International Journal of Antimicrobial Agents 54 (2019) 189–196

Contents lists available at ScienceDirect

International Journal of Antimicrobial Agents

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

Non-intravenous carbapenem-sparing antibiotics for definitive treatment of bacteraemia due to Enterobacteriaceae producing extended-spectrum β-lactamase (ESBL) or AmpC β-lactamase: A propensity score study ☆

Yolanda Meije[a,*], Carles Pigrau[b,c], Núria Fernández-Hidalgo[b,c], Mercedes Clemente[a], Lucía Ortega[a], Xavier Sanz[a], Jose Loureiro-Amigo[a], Montserrat Sierra[d], Ana Ayestarán[e], Alejandra Morales-Cartagena[a], Alba Ribera[a], Alejandra Duarte[a], Gabriela Abelenda[a], Jesús Rodríguez-Baño[c,f], Joaquim Martínez-Montauti[a]

[a] *Infectious Diseases Unit, Internal Medicine Department, Hospital de Barcelona, Societat Cooperativa d'Instal·lacions Assistencials Sanitàries (SCIAS), Diagonal 660, 08034 Barcelona, Spain*
[b] *Infectious Diseases Department, Hospital Universitari Vall d'Hebron, Universitat Autònoma de Barcelona, Barcelona, Spain*
[c] *Spanish Network for the Research in Infectious Diseases (REIPI RD12/0015), Instituto de Salud Carlos III, Madrid, Spain*
[d] *Microbiology Department, Hospital de Barcelona, Societat Cooperativa d'Instal·lacions Assistencials Sanitàries (SCIAS), Barcelona, Spain*
[e] *Pharmacy Department, Hospital de Barcelona, Societat Cooperativa d'Instal·lacions Assistencials Sanitàries (SCIAS), Barcelona, Spain*
[f] *Clinical Unit of Infectious Diseases, Microbiology and Preventive Medicine, Hospital Universitario Virgen Macarena/Departamento de Medicina, Universidad de Sevilla/Instituto de Biomedicina de Sevilla, Seville, Spain*

ARTICLE INFO

Article history:
Received 27 January 2019
Accepted 1 May 2019

Editor: Professor J Roberts

Keywords:
Carbapenem-sparing antibiotics
Enterobacteriaceae bacteraemia
Stewardship
Extended-spectrum β-lactamase
AmpC β-lactamase
Trimethoprim/sulfamethoxazole

ABSTRACT

Carbapenems are considered the treatment of choice for extended-spectrum β-lactamase (ESBL)- or AmpC β-lactamase-producing Enterobacteriaceae bacteraemia. Data on the effectiveness of non-intravenous carbapenem-sparing antibiotic options are limited. This study compared the 30-day mortality and clinical failure associated with the use of carbapenems versus alternative non-intravenous antibiotics for the definitive treatment of ESBL/AmpC-positive Enterobacteriaceae bacteraemia. This 12-year retrospective study (2004–2015) included all patients with bacteraemia due to ESBL/AmpC-producing Enterobacteriaceae at a Spanish hospital. Given the lack of randomisation of initial therapies, a propensity score for receiving carbapenems was calculated. There were 1115 patients with a first episode of bacteraemia due to *Escherichia coli* or *Klebsiella pneumoniae*, of which 123 (11.0%) were ESBL/AmpC-positive. There were 101 eligible patients: 59 in the carbapenem group and 42 in the alternative treatment group (trimethoprim/sulfamethoxazole 59.5%, quinolones 21.4%). The most frequent sources of infection were urinary (63%) and biliary (15%). Compared with the carbapenem group, patients treated with an alternative regimen had a shorter hospital stay [median (IQR) 7 (5–10) days vs. 12 (9–18) days; $P < 0.001$]. Use of an alternative non-intravenous therapy did not increase mortality (OR = 0.27, 95% CI 0.05–1.61; $P = 0.15$). After controlling for confounding factors with the propensity score, the adjusted OR of carbapenem treatment was 4.95 (95% CI 0.94–26.01; $P = 0.059$). Alternative non-intravenous carbapenem-sparing antibiotics could have a role in the definitive treatment of ESBL/AmpC-positive Enterobacteriaceae bacteraemia, allowing a reduction in carbapenem use. Use of trimethoprim/sulfamethoxazole in this series showed favourable results.

1. Introduction

Extended-spectrum β-lactamase (ESBL)- or AmpC β-lactamase-producing Enterobacteriaceae have been increasingly implicated in healthcare- and community-associated bacteraemia [1]. Effective treatment of ESBL or AmpC bacteraemia has become a major

☆ Part of these data were presented at the 55th Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC)/28th International Congress of Chemotherapy (ICC) Meeting, 17–21 September 2015, San Diego, CA.

* Corresponding author. Tel.: +34 932 54 24 00.
E-mail address: yolandameije@gmail.com (Y. Meije).

https://doi.org/10.1016/j.ijantimicag.2019.05.004
0924-8579/

challenge owing to frequent resistance to various antimicrobial agents as well as the existence of mechanisms of co-resistance in this setting [2]. At present, carbapenems are the safest treatment for ESBL bacteraemia [3,4]. However, increasing carbapenem resistance among Enterobacteriaceae as well as in other bacteria calls for a more judicious approach to carbapenem use [5,6].

Previous studies on empirical or definitive treatment of ESBL Enterobacteriaceae bacteraemia with β-lactam/β-lactamase inhibitor (BL/BLI) combinations are contradictory [3,4,7–9]. These discrepant results may be due to differences in the source of infection, the genetic background of the causative micro-organism and local epidemiology [10].

Although several studies support the non-inferiority of BL/BLIs compared with carbapenems for definitive treatment in the setting of ESBL Enterobacteriaceae (*Escherichia coli* or *Klebsiella pneumoniae*) bacteraemia [11–14], a recent study [4] with several methodological criticisms [15] has sown fresh doubt regarding the safest option. Nevertheless, studies on non-carbapenem options for stewardship strategies are required to identify safe and effective therapies that limit carbapenem exposure [6].

Data regarding the usefulness of carbapenem-sparing antibiotics other than BL/BLIs for definitive treatment have also been reported, still with an intravenous (i.v.) regimen [16–18]. The effectiveness of non-i.v. (oral or intramuscular) antibiotic treatment for the management of ESBL or AmpC bacteraemia has not been widely assessed to date [3,19].

At our co-operative non-profit private hospital, patients with ESBL or AmpC Enterobacteriaceae bacteraemia frequently undergo definitive treatment with an orally administered antimicrobial agent. This hospital encourages close follow-up of patients, who may re-contact their doctor directly by telephone if fever or other signs of possible infection appear after discharge.

The aim of this study was to compare the 30-day mortality and clinical failure in two groups of patients, i.e. those receiving carbapenems versus an alternative therapy based on a non-i.v. carbapenem-sparing antibiotic regimen, for the definitive treatment of ESBL- or AmpC-positive Enterobacteriaceae bacteraemia.

2. Methods

2.1. Study design, setting and participants

This 12-year retrospective study (January 2004 to December 2015) was conducted at a 250-bed tertiary general hospital in Barcelona, Spain. Patients aged >15 years with community-acquired or healthcare-associated bacteraemia due to ESBL- or AmpC-producing Enterobacteriaceae were included. Patients who died in the first 72 h or those without 1-month follow-up were excluded. If patients experienced more than one bacteraemic episode, only the first episode was included. The prescribed antibiotic was recorded in each case, as selected by the patient's attending physician. All episodes were identified from the electronic microbiological database. Patients' clinical information was collected from electronic clinical charts and the electronic pharmacological database. Follow-up was performed by either the electronic clinical charts or by telephone if the patient had been discharged. This study was approved by the institutional review board for clinical trials.

2.2. Study endpoints

The primary outcome measure was the 30-day mortality rate. Secondary outcomes were clinical failure within 30 days of bacteraemia onset and hospital length of stay (LOS).

2.3. Variables and definitions

Bacteraemia was defined as the isolation of a micro-organism in one or more separately obtained blood cultures with compatible clinical features. Cases of bacteraemia were categorised as nosocomial, healthcare-associated or community-acquired in accordance with the criteria of Friedman et al. [20]. Infection sources were defined as urinary tract, biliary tract, incisional wound, soft tissue, catheter-related or primary bloodstream infection in accordance with US Centres for Disease Control and Prevention (CDC) guidelines [21]. The following patients were considered immunocompromised: those receiving corticosteroids at a dose of ≥20 mg prednisone or equivalent for ≥2 weeks; those with neutropenia (absolute neutrophil count <500/mm^3); or those receiving anticancer chemotherapy in the previous 6 months. Chronic kidney disease (CKD) was defined and staged according to the Kidney Disease: Improving Global Outcomes (KDIGO) definition and classification [22]. The Charlson comorbidity index was defined as previously described by Charlson et al. [23]. The severity of bacteraemia on the day of onset was graded using the Pitt bacteraemia score [24]. Source control was defined as any kind of intervention apart from antibiotic treatment applied to solve the infection, such as surgical treatment, abscess drainage or catheter withdrawal. Sepsis or septic shock was defined according to current definitions based on Sequential [Sepsis-related] Organ Failure Assessment (SOFA) criteria [25].

Antimicrobial therapy was regarded as empirical if administered before the susceptibility test results were available. Modification of treatment was defined as a change to an active antibiotic after the culture result became available in accordance with the pathogen's in vitro susceptibility pattern. Definitive therapy was defined as an active antibiotic administered for >50% of the total duration of antimicrobial therapy after the antibiogram result [7]. Treatment was defined as appropriate when an active antimicrobial agent, determined by in vitro antimicrobial susceptibility testing, was administered at the usual recommended dose. Clinical failure was defined as persistence of bacteraemia (i.e. positive blood culture for the same Enterobacteriaceae after 72 h of active antibiotic treatment by in vitro susceptibility), persistence of fever or sepsis (also after 72 h), death, or relapse during a 30-day follow-up defined as positive blood culture for the same micro-organism (after a previous negative result). Hospital LOS was defined as the time from the first positive blood culture to discharge.

2.4. Microbiological analysis

Microbiological identification and antimicrobial susceptibility testing were carried out using a MicroScan WalkAway system (Beckman Coulter, Inc., Brea, CA). The presence of ESBL and/or AmpC β-lactamase was screened in all isolates with reduced susceptibility to cephalosporins by MicroScan system and was confirmed by double-disk synergy test, combination disk test, gradient test method or molecular characterisation by PCR according to Clinical and Laboratory Standards Institute (CLSI) and European Committee on Antimicrobial Susceptibility Testing (EUCAST) guidelines. The β-lactams used for confirmation, testing their synergistic effect with amoxicillin/clavulanic acid (AMC) were ceftazidime, cefotaxime and aztreonam. All samples were analysed using the same confirmation procedure.

During the period 2004–2006, in vitro susceptibility tests were interpreted based on CLSI breakpoints [26] and during 2007–2015 based on the EUCAST breakpoints [27].

During the study period, the microbiology department at our hospital did not have access to PCR for the distinction of the type of AmpC β-lactamase encoded by *E. coli* strains (either chromosomal or plasmidic). Given that this distinction could be a

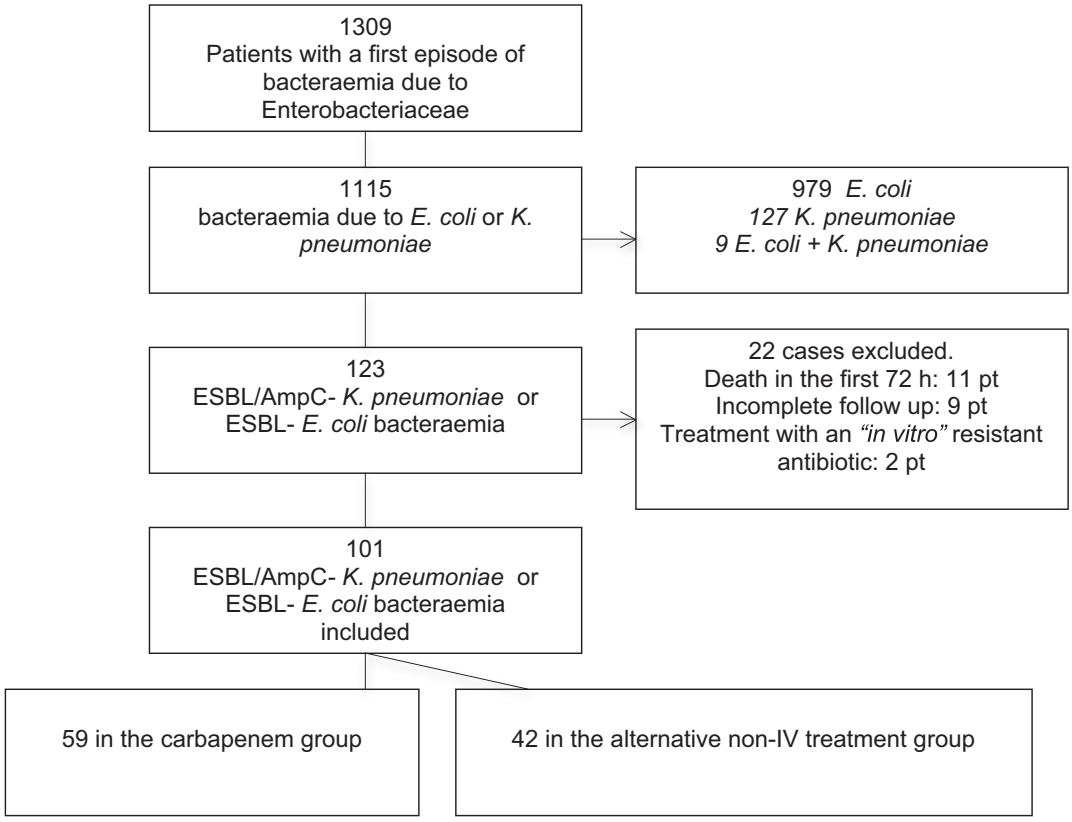

Fig. 1. Flow chart of patient (pt) selection for the study. ESBL, extended-spectrum β-lactamase; IV, intravenous.

possible confounder in the clinical prognosis, all AmpC-producing *E. coli* were excluded. However, all plasmidic AmpC-producing *K. pneumoniae* were included.

2.5. Statistical analysis

Quantitative variables were expressed as the median and interquartile range (IQR), and categorical variables were reported as absolute number and percentage. To detect significant differences between groups, the χ^2 test or Fisher's exact test for categorical variables and the Student's *t*-test or Mann–Whitney *U*-test for continuous variables were used, as appropriate. Independent predictors of 30-day mortality were identified by logistic regression analysis.

Given the lack of randomisation of the initial therapies, a propensity score for receiving carbapenems was estimated using a backward stepwise logistic regression model that included variables with a *P*-value of $\leq$0.25 in the univariate analysis as well as other variables considered relevant in deciding the empirical treatment. The following variables were included: age; sex; Pitt bacteraemia score; active cancer; CKD; source of bloodstream infection; empirical treatment (as appropriate or not); and time without effective treatment. An inverse probability of treatment weighting (IPTW) logistic regression using the propensity score was fitted to estimate the risk of mortality due to carbapenem administration. The weights to the propensity score were finally obtained after fitting a logistic regression model for use of carbapenem as outcome. The model obtained had an area under the receiver operating characteristic curve (AUC) of 0.77. Once the IPTW was obtained, a univariate weighted logistic regression with mortality as outcome was fitted to obtain the effect of carbapenem administration.

Statistical analysis was performed using SPSS Statistics for Windows v.17.0 (SPSS Inc., Chicago, IL) and STATA 13.1 (StataCorp LP, College Station, TX).

3. Results

3.1. Main results

During the study period (2004–2015), there were 1309 patients with a first episode of bacteraemia due to Enterobacteriaceae. Of these, 1115 were due to *E. coli* or *K. pneumoniae*, of which 123 (11.0%) were ESBL or AmpC-positive. Of the 123 patients, 22 were excluded (Fig. 1), resulting in a final cohort of 101 patients who were grouped according to type of treatment, including 59 in the carbapenem group and 42 in the alternative non-i.v. treatment group [25 trimethoprim/sulfamethoxazole (SXT), 9 quinolones, 5 aminoglycosides, 2 fosfomycin and 1 AMC].

The in vitro susceptibility rate for various antibiotics for ESBL/AmpC-producing strains was as follows: carbapenems, 100%; aminoglycosides, 76%; piperacillin/tazobactam, 59%; SXT, 38%; AMC, 27%; and quinolones 14%.

The most frequent infection sources were urinary (63%), biliary (15%) and unknown source (8%), followed by catheter-related (6%), intra-abdominal (5%), surgical wound/soft tissues (2%) and prosthetic joint infection (1%). The clinical and demographic characteristics of each group are shown in Table 1. There were no differences between groups (carbapenem versus alternative therapy) in terms of age, co-morbidities, infection source, severity of underlying disease, and duration of empirical or definitive treatment. Compared with the carbapenem group, patients treated with an alternative regimen had a lower median Pitt bacteraemia score.

Table 1
Characteristics of patients with bloodstream infection (BSI) caused by extended-spectrum β-lactamase (ESBL)- or AmpC β-lactamase-producing Enterobacteriaceae according to definitive therapy[a].

Characteristic	Definitive treatment		*P*-value
	Carbapenem (*n* = 59)	Alternative treatment (*n* = 42)	
Age (years) [median (IQR)]	79 (70–86)	72 (66–84)	0.27
Male sex	34 (58)	28 (67)	0.36
Co-morbidities			
Diabetes mellitus	11 (19)	7 (17)	0.80
Chronic kidney disease	24 (41)	11 (26)	0.13
Immunosuppression	6 (10)	5 (12)	1.00
Cancer	11 (19)	13 (31)	0.15
Charlson comorbidity index [median (IQR)]	4 (3–6)	4 (2–7)	0.69
Sepsis/septic shock	15 (25)	7 (17)	0.29
Pitt bacteraemia score [median (IQR)]	0 (0–2)	0 (0–1)	0.004
Nosocomial acquisition	19 (32)	15 (36)	0.71
Healthcare-associated	21 (36)	11 (26)	0.32
Micro-organism			0.89
Escherichia coli	47 (80)	33 (79)	
Klebsiella pneumoniae	12 (20)	9 (21)	
Bloodstream infection source			0.12
Urinary tract	34 (58)	30 (71)	
Biliary tract	12 (20)	3 (7)	
Catheter-related	2 (3)	4 (10)	
Source control[b]	10 (17)	5 (12)	0.48
Appropriate empirical therapy	32 (54)	13 (31)	0.074
Partially appropriate[c]	3 (5)	4 (10)	
Delay in appropriate therapy (days) [median (IQR)][d]	0 (0–3)	2 (0–3)	0.006
Duration of empirical treatment (days) [median (IQR)]	2 (2–4)	3 (2–3)	0.79
Duration of definitive treatment (days) [median (IQR)]	12 (7–14)	12 (10–14)	0.23
Outcomes			
Hospital stay after BSI [median (IQR)]			
Overall	12 (9–18)	7 (5–10)	<0.0001
Survivors	12 (8.5–18)	7 (4.25–10)	<0.0001
Cure failure[e]	9 (15)	2 (5)	0.12
Relapse (30-day follow-up)	3 (5)	1 (2)	0.64
Mortality (30-day follow-up)	6 (10)	2 (5)	0.46

IQR, interquartile range.
[a] Data are *n* (%) unless otherwise stated.
[b] Includes any kind of intervention apart from antibiotic treatment to resolve the bloodstream infection, e.g. surgical treatment, abscess drainage or catheter withdrawal.
[c] The antibiotic was appropriate for part of the duration of empirical treatment (e.g. the patient received some days of appropriate treatment and some days of a non-appropriate antibiotic during empirical therapy).
[d] Days without active treatment in terms of antibiotic susceptibility.
[e] Includes bacteraemia persistence or recurrence/relapse.

Source control was performed in 5 (12%) of 42 patients in the alternative group: 3 underwent catheter removal due to catheter-related bacteraemia and 2 underwent endoscopic retrograde cholangiopancreatography (ERCP) due to bacteraemia of biliary source. Source control was performed in 10 (17%) of 59 patients in the carbapenem group: 3 underwent ERCP, 5 required a double J catheter or percutaneous nephrostomy, 1 required debridement and implant retention and 1 underwent abdominal surgery.

During the 30-day follow up, among the 59 carbapenem-treated patients, 9 (15%) were considered as clinical failure, of which 6 patients died (10%) and 3 (5%) had a relapse. Among the 42 patients in the non-carbapenem group, 2 patients (5%) died, who were also considered as clinical failure, 1 of which had also previously developed bacteraemia relapse (Table 1). The two patients who died in the alternative treatment group had disseminated cancer (bladder and colon cancer). Among the six patients who died in the carbapenem group, one had a pancreatic tumour and the others had multiple co-morbidities.

Compared with the carbapenem group, patients treated with an alternative regimen had a shorter hospital LOS [median 7 days (IQR 5–10 days) vs. 12 days (IQR 9–18 days); $P < 0.001$] (Table 1).

In the alternative treatment group, 2/25 patients (8%) receiving SXT died due to ESBL-producing *E. coli* bacteraemia, both of whom had advanced neoplastic disease (as previously described). This percentage is not higher than the 30-day mortality observed in the carbapenem group (Table 1).

3.2. Alternative treatment group

SXT was the most frequent therapeutic agent selected in these patients. The clinical characteristics and source of bacteraemia of patients who received alternative therapy as definitive treatment are shown in Table 2, and the complete therapy regimen and length of therapy in the alternative group are shown in Table 3. When patients were switched to non-i.v. antibiotics, they had received a median of 2.5 days (IQR 0–6 days) of appropriate i.v. therapy.

3.3. Multivariate and propensity score analysis

In the univariate analysis, nosocomial acquisition [odds ratio (OR) = 4.08, 95% confidence interval (CI) 1.10–15.11; $P = 0.035$), CKD (OR = 6.22, 95% CI 1.53–25.27; $P = 0.011$) and the type of micro-organism (*K. pneumoniae* compared with *E. coli*) (OR = 3.85, 95% CI 1.05–14.20, $P = 0.042$) were independent predictors of clinical failure. Use of an alternative non-i.v. treatment was not related to mortality (OR = 0.27, 95% CI 0.05–1.61; $P = 0.15$) (Table 4). After controlling for confounding with the propensity score, the adjusted OR of carbapenem treatment was 4.95 (95% CI 0.94–26.01; $P = 0.059$).

Table 2
Clinical characteristics of patients with bloodstream infection (BSI) caused by extended-spectrum β-lactamase- or AmpC β-lactamase-producing Enterobacteriaceae who received an alternative therapy as definitive treatment (carbapenem-sparing).

Patient	Definitive treatment	Sepsis/septic shock	Micro-organism	BSI source	Death	Cure	Relapse
1	SXT p.o./1 DS t.i.d.	No	*Escherichia coli*	Urinary	No	Yes	No
2	SXT p.o./1 DS b.i.d.	No	*E. coli*	Urinary	No	Yes	No
3	SXT p.o./1 DS b.i.d.	No	*E. coli*	Urinary	No	Yes	No
4	SXT p.o./1 DS b.i.d.	Septic shock	*Klebsiella pneumoniae* AmpC	Catheter	No	Yes	No
5	SXT p.o./1 DS b.i.d.	Sepsis	*K. pneumoniae* AmpC	Urinary	No	Yes	No
6	SXT p.o./1 DS b.i.d.	No	*E. coli*	Biliary	No	Yes	No
7	SXT p.o./1 DS b.i.d.	No	*E. coli*	Urinary	No	Yes	No
8	SXT p.o./1 DS b.i.d.	No	*E. coli*	Urinary	Yes	No	No
9	SXT p.o./1 DS b.i.d.	No	*E. coli*	Urinary	No	Yes	No
10	SXT p.o./1 DS b.i.d.	No	*K. pneumoniae* AmpC	Biliary	No	Yes	No
11	SXT p.o./1 DS b.i.d.	No	*K. pneumoniae* AmpC	Urinary	No	Yes	No
12	SXT p.o./1 DS b.i.d.	No	*E. coli*	Primary[a]	No	Yes	No
13	SXT p.o./1 DS b.i.d.	No	*E. coli*	Urinary	No	Yes	No
14	SXT p.o./1 DS b.i.d.	Sepsis	*E. coli*	Urinary	No	Yes	No
15	SXT p.o./1 DS b.i.d.	No	*E. coli*	Bowel	No	Yes	No
16	SXT p.o./1 DS b.i.d.	No	*E. coli*	Biliary	No	Yes	No
17	SXT p.o./1 DS b.i.d.	No	*E. coli*	Urinary	No	Yes	No
18	SXT p.o./1 DS b.i.d.	No	*E. coli*	Urinary	No	Yes	No
19	SXT p.o./1 DS b.i.d.	Septic shock	*E. coli*	Urinary	No	Yes	No
20	SXT p.o./1 DS b.i.d.	No	*K. pneumoniae*	Urinary	No	Yes	No
21	SXT p.o./1 DS b.i.d.	Septic shock	*E. coli*	Urinary	No	Yes	No
22	SXT p.o./1 DS b.i.d.	No	*E. coli*	Urinary	Yes	No	Yes
23	SXT p.o./1 DS b.i.d.	No	*K. pneumoniae*	Primary	No	Yes	No
24	SXT p.o./1 DS b.i.d.	No	*E. coli*	Primary	No	Yes	No
25	SXT p.o./1 DS b.i.d.	No	*E. coli*	Urinary	No	Yes	No
26	Fosfomycin p.o. 500 mg t.i.d.	No	*K. pneumoniae*	Urinary	No	Yes	No
27	Fosfomycin p.o. 500 mg t.i.d.	No	*E. coli*	Urinary	No	Yes	No
28	Ciprofloxacin p.o. 500 mg b.i.d.	No	*E. coli*	Urinary	No	Yes	No
29	Ciprofloxacin p.o. 500 mg b.i.d.	Septic shock	*E. coli*	Urinary	No	Yes	No
30	Ciprofloxacin p.o. 500 mg b.i.d.	No	*K. pneumoniae* AmpC	Catheter	No	Yes	No
31	Ciprofloxacin p.o. 500 mg b.i.d.	No	*K. pneumoniae*	Catheter	No	Yes	No
32	Ciprofloxacin p.o. 500 mg b.i.d.	No	*E. coli*	Urinary	No	Yes	No
33	Ciprofloxacin p.o. 750 mg b.i.d.	No	*E. coli*	Catheter	No	Yes	No
34	Ciprofloxacin p.o. 500 mg b.i.d.	No	*E. coli*	Urinary	No	Yes	No
35	Ciprofloxacin p.o. 500 mg b.i.d.	No	*E. coli*	Abdominal	No	Yes	No
36	Ciprofloxacin p.o. 500 mg b.i.d.	No	*E. coli*	Urinary	No	Yes	No
37	AMC ER p.o. 1000/62.5 mg t.i.d.	No	*E. coli*	Urinary	No	Yes	No
38	Gentamicin i.m. 240 mg qd	No	*E. coli*	Urinary	No	Yes	No
39	Gentamicin i.m. 240 mg qd	Sepsis	*E. coli*	Urinary	No	Yes	No
40	Gentamicin 240 mg qd	No	*E. coli*	Urinary	No	Yes	No
41	Amikacin i.m. 1 g qd	No	*E. coli*	Urinary	No	Yes	No
42	Gentamicin 240 mg qd	No	*E. coli*	Urinary	No	Yes	No

SXT, trimethoprim/sulfamethoxazole; p.o., oral; DS, double strength; t.i.d., three times a day; b.i.d., twice a day; AMC, amoxicillin/clavulanic acid; ER, extended release; i.m., intramuscular; qd, once daily.
[a] Primary indicates no source identified.

4. Discussion

In this study, use of alternative non-i.v. carbapenem-sparing antibiotics for the definitive treatment of ESBL- or AmpC-positive Enterobacteriaceae bloodstream infection in clinically stable patients was not observed to be related to greater mortality. In fact, no differences in either the primary outcome of 30-day mortality [6/59 (10%) vs. 2/42 (5%); $P = 0.46$] or in the secondary outcome of clinical failure [9/59 (15%) vs. 2/42 (5%); $P = 0.12$] were found for the carbapenem group versus the non-i.v. carbapenem-sparing antibiotic group. Moreover, use of alternative treatment was associated with a shorter hospital LOS.

Some reports have evaluated the efficacy of i.v. carbapenem-sparing antibiotics in this setting, including cephamycins, BL/BLIs or fluoroquinolones, and have presented both positive [7,11,16,17,28] and negative [4,29,30] outcomes. To date, there are fewer data for non-i.v. options. In a metanalysis [3], use of empirical quinolones (oral or i.v.) for ESBL Enterobacteriaceae bacteraemia was associated with a higher mortality than carbapenems, but mortality was similar when quinolones were used as definitive therapy. Some studies have shown prior exposure to fluoroquinolones or β-lactams to be independent risk factors for ESBL-producing or carbapenem-resistant Enterobacteriaceae infections [31,32]. Taking this into consideration, other non-i.v. treatments such as SXT or fosfomycin could be a better option for definitive therapy. To our knowledge, there is no published experience with these oral alternatives for the treatment of ESBL Enterobacteriaceae bacteraemia [33]. Published experience with SXT for the treatment of ESBL- or AmpC-producing infections in patients without bacteraemia is also scarce. Park et al. showed that non-carbapenem antibiotics (including five patients treated with SXT) had a similar efficacy to carbapenems among a case series of pyelonephritis, however the outcome of patients treated with SXT was not specified [34]. SXT was the most frequent option chosen as non-i.v., carbapenem-sparing, definitive treatment in the current study (mainly for urinary and biliary sources); no complications were found related to this use. Our experience with SXT as definitive treatment in clinically stable patients, after confirming antibiotic susceptibility (38% of the strains of ESBL infections in our setting) is promising. This option may prevent the emergence of resistance, allows for the administration of an oral regimen and could shorten the hospital LOS.

Studies of the efficacy of non-i.v. carbapenem-sparing agents for infections caused by ESBL/AmpC-producing Enterobacteriaceae

Table 3
Complete therapy regimen and duration of treatment of patients with bloodstream infection caused by extended-spectrum β-lactamase- or AmpC β-lactamase-producing Enterobacteriaceae who received an alternative therapy as definitive treatment (carbapenem-sparing).

Patient	Empirical treatment (appropriate)	Duration (days)	Effective modification treatment (same as definitive)	Duration (days)	Definitive treatment	Duration (days)
1	BL/BLI, cephalosporin (No)	2	Carbapenem (No)	1	SXT	28
2	Quinolone, AMG (No)	5	SXT (Yes)	10		
3	Cephalosporin, carbapenem (Partially[a])	4	Carbapenem (No)	5	SXT	14
4	Carbapenem (Yes)	3	Carbapenem (No)	6	SXT	10
5	BL/BLI (Yes)	3	BL/BLI (No)	2	SXT	8
6	Carbapenem, BL/BLI (Yes)	6	SXT (Yes)	8		
7	BL/BLI (Yes)	3	SXT (Yes)	9		
8 (Death)	BL/BLI (No)	3	Carbapenem (No)	3	SXT	11
9	BL/BLI (No)	1	SXT (Yes)	11		
10	BL/BLI (No)	4	SXT (Yes)	13		
11	BL/BLI (No)	3	Carbapenem (No)	1	SXT	27
12	Quinolone (No)	3	SXT (Yes)	14		
13	Cephalosporin (No)	2	SXT (Yes)	21		
14	Carbapenem (Yes)	2	Carbapenem (No)	4	SXT	14
15	BL/BLI, quinolone (No)	1	Carbapenem (No)	3	SXT	7
16	BL/BLI (No)	2	Carbapenem (No)	6	SXT	11
17	Cephalosporin, quinolone (No)	2	SXT (Yes)	14		
18	Cephalosporin (No)	3	Carbapenem (No)	1	SXT	13
19	Carbapenem, SXT (Yes)	4	SXT (Yes)	11		
20	BL/BLI, carbapenem (Yes)	3	Carbapenem (No)	2	SXT	9
21	Carbapenem (Yes)	3	Carbapenem (No)	8	SXT	14
22 (Death)	BL/BLI, quinolone (No)	2	SXT (Yes)	12		
23	Cephalosporin (No)	3	SXT (Yes)	18		
24	Cephalosporin (No)	5	SXT (Yes)	19		
25	Quinolone (No)	4	SXT (Yes)	15		
26	BL/BLI, carbapenem (Partially)	4	Fosfomycin (Yes)	14		
27	Cephalosporin, AMG (Partially)	2	Carbapenem (No)	5	Fosfomycin	15
28	BL/BLI (No)	1	Quinolone (Yes)	14		
29	Carbapenem (Yes)	3	Carbapenem (No)	7	Quinolone	10
30	BL/BLI (No)	2	Carbapenem (No)	2	Quinolone	10
31	Aztreonam (No)	2	Quinolone (Yes)	14		
32	BL/BLI (Yes)	3	Quinolone (Yes)	25		
33	Aztreonam (No)	2	AMG (No)	2	Quinolone	10
34	BL/BLI (No)	2	Quinolone (Yes)	16		
35	BL/BLI (Yes)	2	Carbapenem (No)	6	Quinolone	8
36	Cephalosporin (No)	5	Quinolone (Yes)	10		
37	BL/BLI (Yes)	2	Carbapenem (No)	2	AMC	10
38	BL/BLI, AMG (Partially)	2	AMG (gentamicin) (Yes)	12		
39	Cephalosporin (No)	2	Carbapenem (No)	5	AMG (gentamicin)	8
40	Cephalosporin (No)	3	AMG (gentamicin) (Yes)	21		
41	Cephalosporin (No)	2	Carbapenem (No)	5	AMG (amikacin)	8
42	Carbapenem (Yes)	1	Carbapenem (No)	5	AMG (gentamicin)	7

BL/BLI, β-lactam/β-lactamase inhibitor; SXT, trimethoprim/sulfamethoxazole; AMG, aminoglycoside; AMC, amoxicillin/clavulanic acid.
[a] Partially indicates the antibiotic was appropriate for part of the empirical treatment.

Table 4
Univariate and multivariate analysis: relationship between variables and treatment failure.

	OR (95% CI)	*P*-value
Univariate analysis		
Age	0.99 (0.94–1.03)	0.57
Sex (male)	1.79 (0.44–7.14)	0.42
Diabetes mellitus	0.43 (0.05–3.59)	0.43
Chronic kidney disease	6.22 (1.53–25.27)	0.011
Immunosuppression	2.00 (0.37–10.73)	0.42
Cancer	1.23 (0.30–5.07)	0.77
Charlson comorbidity index	1.08 (0.86–1.35)	0.49
Sepsis/septic shock	0.33 (0.04–2.72)	0.30
Pitt bacteraemia score	0.84 (0.54–1.29)	0.42
Nosocomial acquisition	4.08 (1.10–15.11)	0.035
Healthcare-associated	1.94 (0.55–6.92)	0.30
ESBL micro-organism *Klebsiella pneumoniae*	3.85 (1.05–14.20)	0.042
Bloodstream infection source		
Urinary tract	1	0.52
Catheter-related	1.000 (1.00–1.00)	
Biliary tract	2.42 (0.53–11.04)	
Other	1.38 (0.25–7.59)	
Appropriate empirical therapy		
Yes	0.70 (0.18–2.66)	0.84
Partially[a]	1.19 (0.12–11.71)	
Delay in appropriate therapy[b]	1.07 (0.73–1.57)	0.74
Duration of empirical treatment	1.004 (0.58–1.72)	0.99
Duration of definitive treatment	0.98 (0.89–1.09)	0.75
Alternative non-i.v. treatment	0.28 (0.06–1.35)	0.11
Hospital LOS after BSI	1.01 (0.99–1.04)	0.34
Multivariate analysis		
Chronic kidney disease	11.19 (1.84–67.94)	0.009
ESBL micro-organism *K. pneumoniae*	7.86 (1.16–53.41)	0.035
Alternative non-i.v. treatment	0.27 (0.05–1.61)	0.15

OR, odds ratio; CI, confidence interval; ESBL, extended-spectrum β-lactamase; i.v., intravenous; LOS, length of stay; BSI, bloodstream infection.
[a] Partially indicates the antibiotic was appropriate for part of the duration of the empirical treatment (e.g. the patient received some days of appropriate treatment and some days of a non-appropriate antibiotic during empirical therapy).
[b] Days without active treatment in terms of antibiotic susceptibility.

have focused mainly on urinary tract infections [35,36], have not assessed cases of bacteraemia and have addressed mainly patients with ESBL-producing *E. coli* infections. Since most of the available drugs (SXT, quinolones, fosfomycin) have high urinary levels, further studies should determine whether these alternative non-i.v. carbapenem-sparing agents are also useful for the treatment of other bacteraemic foci (abdominal) and for ESBL-producing *Klebsiella* infections.

Data on non-i.v. carbapenem-sparing treatments could help reduce carbapenem use, which is crucial in order to contain the spread of carbapenem resistance [37], to reduce its impact on global hospital ecology [38] and to shorten hospital LOS. As demonstrated, hospital LOS in the alternative treatment group was significantly shorter in the current study population without a negative impact in terms of relapse or early re-admission. The benefits associated with non-prolonged hospitalisation in terms of cost effectiveness and co-morbidity have been already demonstrated [39].

Finally, in a recent study [40], the idea of shorter duration for Enterobacteriaceae bacteraemia in general (not focused on ESBL) arises. In the current study, when patients were switched to non-i.v. antibiotics they had received a median of 2.5 days (IQR 0–6 days) of appropriate i.v. therapy. We could say that some of them would already be treated correctly with the i.v. therapy, however these results also support the possibility of step-down therapy in stable patients with ESBL bacteraemia.

This study has several limitations. The retrospective design could not exclude the possibility that patients with more severe infections were preferably treated with carbapenems without subsequent treatment with a non-carbapenem, however all cases were included. Moreover, the sample size may be too small to achieve adequate statistical power, and selection by indication may bias the results. We tried to balance this limitation by adjusting the results using a propensity score analysis, and did not observe changes in estimation effects. This study may not account for all of the variables that may have influenced the decision to use carbapenems and thus might influence the OR; similarly, the goodness-of-fit model for calculating propensity score weights might be underpowered (AUC = 0.77). We also could not characterise the ESBL genes or investigate the minimum inhibitory concentration (MIC) distribution for all study isolates. Furthermore, the study included mostly bloodstream infections due to *E. coli*, which means that these results cannot be extrapolated to *K. pneumoniae* and mixed ESBL/AmpC-positive Enterobacteriaceae or other species of the Enterobacteriaceae family. Finally, the majority of sources of bloodstream infection were urinary, so these results may be not be extrapolated to other bacteraemic foci.

5. Conclusions

Despite these limitations, the possibility that non-i.v. antibiotics could be used in selected patients for the definitive treatment of ESBL/AmpC-positive Enterobacteriaceae bloodstream infections is promising, particularly in the urinary focus setting and in clinically stable patients. This series supports the use of SXT as a carbapenem-sparing alternative therapy that could reduce carbapenem use and shorten hospital LOS. Larger prospective interventional studies are now required to definitively assess the efficacy of oral carbapenem-sparing antibiotics for the treatment of ESBL/AmpC-positive Enterobacteriaceae bacteraemia.

Acknowledgments

The authors thank Jay A. Fishman for his critical review, Santi Pérez Hoyos and Alex Sànchez for the statistical analysis, and Michael Maudsley for English language support and editorial assistance.

Funding

CP, NF-H and JR-B are supported by Plan Nacional de I+D+i 2013–2016 and Instituto de Salud Carlos III, Subdirección General de Redes y Centros de Investigación Cooperativa, Ministerio de Economía, Industria y Competitividad, Spanish Network for Research in Infectious Diseases [REIPI RD16/0016/0001 and 0003], which is co-financed by the European Regional Development Fund 'A way to achieve Europe', Operative Programme Intelligent Growth 2014–2020.

Competing interests

None declared.

Ethical approval

This study was approved by the institutional review board for clinical trials.

References

[1] Arnaud I, Maugat S, Jarlier V, Astagneau PNational Early Warning, Investigation and Surveillance of Healthcare-Associated Infections Network (RAISIN)/Multidrug Resistance Study Group. Ongoing increasing temporal and geographical trends of the incidence of extended-spectrum β-lactamase-producing Enterobacteriaceae infections in France, 2009 to 2013. Euro Surveill 2015;20. doi:10.2807/1560-7917.ES.2015.20.36.30014.
[2] Pitout JD, Laupland KB. Extended-spectrum b-lactamase-producing Enterobacteriaceae: an emerging public-health concern. Lancet Infect Dis 2008;8:159–66. doi:10.1016/S1473-3099(08)70041-0.

[3] 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. doi:10.1093/jac/dks301.

[4] Harris PNA, Tambyah PA, Lye DC, Mo Y, Lee TH, Yilmaz M, et al. Effect of piperacillin–tazobactam vs meropenem on 30-day mortality for patients with E coli or *Klebsiella pneumoniae* bloodstream infection and ceftriaxone resistance: a randomized clinical trial. JAMA 2018;320:984–94. doi:10.1001/jama.2018.12163.

[5] Albiger B, Glasner C, Struelens MJ, Grundmann H, Monnet DLEuropean Survey of Carbapenemase-Producing Enterobacteriaceae (EuSCAPE) Working Group. Carbapenemase-producing Enterobacteriaceae in Europe: assessment by national experts from 38 countries, May 2015. Euro Surveill 2015;20 Erratum in: Euro Surveill 201;21. doi:10.2807/1560-7917.ES.2016.21.38.30344. doi:10.2807/1560-7917.ES.2015.20.45.30062.

[6] Hayden MK, Won SY. Carbapenem-sparing therapy for extended-spectrum β-lactamase-producing *E coli* and *Klebsiella pneumoniae* bloodstream infection: the search continues. JAMA 2018;320:979–81. doi:10.1001/jama.2018.12565.

[7] Rodríguez-Baño J, Navarro MD, Retamar P, Picón E, Pascual ÁExtended-Spectrum Beta-Lactamases–Red Española de Investigación en Patología Infecciosa/Grupo de Estudio de Infección Hospitalaria Group. β-Lactam/β-lactam inhibitor combinations for the treatment of bacteremia due to extended-spectrum β-lactamase-producing *Escherichia coli*: a post hoc analysis of prospective cohorts. Clin Infect Dis 2012;54:167–74. doi:10.1093/cid/cir790.

[8] 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;60:1319–25. doi:10.1093/cid/civ003.

[9] Ofer-Friedman H, Shefler C, Sharma S, Tirosh A, Tal-Jasper R, Kandipalli D, et al. Carbapenems versus piperacillin–tazobactam for bloodstream infections of nonurinary source caused by extended-spectrum β-lactamase-producing Enterobacteriaceae. Infect Control Hosp Epidemiol 2015;36:981–5. doi:10.1017/ice.2015.101.

[10] Perez F, Bonomo RA. Bloodstream infection caused by extended-spectrum β-lactamase-producing Gram-negative bacteria: how to define the best treatment regimen? Clin Infect Dis 2015;60:1326–9. doi:10.1093/cid/civ007.

[11] Gutiérrez-Gutiérrez B, Pérez-Galera S, Salamanca E, de Cueto M, Calbo E, Almirante B, et al. A multinational, preregistered cohort study of β-lactam/β-lactamase inhibitor combinations for treatment of bloodstream infections due to extended-spectrum-β-lactamase-producing Enterobacteriaceae. Antimicrob Agents Chemother 2016;60:4159–69. doi:10.1128/AAC.00365-16.

[12] Ng TM, Khong WX, Harris PNA, De PP, Chow A, Tambyah PA, et al. Empiric piperacillin–tazobactam versus carbapenems in the treatment of bacteraemia due to extended-spectrum β-lactamase-producing Enterobacteriaceae. PLoS One 2016;11:e0153696. doi:10.1371/journal.pone.0153696.

[13] Gudiol C, Royo-Cebrecos C, Abdala E, Akova M, Álvarez R, Maestro-de la Calle G, et al. Efficacy of β-lactam/β-lactamase inhibitor combinations for the treatment of bloodstream infection due to extended-spectrum-β-lactamase-producing Enterobacteriaceae in hematological patients with neutropenia. Antimicrob Agents Chemother 2017;61 e00164-17. doi:10.1128/AAC.00164-17.

[14] Muhammed M, Flokas ME, Detsis M, Alevizakos M, Mylonakis E. Comparison between carbapenems and β-lactam/β-lactamase inhibitors in the treatment for bloodstream infections caused by extended-spectrum β-lactamase-producing Enterobacteriaceae: a systematic review and meta-analysis. Open Forum Infect Dis 2017;4:ofx099. doi:10.1093/ofid/ofx099.

[15] Rodríguez-Baño J, Gutiérrez-Gutiérrez B, Kahlmeter G. Antibiotics for ceftriaxone-resistant Gram-negative bacterial bloodstream infections. JAMA 2019;321:612–13. doi:10.1001/jama.2018.19345.

[16] Matsumura Y, Yamamoto M, Nagao M, Komori T, Fujita N, Hayashi A, et al. Multicenter retrospective study of cefmetazole and flomoxef for treatment of extended-spectrum-β-lactamase-producing *Escherichia coli* bacteremia. Antimicrob Agents Chemother 2015;59:5107–13. doi:10.1128/AAC.00701-15.

[17] Lo C-L, Lee C-C, Li C-W, Li M-C, Hsueh P-R, Lee N-Y, et al. Fluoroquinolone therapy for bloodstream infections caused by extended-spectrum β-lactamase-producing *Escherichia coli* and *Klebsiella pneumoniae*. J Microbiol Immunol Infect 2017;50:355–61. doi:10.1016/j.jmii.2015.08.012.

[18] Palacios-Baena ZR, Gutiérrez-Gutiérrez B, Calbo E, Almirante B, Viale P, Oliver A, et al. Empiric therapy with carbapenem-sparing regimens for bloodstream infections due to extended-spectrum β-lactamase-producing Enterobacteriaceae: results from the INCREMENT cohort. Clin Infect Dis 2017;65:1615–23. doi:10.1093/cid/cix606.

[19] Rodríguez-Baño J, Cisneros JM, Cobos-Trigueros N, Fresco G, Navarro-San\sFrancisco C, Gudiol C, et al. Executive summary of the diagnosis and antimicrobial treatment of invasive infections due to multidrug-resistant Enterobacteriaceae. Guidelines of the Spanish Society of Infectious Diseases and Clinical Microbiology (SEIMC). Enferm Infecc Microbiol Clin 2015;33:338–41. doi:10.1016/j.eimc.2014.11.015.

[20] Friedman ND, Kaye KS, Stout JE, McGarry SA, Trivette SL, Briggs JP, et al. Health care-associated bloodstream infections in adults: a reason to change the accepted definition of community-acquired infections. Ann Intern Med 2002;137:791–7.

[21] Garner JS, Jarvis WR, Emori TG, Horan TC, Hughes JM. CDC definitions for nosocomial infections, 1988. Am J Infect Control 1988;16:128–40.

[22] Levey AS, Eckardt K-U, Tsukamoto Y, Levin A, Coresh J, Rossert J, et al. Definition and classification of chronic kidney disease: a position statement from Kidney Disease: Improving Global Outcomes (KDIGO). Kidney Int 2005;67:2089–100. doi:10.1111/j.1523-1755.2005.00365.x.

[23] Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987;40:373–83.

[24] Hilf M, Yu VL, Sharp J, Zuravleff JJ, Korvick JA, Muder RR. Antibiotic therapy for *Pseudomonas aeruginosa* bacteremia: outcome correlations in a prospective study of 200 patients. Am J Med 1989;87:540–6.

[25] Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA 2016;315:801–10. doi:10.1001/jama.2016.0287.

[26] Clinical and Laboratory Standards Institute. Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically. ninth edition. Wayne, PA: CLSI; 2012. *approved standard*CLSI document M07-A9.

[27] European Committee on Antimicrobial Susceptibility Testing. *Breakpoint tables for interpretation of MICs and zone diameters. Version 5.0*, 2015. http://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/Breakpoint_tables/v_5.0_Breakpoint_Table_01.pdf [accessed 18 June 2019].

[28] Fukuchi T, Iwata K, Kobayashi S, Nakamura T, Ohji G. Cefmetazole for bacteremia caused by ESBL-producing Enterobacteriaceae comparing with carbapenems. BMC Infect Dis 2016;16:427. doi:10.1186/s12879-016-1770-1.

[29] Lee C-H, Su L-H, Chen F-J, Tang Y-F, Chien C-C, Liu J-W. Clinical and microbiologic characteristics of adult patients with recurrent bacteraemia caused by extended-spectrum β-lactamase-producing *Escherichia coli* or *Klebsiella pneumoniae*. Clin Microbiol Infect 2015;21:1105 e1–8. doi:10.1016/j.cmi.2015.07.025.

[30] Wu U-I, Chen W-C, Yang C-S, Wang J-L, Hu F-C, Chang S-C, et al. Ertapenem in the treatment of bacteremia caused by extended-spectrum β-lactamase-producing *Escherichia coli*: a propensity score analysis. Int J Infect Dis 2012;16:e47–52. doi:10.1016/j.ijid.2011.09.019.

[31] Falagas ME, Rafailidis PI, Kofteridis D, Virtzili S, Chelvatzoglou FC, Papaioannou V, et al. Risk factors of carbapenem-resistant *Klebsiella pneumoniae* infections: a matched case control study. J Antimicrob Chemother 2007;60:1124–30. doi:10.1093/jac/dkm356.

[32] Chopra T, Marchaim D, Johnson PC, Chalana IK, Tamam Z, Mohammed M, et al. Risk factors for bloodstream infection caused by extended-spectrum β-lactamase-producing *Escherichia coli* and *Klebsiella pneumoniae*: a focus on antimicrobials including cefepime. Am J Infect Control 2015;43:719–23. doi:10.1016/j.ajic.2015.02.030.

[33] Rodríguez-Baño J, Gutiérrez-Gutiérrez B, Machuca I, Pascual A. Treatment of infections caused by extended-spectrum-β-lactamase-, AmpC-, and carbapenemase-producing Enterobacteriaceae. Clin Microbiol Rev 2018;31 pii: e00079-17. doi:10.1128/CMR.00079-17.

[34] Park SH, Choi S-M, Chang YK, Lee D-G, Cho S-Y, Lee H-J, 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;69:2848–56. doi:10.1093/jac/dku215.

[35] Ipekci T, Seyman D, Berk H, Celik O. Clinical and bacteriological efficacy of amikacin in the treatment of lower urinary tract infection caused by extended-spectrum β-lactamase-producing *Escherichia coli* or *Klebsiella pneumoniae*. J Infect Chemother 2014;20:762–7. doi:10.1016/j.jiac.2014.08.007.

[36] de la Blanchardière A, Dargère S, Guérin F, Daurel C, Saint-Lorant G, Verdon R, et al. Non-carbapenem therapy of urinary tract infections caused by extended-spectrum β-lactamase-producing Enterobacteriaceae. Med Mal Infect 2015;45:169–72. doi:10.1016/j.medmal.2015.03.003.

[37] Lim CL-L, Lee W, Lee AL-C, Liew LT-T, Nah SC, Wan CN, et al. Evaluation of ertapenem use with impact assessment on extended-spectrum β-lactamases (ESBL) production and Gram-negative resistance in Singapore General Hospital (SGH). BMC Infect Dis 2013;13:523. doi:10.1186/1471-2334-13-523.

[38] Pletz MWR, 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. doi:10.1128/AAC.48.10.3765-3772.2004.

[39] Conley J, O'Brien CW, Leff BA, Bolen S, Zulman D. Alternative strategies to inpatient hospitalization for acute medical conditions: a systematic review. JAMA Intern Med 2016;176:1693–702. doi:10.1001/jamainternmed.2016.5974.

[40] Chotiprasitsakul D, Han JH, Cosgrove SE, Harris AD, Lautenbach E, Conley AT, et al. Comparing the outcomes of adults with Enterobacteriaceae bacteremia receiving short-course versus prolonged-course antibiotic therapy in a multicenter, propensity score-matched cohort. Clin Infect Dis 2018;66:172–7. doi:10.1093/cid/cix767.