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“Swimming in resistance”: Co-colonization with carbapenem-resistant *Enterobacteriaceae* and *Acinetobacter baumannii* or *Pseudomonas aeruginosa*

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Abstract

Background—Co-colonization of patients with carbapenem-resistant *Enterobacteriaceae* (CRE) and *Acinetobacter baumannii* (AB) or *Pseudomonas aeruginosa* (PA) is reported to be associated with increased antibiotic resistance and mortality.

Methods—CREs isolated between September 2008 and September 2009 were analyzed at Detroit Medical Center. Patients who had an additional isolation of AB or PA during the period spanning 7 days before to 7 days after CRE isolation were considered co-colonized. Molecular typing was used to determine genetic similarity among CRE strains.

Results—Eighty-six unique patient isolates of CREs were analyzed. Thirty-four patients (40%) were co-colonized, and 26 (79%) had AB or PA isolated on the same day as the CRE. High Charlson Comorbidity Index score was an independent predictor for co-colonization. Recent stay at a long-term acute-care facility and previous therapy with antimicrobials with activity only against gram-positive microorganisms also were associated with co-colonization, but did not remain significant independent predictors. Co-colonization was associated with higher levels of resistance to carbapenems among CREs and increased 90-day mortality. Molecular typing revealed CRE polyclonality in co-colonized patients.

Conclusions—Co-colonization is found in patients with the greatest disease burden in the hospital and occurs due to the dissemination of multiple CRE strains. This finding calls into question the practice of cohorting patients with CRE in close proximity to patients with AB or PA.

Keywords

KPC; CRE; Nonfermenter; Multidrug resistance; Gram negative; HAI; MDRO

Carbapenem-resistant Enterobacteriaceae (CRE) and non-glucose-fermenting gram-negative bacilli, such as *Acinetobacter baumannii* (AB) and *Pseudomonas aeruginosa* (PA), are among the most challenging pathogens to treat and contain in the hospital. Because of a lack of effective therapeutic agents, infections due to these pathogens (CREs, carbapenem-resistant AB [CRAb], and carbapenem-resistant PA [CRPa]) are associated with devastating outcomes.¹⁻⁶ Data on the prevalence and epidemiology of patients co-colonized with both CRE and CRAb and/or CRPa are limited,^{7,8} and the significance of this epidemiologic feature has not been thoroughly evaluated.

Among patients with colonization or infection due to CRE in metropolitan Detroit, co-colonization with a CRAb and/or CRPa was found to be a significant predictor for isolating a strain of colistin-resistant CRE,⁹ to have an elevated minimal inhibitory concentration (MIC) to carbapenems,¹⁰ and to be a strong independent predictor for in-hospital mortality.¹⁰ These findings were extracted from analyses of 2 different patient cohorts.^{9,10} A possible factor in the association between co-colonization and multidrug resistance (MDR) might be related to the transfer of genetic elements conferring antibiotic resistance to and/or from nonfermenters and CRE carriers, which is of concern. Because carriers of CRE and nonfermenter might sometimes be cohorted together or in close proximity due to a lack of single-occupancy rooms or dedicated cohort units, there is the potential risk for dissemination of antibiotic resistance determinants. In one Detroit Medical Center (DMC) hospital where MDR gram-negative bacilli are particularly endemic, the patients who required care in an intensive care unit and were carriers of AB and/or CRE were cohorted together in the same unit in single-occupancy rooms. Health care staff in this unit often cared for patients with both CRE and AB. The transfer of *vanA* from vancomycin-resistant enterococci (VRE) to methicillin-resistant *Staphylococcus aureus* (MRSA) in patients co-colonized with these organisms resulted in the development of vancomycin-resistant *S. aureus*.¹¹ The possibility that a similar scenario could involve MDR gram-negative organisms is of particular concern, given the lack of therapeutic options for CRE and similar organisms.

The aim of the present study was to analyze the epidemiology of patients co-colonized with a CRE and CRAB and/or CRPa in an endemic US location, to further explore the significance of co-colonization.

METHODS

Study settings and design

The DMC health care system comprises 8 hospitals with more than 2,200 inpatient beds and serves as a tertiary referral hospital for metropolitan Detroit and southeastern Michigan. Patients with CRE isolated between September 1, 2008, and August 31, 2009 were included in the study. The Institutional Review Boards of Wayne State University and DMC approved the study before the start of data collection.

Patients and clinical variables

The study cohort comprised all patients who had a culture positive for CRE during the study period. Cultures from all anatomic sites, including both infected and colonized patients, were included in the final cohort.¹² For patients who had more than one CRE isolated during the study period, only the first CRE isolate was analyzed (eg, only unique patient episodes were included). Patients co-colonized with a CRE and CRAB and/or CRPa were compared with patients with CRE not co-colonized with CRAB and/or CRPa. Co-colonization was defined as recovery of CRE and CRAB and/or CRPa within a 7-day window. CRE and CRAB or CRPa did not have to be recovered from the same anatomic site.

Data retrieved from patient charts included (1) demographic information; (2) background condition, immunosuppressive status, and comorbidities, including Charlson Comorbidity Index score¹³; (3) severity of acute illness indices, including McCabe score¹⁴ and sepsis level¹²; (4) recent health care-associated exposures; and (5) factors related to antimicrobial therapy, including recent exposures (past 3 months), empiric regimen (defined as therapy administered from 48 hours before to 72 hours after the date of CRE culture), “definitive” antimicrobial regimen (ie, antibiotics provided more than 72 hours after CRE isolation and up to 14 days after isolation), and time to initiation of effective therapy (defined as time to the initiation of therapy with an antimicrobial agent that demonstrated in vitro activity against all isolates being recovered).

Patient outcomes, including 90-day mortality, length of hospital stay, functional status deterioration (defined as deterioration after the isolation of CRE in one or more activities of daily living according to the Katz criteria¹⁵), discharge to a long-term facility (LTCF) after being admitted from home, and microbiological failure (defined as additional isolations of the same CRE and/or nonfermenter in the 6 months after the culture date) were analyzed as well.

Microbiology

DMC’s clinical microbiology laboratory processes ~500,000 samples annually. Bacteria were identified to the species level, and susceptibilities to predefined antimicrobials were determined using an automated broth microdilution system (MicroScan; Siemens, Munich,

Germany), and in accordance with Clinical and Laboratory Standards Institute (CLSI) criteria.¹⁶ During the study period, MICs to colistin and tigecycline were determined using E-test strips (bioMérieux, Marcy l'Etoile, France) in Mueller-Hinton media. Breakpoints to define nonsusceptibility were set to 4 µg/dL for both drugs, in accordance with the manufacturer's instructions and Food and Drug Administration recommendations. Carbapenem resistance was considered low if the MIC of imipenem and meropenem was 2 µg/dL,¹⁷ in accordance with the CLSI's 2009 breakpoint recommendation for carbapenems.¹⁶ All Enterobacteriaceae that were resistant to one or more extended-spectrum cephalosporins and had an MIC 2 µg/dL against ertapenem were screened for carbapenemase production with the modified Hodge test performed according to CLSI 2009 criteria.¹⁶ Subsequently, CREs were examined for the presence of *Klebsiella pneumoniae* carbapenemase (KPC) enzyme (*bla_{KPC}*) by polymerase chain reaction (PCR).¹⁸ Previously characterized KPC-producing *K. pneumoniae* isolates were used as controls.^{18,19}

Repetitive extragenic palindromic PCR (rep-PCR) was performed with an automated system (DiversiLab; bioMérieux). Band patterns were compared with a modified Kullback-Leibler method to generate a dendrogram, using the DiversiLab software. Isolates with 95% band pattern similarity were considered genetically related.¹⁹ Results of rep-PCR typing were compared with those of previously characterized KPC-producing *K. pneumoniae* isolates.^{18,19}

Statistical analysis

All analyses were performed with SAS 9.2 (SAS Institute, Cary, NC). Bivariate analyses were performed using Fisher's exact test for categorical variables and the independent-samples *t* test or Wilcoxon's rank-sum test for continuous variables. Multivariate models for risk factors for co-colonization and for the various outcomes were constructed using logistic regression. All variables with a *P* value <.10 in bivariate analyses were considered for inclusion in the multivariate analysis. A stepwise selection procedure was used to select variables for inclusion in the final model. The final selected model was tested for confounding. If a covariate affected the β -coefficient of a variable in the model by >10%, then the confounding variable was maintained in the multivariate model. All *P* values were 2-sided.

RESULTS

A total of 92 unique single patient-isolates of CRE were obtained during the 1-year study period at DMC. Only partial microbiological data were available for 6 outpatients, and thus the final cohort comprised 86 patients. Sixty-nine of the CREs were *K. pneumoniae*, 15 were *Enterobacter* spp, and 2 were *Escherichia coli*. The study population was predominately elderly (59% aged ≥ 65 years), debilitated (79% not fully independent¹⁵), African-American (80%) individuals with permanent residence in an LTCF (67%). Many study subjects had been hospitalized in a long-term acute care facility (LTAC) during the previous year (56%). Most patients had undergone an invasive procedure in the 6 months before CRE isolation (86%) and had been hospitalized in an acute care hospital sometime in the 3 months before CRE isolation (75%). Based on McCabe score,¹⁴ life expectancy was <2 months for 16

patients (17%). Twenty-six 26 patients (30%) had dementia and 26 (30%) were in an immunosuppressed state before the index hospitalization.

Comparison of co-colonizers and non-co-colonizers

Thirty-four (40%) CRE-positive patients were co-colonized with CRAb or CRPa. Eighteen of these CRAb or CRPa isolates were isolated from the same culture as the CRE, 8 were isolated on the same day from a different culture, and 8 were cultured sometime during the period from 5 days before to 5 days after CRE culture. In the co-colonized patients, 30 (88%) of the CRE isolates were *K pneumoniae* and 4 (12%) were *Enterobacter* spp. Twenty (59%) of the co-colonized patients had CRPa isolated, 10 (29%) had CRAb, and 4 (12%) had both CRPa and CRAb.

Results of bivariate analysis comparing the 34 co-colonized patients and the 52 non-co-colonized patients are displayed in Tables 1-4. Variables associated with co-colonization included LTAC stay in the preceding year, documented isolation of an MDR pathogen in the previous 6 months (including MRSA, VRE, extended-spectrum β -lactamase producing *Enterobacteriaceae* [ESBL], AB, and PA), and a high Charlson Comorbidity Index score¹³ (Table 1). Invasive procedures or surgeries in the previous 6 months, indwelling permanent foreign devices or implants, and an intensive care unit (ICU) stay in the 3 months before admission also were associated with co-colonization (Table 2). Elevated MIC to group 2 carbapenems among the CREs was more common in co-colonizers compared with non-co-colonizers (Table 1).

Recent use of antimicrobial agents with solely gram-positive activity (ie, glycopeptides, linezolid, and daptomycin) was significantly associated with co-colonization (Table 3). We found no association between exposure to antibiotics with gram-negative activity. Co-colonized patients also had an increased severity of illness at the CRE culture date, as demonstrated by reduced consciousness and the need for transfer to an ICU (Table 4).

In a multivariate analysis of risk factors for co-colonization, independent predictors of co-colonization included a high (4) weighted Charlson Comorbidity Index score (odds ratio [OR], 4.56; 95% confidence interval [CI], 1.18-17.70; $P = .03$).¹³ Isolation of CRE from the urine was associated with decreased risk for co-colonization (OR, 0.23; 95% CI, 0.06-0.85; $P = .03$). This model was controlled for recent stay in an LTAC, recent surgery, level of resistance to group 2 carbapenems among the CREs, and recent exposure to antibiotics with solely gram-positive activity (ie, glycopeptides, linezolid, or daptomycin).

Ninety-day mortality

There were 17 patients (53%) who died in the group that was co-colonized, compared with 11 patients (24%) who had CRE but were not co-colonized with aCRAb and/or CRPa (OR, 3.2; (95% CI, 1.3-9.3); $P = .02$) (Table 4). In multivariate analysis, co-colonization remained an independent significant predictor for 90-day mortality (OR, 9.9; 95% CI, 2.1-48.7; $P = .005$). Other independent predictors included lower McCabe score (OR, 4.4; $P = .04$) and ICU stay during the current hospitalization (OR, 3.8; $P = .05$). This model was controlled for the confounding effects of age.

Rep-PCR

Twenty-eight of the 30 *K pneumoniae* isolates from the co-colonized patients were available for genotyping by rep-PCR. Genetic relatedness is displayed in Figure 1. Of the 63 *K pneumoniae* isolates that were genotyped (28 from co-colonized patients and 35 from non-co-colonized patients), 45 were defined as clone 1, 13 as clone 2, 3 as clone 3, and 2 as clone 4. None of the clones was significantly associated with co-colonization. Because of the low number of patients co-colonized with *Enterobacter* spp (n = 4) and preliminary data showing a wide genetic diversity of *Enterobacter* CRE strains in southeast Michigan,¹⁰ rep-PCR was not performed in the co-colonized patients with CRE due to *Enterobacter* spp.

DISCUSSION

In this study, co-colonization with CRE and CRAb and/or CRPa was the strongest independent predictor for 90-day mortality. The reason for this association is unclear, but evidently patients co-colonized with CRE and CRAb and/or CRPa are one of the most severely ill groups of patients seen in hospitals. Compared with the non-co-colonized patients, the co-colonized patients were older, had more encounters with the health care system and more likely to have been hospitalized in an ICU at the time of culture, to have undergone surgery, and to reside in an LTCF and/or to have had a recent LTAC stay. The co-colonized patients also had more severe underlying chronic diseases,¹³ and were more likely to have had an indwelling device in place for a long period before CRE isolation. These patients also had more invasive infections, including pneumonia and bacteremia, which also might have contributed to the poor outcomes in this group.

Interestingly, co-colonized patients were more often exposed to antibiotics with solely gram-positive activity (ie, glycopeptides, daptomycin, and linezolid) before CRE isolation. Administration of these agents might facilitate, through selective pressure and inhibition of competing gram-positive flora, the appropriate conditions for propagation of MDR gram-negative organisms, including CRE and MDR gram-negative bacilli.²⁰ Patients with isolation of any MDR organism (MDRO) in the past 3 months, including gram-positive pathogens like MRSA and VRE, were at increased risk for co-colonization. Possible explanations for this association are that previous MDRO isolation may be a marker for antecedent antimicrobial exposure, and also that many MDROs share similar risk factors; both of these issues might be confounders by indication.²¹ In multivariate analysis, recent MDRO isolation and recent antimicrobial therapy with gram-positive activity did not remain significant independent predictors of co-colonization.

Another important finding of the present study is the association between co-colonization and elevated MICs against various types of antibiotics among the isolated CREs. In the co-colonization patients, CRE strains had higher MICs to group 2 carbapenems. The resistance determinant *bla_{KPC}* mediates resistance to carbapenems in the vast majority of CRE cases in the United States.²² Until recently, the median MIC to carbapenems reported from various US locations was low (ie, 2 µg/mL).²² The high MICs to carbapenems in our co-colonized patients might indicate that other mechanisms of resistance to carbapenems are present in the CREs isolated from these patients. In CRAb and CRPa there are other recognized mechanisms for carbapenem resistance apart from Ambler-A β-lactamases like *bla_{KPC}*,

including class D β -lactamase production, loss of outer membrane proteins, metallo- β -lactamase production, and efflux pumps.²³ One possible explanation for the increased MICs to carbapenems among CREs isolated from the co-colonized patients is that the CRE-acquired resistance determinants derive from gene exchange with CRAb and CRPa. This hypothesis awaits further molecular investigation.

The increased MICs to carbapenems in CRE has important clinical implications. In vitro synergy tests and time-kill curve trials have demonstrated that imipenem or meropenem can be used as an adjunct to colistin in the treatment of CRE, CRAb, and CRPa infections.^{24,25} If increased resistance to carbapenems becomes more common and widespread, the role of carbapenems, even as therapeutic adjuncts, might be greatly diminished.

The retrospective nature of this study presented some inherent limitations. The patients included in our analysis had a large disease burden, with multiple comorbidities and hospital exposures. It was difficult to separate the impact on clinical outcomes of severity of illness and health care exposure from the impact of co-colonization, although our multivariate model attempted to address this limitation.

Most importantly, this study raises new questions regarding the impact of co-colonization on clinical outcomes and infection control management. Although the potential transfer of resistance determinants from non-lactose fermenters (CRAb and CRPa) to CRE was not demonstrated to be the reason for increased antimicrobial resistance, the possibility of genetic exchange is of concern. It has been shown that many resistance genes can cross the interspecies barrier in gram-negative and gram-positive bacteria.²⁶ The example of the transfer of *vanA* from VRE to MRSA, resulting in vancomycin-resistant *S aureus* in patients co-colonized with both MRSA and VRE, should serve as a warning of the possibility of these events among MDR gram-negative organisms as well. Consequently, MICs to carbapenems and to other antibiotics should be monitored among CREs (even as the new CLSI breakpoints and recommendations are implemented¹⁶) to allow early detection of increases and appropriate adjustments to treatment strategies. Until more is known regarding the transfer of resistant determinants between genera, it seems prudent to avoid cohorting patients colonized with CRE together with patients colonized with PA and/or AB.

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Fig 1.
rep-PCR of *K pneumoniae* isolates that were cultured concurrently or within 7 days of AB and/or PA at DMC between September 2008 and September 2009.

Table 1

Bivariate analysis comparing demographics, microbiologic characteristics, and background conditions in patients co-colonized with a CRE and AB or PA and patients with CRE not co-colonized, DMC, September 2008 to September 2009

Parameter	Co-colonized (n = 34)	Noneco-colonized (n = 52)	OR	95% CI	P
Demographics					
Age, years, mean $\pm$ SD	65.2 $\pm$ 17.4	61.9 $\pm$ 21.2			.76
Female sex, n (%)	21 (68)	24 (46)	1.89	0.78-4.55	.19
Stay at adult ICU at CRE culture date, n (%)	8 (24)	4 (8)	0.27	0.07-0.99	.06
African-American race, n (%)	26 (77)	43 (84)	0.68	0.23-1.98	.58
Permanent residence in an LTCF, n (%)	27 (79)	31 (60)	2.63	0.96-7.14	.06
LTAC stay in the past year, n (%)	24 (71)	24 (47)	2.7	1.06-6.78	.04
Microbiology parameters of the CREs isolated					
<i>K pneumoniae</i> CRE, n (%)	30 (88)	39 (75)	2.5	0.66-10.2	.13
Anatomic site of CRE culture, n (%)					
Respiratory	13 (38)	9 (17)	2.96	1.09-8.02	.04
Urine	8 (24)	26 (50)	0.31	0.12-0.80	.02
Number of coslitin-resistant strains, n (%)	7 (22)	7 (14)	1.72	0.54-5.47	.38
Meropenem MIC, median (IQR)	7.3 (2.7-13.9)	4.3 (2.8-8)			.06
Not lowered group 2 carbapenem resistance, n (%) [†]	19 (58)	16 (32)	2.88	1.16-7.17	.03
Recent isolation of resistant organism, n (%) [‡]	31 (91)	28 (57)	7.75	2.08-28.82	.001
Background conditions and comorbidities					
Dependent functional status, n (%)	30 (88)	38 (73)	2.77	0.82-9.27	.11
Reduced consciousness at admission, n (%)	19 (56)	20 (38)	2.03	0.84-4.88	.13
Congestive heart failure, n (%)	20 (61)	16 (31)	3.46	1.39-8.63	.01
Diabetes mellitus, n (%)	26 (79)	30 (58)	2.72	1.00-7.40	.06
Cerebrovascular disease, n (%)	19 (58)	16 (31)	3.05	1.23-3.57	.02
Hemiplegia, n (%)	16 (48)	14 (27)	2.55	1.02-6.39	.06
Chronic skin ulcers, n (%)	24 (73)	21 (40)	3.94	1.5-10.1	.004
Charlson weighted Comorbidity Index score, median (IQR) ¹³	5.9 (4.6-8.3)	4.3 (2.5-6.4)			.002
Charlson combined condition score, median (IQR) ¹³	8.4 (6.6-10.8)	6.5 (4.2-9)			.005
Charlson 10-year survival, median (IQR) ¹³	0.6 (0-1.7)	1.6 (0-47)			.01

IQR, interquartile range.

All information on MIC and resistance status refers to the CRE, not to the nonfermenter.

[†] Defined as not lowered if the MIC of imipenem or meropenem exceeded 2 μ g/dL.

[‡] Isolation of any of the following in the preceding 3 months: MRSA, vancomycin-intermediate *S aureus*, VRE, ESBL-producing organism, AB (from 7 days to 3 months earlier), or PA (from 7 days to 3 months earlier).

Table 2

Exposures pertaining to health care settings and foreign devices in patients co-colonized with a CRE and AB or PA and patients with CRE not co-colonized, DMC, September 2008 to September 2009

Parameter	Co-colonized (n = 34)	Nonco-colonized (n = 52)	OR	95% CI	P
Hospitalization in past 3 months, n (%)	29 (85)	36 (69)	2.58	0.84~7.88	.12
ICU stay in the past 3 months, n (%)	24 (77)	22 (54)	2.96	1.04~8.39	.05
Invasive procedure in past 6 months, n (%) [*]	33 (100)	41 (82)	15.31	0.86~273.22	.01
Surgery in past 6 months, n (%)	32 (97)	36 (72)	12.44	1.55~100	.003
Permanent foreign devices, n (%) [†]	33 (100)	38 (78)	20.01	1.14~352.63	.002

^{*} Any type of invasive procedure, including endoscopy, permanent central line insertion, gastrostomy tube insertion, tracheotomy, biopsy, and transcutaneous procedures conducted by invasive radiologists.

[†] Devices (eg, tracheotomies, central lines, urinary catheters, orthopedic external fixators, pacemakers) had to be in place at least 48 hours before CRE isolation.

Table 3

Antibiotic use during the previous 3 months in patients co-colonized with CRE and AB or PA and patients with CRE not co-colonized, DMC, September 2008 to September 2009

Parameter	Co-colonized (n = 34)	Nonco-colonized (n = 52)	OR	95% CI	P
Use of any antibiotics, n (%)	31 (100)	40 (93)	5.44	0.27~109.31	.26
Days from last antibiotic, median (IQR)	0.92 (0.04-2.9)	1.5 (0.1-19.8)			.40
Penicillins, n (%)	19 (63)	17 (43)	2.34	0.88~6.18	.10
Cephalosporins, n (%)	27 (90)	34 (84)	1.85	0.44~7.85	.50
Carbapenems, n (%)	8 (27)	7 (18)	1.71	0.54~5.41	.39
Fluoroquinolones, n (%)	9 (30)	13 (30)	0.89	0.32~2.48	1.00
Glycopeptides, n (%)	26 (84)	21 (51)	4.95	1.59~15.4	.01
Tetracyclines including tigecycline, n (%)	5 (17)	2 (5)	3.80	0.68~21.1	.13
Polymixins, n (%)	4 (14)	1 (3)	6.24	0.66~59.1	.15
Aminoglycosides, n (%)	7 (24)	4 (10)	2.94	0.77~11.2	.18
Trimethoprim/sulfamethoxazole, n (%)	2 (7)	2 (5)	1.41	0.19~10.6	1.00
Daptomycin, n (%)	3 (10)	0 (0)			.05
Linezolid, n (%)	9 (31)	3 (8)	5.55	1.35~22.8	.02
Macrolides, n (%)	3 (10)	3 (8)	1.42	0.27~7.61	.69
Clindamycin, n (%)	6 (21)	7 (17)	1.27	0.38~4.26	.76
Metronidazole, n (%)	8 (28)	6 (15)	2.22	0.68~7.30	.23
Rifampin, n (%)	2 (7)	0 (0)			.17

IQR, interquartile range.

Table 4

Indices of acute illness, time to effective therapy, and outcomes in patients co-colonized with a CRE and AB or PA and patients with CRE not co-colonized, DMC, September 2008 to September 2009

Parameter	Co-colonized (n = 34)	Noneco-colonized (n = 52)	OR	CI-95%	P
Indices of acute illness					
McCabe score, mean $\pm$ SD ¹⁴	1.9 $\pm$ 0.6	2.1 $\pm$ 0.7			.19
Reduced consciousness at initial CRE culture date, n (%)	19 (56)	17 (33)	2.61	1.07-6.36	.04
Severe sepsis level, n (%) [*]	7 (24)	4 (12)	2.33	0.60-9.09	.32
Necessitates transfer to an ICU, n (%)	6 (25)	3 (7)	4.56	1.02-20.27	.06
Clinical syndrome, n (%)					
Colonization only	9 (31)	12 (28)	1.2	0.44-3.26	.80
Central line-associated bloodstream infection	3 (10)	5 (12)	0.91	0.20-4.08	1.00
Pneumonia	8 (28)	6 (14)	2.36	0.74-7.55	.23
Urinary tract infection	2 (7)	12 (28)	0.21	0.04-1.00	.04
Effective therapy parameters [†]					
Hours to effective therapy, median (IQR)	101.5 (50-128)	100.5 (77-120)			.78
Effective therapy given at all during the course of infection, n (%)	12 (67)	17 (71)	0.82	0.22-3.07	1.00
Effective therapy options available, n (%)	30 (94)	50 (100)			.15
Outcomes					
90-day mortality, n (%)	17 (53)	11 (24)	3.50	1.33-9.26	.02
Functional status deterioration at discharge date, n (%) [‡]	11 (63)	20 (57)	2.06	0.55-7.77	.35
Discharge to LTCF, n (%) [§]	9 (82)	18 (58)	3.25	0.60-17.62	.27
Discharge to LTAC, n (%) ^{**}	3 (25)	13 (39)	0.51	0.12-2.27	.49
Invasive procedure [¶] or surgery in the 6 months after CRE culture, n (%)	14 (48)	26 (57)	0.72	0.28-1.82	.64
Bacteriologic failure, n (%) ^{//}	19 (56)	23 (44)	1.60	0.67-3.81	.38
LOS from infection to discharge after excluding the dead, days, median (IQR)	8 (4.25-16.75)	13 (5-25.2)			.36

IQR, interquartile range; LOS, length of stay.

^{*} From severe sepsis to multiorgan failure in accordance with established definitions.¹²

[†] Defined as administration of a drug to which both CRE and a nonfermenter (if present) were susceptible according to in vitro results.

[‡] Deterioration compared to initiation of acute illness in one or more activities of daily living.¹⁵

[§] After being admitted from home.

[¶] Any type of invasive procedure, including endoscopies, permanent central line insertion, gastrostomy tube insertion, tracheotomy, biopsies, and transcatheter procedures conducted by invasive radiologists.

^{//} Additional isolations of the same CRE-producing organism in the subsequent 3 months.

^{**} After being admitted from a non-LTAC residence.