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Implementation of an infection control program with emphasis on cohorting to patients with carbapenemase-producing Enterobacteriaceae. The experience of 2 years in a tertiary teaching hospital in northern Portugal

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Abstract

Background: The emergence of carbapenemase-producing Enterobacterales (CPE) represents a major public health threat. Our purpose was to evaluate a surveillance and cohorting program implemented in patients infected or carriers of CPE.

Methods: A prospective registry of CPE carriers or infected patients was analyzed from October 2015 until December 2017. All inpatients presenting with CPE were included in a hospital cohort with dedicated healthcare staff and contact precaution measures.

Results: A total of 480 patients were identified, of which 15.8% (n = 76) were infected. Men comprised 56.7% of the cohort (n = 272) and 69.2% (n = 332) were elderly. About 46.3% (n = 222) had a previous hospital admission and 81.7% (n = 392) had at least 1 antibiotic course in the previous 90 days. There was a decline in infected patients in 2017. Periodic and admission screenings accounted for 63% and 74% of cases in 2016 and 2017, with increased detection rate comparing with contact/investigation screenings. In 2017, significantly fewer patients were identified outside the admission/point of prevalence screening (P = .009). In 2017 the proportion of invasive carbapenem-resistant *Klebsiella pneumoniae* amongst CPE in our center was below the national average (2016: 13.3% vs 5.2%; 2017: 6.6% vs 8.6%). A reduction of the consumption of carbapenems was also observed in 2017.

Conclusion: The implementation of the program has increased the number of patients identified by the preventive method and stabilized the emergence of new CPE cases. Furthermore, the program cohort compared well with the national picture, with a lower number of infected patients and a lower proportion of carbapenem-resistant *K pneumoniae* in invasive specimens. These indicators reflect the added value of the CPE surveillance and cohorting program.

Keywords: active screening, carbapenemase-producing Enterobacteriaceae, infection control, surveillance and isolation program, antimicrobial stewardship

Introduction

The emergence of carbapenemase-producing Enterobacterales (CPE) represents a major public health threat, because they show large spectrum antimicrobial resistance and have the potential to spread widely.[1] The mechanism of resistance is mostly the production of carbapenemases.[2] These organisms cause infections that are associated with high mortality rates.[3] Decreasing the impact of these organisms requires a coordinated effort involving healthcare facilities and providers, public health, and industry.[4]

For *Klebsiella pneumoniae*, data from the European Antimicrobial Resistance Surveillance Network (EARS-Net) for 2017 show large variability in the national percentages of carbapenem resistance in isolates from invasive infections, ranging from 0% to 64.7%. Increasing national trends in carbapenem resistance in *K pneumoniae* for the period 2014 to 2017 were observed in Slovakia, Poland and Portugal, whereas there was a decreasing trend in Croatia, Slovenia, and Italy.[5] For *Escherichia coli*, EARS-Net data for 2017 show a lower overall EU/EEA population-weighted mean percentage (0.1%) of carbapenem resistance in invasive isolates, with national percentages ranging from 0% to 1.6% (2017). Between 2014 and 2017, a slightly decreasing trend was observed for the EU/EEA population-weighted mean of national percentages.[1] In comparison to a previous assessment in 2015, 11 countries reported a higher epidemiological stage of CPE indicating increasing spread between 2015 and 2018.[6] Despite the low percentages in many

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European countries of carbapenem resistance in *K pneumoniae* and *E coli* in invasive isolates from blood and cerebrospinal fluid, a national self-assessment of epidemiologic stages conducted in 2018 that considered all types of infection as well as carriage documented an evolving pattern of spread of carbapenem-resistant Enterobacteriaceae (CRE) in Europe.[6] Sixteen (43%) of 37 participating countries reported regional or interregional spread of CPE, in which Portugal was included, and 4 countries reported an endemic situation. On the percentage of invasive *K pneumoniae* isolates with resistance to carbapenems, EU/EEA, 2017 (EARS Net), Portugal had 8.6% of invasive infections, above the EU.[5]

Institutional prevention programs were developed based on the early identification of CPE carriers through rectal swab cultures, for strict contact precautions to minimize CRE transmission in the hospital. This approach has shown to reduce the frequency of CRE infections in acute-care and long-term-care settings.[7–11] Reduction of carbapenem use through an antimicrobial stewardship program has shown to be beneficial for CPE control.[12]

In our hospital, first cases were identified in late 2015. Since then, active surveillance of CPE has been a priority. Coordinated by the infection control committee, a comprehensive program that included inpatient risk evaluation, contact precautions, screening, training of patients, and healthcare workers and antibiotic stewardship was delineated to identify and cohort these patients in the cohort, which are believed to be fundamental tools for the contention of infection and carrier state.

Our purpose was to evaluate the impact of a surveillance and cohorting program of patients infected or with carrier state of CPE.

Methods

Our institutional clinical committee approved this study and the informed consent was waived. The study follows the "Strengthening the Reporting of Observational Studies in Epidemiology (STROBE)" checklist for observational studies and reports the required information accordingly (see checklist, http://strobe-statement.org/).

Setting

Centro Hospitalar e Universitário do Porto is a 781-bed tertiary-care university hospital in Oporto (northern Portugal). The hospital comprises 5 (10–12-bed) intensive care units (ICUs), 12 surgical units, 2 transplant units, a dialysis center, medicine wards (including pediatrics), day-hospital services, and rehabilitation units. In 2017 the hospital had about 34,599 admissions per year. Patients are admitted in 2- to 8-beds general wards, whereas ICUs are organized in open space with 1 to 4 isolation rooms. The infection control and antibiotic stewardship team comprised 2 dedicated internists, an infectiologist, 3 fully dedicated nurses, and consultants from different clinical areas, that is, Pediatrics and Neonatology, Intensive care, Microbiology, Surgery, and Pharmacy Department.

Study design

A prospective registry of carriers or infected CPE patients was analyzed from October 2015 until December 2017. Clinical records were reviewed by authors and the information was stored in a confidential database.

The surveillance program

Admission screening. A rectal swab was obtained and analyzed by molecular biology method from all patients admitted to the ICU and hepatic transplant unit. Differently, patients admitted to general wards were selected to molecular biology method if they presented the following risks: (a) transfer from another hospital (≥72 h); (b) transfer from postacute care and long-term facilities or elderly home care (≥72 h); (c) hospital stay in the previous 6 months.

Contact screening. If a new patient was identified as carrier or infected by CPE, contact precaution measures were applied to the ones in the same nursery, and rectal swab cultures were obtained and analyzed by culture examination in chromogenic agar (see the section Microbiology).

Point prevalence screening ICU and hepatic transplant patients were tested every 7 days, with a culture examination in chromogenic agar.

Cohorting. All the patients identified as carriers or infected by CPE were isolated in a cohort, with dedicated healthcare staff and contact precaution measures. Some of the carriers were identified in other institutions. Several cohorts were created: a cohort for medical patients with a variable capacity between 4 and 25 beds, a polyvalent cohort with 7 to 14 beds, and an ICU cohort with a capacity of up to 7 beds.

Outbreak management. The detection of an increased number of new cases in a specific ward, warranted the visit of the Comissão de Controlo de Infeção e Resistência aos Antimicrobianos, for identification and discussion of the problems, and training of the health staff.

Antibiotic stewardship. A program was implemented, including: medical training, tailored to each medical team; and a prescription validation system. Since 2015, all carbapenem prescriptions were analyzed and validated by Comissão de Controlo de Infeção e Resistência aos Antimicrobianos, and annual consumption was calculated by defined daily dose per 1000 bed-days (DDD‰).

Definitions

Carrier patients were defined as patients with CPE-positive active screening from the rectal swab or positive culture test from other biologic product decided for any reason in the absence of infection. The term carrier was applied to patients with or without infection. Infection was considered when gathering suggestive clinical features and identification of a CPE in a biological sample, whenever considered by the patient medical team.

Microbiology

CPE carriers were identified by rectal swabs, which were inoculated with 1 of 2 methods: on a chromogenic agar plate (Oxoid Brilliance CRE, Thermo Scientific) containing a carbapenem antibiotic as the selective agent (culture test); or by molecular biology using GeneXpert Cepheid Xpert CARBA R. Clinical specimens were processed following the European Committee on Antimicrobial Susceptibility Testing guidelines, and isolates were identified with the Vitek 2 semiautomated system (bioMeriéux). Confirmation was made by GeneXpert Cepheid Xpert CARBA R; BlueCarba; diffusion with ε-test

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Table 1

Epidemiologic features and comorbidities

Epidemiologic features	
Sex (male) n	272 (56.7%)
Age (median), yr (IQR)	73 (2–101)
Elderly (≥65 years old) n	332 (69.2%)
Very elderly (≥80 yr old) n	152 (31.7%)

Comorbidities	n
Dialysis	42 (8,8%)
Chronic algaliation	20 (4.2%)
Heart failure	192 (40.2%)
COPD	61 (12.7%)
Dementia	86 (17.9%)
Diabetes mellitus	180 (37.5%)
Active cancer	80 (16.7%)
Chronic ulcers	58 (12.1%)
Charlson Comorbidity Index (mean)	3.4

COPD = Chronic obstructive pulmonary disease.

(minimum inhibitory concentration). Enterobacterales producing carbapenemases were defined as CPE. All minimum inhibitory concentrations were interpreted according to European Committee on Antimicrobial Susceptibility Testing guidelines.

Statistical analysis

Kolmogorov-Smirnov test was used to test the distribution of continuous variables. Normally distributed continuous variables are presented with means and standard deviation and were compared with a *t* test. Non-normal distributed variables are represented with medians and interquartile range and compared with Mann-Whitney *U* test. Nominal variables were compared with the chi-square test when the expected count in each cell of the 2×2 contingency table was ≥5. For variables with expected counts <5, Fisher exact test was performed. For all calculations, a 2-sided *P* value of <0.05 was considered to be significant. All statistical analyses were performed with IBM SPSS Statistics version 23.0 (IBM Corp, Armonk, NY).

Results

A total of 13,874 screening tests were made (a mean of 19 tests per day). Four hundred eighty carrier patients were identified: 356 by active screening; 93 by clinical tests asked for any reason; 31 were identified in other settings.

The demographic data are presented in Table 1. About 46.3% (n=222) had a previous hospital admission in the previous 90 days and 81.7% (n=392) had at least 1 antibiotic course in the previous 90 days.

Table 2

Cohort description

Cohort description	2016 (n, %)	2017 (n, %)
Total of patients	239; 49.8	241; 50.2
Surveillance method		
Admission and periodic screenings	151; 63.2	178; 73.9
Contact and investigation screenings	88; 36.8	63; 26.1
Identification in other hospital	7; 2.9	23; 9.5
Patients identified		
Infected	58; 24.3	48; 19.9
Carrier only	181; 75,7	193; 80.1

Table 3

Carbapenem consumption presented by daily dose per 1000 bed-days

Carbapenem consumption presented by DDD‰				
Year	All carbapenems	Imipenem	Meropenem	Ertapenem
2015	68.8	52.6	7.3	8.9
2016	52.0	33.2	8.3	10.5
2017	43.4	25.3	9.9	8.1

DDD‰ = daily dose per 1000 bed-days.

Table 1 summarizes the epidemiologic data and the principal comorbidities of the patients included.

Comparing the first and second year of the surveillance and isolation program (2016 and 2017, respectively), the number of patients identified was similar (50.2%, n=241 in 2017). In this period, the percentage of patients identified as CRE carriers in another hospital increased from 2.9% (n=7) to 9.5% (n=23) (*P* < .007). Periodic and admission screenings accounted for 63.2% and 73.9% of cases in 2016 and 2017, which represents an increase of identification by these methods. Contact or investigation screenings accounted for 36.8% and 26.1% in 2016 and 2017, respectively. Thus, in 2017, significantly fewer patients were identified outside the admission/point of prevalence screening (*P* = .009). There was a nonsignificant tendency for a lower proportion of identification in microbial investigations. Concerning carbapenem consumption in DDD‰ days of hospital stay, it was 52.0 in 2016 and 43.4 in 2017 (Table 2). The carbapenem consumption reduction is presented by DDD‰, in Table 3.

Since May of 2016 the emergence of new cases per month has become fluctuant between a minimum of 8 cases and a maximum of 34. From January to April of 2016, the average of new cases was 9.5 (8–12); between May and December of 2016 the average was 23.1 (14–34); in 2017 the average was 19.8 (8–32). The monthly average variations were attributed to outbreaks occurring in several wards.

Figure 1 represents the evolution of new appearances throughout both years of surveillance and isolation program.

The average of CPE inpatients in 2017 was 18 per day (3–24), with an average of 13 per day in January and 16 per day in December, reflecting a relatively stable evolution. Figure 2 illustrates these facts. Data from January to May of 2016 was not included due to inaccurate records.

In 2016, the rate of invasive carbapenem-resistant *K pneumoniae* was 5.2% in Portugal and 13.3% in our center, and an inversion was observed in 2017 with 8.6% and 6.6%, respectively.[13,14]

There were no differences between 2016 and 2017 regarding the number of readmissions at 30 days (15.3% vs 11.9%, *P* = .385) and mortality during hospital stay (21.6% vs 24.8%, *P* = .430).

Discussion

The widespread and indiscriminate use of broad-spectrum antibiotic therapy has favored the emergence and spread of CRE, a growing source of infections, and a serious threat to public health. A significant association was seen between carbapenem consumption (ESAC-Net) and the percentage of invasive carbapenem-resistant *K pneumoniae* (EARS-Net) in EU countries participating in these 2 epidemiological surveillance
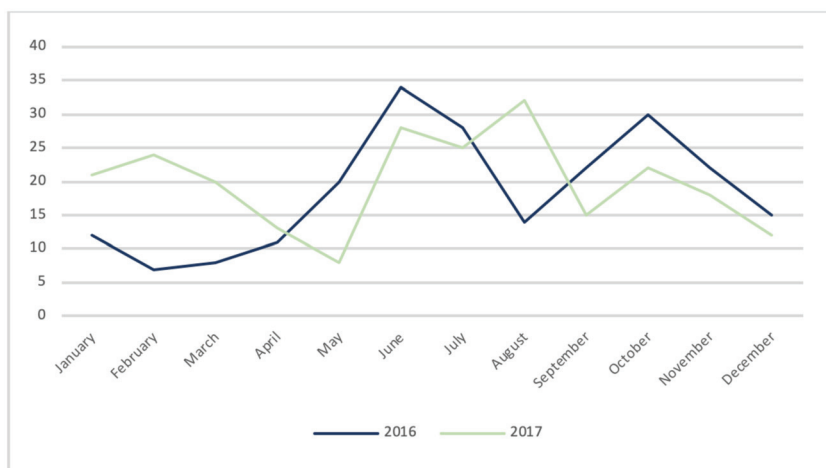
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Figure 1. Appearance of new cases of CPE carriers by month, in 2016 and 2017.

programs.[1] The consumption of carbapenems is rising in the EU as a whole but was declining in Portugal for the first time in 2014 (5%). Even though, in Portugal it was still 2.3 times higher than the EU average, according to European Centre for Disease Prevention and Control data.[15]

The observed population was homogeneous in sex, with a slight men preponderance. Patients were predominantly elderly (Table 1), with one third of the population being very elderly and therefore corresponding to more comorbid and fragile patients. Regarding comorbidities, approximately 40% of patients had heart failure and diabetes (40.2%; 37.5%), and almost one fifth had the diagnostic of dementia (17.9%), and active cancer (16.7%) which reflects the frailty of these patients. In addition, 42 (8.8%) patients were on dialysis, 58 (12.1%) were treating chronic ulcers, and 20 (4.2%) reported a long-term indwelling urinary catheter, reminding that the chronic invasive devices and procedures may have a role in the predisposition for CPE infection or carrier state.

The percentage of patients identified in another hospital increased from 2.9% to 9.5%, and it can be stated that in 2017 a significantly larger number of patients were identified outside our center ($P = .007$). In 2017, significantly fewer patients were

identified outside the admission and periodic screening ($P = .009$), meaning that the program is identifying patients at earlier stages and therefore playing a preventive role. There is, however, still a large proportion of patients identified by contact screening, which also reveals the concern of the infection control committee in actively identifying these cases.

The higher number of cases observed between July and September 2017 was due to an outbreak in the medical wards. Excluding the outbreak period in 2017 and, the lower identification in the first months of 2016 (attributable to lower team sensitivity to the screening program), we observed tendentially fewer new cases in 2017 when compared to the last months of 2016 (19.8 vs 23.1). These results may have been influenced by numerous uncontrolled internal or external factors related to hospital activity open to the community and other hospitals. The carbapenem-resistant Enterobacterales ratio in invasive infections evolved favorably in our center, in contrary to that observed in Portugal. In 2016, the rate of invasive carbapenem-resistant *K pneumoniae* was 5.2% in Portugal and 13.3% in our center. In 2017, the local rate was lower than the national rate (6.6% and 8.6%, respectively), suggesting that
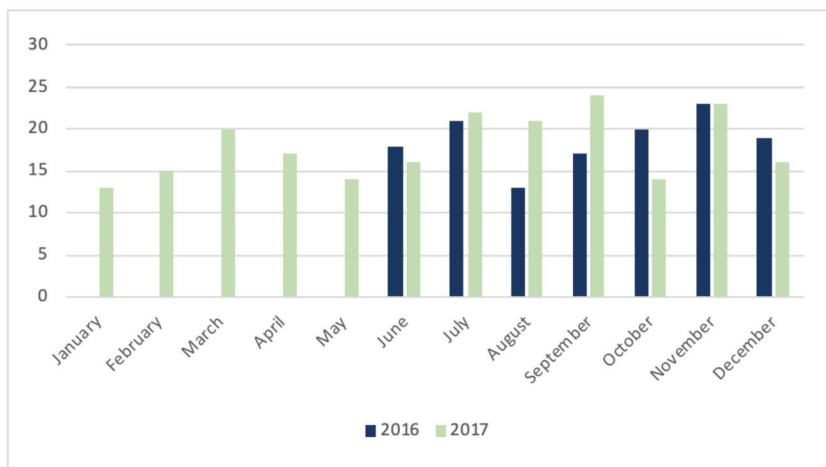

Figure 2. Mean of carriers/infected CPE patients, per month in 2016 and 2017.

our center performed better containment of the spread of these multiresistant microorganisms. The rate of carbapenem-resistant *K pneumoniae* in invasive specimens reflects the proportion of strains resistant to at least 1 carbapenem among all species colonies identified in blood and cerebrospinal fluid samples. It is the most reliable index, allowing monitoring and benchmarking, valuing the impact of the most serious infections and devaluing local factors such as carrier state, contamination, and rate of microbiological examinations performed in each institution.

As the main limitations of our program, we identify the resistance of medical teams to accomplish the screening program and the high carbapenem prescription rate. However, a declining tendency of carbapenem consumption was observed, which may have been a contributor factor to the favorable evolution of invasive carbapenem-resistant *K pneumoniae* rate. On the contrary, the accountability of the teams in identifying these patients made them aware of this problem. Being an observational and nonblind study, this work did not surpass the heterogeneity of the therapeutic attitudes of medical teams and the change of strategy whenever patients were mobilized to cohorts.

These data highlight the importance of the implementation of surveillance programs and isolation of identified patients. A long path is still ahead, and efforts in reducing carbapenem use must be a priority.

Acknowledgments

Conflicts of interest

The authors declare no conflicts of interest.

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