

Community-Onset Bloodstream and Other Infections, Caused by Carbapenemase-Producing *Enterobacteriaceae*: Epidemiological, Microbiological, and Clinical Features

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Background. Because most infections caused by carbapenemase-producing *Enterobacteriaceae* (CPE) begin during hospitalization, there are limited data about community-onset (CO) infections caused by CPE. Our aim is to describe the frequency of CO infections caused by CPE as well as the clinical features of CO bloodstream infections (CO-BSIs).

Methods. This study includes retrospective case series of CO infections caused by CPE in a tertiary hospital from January 2010 to July 2014. Any clinical sample with a positive culture for CPE that had been ordered by primary care doctors or by doctors at the emergency room (ER) were classified as CO. Epidemiological and microbiological features of CO cases were assessed as were clinical features of CO-BSIs.

Results. Of 780 clinical samples with CPE, 180 were requested at the ER or by primary care doctors (22.9%), 150 of which were produced by *Klebsiella pneumoniae* (83.3%). The *bla*_{OXA-48} gene was detected in 149 isolates (82.8%) followed by the *bla*_{VIM} gene, 29 (16.1%). Sixty-one patients (33.9%) had a prior history of CPE infection/colonization. Thirty-four of the 119 (28.6%) patients without prior history of CPE infection/colonization did not fulfill Friedman criteria for healthcare-associated infections (HAIs). Considering previous hospitalization of up to 12 months as a criterion for defining HAI, only 16 (13.4%) cases were identified as community-acquired infections. The most frequent positive sample was urine (133 of 180; 73.9%). Twenty-one (11.7%) patients had a BSI, 9 of them secondary to urinary tract infections (42.9%). Thirty-day crude mortality among patients with BSI was 23.8% (5 of 21).

Conclusions. Community-onset infections caused by CPE are an important subgroup of all CPE infections. The urinary tract is the main source. Bloodstream infections accounted for more than 10% of the cases.

Keywords. bloodstream infections; carbapenemase-producing *Enterobacteriaceae*; community-onset infections; epidemiology.

Carbapenems are among the most potent, broadest-spectrum antimicrobials. As such, they are useful for the empirical therapy of severe infections potentially caused by several multidrug-resistant microorganisms (MDROs) and for targeted therapy when MDROs are isolated in patients with severe infections. Infections caused by carbapenem-resistant Gram-negative bacteria have significantly increased in recent years, especially due to carbapenemase-producing *Enterobacteriaceae* (CPE) [1]. Patients with severe infections caused by CPE face alarming

mortality rates because they are currently one of the main challenges for healthcare institutions and public health authorities [2].

The epidemiology of carbapenemases, which have spread worldwide, is complex. In Spain, the interregional spread of CPE—mainly OXA-48-producing *Klebsiella pneumoniae*—has occurred since 2011 [3, 4]. In our institution, we first detected CPE in 2005: VIM-producing *K pneumoniae*. Since then, we have observed a multispecific and polyclonal pattern of VIM-producing *Enterobacteriaceae* [5]. In December 2010, an outbreak of OXA-48-producing *K pneumoniae* started in our hospital. After the outbreak had begun, we detected a hyperendemic pattern of patients with OXA-48-producing *Enterobacteriaceae* in clinical or surveillance samples [6]. Since 2013, we have detected 7 patients infected or colonized with NDM-producing *Enterobacteriaceae* [7]. KPC-producing *Enterobacteriaceae* have been described sporadically.

Although CPE infections have been found predominantly in healthcare and nosocomial settings, the frequency of community-onset (CO) infections by these microorganisms is expected to increase, as reported for extended-spectrum β -lactamases.

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Not only do carbapenemases have a significant capability for horizontal transfer, but the clones on which carbapenemases settle are frequently successful from the epidemiological standpoint. In addition, gastrointestinal colonization can last for months [8–10]. In this scenario, CO infections can either arise in patients who were colonized during a previous hospitalization or after significant contact with healthcare or represent true community-acquired infections, which is a step further in the spread of CPE. Unfortunately, CO infections caused by other multidrug-resistant *Enterobacteriaceae* have been repeatedly associated with a delay in appropriate antimicrobial therapy and, subsequently, with poorer outcomes [11, 12].

Despite ongoing antimicrobial resistance surveillance programs, there is very limited information about the epidemiology of CO infections caused by CPE [13]. The proportion of infections caused by CPE that have a CO is not well known, nor is the proportion of these infections that are truly community associated (CA), representing transmission in the community. From a clinical standpoint, there is little information on the burden of CO CPE infections and their presentation and severity. Case series of CPE BSI have seldom included CO infections [8].

To assess the frequency and epidemiological features of CO infections caused by CPE, we conducted a 4-year retrospective study in our center. In addition, we focused on the clinical features of bloodstream infections (BSIs) caused by CPE.

METHODS

Setting

Hospital Universitario La Paz (HULP) is a 1200-bed tertiary hospital of the Spanish National Health System. It is the reference hospital for a mixed urban and periurban population of approximately 500 000 people in northern Madrid. Twenty public primary care practices located in the hospital reference area share the same microbiology laboratory.

Inclusion Criteria

Consecutive, nonhospitalized, adult patients (≥ 18 years old) with CPE isolated from clinical samples in the HULP Microbiology Department from January 2010 to July 2014 were included. Patients were considered to be nonhospitalized at the time the sample was obtained if the sample was requested by a physician from the emergency room (ER) or from primary care practices. For epidemiological purposes, only the first CPE isolated in each patient was considered. For clinical purposes, all patients with CO BSIs caused by CPE were included.

Bacterial Isolates and Microbiological Workup

Enterobacteriaceae isolates were suspected of producing a carbapenemase if imipenem and/or meropenem minimum inhibitory concentrations (MICs), determined by automated broth microdilution, were >1 mg/L and/or >0.5 mg/L in the case of ertapenem. For all suspected isolates, a Modified Hodge Test (MHT) was performed. All positive MHTs were confirmed by

polymerase chain reaction (PCR) (OXA-48-, VIM-, KPC-, NDM-specific primers). The genetic relationships between the isolates of OXA-48-producing *K pneumoniae* were determined by clone-specific PCR, multilocus sequence typing (MLST), and by automated repetitive sequence-based PCR using the DiversiLab (bioMérieux) system [14, 15].

Clinical and Epidemiological Data

We assessed the demographic and epidemiological features related to the first episode of CPE in clinical samples obtained from nonhospitalized patients. Age, gender, the existence of previous isolates of CPE, hospitalizations (≥ 48 hours) within 1 year, residence in a nursing home, and the receipt of hemodialysis and home care were reviewed. For this purpose, HULP and regional healthcare health information systems were reviewed. Primary Care medical records were available through an online electronic medical records platform provided by the Comunidad de Madrid regional healthcare system. This platform provides information on every visit paid to primary care doctors (PCDs) or nurses within the geographical area tributary to our Microbiology Laboratory. Information regarding antibiotics prescribed by PCDs was available through this system. In addition, for all episodes of CO CPE BSI, demographic characteristics, comorbidity, clinical presentation, source of infection, recent exposure to antimicrobials, and clinical outcomes were retrieved from the medical records by the investigators.

Definitions

Episodes in patients with CPE CO infections and no history of infection/colonization during previous hospitalizations were primarily classified according to Friedman [16] as healthcare associated (HCA) if any of the following criteria were present: ≥ 48 -hour hospital admission during the previous 90 days; receipt of hemodialysis, intravenous medication, or home wound care in the previous 30 days; and residence in a nursing home or long-term care facility. Given the duration of gastrointestinal colonization by CPE, an alternative definition of HCA, increasing the time since the last hospitalization to 1 year, was used as well (modified Friedman's [16] criteria). For BSI, the Charlson Comorbidity Index [17] and McCabe-Jackson [18] classification (nonfatal, ultimately fatal, or rapidly fatal) were used to evaluate comorbidity and prognosis. Acute severity of illness was evaluated with the Pitt bacteremia score [19]. Sepsis level was graded as sepsis, severe sepsis, or septic shock, following the definition of systemic inflammatory response syndrome [20]. The source of bacteremia was determined according to the clinical presentation or by the evidence of an identical strain cultured near to, or on the same date as, the onset of BSI from other body sites. If the source of bacteremia could not be identified, it was classified as primary bacteremia. Antimicrobial therapy was considered (1) microbiologically appropriate if the patient received at least 1 active agent against the isolate (MIC within the susceptible range) and (2) clinically

adequate if the patient received a combination of 2 active antibiotics, at the right dose and route according to the source of infection. Use of imipenem or meropenem if MIC was ≤ 8 mg/L was considered adequate if high-dosed and associated with a second microbiologically active agent [21].

Statistics

Mean, median, and range were calculated when appropriate. Categorical variables were compared using the χ^2 test. Statistical software program SPSS, version 17.0 for Windows (SPSS, Chicago, IL) was used to perform all analyses.

Ethic

The HULP Institutional Review Board evaluated and approved the study protocol. Given its observational retrospective design, informed consent was waived.

RESULTS

During the study period, 1866 patients infected and/or colonized by CPE were detected in our institution. Of these, 780 had CPE in at least 1 clinical sample. Carbapenemase-producing *Enterobacteriaceae* were detected in clinical samples of 180 non-hospitalized patients (23.1%). Sixty-one samples (33.9%) had been requested by PCDs and 119 (66.1%) by the ER doctors, representing 0.36% and 2.96% of all patients from whom *Enterobacteriaceae* were isolated, respectively (Tables 1 and 2).

The most frequent carbapenemase identified in CO infections was OXA-48 (149 of 180; 83.3%), followed by VIM (29 of 180; 16.1%). The most frequent CPE-positive sample was urine (133 of 180; 73.9%), followed by blood (21 of 180; 11.7%). *Klebsiella pneumoniae* accounted for the majority

(149 of 180; 82.8%) of CPE isolates. Most (119 of 180; 66.1%) of the nonhospitalized patients with positive cultures for CPE had no prior history of CPE colonization or infection, although this proportion decreased during the study period, from 83.3% in 2010 and 2011 to 51.1% in 2014 ($P = .017$). The main epidemiological features of patients with CPE in clinical samples requested by PCDs or at the ER are summarized in Tables 1 and 2, respectively. Among the patients without prior history of infection/colonization by CPE, 34 of 119 (28.6%) did not fulfill any of the Friedman [16] criteria and thus would not be considered to be HCA (Figure 1). Nevertheless, if the interval since the last significant hospitalization was increased to 12 months, only 16 of 119 (13.4%) would not be considered to be HCA. In all of them, CPE harbored OXA-48. Of these, at least 2 patients with CO OXA-48-producing *K pneumoniae* urinary tract infections were household members of individuals infected with or colonized by CPE or who had been hospitalized in units with ongoing CPE transmission as their sole healthcare relationship.

Among the 150 cases of carbapenemase-producing *K pneumoniae*, 124 were OXA-48 producers. Of these, 54 were typed and found to belong to 6 different clones: 16 isolates belonged to ST405, 31 to ST11, 4 to ST323, and the remaining 3 belonged to 3 different clones by Diversilab but were not typed by MLST. These 3 predominant clones matched the major clones detected in hospital samples. Cumulative curves of ST405 and ST11 detected in samples obtained from nonhospitalized patients paralleled those found in the hospital (Figure 2).

Twenty-one patients had a CO CPE BSI. All blood cultures were requested at the ER. Fifteen episodes (71.4%) were caused by *K pneumoniae*, 4 (19%) by *Serratia marcescens*, 1 by

Table 1. Frequency, Distribution, and Main Epidemiological Features of Clinical Isolates of CPE in Microbiological Samples Requested by Primary Care Physicians From a Healthcare District in Northern Madrid

	2010	2011	2012	2013	2014 (January–July)	Total
<i>Enterobacteriaceae</i>	3712	3630	3352	3905	2432	17031
KP (KP/ <i>Enterobacteriaceae</i> %)	453 (12.2)	496 (13.6)	451 (13.4)	552 (14)	327 (13.4)	2279 (13.4)
CPE (CPE/ <i>Enterobacteriaceae</i> %)	1 (0.03)	6 (0.17)	15 (0.45)	16 (0.41)	23 (0.95)	61 (0.36)
CP-KP (CP-KP/CPE %)	0 (0)	4 (66.7)	14 (93)	12 (66.7)	20 (87)	50 (82)
OXA	0	4	11	13	18	46
VIM	0	2	4	3	5	14
KPC	1	0	0	0	0	1
Urine	1	5	15	15	21	57
Other samples	0	1	0	1	2	4
Prior CPE colonization/infection (Prior CPE/CPE %)	0 (0)	0 (0)	2 (13.3)	4 (25)	8 (34.8)	14 (23)
Healthcare-associated ^a (Friedman [16] criteria) (%)	1 (100)	4 (66.7)	7 (58.3)	8 (66.7)	7 (46.7)	27 (57.4)
Hospitalization within 90 d	1	4	7	6	5	23
Hemodialysis	0	0	0	0	0	0
Outpatient IV therapy	0	0	0	0	0	0
Home wound care	0	0	0	0	0	0
Nursing home/LTCF	0	1	1	2	5	9
Healthcare-associated ^a (modified criteria) ^b (%)	1 (100)	5 (83.3)	11 (84.6)	9 (75)	11 (84.6)	37 (78.7)

Abbreviations: CPE, carbapenemase-producing *Enterobacteriaceae*; KP, *Klebsiella pneumoniae*; CP-KP, carbapenemase-producing *K pneumoniae*; IV, intravenous; LTCF, long-term care facility.

^a Among patients without prior history of CPE infection/colonization.

^b Includes history of hospitalization in the previous year.

Table 2. Frequency, Distribution, and Main Epidemiological Features of Clinical Isolates of CPE in Microbiological Samples Requested at the Emergency Room of a Tertiary Academic Center in Northern Madrid

	2010	2011	2012	2013	2014 (January–July)	Total
<i>Enterobacteriaceae</i>	468	714	965	1108	761	4016
KP (KP/ <i>Enterobacteriaceae</i> %)	54 (11.5)	99 (13.9)	136 (14.1)	192 (17.3)	118 (15.5)	599 (14.9)
CPE (CPE/ <i>Enterobacteriaceae</i> %)	1 (0.21)	12 (1.68)	33 (3.42)	49 (4.42)	24 (3.15)	119 (2.96)
CP-KP (CP-KP/CPE %)	0 (0)	12 (100)	27 (81.8)	40 (81.6)	21 (87.5)	100 (84)
OXA	0	11	25	45	22	103
VIM	1	1	8	4	2	15
NDM	0	0	0	1	1	1
Urine	1	7	21	31	16	76
Blood	0	3	8	6	4	21
Other samples	0	2	4	12	4	22
Prior CPE colonization/infection (Prior CPE/CPE %)	0 (0)	3 (25)	9 (27.3)	20 (40.8)	15 (62.5)	47 (39.5)
Healthcare-associated ^a (Friedman [16] criteria) (%)	1 (100%)	9 (100)	17 (70.9)	25 (86.2)	6 (66.7)	58 (80.6)
Hospitalization within 90 d	1	9	20	21	5	56
Hemodialysis	0	1	2	1	0	4
Outpatient IV therapy	0	2	8	7	0	17
Home wound care	0	0	0	0	0	0
Nursing home/LTCF	1	1	4	7	1	14
Healthcare-associated ^a (modified criteria) ^b (%)	1 (100%)	9 (100%)	22 (91.7)	27 (93.1)	7 (77.8)	66 (91.7)

Abbreviations: CPE, carbapenemase-producing *Enterobacteriaceae*; KP, *Klebsiella pneumoniae*; CP-KP, carbapenemase-producing *K pneumoniae*; IV, intravenous; LTCF, long-term care facility.

^a Among patients without prior history of CPE infection/colonization.

^b Includes history of hospitalization in the previous year.

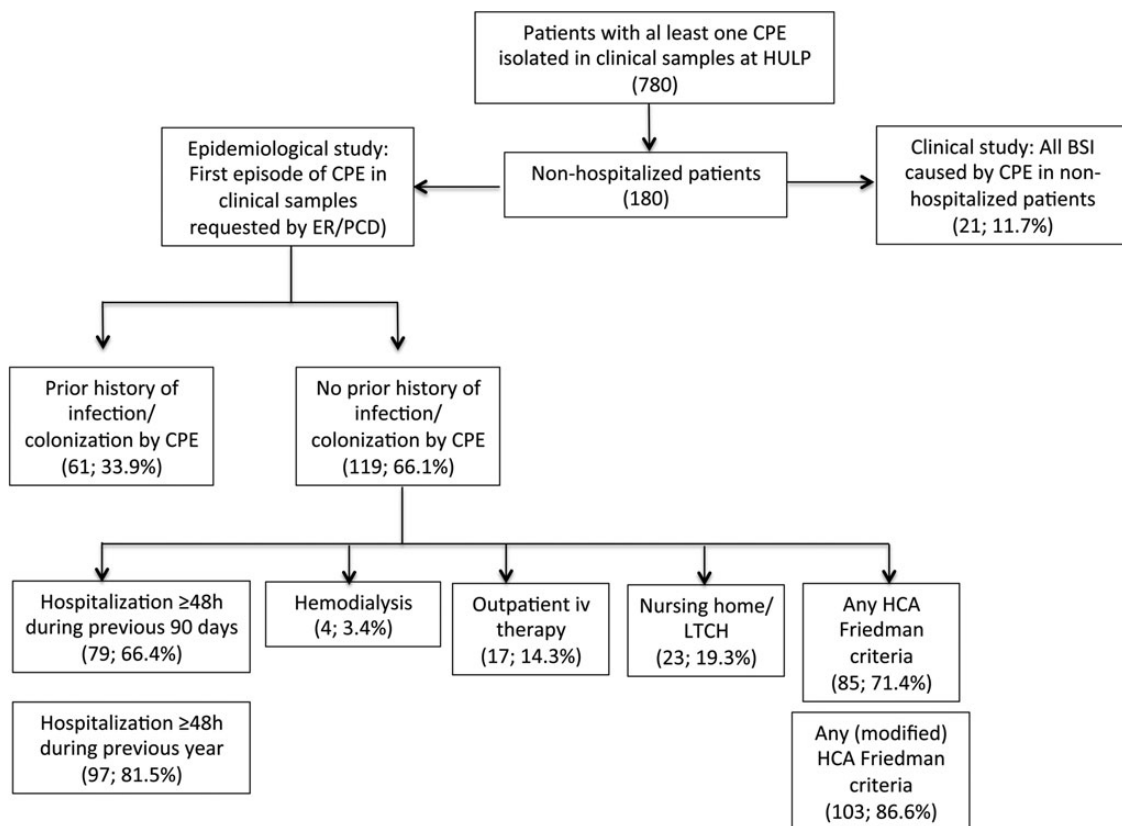


Figure 1. Flow chart of patients included in the study and distribution of factors associated with healthcare among them. Abbreviations: BSI, bloodstream infection; CPE, Carbapenemase-producing *Enterobacteriaceae*; HCA, healthcare-associated; HULP, hospital universitario La Paz; LTCF, long-term care facility.

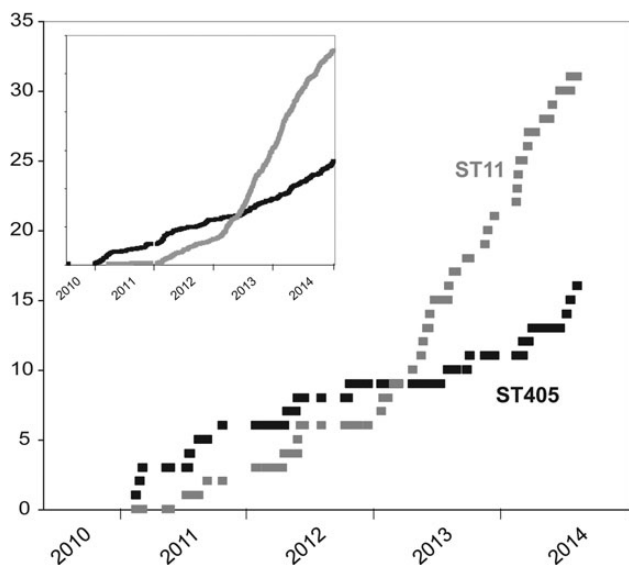


Figure 2. Cumulative distribution of isolates of *K. pneumoniae* OXA-48 belonging to ST405 (black) and ST11 (grey) sequence types in samples from ER and PCP compared with hospital isolates (inset).

Enterobacter cloacae, and 1 by *Klebsiella oxytoca*. The *bla*_{OXA-48} gene was identified in 15 (71.4%) isolates, and the *bla*_{VIM} gene was identified in the remaining 6 (28.6%). Median age at onset of infection was 77 (range, 49–90), and most of the patients were male (18 of 21; 85.8%). Median Charlson score was 4 (range, 1–11). Seven (33.3%) were oncohematological patients, and 6 (28.6%) had other types of cancer. Prior rectal colonization was known in 5 (23.8%) patients, and the median time from rectal colonization to infection was 11 days (range, 7–114 days). Systemic antibiotic exposure within 90 days before the onset of infection was documented in 15 (71.4%) patients, whereas hospitalization for more than 48 hours was observed in 13 (62%) patients. Median Pitt score at onset of infection was 2 (range, 0–4). Three patients (14.3%) were in septic shock at the onset of infection, and 5 patients had severe sepsis (23.8%). Nine (42.9%) BSIs had a urinary source, whereas 2 patients each (9.5%) had a surgical site, catheter, or intra-abdominal source, respectively. In 4 (19%) patients, bacteremia was apparently primary. Thirty-day crude mortality was 23.9% (5 of 21). Eighteen patients received appropriate therapy in a median time of less than 1 day (0–3 days). Sixteen patients (16 of 21) received adequate therapy in a median time of 3 days (0–6 days) since onset of bacteremia. Detailed features of patients with CO BSI caused by CPE are presented in Table 3.

DISCUSSION

We found that more than 20% of all clinical samples positive for CPE at our institution were obtained from nonhospitalized patients. This finding depicts the existence of a pool of nonhospitalized patients at risk of developing infections by CPE, as a

consequence of persistent gastrointestinal colonization by these microorganisms. It is worth noting that this pool of patients colonized by CPE can be considered one of the main reservoirs for the spread of these resistance genes in the community. In addition, because these patients might need further hospitalization, they could be responsible for further transmission within the hospital too. Given their epidemiological relevance and the paucity of available information about CO CPE infections, antimicrobial resistance surveillance programs should probably increase their focus on this epidemiological setting.

It is remarkable that almost 30% of patients with CO CPE infections did not fulfill any of the Friedman [16] criteria for HCA infections and would therefore be classified as CA. Because prolonged gastrointestinal colonization can occur, it is reasonable to increase the interval between infection onset and previous hospitalization to better identify HCA CPE infections. Indeed, if the previously mentioned interval was increased to 1 year, almost 90% of CO CPE infections in our series would be considered to be HCA. Therefore, from an epidemiological perspective, our study suggests that the most widely used criteria for classifying infections as HCA might not be precise enough in the case of CPE.

Even after increasing the interval between the onset of infection and prior hospitalization, 10% of CO CPE infections—all of which were caused by OXA-48-producing *K pneumoniae*—would not fulfill the criteria for HCA. It is interesting to note that 2 of the patients without any classic risk factors for HCA infections had been taking care of other patients or had close contact in an environment where CPE were circulating and, thus, should be considered to have been transmitted within the household. Further research into the risk of transmission of CPE to household contacts (human or animal) is definitely needed.

Overall, OXA-48- and VIM-producing *Enterobacteriaceae* were detected in a relatively similar number of patients at our institution. However, among CO CPE infections, the predominance of OXA-48-producing *Enterobacteriaceae* is surprising. Whether this predominance is related to a survival advantage of *bla*_{OXA48} gene carriers, to the high horizontal transfer of the *bla*_{OXA48} gene, or other unidentified reasons remains unknown and also deserves further research [22–24].

To the best of our knowledge, this is the largest series of CO CPE BSIs reported to date. From a clinical perspective, although the most frequent sample among nonhospitalized individuals with suspected CPE infections was the urine, BSIs accounted for more than one third of all of the episodes in which CPE were identified in clinical samples requested at the ER. Indeed, more than 15% of all CPE BSIs in our institution had a CO, which is higher than that which has been described by Daikos et al [8]. Among patients with BSI, the most frequently identified source was the urinary tract. Nevertheless, as recently

Table 3. Clinical Features of Patients With Community-Onset Carbapenemase-Producing *Enterobacteriaceae* Bloodstream Infections

	Age/ Gender (M/F)	Comorbidity	Neutropenia	Prior Infection/ Colonization	Severity at Presentation (Pitt Score)	Source	Microorganism (Carbapenemase)	Empiric Therapy	Definitive Therapy	Time to Appropriate Therapy	Time to Adequate Therapy	Death at 30 d	Death at 6 months
1	63/M	Lymphoma (allo-BMT)	Y	N	Septic shock (2)	Intra-abdominal	<i>Klebsiella pneumoniae</i> (VIM)	Amikacin	Tigecycline + amikacin	0	0	N	Y (90 d)
2	76/M	Diabetes	N	N	Sepsis	Respiratory	<i>Klebsiella oxytoca</i> (VIM)	Meropenem + amikacin	Meropenem + ciprofloxacin	0	0	N	N
3	56/M	Lymphoma	N	Y	Sepsis (3)	Catheter	<i>Serratia marcescens</i> (VIM)	Meropenem	Meropenem + amikacin	0	4	N	N
4	64/M	Lymphoma, HIV, diabetes, COPD	N	N	Severe sepsis (2)	Urinary	<i>K pneumoniae</i> (OXA-48)	Meropenem	Meropenem + colistin	0	6	N	N
5	51/M	Chronic kidney disease (hemodialysis), diabetes	N	N	Sepsis	Intra-abdominal	<i>K pneumoniae</i> (OXA-48)	Meropenem	Meropenem + amikacin	0	3	N	Y (32 d)
6	77/M	Chronic kidney disease, Connective-tissue disease	N	N	Severe sepsis (0)	Skin and soft tissue	<i>K pneumoniae</i> (OXA-48)	Amikacin	Meropenem + tigecycline	1	6	N	Y (36d)
7	79/M	Coronary artery disease, COPD dementia	N	N	Sepsis (3)	Skin and soft tissue	<i>K pneumoniae</i> (OXA-48)	Meropenem	Meropenem + levofloxacin	1	2	Y (14 d)	
8	49/F	Cancer	N	N	Sepsis (1)	Catheter	<i>Enterobacter cloacae</i> (VIM)	Cefepime		No appropriate therapy	No adequate therapy	N	N
9	90/M	Cancer	N	N	Sepsis (2)	Urinary	<i>K pneumoniae</i> (OXA-48)	Ertapenem		No appropriate therapy	No adequate therapy	Y (14 d)	
10	78/M	Cancer, cerebrovascular disease, chronic kidney disease	N	N	Severe sepsis (1)	Urinary (prostatitis)	<i>K pneumoniae</i> (OXA-48)		Meropenem + amikacin	1	1	N	N
11	65/M	Cancer, diabetes, cerebrovascular disease	N	Y	Severe sepsis (2)	Urinary	<i>K pneumoniae</i> (OXA-48)	Meropenem	Meropenem + colistin	0	1	N	N
12	86/M	Chronic renal disease	N	N	Sepsis (1)	Urinary	<i>K pneumoniae</i> (OXA-58)	Meropenem	Meropenem + amikacin	0	1	N	Y (39 d)
13	60/M	Diabetes, chronic kidney disease	N	N	Septic shock (2)	Urinary	<i>K pneumoniae</i> (OXA-48)	Meropenem	Meropenem + amikacin	1	1	Y (19 d)	
14	77/M	Cancer	Y	N	Severe sepsis (4)	Primary	<i>S marcescens</i> (OXA-48)	Meropenem	Meropenem	0	No adequate therapy	Y (1 d)	
15	88/F	Lymphoma	N	N	Sepsis (2)	Primary	<i>K pneumoniae</i> (OXA-48)		Meropenem	3	No adequate therapy	N	N
16	82/M	Lymphoma, diabetes, COPD	Y	N	Sepsis (1)	Primary (febrile neutropenia)	<i>S marcescens</i> (VIM)	Meropenem	Ciprofloxacin + gentamicin	1	2	N	Y (45 d)
17	59/M	Lymphoma	Y	Y	Sepsis (2)	Primary (febrile neutropenia)	<i>K pneumoniae</i> (OXA-48)	Meropenem	Meropenem + colistin	0	1	Y (24 d)	
18	82/F	Lymphoma	Y	Y	Septic shock (4)	IV catheter	<i>S marcescens</i> (VIM)	Meropenem + amikacin	Aztreonam + ciprofloxacin	0	3	N	N
19	89/M	Cerebrovascular disease, chronic kidney disease	N	N	Sepsis (0)	Urinary	<i>K pneumoniae</i> (OXA-48)	Meropenem	Meropenem + amikacin	0	3	N	N
20	82/M	Diabetes, COPD, Connective-tissue disease	N	N	Sepsis (0)	Urinary (prostatitis)	<i>K pneumoniae</i> (OXA-48)	Meropenem	Meropenem + amikacin	0	3	N	N
21	66/M	Cancer, diabetes, chronic kidney disease	N	Y	Sepsis (1)	Urinary	<i>K pneumoniae</i> (OXA-48)	Meropenem + colistin	Meropenem + amikacin	1	3	N	Y (35 d)

Abbreviations: allo-BMT, allogeneic bone marrow transplant; COPD, chronic obstructive pulmonary disease; HIV, human immunodeficiency virus; IV, intravenous.

described, a significant proportion of BSIs did not have an identifiable source [2]. It is interesting to note that 30-day crude mortality in patients with CO BSI caused by CPE in our study was slightly over 20%, which is significantly lower than in most series of CPE BSIs reported to date [25]. We believe that observed mortality is accurate because we had proof of life of all patients classified as 30-day survivors (results of a blood test, radiological exam, or a nonmissed doctor's appointment). The predominance of low-risk sources, such as urine, the existence of an ongoing antimicrobial stewardship program actively targeting CPE BSI, and host-related factors are circumstances that might have influenced the lower-than-expected 30-day crude mortality among patients with CO CPE BSI.

The main limitations of our study are derived from its retrospective design. Although it is unlikely that the most relevant epidemiological data (ie, Friedman [16] criteria) were missed, this could have happened with subtler epidemiological information, such as household or pet contacts. Unfortunately, this study does not provide definitive evidence of individual risk factors for these types of infections, because we did not use any control group. From the clinical standpoint, there are some limitations with regard to describing the features of the least severe infections because differentiating colonization from true infection retrospectively was expected to be problematic. A prospective design would, unquestionably, provide more relevant clinical data on this subset of CO CPE infections.

CONCLUSIONS

To summarize, CO CPE infections are an important subgroup of all CPE infections at our institution. Although most were HCA, no association with healthcare was found in almost one tenth of the cases, suggesting the transmission of CPE in the community. The most frequent CO CPE infections are urinary tract infections, which can present as BSIs. Our study emphasizes the importance of prompt identification and management of patients at risk of contracting these CO CPE infections.

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