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Concise Communication

The burden of colonization and infection by carbapenemase-producing *Enterobacteriaceae* in the neuro-rehabilitation setting: a prospective six-year experience

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Abstract

We describe the high burden of carbapenemase-producing *Enterobacteriaceae* (CPE) colonization and infection in a neuro-rehabilitation hospital in Italy over a 6-year period. Overall, 9.3% of patients were found to be CPE carriers on admission; the rates of CPE in-hospital acquisition and CPE-BSI were 9.2 and 2.9 cases per 10,000 patient days, respectively.

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Long-term acute-care hospitals (LTACHs) and other post-acute care facilities have been shown to be a major contributor to the dissemination of carbapenemase-producing *Enterobacteriaceae* (CPE).[1] In this context, patients with spinal cord injuries (SCIs) and acquired brain injuries (ABIs) in neuro-rehabilitation units are at increased risk because they usually have experienced a prolonged stay in an acute-care hospital, they have been exposed to antimicrobials, and they have had invasive medical devices placed. Preventing CPE cross transmission may be extremely difficult in this population because caregivers and several healthcare workers with different cultural backgrounds are involved in the patient care, and the usual interventions (eg, strict infection control measures and isolation) could reduce patients' access to rehabilitation activities, hampering rehabilitation programs and adversely affecting outcomes.[2]

To date, epidemiology of CPE in the neuro-rehabilitation setting is largely unknown. The aim of this study was to assess the burden of CPE colonization and infection in a neuro-rehabilitation hospital in Italy and to describe a tailored infection control program.

Materials and methods

Study design and setting

We performed a prospective, observational study from January 2012 to December 2017 on all patients admitted to Montecatone Rehabilitation Institute (MRI). MRI is a 150-bed rehabilitation hospital in Northern Italy with ~700 admissions per year; it is dedicated to the intensive rehabilitation of patients with SCI and ABI. The hospital has an 8-bed intensive care unit, an 11-bed respiratory intensive care unit, a 23-bed ward dedicated to patients with ABI, a 108-bed spinal unit, a rehabilitation day hospital, and an outpatient clinic.

Since 2012, the management of the infectious risk has been committed to an infectious disease consultant, who is on site 3 times per week, performs bedside patient evaluations, and coordinates a persuasive antimicrobial stewardship program and the infection control activities, as described elsewhere.[3]

Infection control measures to contain the spread of CPE

The implementation of a tailored infection control program started in 2012. Considering that patients admitted to MRI come from other hospitals and/or have had frequent readmissions, surveillance culture (SC) for ruling out CPE colonization are performed on admission in all patients. Contact precaution are maintained until SC result; if the SC is negative, contact precautions are removed and the test is repeated every 2 weeks. Surveillance culture consists of only rectal swab; however, patients with CPE positive cultures from clinical specimens are considered carriers also if the rectal swab is negative.

For those patients who are found to be CPE carriers, contact isolation and geographic separation in a ward cohort are applied; environmental cleaning is performed thrice daily, including bathroom and areas close to the patient (eg, bed rails and bedside table) using chlorhexidine solution. Also, when CPE carriers attend rehabilitation activities into the gyms in dedicated areas and after the other patients, all the surfaces are cleaned with chlorhexidine

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Table 1. Number of Admissions and Demographic Characteristics of the Study Population

Variable	Total	2012	2013	2014	2015	2016	2017
Patients, no.	4,180	655	721	740	725	687	652
Male, no. (%)	3,114 (74.5)	502 (77)	540 (75)	559 (75.5)	540 (74.5)	480 (70)	493 (75.5)
SCI, no. (%)	3176 (76)	499 (76)	558 (77.5)	544 (73.5)	561 (77.5)	531 (77)	483 (74)
Age, no. (%)	710 (17)	115 (17.5)	120 (17)	118 (16)	121 (17)	136 (20)	100 (15)
<30 y	1,358 (32.5)	249 (38)	227 (31.5)	248 (33.5)	210 (29)	200 (29)	224 (34)
30–49 y	1170 (28)	168 (26)	200 (28)	210 (28.5)	194 (27)	204 (30)	194 (30)
50–64 y	940 (22.5)	121 (18.5)	172 (24)	161 (22)	198 (27)	145 (21)	143 (22)
≥65 y							

Note. SCI, spinal cord injury.

Table 2. Colonization and Infection by Carbapenemase-Producing *Enterobacteriaceae*

Variable	Total	2012	2013	2014	2015	2016	2017
Patients admitted, no.	4,180	655	721	740	725	687	652
CPE carriers, no. (%)							
On admission	391 (9.3)	66 (10)	68 (9.4)	56 (7.5)	68 (9.3)	69 (10)	64 (9.8)
During hospitalization	308 (8.1)	58 (9.8)	51 (7.8)	44 (6.4)	53 (8)	60 (9.7)	42 (7.1)
Incidence of CPE colonization during hospitalization/10,000 patient days	9.2	10.4	9.2	7.9	9.5	10.7	7.5
Incidence of CPE-BSI/10,000 patient days	2.9	4.1	2.9	1.4	3.2	2.9	2.7

solution afterward. CPE carriers can participate in the activities that take place in common spaces (eg, occupational and recreational therapy, meals) if they are able to comply with hand hygiene and are able to contain their stool and secretions.

In ICU and RICU, where geographic separation of CPE-carriers is not possible and patient's clinical conditions usually do not allow participation in social activities, functional contact isolation is applied for all patients.

Healthcare personnel receive periodic education (every 6 months) regarding hand hygiene practices and proper use of contact precaution. Adherence monitoring by direct observation is performed weekly by the infection control nurse. Patients and/or their caregivers are involved in the infection control practices: they receive information about CPE-carriage, hand hygiene practices and proper use of contact precautions during dedicated educational meetings conducted by a charge nurse and ward physicians every 2 weeks.

Microbiology

Rectal swabs were collected using ESwab (Copan, Brescia, Italy). The swabs were plated into chromogenic plates, BBL CHROMagar CPE (Becton Dickinson, Erembodegem-Aalst, Belgium) or CHROMagar KPC (MEUS S.r.l. Kima, Padua, Italy), which were incubated aerobically at 37°C for 18–24 hours. Detection of CPE in blood cultures was performed using the BACTEC instrument (Becton Dickinson). Bottles were incubated for 6 days or until the instrument signaled a positive result.

Identification and susceptibility testing of the presumptive CPE colonies identified on the chromogenic plates and the positive blood cultures were performed using the Vitek-2 automated system (BioMérieux, Marcy l'Etoile, Craponne, France). Results were interpreted in accordance with the European Committee on Antimicrobial Susceptibility Testing (EUCAST) clinical break points. From January 2012 to June 2016 mechanism of resistance to carbapenems was confirmed with phenotypic test using combined-disk commercially available kits (Biorad, Milan, Italy) and, as confirmatory method, the modified Hodges test, as described previously.[4]

From July 2016 to the end of the study period, presumptive CPE colonies were tested with a first-level colorimetric test, Neo-Rapid CARB Screen Kit (Biolife Italiana, Milan, Italy). Carbapenem-resistant strains that yielded negative results to this first-level colorimetric test were also tested using a disk-diffusion method, KPC+MBL detection kit (Biolife Italiana, Milan, Italy) to confirm the mechanism by which the organism gained resistance to carbapenems. In case of inconclusive results or suspected production of OXA-48, colonies were submitted to a molecular test, Xpert CarbaR (Cepheid, Milan, Italy).

Statistical analysis

Our endpoints were (1) prevalence of CPE rectal colonization on admission, (2) incidence of in-hospital acquisition of CPE colonization, and (3) incidence of CPE-BSI. Descriptive statistics were obtained for all variables analyzed. Continuous variables were expressed using mean ± standard deviation (SD) if normally distributed an using median and interquartile range (IQR) if nonnormally distributed. Categorical variables were expressed using absolute numbers and proportions. The $\chi 2$ for trend test was used to compare differences in the rates of CPE colonization and BSI during the study period.

Ethics

The study was conducted according to the principles of the Helsinki Declaration and was approved by the local institutional review board.

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Results

During the study period, we observed 4,180 patients with a mean length of stay of 79 ± 4 days, for overall 333,484 patient days (Table 1). Overall, 9.3% of patients were CPE rectal carriers on admission, and 8.1% acquired colonization during hospitalization. A CPE-BSI was diagnosed in 96 of 699 colonized patients (14%). No CPE-BSI occurred among subjects who were not colonized, and during the study period no other CPE infections were identified.

A slight decrease of CPE prevalence on admission (from 10% to 7.5%; $P = .06$) was observed from 2012 to 2014, but this trend was not confirmed in 2015. Likewise, the incidence of CPE colonization and CPE-BSI decreased significantly from 2012 to 2014: from 10.4 to 7.9 per 10,000 patient days ($P = .03$) and from 4.1 to 1.4 per 10,000 patient days ($P = .02$), respectively. However, these rates increased in 2015, when the burden of CPE carriers was higher.

During 2016, the number of CPE carriers on admission increased together with the rates of CPE colonization during hospitalization, whereas in 2017 the number of CPE carriers on admission remained stable but the incidence of CPE cross transmission decreased. Finally, a statistically nonsignificant reduction of the incidence of CPE-BSI was observed from 2015 to 2017: from 3.2 to 2.6 per 10,000 patient days ($P = .10$) (Table 2). Overall, the differences in the rates of CPE colonization and CPE-BSI observed during the study period were not statistically significant ($P = .36$ and $P = .41$, respectively).

Discussion

In this study, we described the burden of CPE in an Italian neurorehabilitation hospital during a 6-year period. At our knowledge, this is the first longitudinal report on the epidemiology of CPE in this setting. Our findings show a reduction of the CPE burden during the first 3 years of the study period that was not confirmed subsequently, which illuminates the underlying difficulties in maintaining the results over time, especially in the face of the increase of colonized patients entering the hospital.

In 2015, Hayden *et al*[1] described the implementation of a bundled intervention to reduce KPC colonization and infection in LTCAHs that led to a sustained decrease in KPC cross transmission and bloodstream infections. Our results were not as favorable, but the length of study period (6 years vs 12–19 months) and the epidemiological context (prevalence of CPE carriers on admission the baseline incidence of CPE-BSI of 9% vs 20% and 0.4 vs 0.9 per 1,000 patient days, respectively) are different. Moreover, some effective infection control measures could not be applied routinely. Strict patient isolation could not be routinely applied because reintegration in the community is a main goal of rehabilitation programs and because participation in social activities is a cornerstone of the rehabilitation process. In addition, universal chlorhexidine bathing cannot be routinely carried out because open wounds (eg, pressure ulcers and surgical and traumatic wounds) are extremely frequent in our population. Finally, the attendance at educational activities regarding infection control practices was mandatory for healthcare workers but voluntary for patients' relatives and caregivers, who are directly involved in patient care.

In our study, the application of the infection control measures was effective in containing in-hospital CPE colonization, especially when the amount of imported CPE carriers was lower. Their number can be considered related to the effectiveness of the infection control measures applied in the acute-care setting, and the reduction observed in 2014 is probably related to some successful Italian experiences.[5,6] These measures, however, had been implemented only at a hospital or local level, and their effectiveness was not sustained overtime.[7] Colonization pressure is an important risk factor for acquiring colonization,[8] which underscores the need for comprehensive infection control programs implemented on a national level. Such programs are lacking in Italy.

The first limitation of this study is its single-center design. However, MRI is one of the largest rehabilitation hospitals in Italy, and it admits patients coming from acute-care hospitals located all over the country. Thus, our data can be considered representative of the national epidemiology. Second, molecular tests for the detection of resistance genes were not routinely available during the study period. These techniques have been shown to be more sensitive than culture on chromogenic media to identify CPE on surveillance rectal swabs, so we could have underestimated the real burden of CPE colonization.[9]

To conclude, our study has demonstrated a high burden of CPE colonization and infection in the neurorehabilitation setting in Italy, consistent with national epidemiology. The effectiveness of infection control measures was directly affected by the CPE epidemiology outside the facility: the higher the rate of CPE carriers on admission, the higher the rates of new CPE carriers during the hospital stay and of CPE infections. However, during the study period, the rates of CPE-BSI decreased below the initial rate of 4.2 per 10,000 patient days, suggesting that infection control measures may have failed in reducing cross transmission but, together with the reduction of the antibiotic pressure reached with a concomitant antimicrobial stewardship program,[3] they may have contributed to prevent CPE infections among CPE carriers.

Surely, improving the attention to CPE colonization prevention and management in acute-care hospitals, thus reducing the burden of CPE carriers who access the rehabilitation setting, remains of pivotal value.

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