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Clinical, microbiological characteristics and predictors of mortality in patients with carbapenemase-producing Enterobacterales bloodstream infections: a multicentre study

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SUMMARY

Objectives: To investigate the clinical, microbiological characteristics and outcomes of patients with bloodstream infections (BSI) due to carbapenemase-producing Enterobacterales (CPE).

Methods: A multicentre retrospective observational study of patients with BSIs due to CPE admitted to six UK hospitals was conducted between 2011 and 2021. Multivariate analysis was used to identify factors predicting 30-day case fatality rate (CFR).

Results: There were 84 episodes of CPE-BSIs, 37 (44%) due to OXA-48, 35 (42%) to metallo-betalactamases (MBL) and 12 (14%) to KPC. 63% of patients were male with a median age of 64 years. Common organisms included *Klebsiella* spp. (61%), *Escherichia coli* (20%) and *Enterobacter* spp. (13%). Urinary devices were more often involved in OXA-48 BSIs (12/37; 32%) compared to infections caused by MBL and KPC (4/35; 11% and 1/12; 8%; $P = 0.046$). In contrast, central venous catheters were more frequently present in KPC-BSIs (10/12; 92%) compared with OXA-48 and MBL (11/37; 30% and 20/35; 57%; $P = 0.002$). Effective definitive antimicrobials were received by 72/84 (86%) patients, comprising monotherapy (32/72; 44%) or combination therapy (40/72; 56%). 30-day case fatality rate (CFR) was 38%. Sepsis or septic shock was associated with death [OR 3.81 (CI 1.19—12.14), $P = 0.024$].

Conclusion: Strategies targeting high-risk patients and adherence to infection prevention bundles for urinary devices and central venous catheters can reduce OXA-48 and KPC-BSIs.

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Early recognition and management of severe sepsis, prompt initiation of appropriate antimicrobial therapy and development of novel antimicrobials are crucial to mitigate the high CFR associated with CPE-BSIs.

Introduction

Bloodstream infections (BSIs) caused by carbapenemase-producing Enterobacterales (CPE) are a public health concern associated with a 75% increase in in-hospital mortality [1,2], prolonged hospitalisation and increased healthcare costs [3]. The most common carbapenemases are oxacillinase-48 (OXA-48), *Klebsiella pneumoniae* carbapenemase (KPC), Guiana extended-spectrum beta-lactamase (GES) and the metallo-beta-lactamases (MBL) known as New Delhi metallo-beta-lactamase (NDM), Verona integron-mediated metallo-beta-lactamase (VIM), and active-on-imipenem carbapenemase (IMP); these have considerable geographical variation. Indeed, the distribution of CPE is variable across the UK, with 11% of referred isolates coming from the Southeast of England and 38% of isolates being from London [3]. In the UK, the prevalence of CPE bloodstream infections has progressively risen in the last decade, accounting for 10.4% of the total reported CPE infections under surveillance in 2020 [3].

Clinical management and antibiotic choices in patients with CPE bloodstream infection are not yet standardised. The European Society of Clinical Microbiology and Infectious Diseases (ESCMID) and the Infectious Diseases Society of America (IDSA) recently published guidelines with recommendations on the treatment of resistant Gram-negative infections, including infections caused by CPE [4,5]. However, there are limited options available for the treatment of some CPE infections, particularly those harbouring MBL, where therapeutic failure is not uncommon [6]. Furthermore, studies of CPE-BSIs are scarce in the literature and most focus on one specific class of carbapenemase, and often do not report detailed antimicrobial susceptibility data. For this reason, studies providing detailed analysis of CPE-BSI sensitivity data combined with clinical outcomes across regions with high incidence may have the potential to improve clinical management for these patients in the short-term.

We aimed to investigate the clinical, microbiological characteristics and clinical outcomes and to identify factors associated with 30-day case fatality rate (CFR) in patients with different classes of CPE-BSI presenting to hospitals in London, UK over a decade.

Methods

Study design and participants

A multicentre retrospective observational study of patients with BSIs due to CPE admitted to four university hospitals and two district general hospitals in London was conducted from 1st November 2011 to 31st October 2021. Adult patients (>18 years old) with monomicrobial BSIs due to CPE were included. Samples were excluded if: (i) more than one organism grew in the blood culture (polymicrobial sample); or (ii) a second or subsequent repeat sample was positive for the same CPE during the same hospital admission. Each patient had only one episode/admission with CPE BSI.

Study outcomes

The main outcome was descriptive: demographics, microbiological characteristics, antimicrobial and clinical outcomes of patients with bloodstream infections due to CPE were compared between the three classes of carbapenemase identified (OXA-48, KPC and MBL). Note that some isolates harboured more than one resistance mechanism, and for the purpose of this study, MBL took precedence over KPC, and KPC over OXA-48 - recognising the typically broader resistance patterns and clinical significance of each carbapenemase. A subsequent analysis was undertaken to identify risk factors associated with 30-day CFR.

Data collection and demographic variable definitions

Cases were identified by searching laboratory information management systems, or other available databases, at individual hospitals. Presence of CPE genes was confirmed by nucleic acid amplification assays (NAATs) or lateral flow immunochromatographic methods (https://www.eucast.org/resistance_mechanisms) in UKAS-accredited diagnostic laboratories. Demographic, clinical, microbiological and treatment data were extracted from the medical records by investigators at each centre and entered into a secure data collection tool. Further laboratory results were collected at each site from laboratory information management systems. All collected data from individual sites were pseudonymised and collated into a single secure data collection sheet for analysis.

The demographic and baseline variables collected were age, gender, previous colonisation by CPE, underlying medical conditions and Charlson comorbidity index for adults [7]. Immunosuppression was defined as the presence of diabetes mellitus, neutropenia, HIV infection, or receipt of steroids (at any dose) or other immunosuppressive agents in the 30 days prior to bacteraemia. Severity of illness at the time of onset of infection was assessed by the presence of severe sepsis or septic shock, defined as sepsis with hypotension (systolic blood pressure BP <90 mmHg) or requiring vasopressors with elevated lactate (>2 mmol/L). Invasive procedures included mechanical ventilation, insertion of central venous catheter, urinary devices, intra-abdominal or prosthetic devices. Source of infection was determined as pneumonia, urinary tract infection, intra-abdominal, line-related infection, bone and joint, using the definitions of the Centers for Disease Control and Prevention [8]. Early source control was determined as an intervention that contributed to achieving control of the infection (e.g. drainage of a collection, indwelling device removal) that occurred within 72 hours of the positive blood

culture. Infection onset was defined as the date and time that the index CPE blood culture was collected.

Microbiological data

Bacterial identification and antibiotic susceptibilities were performed and reported by UKAS-accredited laboratories according to the protocols extant at the time, with additional identification of resistance mechanisms and antimicrobial susceptibility by the reference laboratory where required (UK Health Security Agency (UKHSA) (formerly Public Health England), Colindale, UK). Isolate sensitivity tests reported as intermediate were deemed not sensitive. In instances of antimicrobial susceptibility discrepancies between the local and the reference laboratories, the result from the reference laboratory took precedence.

Antimicrobial outcomes

Antimicrobial therapy was defined as effective if the isolate was susceptible *in vitro* to that antibiotic. We defined effective combination therapy as a regimen including two or more *in vitro* active antimicrobial, and monotherapy as including only a single active drug. Effective antimicrobial treatment was categorised as i) effective *empirical* treatment which was administered before antimicrobial susceptibility results were available, and ii) effective *definitive* treatment, which was administered following susceptibility results. Early effective therapy was defined as the receipt of at least one *in vitro* active antibiotic within 48 hours of blood culture collection.

Clinical outcomes

Case fatality was defined as all-cause death within 7, 30 or 90 days after the positive blood culture. Length of stay was time to discharge from hospital after positive blood culture.

Statistical analysis

For descriptive analysis, categorical variables were presented as absolute numbers and their relative percentages; continuous variables were summarised as mean ± standard deviation (SD) or median and interquartile range (IQR), according to their distribution. Baseline characteristics and treatment outcomes were compared between the groups of patients according to carbapenemase gene. ANOVA tests were used to examine differences across these groups. Multinomial logistic regression was used to build a model to explore which factors might influence 30-day mortality. Variables with a *P*-value of <0.1 on the univariate analysis, were included in the model. Odds ratios (ORs) and 95% confidence intervals (CIs) were estimated. All *P*-values were two-tailed and a *P*-value of <0.05 was considered statistically significant. The statistical analysis was performed using IBM SPSS v21.0.

Ethical approval

The study was initially approved by St. George's Hospitals NHS Foundation Trust as a service evaluation, and approval was also obtained at each participating centre according to local requirements. According to the UK Policy Framework for Health and Social Care Research v3.2 October 2017, service evaluations do not require formal ethical review. Informed consent was not obtained as included patients were not subjected to extra procedures or questions. No personal information was stored in the study database. Samples were collected as part of standard care, which was unchanged during the service evaluation.

Results

Between 1st November 2011 and 31st October 2022, 89 patients with BSI due to CPE were identified. Of these, 5 patients were excluded due to age <18 years (n = 2) and missing key data (n = 3). The remaining 84 patients were included in the main analysis, representing 84 distinct hospital admissions (see Figure 1). The median Charlson score of patients in this cohort was 5 (range 0—14).

Baseline characteristics

Of 84 episodes of BSIs caused by CPE, 37 (44%) were due to OXA-48, 35 (42%) to MBL, and 12 (14%) to KPC. 7 isolates had 2 resistance mechanisms: 4 had both MBL and OXA-48, and a further 3 had KPC and OXA-48. Among the 35 MBL isolates, New Delhi β-lactamase (NDM) accounted for 28, IMP β-lactamase (IMP) accounted for 6 cases, and VIM β-lactamase (VIM) was detected in 1 case (Figure 1). 53/84 (63%) of the patients were male, and the median age of all patients was 64 years (range: 18—95 years). Causative organisms included *Klebsiella* spp. (51/84; 61%), *E. coli* (20/84; 24%), *Enterobacter* spp. (11/84; 13%), *Serratia marcescens* (1/84; 1%) and *Proteus mirabillis* (1/84; 1%). Nosocomial acquisition was identified in 59 (70%) cases. Prior colonisation was reported in 25 (30%) cases, although it is of note that screening policies and their implementation vary between hospitals. The common sources of bacteraemia included urine (21/84; 25%), endovascular (18/84; 21%), intra-abdominal/biliary (20/84; 24%), respiratory (8/84; 10%), and skin and soft tissue (3/84; 4%); the source was

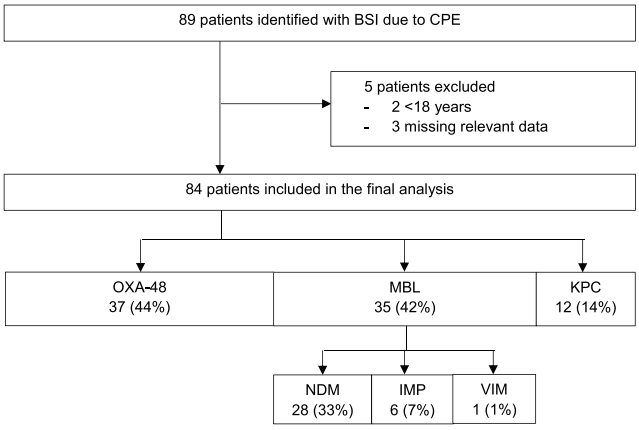

Figure 1. Flow chart of included patients with bloodstream infection (BSI) due to carbapenemase-producing Enterobacterales. BSI - bloodstream infections; CPE - carbapenemase-producing Enterobacterales; OXA-48 - oxacillinase β-lactamases; MBL - metallo-beta-lactamase; KPC - *Klebsiella pneumoniae* carbapenemase, NDM - New Delhi metallo-beta-lactamase, IMP - imipenem beta-lacatamase, VIM - VIM beta-lactamase.

unclear or not identified in 14 (17%) cases. Prior CPE colonisation was significantly associated with pneumonia as the source of BSI, compared with other sources (7/25; 28% vs 1/59; 1.7%, $P<0.001$), with no predominance of any specific class of CPE. Invasive devices were present in 64 patients (76%) at the time of the BSI. Underlying diseases notably included haematological malignancy (29; 35%), diabetes mellitus (26; 31%), chronic liver disease (20; 24%), chronic kidney disease (18; 21%) and organ transplantation (5; 6%). Severe sepsis or septic shock was present in 49 (59%).

Baseline characteristics across groups: OXA-48, KPC and MBL

Klebsiella spp. accounted for 11/12 (92%) of KPC isolates, as expected, 23/37 (62%) of OXA-48 isolates, and 17/35 (49%) of MBL isolates. In contrast, *Enterobacter* spp. harboured MBL almost exclusively, with this resistance mechanism being identified in 10/11 (91%) of all *Enterobacter* isolates. Urinary tract infection was identified as the main source of BSI in 15 (41%) of OXA-48 cases - significantly more commonly than in KPC and MBL (1/12; 8% and 5/35; 14%) ($P = 0.012$). Consistent with this, urinary devices were more frequently present in OXA-48-related BSIs (12/37; 32%) compared to KPC and MBL (1/12; 9% and 4/28; 14%) ($P = 0.046$). Central venous catheters and peripherally inserted central catheters, were the commonest invasive devices identified in this series, and were over-represented in KPC BSIs (10/11; 90%) compared with MBL and OXA-48 (20/35; 57% and 11/37; 30%) ($P = 0.002$) (Table I).

Microbiological characteristics

None of the isolates was sensitive to either piperacillin-tazobactam or ertapenem, and only 8 were sensitive to ceftriaxone — these were all OXA-48-producers. This is notable as these agents are common first-line agents for treating sepsis. Isolates were susceptible to meropenem in 31/84 (37%) of all CPE isolates, including OXA-48 (27/37; 73%) and MBL (4/35; 11%). Ciprofloxacin was susceptible in 25/75 (33%), including OXA-48 (14/36; 40%), MBL (10/31; 33%) and KPC (1/10; 10%). Amikacin was susceptible in 54/84 (64%), including OXA-48 (30/37; 81%), MBL (22/35; 63%) and KPC (2/12; 17%). Fosfomycin was susceptible in 56/71 (79%), for OXA-48 (26/34; 77%), MBL (25/30; 83%) and KPC (5/7; 71%). Tigecycline was susceptible in

Table I
Baseline patient characteristics

	Total N=84	OXA-48 N=37	KPC N=12	MBL N=35	*P*-value
Age (years); median (range)	64 (18—95)	67 (26—95)	50 (18—86)	61 (25—95)	0.074
Male sex	53 (63%)	21 (57%)	9 (75%)	23 (66%)	0.489
Onset BSI >48h from admission	59 (70%)	22 (60%)	10 (83%)	27 (77%)	0.150
Known prior colonisation	25 (30%)	7 (19%)	6 (50%)	12 (36%)	0.093
Charlson score; median (range)	5 (0—14)	5 (0—14)	5 (2—12)	5 (0—12)	0.958
Chronic kidney disease	18 (21%)	6 (17%)	4 (36%)	8 (24%)	0.448
Chronic liver disease	20 (24%)	10 (29%)	5 (46%)	5 (15%)	0.134
Diabetes mellitus	26 (31%)	15 (43%)	2 (18%)	9 (27%)	0.209
Haematology malignancy	29 (35%)	12 (34%)	2 (18%)	14 (42%)	0.348
Organ transplantation	5 (6%)	2 (6%)	2 (18%)	1 (3%)	0.220
Severe sepsis or septic shock	49 (59%)	19 (53%)	10 (83%)	20 (57%)	0.173
Enterobacterales					
Klebsiella spp.[a]	51 (61%)	23 (63%)	11 (92%)	17 (49%)	**0.029**
Escherichia coli	20 (24%)	12 (32%)	1 (8%)	7 (20%)	0.189
Enterobacter spp.[b]	11 (13%)	1 (3%)	0 (0%)	10 (29%)	**0.001**
Serratia marcescens	1 (1%)	1 (3%)	0 (0%)	0 (0%)	0.535
Proteus mirabillis	1 (1%)	0 (0%)	0 (0%)	1 (3%)	0.502
Source					
Urine	21 (25%)	15 (41%)	1 (8%)	5 (14%)	**0.012**
Endovascular	18 (21%)	7 (19%)	3 (25%)	8 (23%)	0.877
Intra-abdominal	20 (24%)	10 (27%)	2 (17%)	8 (23%)	0.760
Pneumonia	8 (10%)	2 (5%)	2 (17%)	4 (11%)	0.462
Skin and soft tissues	3 (4%)	1 (3%)	1 (8%)	1 (3%)	0.639
Unknown	14 (17%)	2 (5%)	3 (25%)	9 (26%)	0.049
Invasive devices	66 (79%)	27 (73%)	11 (92%)	28 (80%)	0.403
Type of invasive devices					
Urinary device	17 (26%)	12 (32%)	1 (8%)	4 (11%)	**0.046**
Central line	41 (62%)	11 (30%)	10 (92%)	20 (57%)	**0.002**
Intra-abdominal catheter	5 (8%)	1 (3%)	0 (0%)	4 (11%)	0.194
Prosthetic joint	2 (3%)	2 (5%)	0 (0%)	0 (0%)	0.280
Mechanical ventilation	1 (2%)	1 (3%)	0 (0%)	0 (0%)	

A *p*-value less than 0.05 was considered statistically significant and marked in bold.
[a] *K. pneumoniae* (n = 45), *K. oxytoca* (n = 2), *K. aerogenes* (n = 1).
[b] *E. cloacae* (n = 9), *E. hormaechei* (n = 2).

41/71 (58%), for OXA-48 (19/31; 61%), MBL (19/28; 68%) and KPC (3/12; 25%). Colistin was susceptible in 68/71 (96%) of all CPE-BSI. Ceftazidime-avibactam was susceptible in 24/38 (63%), for OXA-48 (16/18; 89%), MBL (3/10; 30%) and KPC (5/10; 50%). Ceftolozane-tazobactam was susceptible for OXA-48 (6/10; 60%), MBL (2/5; 40%) and KPC (0/1; 0%) and cefiderocol was susceptible in 2/2 (100%) of MBL isolates (see Figure 2). Antimicrobial susceptibility testing profile for each type of carbapenemase and microorganism is displayed in Figure 3.

Antimicrobial outcomes

Empiric antimicrobials were effective *in vitro* in 16/84 (19%) cases, and effective definitive treatment was received by 72/84 (86%) patients, of which monotherapy was prescribed in 32/72 (44%) and combination therapy in 40/72; (56%). OXA-48 infections were most likely to have effective definitive treatment with monotherapy (24/37; 67%), compared to KPC and MBL (2/12; 22% and 6/27; 22%, respectively) ($P < 0.001$). Almost 3/4 of our patients received effective definitive antimicrobial treatment within three days of blood culture positivity. The most frequent antimicrobials used in monotherapy were ciprofloxacin, meropenem, aminoglycosides and ceftazidime-avibactam. The most common antibiotics used in combination therapy included colistin, aminoglycosides, meropenem, tigecycline, and ceftazidime-avibactam. The specific antimicrobials administered, time to start treatment and duration of antimicrobials are shown in Table II.

Clinical outcomes

Thirty-seven (44%) cases were admitted to intensive care following BSI onset. The median length of hospital stay was 15 days (range: 0—241 days). 7-day CFR after BSI onset was 21%, rising considerably to 38% by day 30, and 44% by day 90. No mortality differences were found across different CPE groups (Table II).

In the univariate analysis for 30-day CFR, we found that severe sepsis or septic shock [OR 3.87 (CI 1.42—10.57), $P = 0.008$] was associated with higher mortality and *in vitro* antimicrobial resistance to meropenem [OR 0.32 (CI 0.12—0.88), $P = 0.024$] was found to be associated with 30-day mortality. However, in the multivariate analysis, only severe sepsis or septic shock [OR 3.81 (CI 1.19—12.14), $P = 0.024$] was associated with higher mortality (Table III).

Discussion

Our study involved a series of 84 patients with CPE-BSI, including 37 patients with OXA-48, 35 patients with MBL and 12 with KPC presenting over a 10-year period. This study identified specific risk factors associated with different classes of CPE-BSIs. Urinary devices were found to be a risk factor for OXA-48, while central venous catheters were identified as risk factor for KPC-BSIs. Additionally, prior colonisation with CPE was associated with a higher risk of pneumonia as the source of CPE-BSI. In terms of antimicrobial treatment, amikacin was effective *in vitro* in 64% of the total CPE isolates and meropenem in nearly 75% of the OXA-48 isolates. Importantly, almost 75% of our patients received effective definitive antimicrobial treatment within three days of blood culture positivity. Our study observed different treatment approaches based on the type of carbapenemase. Monotherapy was more often administered in patients with OXA-48-BSI, whereas combination therapy was more frequently administered in patients with KPC and MBL-BSI. This reflects the fact that preferred agents with reliable activity were more often available in OXA-48 cases. Finally, we did not identify an association between mortality at any time-point and class of carbapenemase, showing that the extent of resistance *per se* is not associated with mortality in our cohort. However, the overall 30-day CFR was 38% and only severe sepsis or septic shock was associated with 30-day mortality.

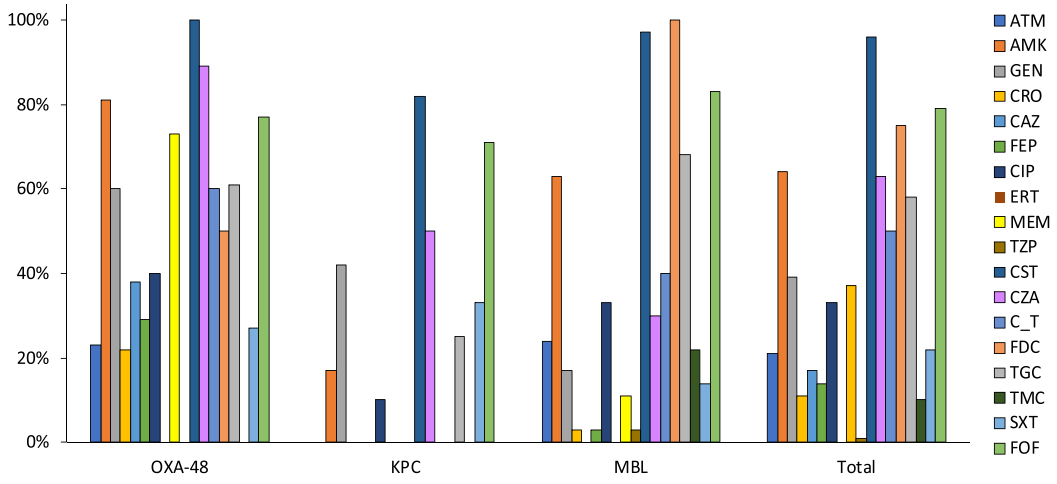

Figure 2. Antimicrobial susceptibility percentages for each type of carbapenemase (MBL, KPC and OXA-48). Each colour represents susceptibility to a given antibiotic, listed on the legend. ATM: aztreonam; AMK: amikacin; GEN: gentamicin; CAZ: ceftazidime, CIP: ciprofloxacin; CRO: ceftriaxone; FEP: cefepime; ERT: ertapenem; MEM: meropenem; TZP: piperacillin/tazobactam; CST: colistin; CZA: ceftazidime/avibactam; C_T: ceftolozane/tazobactam; FDC: cefiderocol; TGC: tigecycline; TMC: temocillin; SXT: trimethoprim-sulfamethoxazole; FOF: fosfomycin.

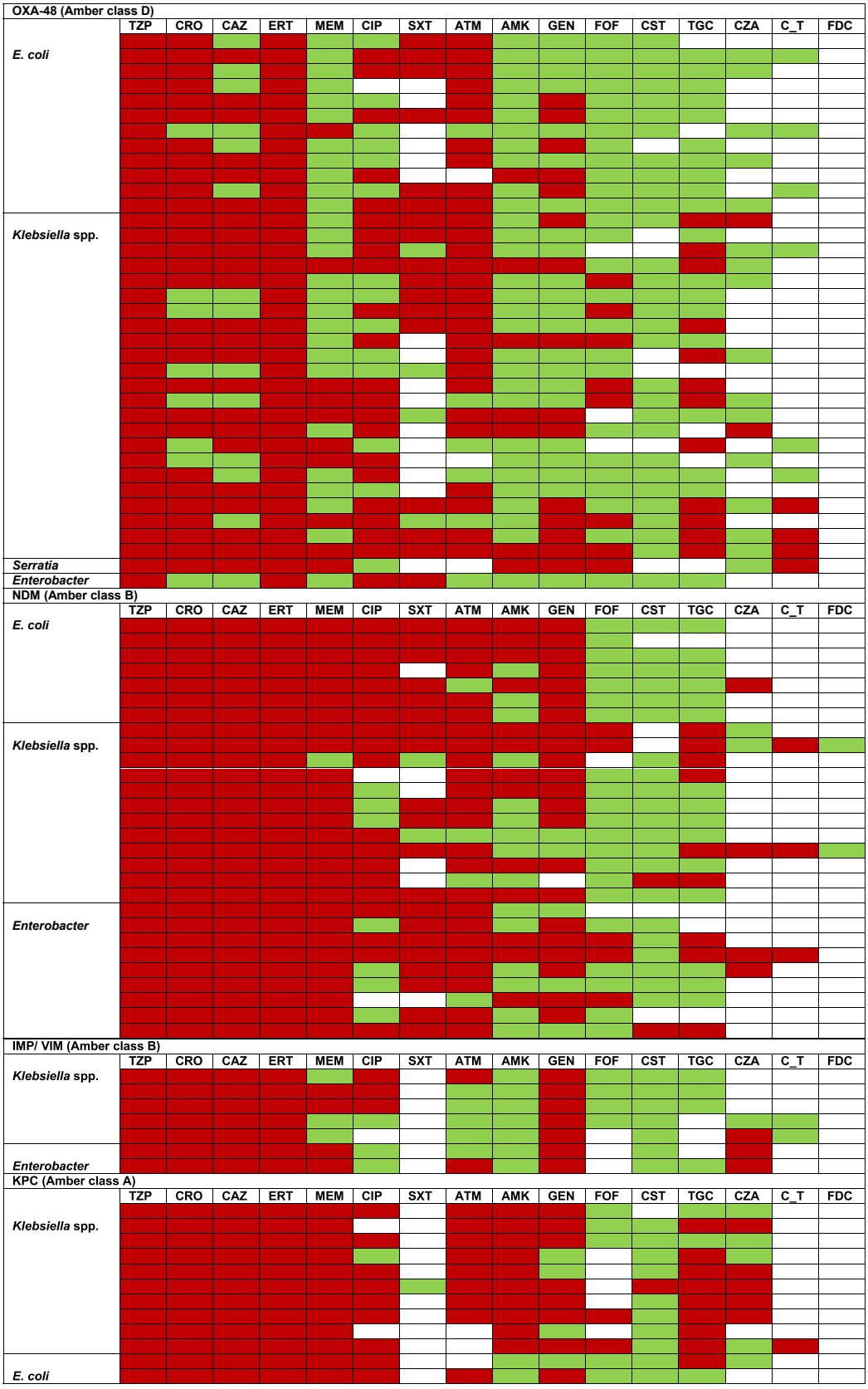

Figure 3. Antimicrobial susceptibility testing profile for each type of carbapenemase and microorganism. Resistant (red squares), susceptible (green squares), not tested (white squares). ATM: aztreonam; AMK: amikacin; GEN: gentamicin; CAZ: ceftazidime, CIP: ciprofloxacin; CRO: ceftriaxone; FEP: cefepime; ERT: ertapenem; MEM: meropenem; TZP: piperacillin/tazobactam; CST: colistin; CZA: ceftazidime/avibactam; C_T: ceftolozane/tazobactam; FDC: cefiderocol; TGC: tigecycline; TMC: temocillin; SXT: trimethoprim-sulfamethoxazole; FOF: Fosfomycin.

Table II
Antimicrobial and clinical outcomes

Antimicrobial and clinical outcomes	Total N=84	OXA-48 N=37	KPC N=12	MBL N=35	*P*-value
Effective empirical antibiotic	16 (19%)	8 (23%)	1 (9%)	6 (19%)	0.473
Time to effective treatment; median (range)	1 (0–6)	1 (0–6)	2 (0–4)	2 (0–6)	0.090
Early effective treatment $\leq$ 3 days	56 (73%)	29 (83%)	7 (64%)	20 (65%)	0.085
Duration of treatment; median (range)	9 (0–30)	7 (0–30)	8.5 (1–14)	10 (1–17)	0.949
Effective definitive antibiotic	**72 (86%)**	**36 (97%)**	**9 (75%)**	**27 (77%)**	**0.022**
Monotherapy	**32 (44%)**	**24 (67%)**	**2 (22%)**	**6 (22%)**	**<0.001**
Meropenem	8 (25%)	8 (33%)	0 (0%)	2 (33%)	**0.041**
Aminoglycosides	5 (16%)	3 (13%)	0 (0%)	2 (33%)	0.675
Ciprofloxacin	16 (50%)	10 (42%)	0 (0%)	6 (22%)	0.185
Ceftazidime/avibactam	4 (13%)	3 (13%)	1 (50%)	0 (0%)	0.163
Colistin	1 (3%)	0 (0%)	1 (50%)	0 (0%)	**0.022**
Combination therapy[a]	**40 (56%)**	**12 (33%)**	**7 (78%)**	**21 (78%)**	**0.004**
Meropenem	15 (38%)	6 (50%)	2 (29%)	7 (33%)	0.425
Ciprofloxacin	3 (8%)	0 (0%)	0 (0%)	3 (14%)	0.226
Fosfomycin	2 (5%)	0 (0%)	0 (0%)	2 (10%)	0.386
Tigecycline	11 (28%)	3 (25%)	2 (29%)	6 (29%)	0.939
Aminoglycosides	18 (45%)	7 (58%)	2 (29%)	9 (43%)	0.569
Colistin	22 (55%)	6 (50%)	5 (71%)	11 (52%)	0.569
Ceftazidime/avibactam	7 (18%)	2 (17%)	3 (43%)	2 (10%)	0.131
Cefiderocol	1 (3%)	0 (0%)	0 (0%)	1 (5%)	0.633
Admitted to ICU (post-bacteraemia episode)	37 (44%)	15 (41%)	8 (67%)	14 (40%)	0.137
Length of stay (days); median (range)	15 (0–241)	15 (0–241)	11 (0–117)	15 (1–76)	0.235
7-day mortality	18 (21%)	8 (22%)	4 (33%)	6 (17%)	0.498
30-day mortality	32 (38%)	13 (35%)	6 (50%)	13 (37%)	0.663
90-day mortality	37 (44%)	14 (38%)	7 (58%)	16 (46%)	0.440

A *p*-value less than 0.05 was considered statistically significant and marked in bold.
[a] Antibiotics listed under combination treatment were part of the combined treatment. The most common combination treatments were meropenem plus aminoglycosides (10/40, 25%), tigecycline plus colistin (8/40; 20%), meropenem plus colistin (4/40; 10%) and ceftazidime/avibactam plus colistin (5/40; 13%).

The patient characteristics were similar to the ones reported in other studies [9–13]. Severe sepsis or septic shock occurred in 59% of cases [14,15]. Although, in our KPC group, severe sepsis was much higher than in other KPC-BSI series [11]. The average Charlson comorbidity score in this cohort was higher than the one reported elsewhere [14,16]. Urinary source and a urinary device in place were more frequently found in OXA-48-BSI compared to KPC and MBL [17]. We had anticipated a greater proportion of patients having a urinary source, but notably 17% of our cohort had no source clearly identifiable on detailed review of their notes, and some of these are likely to have been urinary. Interestingly, another study observed an association between pneumonia and prior CPE colonisation [18].

Klebsiella spp. was the most prevalent organism in patients with KPC, followed by OXA-48 and MBL-BSI; this is similar to other series [15]. Antimicrobial susceptibility results of CPE showed moderate susceptibility to aminoglycosides, specifically for amikacin (64%). Although this is similar to the susceptibilities found in a previous study [19], it gives cause for concern because aminoglycosides are often depended upon to provide reliable Gram-negative bactericidal activity. Isolates were susceptible to meropenem in vitro in 73% of the OXA-48 clinical isolates. Accordingly, meropenem was the backbone of a great part of the combination treatment regimens.

Almost three-quarters of our patients received effective definitive antimicrobial treatment within three days of blood culture positivity. This compares favorably with other reports, where fewer than half of the patients were initiated on early effective antibiotics [11]. Almost half of the patients who received effective definitive treatment were administered monotherapy and the other half received combination therapy with at least one antibiotic being active in vitro. Monotherapy was more often administered in patients with OXA-48-BSI, whereas combination therapy was more frequently administered in patients with KPC and MBL-BSI. This finding may be related to the fact that OXA-48 blood culture isolates had higher percentages of antimicrobial susceptibility compared to KPC and MBL. This offers a greater choice of preferred antimicrobial options agents with more reliable activity *in vivo*.

The overall 30-day CFR of 38% was very similar to that reported in 2017 [14]. However, mortality for KPC-BSI was lower compared to another series [11]. According to the results of the multivariate analysis, the major predictor of 30-day mortality was severe sepsis or septic shock, as seen previously [14,20]. While the univariate analysis showed blood culture isolates that were *in vitro* susceptible to meropenem were associated with a lower mortality, this association was not shown apparent in the multivariate analysis. Earlier microbiological studies have shown a correlation between carbapenem minimum inhibitory concentration and clinical outcome [21] and this is biologically plausible given the frequent use of carbapenems in this setting. Other factors associated with adverse outcomes identified in other studies include co-morbidities and/or underlying disease [22],

Table III
Univariate and multivariate analysis for 30-day case fatality rate of patients with BSI due to CPE

	Survived N=52	Died N=32	Univariate OR (95% CI), *P*-value	Multivariate OR (95% CI), *P*-value
Age>=60 years (vs <60)	26 (50%)	18 (56%)	1.24 (0.51−3.00), 0.640	-
Male (vs female)	30 (58%)	22 (69%)	1.54 (0.61−3.91), 0.364	-
Onset BSI >48h from admission	32 (62%)	26 (81%)	**2.57 (0.89-7.38), 0.079**	2.60 (0.70−9.67), 0.154
Known prior colonisation	13 (25%)	12 (38%)	1.75 (0.68−4.55), 0.248	-
Source (urine vs others)	16 (31%)	5 (16%)	0.41 (0.13−1.25), 0.115	-
Invasive devices	38 (73%)	25 (78%)	1.22 (0.43−3.49), 0.708	-
Severe sepsis or septic shock	24 (46%)	25 (78%)	**3.87 (1.42-10.57), 0.008**	**3.81 (1.19-12.14), 0.024**
Charlson score >2	40 (77%)	30 (94%)	**4.13 (0.85-20.01), 0.079**	3.94 (0.69−22.51), 0.124
CKD (vs no)	11 (21%)	7 (22%)	1.02 (0.35−2.97), 0.974	-
Liver disease (vs no)	10 (19%)	10 (32%)	1.86 (0.67−5.16), 0.231	-
Onco-haematological malignancy	21 (40%)	8 (25%)	0.48 (0.18−1.26), 0.136	-
Organ transplant (vs no)	4 (8%)	1 (3%)	0.39 (0.04−3.55), 0.395	-
E. coli (vs others)	14 (27%)	5 (16%)	0.49 (0.16−1.52), 0.217	-
Klebsiella spp. (vs others)	29 (56%)	22 (69%)	1.67 (0.66−4.23), 0.281	-
Enterobacter spp. (vs others)	7 (13%)	4 (13%)	0.90 (0.24−3.35), 0.873	-
OXA-48 (vs others)	24 (46%)	13 (41%)	0.77 (0.32−1.89), 0.566	-
MBL (vs others)	21 (40%)	13 (41%)	0.98 (0.40−2.40), 0.960	-
KPC (vs others)	6 (12%)	6 (19%)	1.73 (0.51−5.92), 0.382	-
Meropenem susceptible	24 (46%)	7 (22%)	**0.32 (0.12-0.88), 0.024**	0.36 (0.11−1.21), 0.098
Effective empirical antibiotic	10 (19%)	6 (19%)	0.96 (0.31−2.97), 0.943	-
Effective definitive antibiotic	46 (88%)	26 (96%)	1.69 (0.17−17.15), 0.655	-
Early effective antibiotic (≤72h)	34 (65%)	24 (92%)	**0.41 (0.14-1.22), 0.100**	0.28 (0.07−1.09), 0.096
Combination therapy (vs mono)	24 (46%)	16 (59%)	1.52 (0.59−3.92), 0.391	-
Meropenem-based therapy	7 (13%)	9 (53%)	1.72 (0.64−4.61), 0.282	-
Ciprofloxacin-based therapy	15 (29%)	4 (15%)	0.39 (0.12−1.34), 0.136	-
Fosfomycin-based therapy	1 (2%)	1 (4%)	1.85 (0.11−30.74), 0.669	-
Tigecycline-based therapy	8 (15%)	3 (11%)	0.64 (0.16−2.65), 0.539	-
Aminoglycoside-based therapy	12 (23%)	11 (41%)	2.12 (0.76−5.80), 0.143	-
Colistin-based therapy	14 (27%)	9 (33%)	1.25 (0.45−3.44), 0.666	-
Ceftazidime/avibactam-based	8 (15%)	3 (11%)	0.64 (0.16−2.65), 0.539	-
Early source control (≤72h)	29 (56%)	11 (38%)	**0.40 (0.16- 1.03), 0.058**	0.41 (0.14−1.22), 0.110

A *p*-value less than 0.05 was considered statistically significant and marked in bold.

treatment monotherapy [9,11,20] non-urinary source [17] and delayed effective antimicrobial therapy [14,23]. The relatively small cohort in our study may have contributed to these not being identified as significant in our multivariate analysis. Neither combination treatment nor different treatment regimens showed any impact on mortality in this study [11,24]. Although dose and toxicity were not explored in the present study, new less toxic antibiotics are becoming available with optimised dosing regimens, which may lead to better outcomes than current options.

The main limitations of this study include its retrospective, observational nature. The sample size of each group was relatively small. The absence of a denominator for the population at risk is a limitation that stems from the study design and data collection process. The multivariate analysis may be affected by the low number of cases. Data on new antimicrobial treatment options such as ceftazidime-avibactam, ceftolozane-tazobactam and cefiderocol are scarce, as this study captured data from 2011 when such treatment options were not available in all centres. Antibiotic sensitivity testing was undertaken in several laboratories and over the 10-year period of the study changes in European Committee on Antimicrobial Susceptibility Testing (EUCAST) guidance means there was variation in the testing methods and classification of sensitivity.

The case-mix in this series reflects the hospitals' catchment areas, with a diverse population. Several of the hospitals also offer specialist haemato-oncology services. Whilst rates of CPE infection are highest in London, rates are expected to rise nationally with increased antibiotic use and the global movement of people.

Conclusion

In summary, this study provides valuable insight into the clinical characteristics, management and treatment outcomes of CPE-BSIs. Our findings have implications for infection control strategies, particularly in identifying high-risk patients. Adherence to infection prevention bundles for urinary devices and central venous catheters may help to reduce the risk of OXA-48 BSIs and KPC-BSIs, respectively. In addition, strategies to prevent and closely monitor CPE colonisation may be beneficial in reducing pneumonia as a source of CPE-BSI. The study highlights the high mortality rate associated with CPE-BSIs, emphasising the importance of early recognition and management of severe sepsis in these patients. The high case fatality rate underscores the urgent need to improve timely diagnosis and treatment approaches. This includes prompt initiation of appropriate antimicrobial therapy, which relies on the local detection of

CPEs and rapid susceptibility testing of second- and third-line agents to prevent treatment delays. Furthermore, there is a pressing need to expedite the development and implementation of effective novel antimicrobials targeting the different classes of CPE. Further larger studies should be aimed at characterising and comparing the clinical and microbiological profile of BSIs due to different types of carbapenemases to improve patient care and outcomes in CPE-BSIs.

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Authors' contributions

VAV and TP led the study, including design, analysis and write-up of the manuscript. SF, JE, DS, KD, LH and BD collected clinical and microbiological data. MA, MM, SM-J and MD reviewed the manuscript. All authors approved the final manuscript.

Competing interests

The authors declare no competing interests.

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