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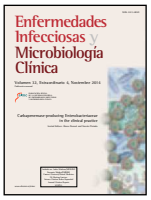

Infections caused by carbapenemase-producing Enterobacteriaceae: Risk factors, clinical features and prognosis

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ABSTRACT

Infections caused by carbapenem-producing Enterobacteriaceae (CPE) can present as several infectious syndromes, but they primarily present as respiratory, urinary and blood stream infections (primary or catheter-related) that are usually found as nosocomial or healthcare-associated infections. The risk of CPE infection is influenced by individual factors, such as the length of the hospital stay and their exposure to invasive procedures and/or to antimicrobials. Of note, exposure to several antimicrobials, not only carbapenems, has been linked to CPE colonization; the duration of antibiotic exposure is one of the primary drivers of CPE acquisition. Individual risk factors must be considered jointly with the local epidemiology of these microorganisms in healthcare institutions. Overall, these infections have a high associated mortality. Mortality is influenced by host factors (e.g., age, comorbidity and immune deficiency), infection-related variables (e.g., type and severity of the infection) and treatment-related factors such as the delay in the initiation of appropriate antimicrobial therapy and the use or monotherapy or combined antimicrobial therapy. Gaining knowledge concerning the epidemiology, clinical features and prognostic features of CPE infection could be useful for improving infection prevention and for the management of patients with infections caused by these microorganisms.

Infecciones causadas por enterobacterias productoras de carbapenemasas: factores de riesgo, características clínicas y pronóstico

Palabras clave:
Enterobacterias productoras de carbapenemasas
Factores de riesgo
Características clínicas
Bacteriemia
Factores pronósticos

RESUMEN

Las infecciones causadas por enterobacterias productoras de carbapenemasas (EPC) se pueden presentar con diferentes cuadros clínicos, aunque suelen ser más frecuentes las infecciones respiratorias, urinarias y la bacteriemia, ya sea primaria o asociada a catéter. Su adquisición es habitualmente nosocomial o relacionada con la asistencia sanitaria. El riesgo de presentar infección por EPC se relaciona con factores individuales como la duración del ingreso hospitalario y la exposición a procedimientos invasivos o antibióticos. El tratamiento previo con diversos antimicrobianos, además de carbapenemas, y en especial su duración son factores de riesgo esenciales para su adquisición. Estos factores individuales se deben valorar teniendo en cuenta la epidemiología local de las EPC en el medio sanitario. La mortalidad global de las infecciones causadas por EPC es generalmente elevada y se relaciona con factores del huésped (edad, inmunodepresión y enfermedades subyacentes), la infección (localización y gravedad) y el tratamiento antibiótico (retraso en el inicio de terapia adecuada y uso de monoterapia o terapia combinada). Un mayor conocimiento de la epidemiología, la presentación clínica y los factores pronósticos de las infecciones causadas por EPC debe contribuir a mejorar su prevención y manejo global.

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Introduction

The spread of antimicrobial-resistant microorganisms is considered by many to be one of the major public health issues worldwide, primarily due to its burden in terms of associated morbidity and mortality.[1] Among these microorganisms, carbapenem-producing Enterobacteriaceae (CPE) are perhaps the most concerning given that CPE can produce a broad spectrum of infections that are typically associated with high mortality, particularly in the acute healthcare setting.

The most clinically important CPE is KPC-producing *Klebsiella pneumoniae,* which has become endemic in many countries around the world; however, other enterobacterial species such as *Escherichia coli* and *Enterobacter* spp. that harbor various types of carbapenemases, such as metallo-beta-lactamases (MBL) and OXA-48, can produce a similar spectrum of disease. Due to the worldwide distribution of CPE, associated with the successful dissemination of the ST258 clone, most clinical and epidemiological studies have been performed with KPC-producing *K. pneumoniae*. In this review we will summarize the risk factors for acquisition of CPE, the clinical features of primary infections, including its presentation in special populations, and the prognostic factors associated with mortality.

Risk factors for colonization and infection caused by CPE

Interventions to prevent CPE acquisition might be more likely to succeed if they are guided by an understanding of the risk factors leading to colonization by these microorganisms. The assessment of independent risk factors for colonization and/or infection is challenging, however, because the data generated have come from studies conducted in different settings with different designs, frequently including small numbers of patients. Furthermore, the outcome is often a composite variable of colonization and infection, hampering the analysis of factors that determine the shift from colonization to infection. In addition, the most common risk factors appear to be time-dependent, so the associations might be confounded by the ease of CPE spread in high-prevalence settings. To evaluate the risk factors for CPE carriage or infection, we reviewed case-control studies,[2-19] retrospective studies and outbreak reports,[6,7,10,15,16,18,20,23] prospective cohorts[13,15-17,19,24-27] and surveillance studies.[28-31]

Influence of local epidemiology on the risk of CPE colonization

CPE infection is usually preceded by colonization, primarily at the level of the gastrointestinal tract; however, other sites such as the respiratory and urinary tracts are also frequently colonized. After colonization with CPE has occurred, it can persist from days to months. It appears that the median carriage time is usually approximately 3 months, but in a significant proportion of carriers, it can be longer.[32] The overall risk for rectal colonization in hospitalized patients is influenced by CPE colonization pressure in that setting, and it is noteworthy that most studies on this topic have been conducted in the context of outbreaks or in areas of high CPE endemicity.[5,6,14] In a context of high endemicity, the overall risk of CPE colonization is estimated to be around 5%, according to the results of a study analyzing more than 5000 patients from the intensive care, medical, surgical and rehabilitation units in two New York hospitals.[4] A similar carriage rate (5.4%) was observed in another prevalence survey from Israel.[14] In addition, the risk of CPE acquisition is time dependent, as demonstrated by two recent reports that have shown that the prevalence of colonization among patients admitted to the intensive care unit (ICU) increased from 6%-7% at admission to 27%-59% during subsequent hospitalization.[5,29] In contrast, the prevalence on admission of rectal colonization by CPE in patients from the community is negligible.[1,12]

Independent individual risk factors for CPE acquisition

The primary risk factors for CPE acquisition are common and universal to other nosocomial microorganisms such as extended-spectrum beta-lactamase-producing Gram-negative bacilli, methicillin-resistant *Staphylococcus aureus,* vancomycin-resistant enterococci, *Clostridium difficile* and *Candida*.[2-19] A number of situations leading to longer exposure to health care and antibiotics as well as susceptibility to infection have been established as independent risk factors for CPE colonization and infection (Table 1).

Broad-spectrum antibiotic use is likely the primary determinant of persistent CPE carriage. Previous use of broad-spectrum antibiotics such as betalactams and cephalosporins,[1,6,7,10,15,16,18,20-23] quinolones,[13,15-17,19,24-27] aminoglycosides,[28-31] metronidazole,[5,6,9,14] vancomycin[4,14] and carbapenems[2-19,25,29] has been recognized as an independent risk factor for CPE colonization. Importantly, the effects of antibiotics on colonization might be driven by the duration of therapy.[2,4,6,7,10,15,16,18,20-23] Although previous exposure to carbapenems is a prominent risk factor, it is not essential, given it ranges from 15% to 75% in patients with CPE colonization.[30,33] In addition, the use of medical devices and other common situations with increased risk of contact with CPE carriers correlates with higher CPE colonization. The primary risk factors associated with a significant risk of colonization are admission to an ICU, transfer between units, extended in-hospital stay and sharing a room with a colonized patient.[6,19,20,22,29,34] Although previous antibiotic use and extended hospital stay are the major risk factors for CPE colonization, clinicians should be aware of the possibility of carbapenem resistance in recent travelers who have received medical care in countries with a high prevalence of CPE.[35,36]

From colonization to infection

The proportion of patients who develop infection following CPE colonization is influenced by the patient's characteristics and by the invasiveness of each type of CPE. Although data regarding the infection/colonization ratio are very limited, it is estimated that 10% to 30% of colonized patients will develop CPE infection.[37] In the series of Borer et al,[7] analyzing 464 patients colonized by CPE, 9% developed infection. This proportion is likely influenced by the severity of the host's comorbidities and appears to be higher for immunocompromised patients. The duration of antibiotic therapy and the use of invasive procedures (e.g., mechanical ventilation and urinary or venous catheters) have been largely associated with a higher risk of infection by CPE.[38] Not surprisingly, many of these conditions also predict mortality in patients colonized by CPE.[18,19,32] Thus, it is unclear whether these conditions themselves induce susceptibility to infection, or whether the association with CPE infection is driven by the greater burden of antibiotic use and hospitalization among patients with poorer health status.

Clinical features

CPE, as most Enterobacteriaceae do, usually colonize the gastrointestinal tract, where they do not cause disease. Their pathogenic role emerges when present in usually sterile sites, such as blood, urine or the peritoneal cavity. CPE can also colonize the skin and respiratory tract, potentially causing infections of the skin and soft tissue, catheter-related infections and respiratory infections. The pathogenicity of these multidrug-resistant bacteria is frequently associated with the use of devices.[39]

The clinical features of infections caused by CPE have been summarized in Table 2 and Table 3, the former including only patients with bloodstream infections (BSIs). CPE can produce a broad spectrum of infections, such as bacteremia, respiratory infections including ventilator-associated pneumonia, urinary infections and

Table 1
Risk factors for colonization or infection by carbapenem-producing Enterobacteriaceae (CPE)

Risk factor	References
Previous CPE colonization	19
Previous antibiotic use	
Broad spectrum betalactams and cephalosporin	6, 10, 15, 16, 18, 25, 38
Fluoroquinolones	13, 15-17, 19
Aminoglycosides	28
Metronidazole	9
Vancomycin	14
Carbapenems	5, 10, 17-19, 25
Length of antimicrobial therapy	2, 4
Severe disease (APACHE score, SOFA score)	15, 29
Comorbidities	
Diabetes, malignancy	38
Neurologic dysfunction	19
Solid organ or stem-cell transplantation	18
Poor functional status	14, 19, 66
Multimorbidity (Charlson index)	19, 22, 25
Children: prematurity, necrotizing enterocolitis	65
Surgical and non-surgical invasive procedures	
Surgery	21
Urinary/intravenous catheters	8, 19, 38, 66
Mechanical ventilation	4, 18, 19, 31
Tracheostomy	38
Hospitalization	
Intensive care units	17, 19, 25
Transfer between units	21
Sharing room with colonized patients, extended stay	12, 14, 18, 22, 25
Hospital transfer	13
Nursing home residency	38
Travel to high-prevalence countries	24

intra-abdominal infections, usually in the acute healthcare setting. CPE infection is typically a late complication of hospitalization; among patients with nosocomial infection, the time from admission to documented infection is approximately 2-4 weeks.[40-42] As previously described, most of the relevant clinical information has been obtained from studies of KPC-producing *K. pneumoniae*, but reports from other species and types of CPE have provided similar data. Nevertheless, delineating the clinical scope of infections caused by CPE as a whole is not straightforward. Clinical studies are quite heterogeneous, not only due to the differences in patient populations, but because of several methodology and design issues. For instance, it is frequently difficult to differentiate infection from colonization in several clinical samples such as the skin, urine and respiratory tract.

Although reports describing the clinical features of BSIs provide significant input concerning the most severe infections and prevent the problems related to colonization/infection uncertainty, they represent only a fraction of the problem regarding infections caused by CPE. The sources of BSI vary among studies: primary bacteremia (which often includes catheter-related infections) is the most frequently observed source, followed by infections of the respiratory and the urinary tract (Table 2). Studies including consecutive patients with various types of clinical samples might provide a different perspective on the scope of the problem but are somewhat more difficult to interpret because these are based on the growth of CPE in samples in which colonization cannot always be easily excluded (Table 3). Overall, the most frequently observed sources of infection are the urinary and respiratory tract and intravenous catheter-associated infections. As might be expected, there is significant variability in the weight that different sites of infection have in the reported case series. For instance, respiratory tract infections are more frequently observed in studies with a higher proportion of critically ill patients, probably due to their exposure to mechanical ventilation. The frequency of catheter-related infections depends, however, on whether these infections are considered primary BSIs.

Urinary tract infection (UTI) is one of the most common types of infection, particularly among non-hospitalized patients (community-onset healthcare-associated infections) and non-critically ill hospitalized patients.[43] Perhaps the most compelling evidence concerning the clinical presentation and epidemiology of UTI caused by CPE was recently summarized by Qureshi et al.[44] This single-center study described the clinical and epidemiological features of 105 consecutive patients with CPE bacteriuria (50% nosocomial and 50% healthcare-associated) in which other sources of infection were reasonably ruled out. Interestingly, most patients with positive urine cultures for CPE were asymptomatic when bacteriuria was diagnosed (84/105; 80%). Among the symptomatic, most had some type of systemic sign or symptom, such as fever and/or altered mental status without alternative explanation (17/21; 81%); nevertheless, only two patients were diagnosed with pyelonephritis and one was diagnosed with prostatitis. In addition, CPE has been described as a cause of other common nosocomial infections, such as surgical site and wound infection, osteoarticular infection, mediastinitis, endocarditis and meningitis.[32]

Mortality and prognostic factors

Most reports have shown that infections due to CPE are typically associated with an adverse outcome, although a wide range of mortality (10% to 72%) has been observed.[32,37,45-51] This might be partially due to heterogeneous patient populations, underlying diseases and the severity of the infections. Varying antimicrobial susceptibilities and therapeutic approaches might also account for these different outcomes. In addition, there has been a wide variability of criteria used to assess the outcome. In most reports, the 28- or 30-day mortality was provided, whereas others have provided the 7- or 14-day mortality, as well as the infection-related, in-hospital, or overall mortality (see Tables 2 and 3).

Prognostic factors associated with mortality include a wide and complex spectrum of host-, infection-, strain- and therapy-related variables (Table 4). Demographic variables commonly described as prognostic factors in other types of infections have also been reported in CPE infections, such as older age[32,40,46,48] and severity of the comorbidities.[37,49,52] In addition, specific diseases such as malignancy, solid organ transplantation (SOT) and heart failure have occasionally been reported as independent prognostic factors in these patients.[18,19,32,40,53]

Among the infection-related factors, some studies have shown that the type and severity of CPE infection have a significant impact on mortality. For instance, the presence of BSI or pneumonia is associated with a higher rate of treatment failure, whereas UTI has a higher treatment success rate;[51] bacteremia has been found to be an independent risk factor for mortality in this population.[54] Previous reports have shown that the occurrence of septic shock at the onset of infection is an independent predictor of death.[32,46,49] Of note, in the subset of patients with BSI, the severity of sepsis[46,49] and underlying diseases (Charlson score and McCabe and Jackson classification),[49,52,54] the Pitt bacteremia score[52,55] and resistance to carbapenems or other antimicrobials were shown to be independent predictors of death.[19,26,40,48,52]

Table 2
Studies describing the clinical features of patients with carbapenem-producing Enterobacteriaceae (CPE) bacteremia

Author		Daikos[49]	Tumbarello[46]	Neuner[55]	Zarkotou[48]	Nguyen[57]	Ben-David[52]	Qureshi[47]	Navarro[67]	Mouloudi[40]	Borer[38]	Corcione[68,a]
Country		Greece	Italy	USA	Greece	USA	Israel	USA	Spain	Greece	Israel	Italy
Year		2014	2012	2011	2011	2010	2012	2012	2012	2010	2009	2014
Study design		RO	RO	RO	RO	RO	RO	RO	RO	CC	CC	CC
Number of cases		205	125	51[b]	53	48	42	41	40	37	32	18
Type of carbapenemase		KPC (127) KPC+ VIM (36) VIM (42)	KPC	KPC	KPC	KPC	KPC	KPC	OXA-48	KPC (19) VIM (18)	KPC	KPC
ICU at onset of infection		57%	43%	43%	72%	52%	57%		22%	100%	37%	0%
Respiratory tract infection		21%	22%	12%	3%			24%	3%		19%	n/a
Urinary tract infection		9%	14%	14%	11%			17%	30%		50%	n/a
CR-BSI		11%	10%	[c]	23%			32%	10%		9%	n/a
Intraabdominal infection		14%		12%					25%			n/a
SSTI		3%			8%				5%			n/a
Primary BSI		41%	60%	55%	45%			15%	18%		22%	n/a
Combination therapy[d]		50%	63%		38%	27%	12%	44%	68%			n/a
Crude mortality	7-day					23%						
	14-day			42%	28%							22%[e]
	28/30-day	40%	42%			42%		39%	50%			
	In-hospital			58%	52%	61%	69%		65%	57%[f]	72%	
Attributable mortality					34%		48%				50%	

BSI: bloodstream infection; CC: case control; n/a: not applicable; CR-BSI: catheter-related BSI; ICU: intensive care unit; RO: retrospective observational; SSTI: skin and soft tissue infection.
[a]Only healthcare-associated BSIs were included.
[b]Only those patients who received at least one active agent were included (51/60).
[c]Included as primary BSI.
[d]More than one active agent against CPE.
[e]21-day mortality.
[f]ICU mortality.

Regarding the carbapenemase type, a comparative study of BSIs caused by KPC- and VIM-producing *K. pneumoniae* showed that isolation of KPC was an independent predictor of ICU death and in-hospital death but not infection-attributable mortality.[40] However, in the series of Daikos et al,[49] no significant differences in 28-day mortality were shown between patients with BSI caused by VIM- or KPC-producing *K. pneumoniae*. Among 216 episodes of infection caused by CPE in the Hospital Ramón y Cajal, no significant differences were observed in the 30-day mortality of patients with VIM-1 (20%), KPC-3 (23%) and OXA-48 (23%).[56]

Adverse outcomes in severe infections could be partly related to a delay in initiating effective antimicrobial therapy. A recent study showed that patients with CPE bacteremia were 4 times more likely to receive inappropriate empiric therapy.[26] Although some reports have shown that inappropriate initial therapy is associated with increased mortality,[46] the timely administration of active antimicrobials against CPE was not associated with survival in other series.[18,48,49,58] Regarding definitive treatment, inappropriate therapy (defined as administration of antibiotics inactive against the study isolate) has been associated with increased mortality in some reports,[46,48] whereas other studies have not confirmed this finding.[18]

A recent systematic evaluation of antimicrobial therapy for CPE infections has shown significant heterogeneity among clinical reports performing statistical analyses of the available evidence.[58] Despite this heterogeneity, some recent observational studies focusing on BSI due to CPE have found that monotherapy is associated with a high rate of clinical failure and/or increased mortality compared with combined antibiotic therapy. In the largest study of Daikos et al,[49] which included 205 patients, combined therapy was associated with lower overall 28-day mortality (27% vs. 44%; p=.01). In the Cox proportion hazard model, the presence of ultimately or rapidly fatal disease and septic shock were independent predictors of death, whereas combination therapy was strongly associated with survival. A similar result was observed by Tumbarello et al[46] among 125 patients with BSI. Combined therapy was associated with lower overall 30-day mortality (34% vs. 54%; p=.02). Logistic regression analysis identified septic shock at infection onset, inadequate initial antimicrobial therapy and high APACHE III scores as independent predictors of 30-day mortality, whereas combination therapy was associated with a lower risk of mortality. Qureshi et al[47] examined the effect of combined antibiotic therapy on all-cause 28-day mortality; combined therapy, defined as administration of ≥2 antimicrobials with Gram-negative activity (regardless of the *in vitro*

Table 3
Studies describing the clinical features of patients with microbiologically-documented carbapenem-producing Enterobacteriaceae (CPE) infections, bacteremic and non-bacteremic

Author		Bratu[69]	Peleg[70]	Patel[18]	Souli[71]	Córdova[72]	Logan[65,a]	Paño[41]	Sbrana[73]	Capone[54]	Kontopopidou[74]
Country		USA	Australia	USA	Greece	Argentina	n/a	Spain	Italy	Italy	Greece
Year		2005	2005	2008	2010	2011	2012	2013	2013	2013	2014
Study design		R-CS (Outbreak report)	R-CS (Outbreak report)	CC	R-CS (Outbreak report)	P-CS	Review	Outbreak report	R-CS	P-CS	R&P-CS
Number of cases		59	12	99	18	27	63	62	26[b]	91[c]	127
Type of carbapenemase		KPC	IMP	KPC	KPC	KPC	NDM, KPC, VIM, OXA-181	OXA-48	KPC	KPC, VIM, CTX-M-15	KPC, VIM
ICU at onset of infection		n/a	83%	69%	50%	19%	53%	n/a	100%	47%	100%
Respiratory tract infection		12%	50%	2%	11%	15%	17%	15%	52%	32%	28%
Urinary tract infection		31%	8%	2%	6%	63%	25%	36%	8%	32%	10%
Intraabdominal infection				34%	6%	15%	19%	7%	4%	15%	5%
SSTI/wound		14%	8%	1%	11%			27%		12%	
Line-related infection			17%	27%[d]	28%		30%	5%	19%		31%
Bloodstream infection		37%	17%	57%	78%	7%	8%	37%	46%	37%	
Crude mortality	14-day	47%									35%
	30-day								9%		
	In-hospital		42%	49%[e]	61%[f]	59%[g]	9%	43%		25%	

CC: case control study; ICU: intensive care unit; n/a: not applicable; P-CS: prospective cohort study; R&P-CS: retrospective and prospective cohort study; R-CS: retrospective cohort study; SSTI: Skin and soft tissue infection.
[a]Only includes pediatric patients.
[b]Episodes, corresponding to 22 patients.
[c]91 infected patients out of 97 patients with positive cultures.
[d]All were BSI.
[e]Mortality among non carbapenem-producing *K. pneumoniae* 20% OR, 3.71 [95% CI, 1.97-7.01]; *P*<.001.
[f]Attributable mortality: 28%.
[g]Attributable mortality: 26%.

susceptibility to each agent), was associated with lower mortality (13% vs. 58%; p=.01). In the multivariate analysis, definitive combination therapy remained the only independent predictor of survival. Finally, in the study by Zarkotou et al,[48] a lower mortality was observed among patients treated with combination therapy, but only in the univariate analysis (0% vs. 47%; p<.001). The mechanisms underlying the effectiveness of combined therapy are not known, but synergistic activity between different antimicrobials has been observed *in vitro* among CPE.[37] With the current available clinical evidence, combined therapy appears to be more effective in terms of increased survival than the use of only one active drug for invasive infections due to CPE.

In addition to antimicrobial therapy, the importance of source control has been addressed in some recent studies. Adjunct procedures performed for control of the source of infection, such as removal of venous or urinary catheters, debridement, drainage and other surgical procedures, have been associated with a favorable clinical response[57] and increased survival.[18,49] In the same way, the lack of microbiologic eradication has been associated with an adverse outcome in BSI.[57]

Specific patient populations

Transplant recipients are a vulnerable population at risk for CPE infections. This vulnerability is due to the increased risk of CPE acquisition, particularly shortly after the transplant, and to the associated immune compromise in these patients.[18] The clinical, epidemiological and therapeutic features of CPE infections in SOT recipients have recently been reviewed by Satlin et al and commented on by Johnson and Boucher.[59,60]

Overall, the site of infection in SOT is influenced by the transplanted organ. For instance, UTI is the most common infection in kidney transplant recipients, whereas pneumonia is the predominant infectious syndrome after a lung transplant. Among liver transplant recipients, the abdomen is the predominant site of infection, and BSI is a frequent complication of CPE infections.

In the aforementioned review, the overall 30-day mortality among the reported 91 SOT recipients infected with CPE was 37%. In liver transplant patients, the excess risk of death among patients with CPE infections has been estimated in a 5-fold increase compared with controls.[61] Given the poor outcomes of CPE infections in this

Table 4
Prognostic factors related to mortality and/or treatment failure in carbapenem-producing Enterobacteriaceae (CPE)-associated infections

Prognostic factor	Comments (increased mortality among patients with risk factor)	References
Age	Older patients	32, 37, 40, 48
Charlson comorbidity index	High score at admission	52, 54
McCabe and Jackson classification	Rapidly or ultimately fatal underlying disease	37, 49
APACHE score	High score at infection onset	42, 46, 48
Pitt score	High score at bacteremia onset	52, 55
Intensive care unit stay	Admission to intensive care unit	37, 54
Site of infection	Higher mortality or treatment failure in patients with bacteremia and pneumonia	2, 38, 54
Severity of infection	Higher mortality in patients with septic shock at infection onset	46, 49
Resistance to carbapenems	Carbapenem-resistant CPE isolate	18, 19, 26, 40, 42, 52
Carbapenemase type	KPC-producing *Klebsiella pneumoniae*	40
Inadequate initial antimicrobial treatment	Antimicrobial inactive against CPE isolate	46
Inappropriate antimicrobial treatment	Antimicrobial inactive against CPE isolate	48
Definitive antimicrobial therapy	Monotherapy (only one antimicrobial active against CPE isolate)	46, 49
Lack of microbiologic eradication	Persistent bacteremia (>7 days)	57
Source control	Lower mortality with catheter removal or wound/abscess debridement	18, 57

patient population, some have questioned whether patients colonized by these bacteria should be offered a SOT.[62] As with other multidrug resistant microorganisms, such as *Pseudomonas aeruginosa,* CPE colonization should not be considered an absolute contraindication for SOT. Perhaps CPE should be included in a comprehensive evaluation considering all other patient-associated factors to determine whether it increases the risk of transplantation above a safe threshold.[63] Donor-related CPE transmission and infection have been described, and targeted perioperative prophylaxis is likely beneficial in this setting.[59,63]

Other specific patient populations to be considered are patients with hematologic malignancies and hematopoietic stem cell transplant recipients. In neutropenic patients, bacterial translocation from the intestinal tract is perhaps the primary mechanism behind bacterial infections. In neutropenic patients colonized by CPE, severe infections caused by these microorganisms, primarily BSIs, do occur. Satlin et al, in the largest study to date, reviewed 18 patients with hematologic malignancies who developed CPE bacteremia.[64] In this study, a mean delay of 55 hours in the initiation of appropriate antimicrobial therapy was observed and a crude mortality of 69% was documented. Active surveillance in hematology wards searching for CPE-colonized patients and specific empiric treatment protocols for patients colonized by CPE might help to decrease time to appropriate antimicrobial therapy, but its clinical impact needs to be clinically evaluated.

Children are another specific population affected by CPE who have distinct epidemiological, clinical and therapeutic issues, which have been recently reviewed by Logan.[65] She provides clinical and demographic information concerning 33 pediatric cases of CPE infections worldwide. As in adults, CPE infections are primarily nosocomial, occurring typically during hospitalization in the ICU (53%), in patients with associated comorbidities such as lung disease or several forms of immunosuppression. The observed mortality rate in children with CPE infections was significantly lower (10%) than that in adults. Nevertheless, the author did not provide enough information about the site of infection and the number of BSIs observed in these patients.

Conclusions

The risk factors for acquisition of CPE are common to other multiresistant microorganisms, particularly to extended spectrum beta-lactamase-producing bacteria. Of note, individual risk factors interact with the epidemiologic setting, primarily endemicity and colonization pressure. The main driver for infection in patients colonized by CPE is exposure to invasive procedures and devices. The presentation of infections caused by CPE is diverse and is influenced by the clinical setting in which they occur. Overall, infections caused by CPE are associated with a high mortality rate that is primarily related to the severity of the infection and underlying comorbidities. Adequate source control and appropriate use of antimicrobial therapy are the most important modifiable risk factors that have shown a survival benefit in this population.

Conflicts of interest

The authors have no conflicts of interest to declare.

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