, was associated with no therapeutic failure and a significantly lower cost of antimicrobials than in patients whose treatment was not de-escalated.

A recent meta-analysis confirmed that an empiric choice of inappropriate antimicrobials to treat bloodstream infections significantly increased the odds of dying [16]. Given the current concerns regarding the production of AmpC beta-lactamase in *Serratia*, *Citrobacter*, and *Enterobacter* sp. and the high prevalence of *Pseudomonas* or *Acinetobacter* sp., one might consider, when suspecting SPACES, the administration of the broadest-spectrum antimicrobials, including carbapenems or piperacillin/tazobactam, alone or in combination with other antipseudomonal agents, to optimise the initial coverage. Based on the results of cultures and whenever possible, however, it is recommended to de-escalate the initial treatment to a single, narrow-spectrum antimicrobial, with a view to limit the use of broad-spectrum therapy and its associated adverse consequences [17–19]. In our earlier study, treatment was safely de-escalated and associated with a trend toward lower treatment failure rates and mortality in patients presenting with antimicrobial-sensitive bacteraemia [20]. It remained uncertain, however, as to whether a de-escalation strategy can be implemented for infections caused by other, potentially antibiotic-resistant pathogens. In previous studies, bacteraemia caused by strains resistant to multiple antimicrobials could not be successfully de-escalated [6, 21]. In a prospective study of ventilator-associated pneumonia, where Gram-negative bacilli potentially resistant to treatment were the main pathogens, the rate of de-escalation was only 22 %, though it was associated with a significantly lower mortality than when treatment was escalated or unchanged [14]. Other studies found the de-escalation of antimicrobials challenging when the causative pathogens were likely to be refractory to treatment [3, 22]. Currently, however, a de-escalation strategy

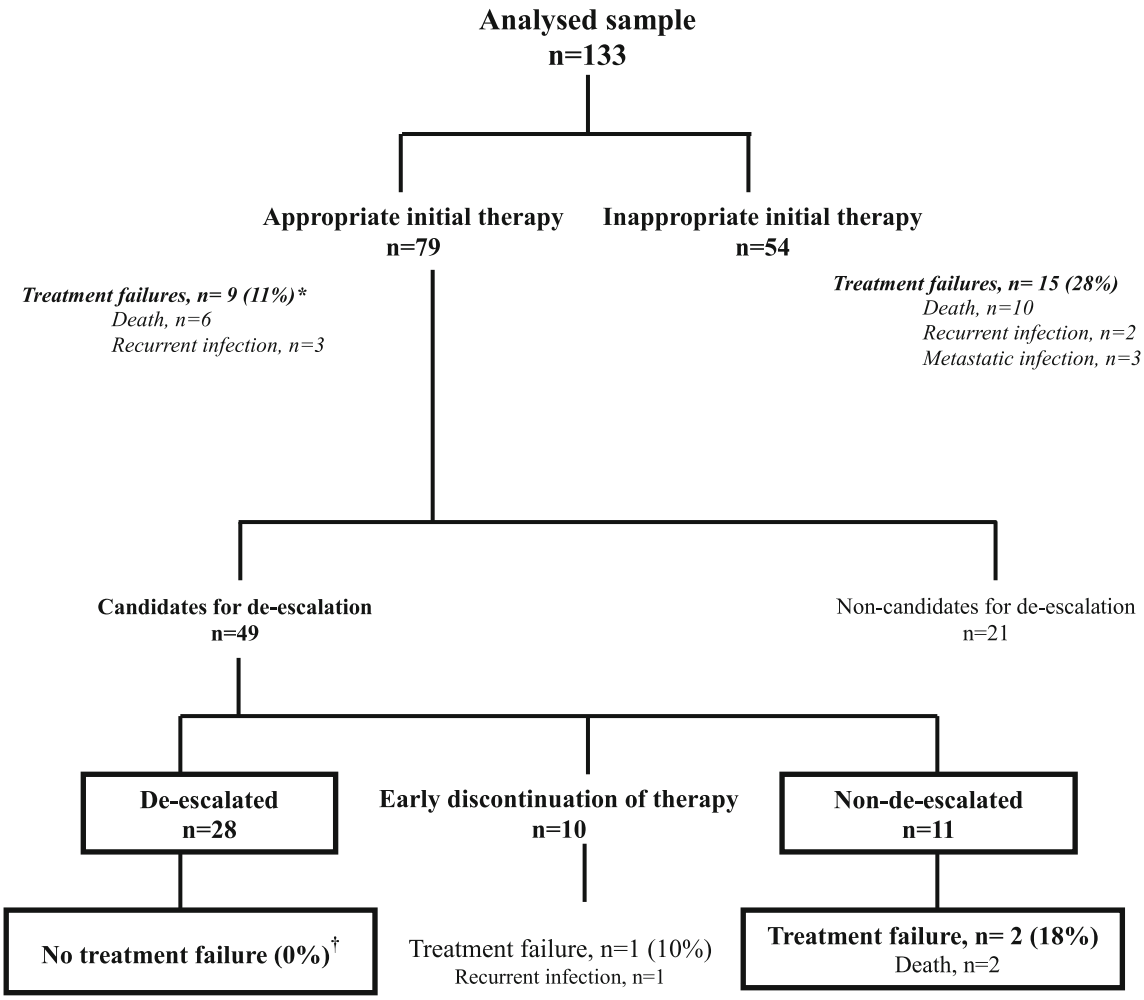

Fig. 2 Flow of patients, from the initial analysable sample to the final escalated and de-escalated study groups. *$p = 0.01$ vs. inappropriate initial therapy group; †$p = 0.13$ vs. non-de-escalated group

seems applicable to a broad spectrum of patients [23]. It is also noteworthy that recent studies of the efficacy of therapy against major infections due to *Pseudomonas aeruginosa* found that, after the confirmation of susceptibility, the administration of a single pathogen-specific antimicrobial, instead of a combination, was associated with favourable clinical outcomes [24, 25].

In our study, 59 % of non-neutropaenic patients infected with SPACES were treated appropriately initially and, therefore, were candidates for de-escalation. Compared with a previous study, in which empiric antipseudomonal therapy rotated monthly and, if necessary, combined with vancomycin was administered to all patients suspected of ventilator-associated pneumonia [26], this rate of appropriate initial therapy in our study (59 % for all pathogens instead of 93 % in the study by Eachempati et al.) was remarkably low. The lower prescription rate of initial antipseudomonal or combined therapy in our study or the different pathologies treated (bacteraemia vs. ventilator-associated pneumonia) might explain this prominent difference.

It is equally noteworthy that the de-escalation of antimicrobials, actually implemented in >50 % of candidates, reduced significantly the costs of antimicrobials. These observations might encourage the caregivers to adhere to this treatment strategy against bacteraemia due to SPACES whenever possible. The implementation of institutional guidelines might contribute to further improving the quality of medical practices [17].

Study limitations

First, the retrospective design of our study is a methodological limitation, which is difficult to overcome because of the obvious ethical issues that have to be considered when studying the management of a life-threatening illness. Second, the suspicion of bacteraemia, the decision to obtain blood cultures or the choice and doses of

antimicrobials depended mostly on the primary care physicians, instead of being guided by a protocol or by recommendations made by infectious disease specialists. These factors might have prominently influenced the choice and timing of therapy and, hence, the clinical outcomes [2, 22, 27]. Third, the appropriateness of dosing of the antimicrobials was not assessed. This might be a concern in patients whose severity of illness was greatest, in whom the pharmacokinetics and pharmacodynamics of treatment might significantly affect the outcome [28]. Fourth, in a recent experimental study, the production of AmpC beta-lactamase by SPACES was induced by exposure to antimicrobials [29]. Isolates of these organisms upregulated their production of beta-lactamase in the presence of antimicrobials or produced beta-lactamase at a constitutive level that rendered the antimicrobials ineffective. Treatment failure or resistance might, therefore, develop in the long term, despite an initial sensitivity observed in vitro. Consequently, some medical institutions have adopted a default resistance reporting system, considering only cefepime, carbapenems, fluoroquinolone and aminoglycosides as appropriate choices, if confirmed by in vitro testing [30]. If we exclude the isolates treated with other antimicrobials from the appropriately treated group, our initial appropriateness calculation decreases to 54 %. Our study has, nevertheless, shown that, based on their in vitro susceptibility, antimicrobials were safely de-escalated during our predefined observation period, without increase in the rate of treatment failure. These observations, however, need to be confirmed in a longer-term study. Finally, the pathogens we studied were limited to five Gram-negative bacilli whose local antimicrobial resistance pattern was relatively low (Table 2). Since the rates of antimicrobial resistance are likely to be variable, one may expect different results among different settings.

In conclusion, our study shows that antimicrobial therapy for bacteraemia due to SPACES could be de-escalated based on the in vitro susceptibility, with no fatal complications and at significantly lower costs of antimicrobials. Studies of the factors associated with unsuccessful de-escalation and of the long-term clinical outcomes of de-escalation or changes in resistance patterns are warranted.

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Conflict of interest The authors have no potential conflict of interest to disclose.

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