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Epidemiology of carbapenemase-producing *Enterobacteriaceae* in a pediatric hospital in a country with high endemicity

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ABSTRACT

Background: Little is known about epidemiology of carbapenemase-producing *Enterobacteriaceae* (CPE) in children. Aim of this study was to describe CPE epidemiology in a tertiary care pediatric hospital in Italy that admits patients coming from geographic areas with high diffusion of CPE.
Methods: Prospective evaluation of the proportion and rates per 100,000 hospital discharges (D) or hospitalization-days (HD) of invasive infections due to CPE from 2013 to 2017 and of CPE infections and colonizations from 2014 to 2017. Disease-preventing strategies comprised patients' screening at admission, pre-emptive contact isolation precautions pending cultures results, and bundles for prevention of healthcare associated infections.
Results: From 2013 to 2017 CPE represented 3.5% of all invasive infections due to *Enterobacteriaceae*, with rates ranging 7.30–14.33 for D and 1.03–2.06 for HD, without major changes over time. On the contrary, overall rates of isolates increased from 83.03 to 191.34 for D and from 12.21 to 28.35 for HD. The intra-hospital diffusion consisted of 2 small outbreaks without invasive diseases in 2014–2015, and sporadic, not epidemiologically-related cases in 2016–2017. Globally, *Escherichia coli* and *Klebsiella pneumoniae* represented 64% of identified CPE, while 70% of carbapenemases identified were metallo-beta-lactamases (VIM or NDM), with changes over time.
Conclusions: In our center metallo-beta lactamases were the most frequently identified carbapenemases in *Enterobacteriaceae* and *E. coli* and *K. pneumoniae* the most frequently isolated pathogens carrying these enzymes. A proactive management strategy was effective in containing in-hospital spreading.

Background

The spreading of antibiotic resistance, especially among Gram-negatives, is an increasing problem in modern medicine all over the world, even if identified pathogens and mechanisms of resistance show geographical variations [1]. The spread of carbapenemase-producing *Enterobacteriaceae* (CPE) is particularly worrisome in Italy: one third of *Klebsiella pneumoniae* strains isolated from blood or cerebrospinal fluid (CSF) are carbapenem-resistant and this diffusion has been described as an endemic situation for *K. pneumoniae* producing *K. pneumoniae* carbapenemase (KPC), or inter-regional spread for strains producing Verona integron-encoded metallo-beta-lactamase (VIM) [2–5]. However, these data mainly derive from studies on adults. Italian pediatric data on epidemiology of CPE colonizations or infections originate mainly from single- or multi-center surveys on invasive infections, mostly in specific populations, but little is known about incidence of colonizations and possible epidemiological variations [6–11]. Moreover, there is little information on the types of carbapenemase identified in children.

The aim of this study was to describe epidemiology of CPE isolates during a 5-year period in a tertiary care pediatric Italian hospital, where patients coming from geographic areas with high diffusion of CPE are admitted.

Materials and methods

The Istituto Giannina Gaslini (IGG), Genoa – Italy is a pediatric tertiary care hospital in northern Italy serving as local pediatric hospital for the Genoa area and as referring hospital for Italy and many foreign countries.

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Table 1
Epidemiological staging system of carbapenem-resistant *Enterobacteriaceae* diffusion.

Stage	Epidemiological scale	Description
0	No case reported	No case reported
1	Sporadic occurrence	Single case, epidemiological unrelated
2a	Single hospital outbreak	Outbreak defined as two or more epidemiologically-associate cases with indistinguishable geno- or phenotype in a single institution
2b	Sporadic hospital outbreak	Unrelated hospital outbreaks with independent, i.e. epidemiologically-unrelated introduction or different strains; no autochthonous inter-institutional transmission reported
3	Regional spread	More than one epidemiologically-related hospital outbreak confined to hospitals that are part of the same region or health district, suggestive of regional autochthonous inter-institutional transmission
4	Inter-regional spread	Multiple epidemiologically-related outbreaks occurring in different health districts, suggesting interregional autochthonous inter-institutional transmission
5	Endemic situation	Most hospitals in a country are repeatedly seeing cases admitted from autochthonous sources

Table 2
Carbapenemase-producing *Enterobacteriaceae*: proportions of resistant strains, rate/100.000 hospital discharges and rate/100.000 hospitalization-days in the 2013–2017 period at Istituto Giannina Gaslini Children's Hospital, Genoa – Italy.

Year	2013	2014	2015	2016	2017
Number of hospital discharges	14750	14452	13704	13954	14633
Number of hospitalization days	99487	98286	97244	97180	98764
	Total isolates after implementation of the screening program				
Overall CPE strains, n	NA	12	15	18	28
CPE/100.000 hospital discharges (95%CI)	NA	83.03 (81.68-84.38)	109.46 (107.64-111.28)	128.99 (126.86-131.12)	191.34 (188.25-194.43)
CPE/100.000 hospitalization days (95%CI)	NA	12.21 (12.14-12.28)	15.42 (15.33-15.51)	18.52 (18.41-18.63)	28.35 (28.18-28.52)
Epidemiological stage	NA	2a	2a	1	1
	Isolates from invasive infections (blood and cerebrospinal fluid)				
Strains of Enterobacteriaceae, n	45	46	54	48	60
Numbers of CPE	2	2	1	2	2
Proportions (%) in invasive diseases	4.4	4.3	1.8	4.2	3.3
Invasive disease/100.000 hospital discharges (95%CI)	13.56 (13.35-13.77)	13.84 (13.62-14.06	7.30 (7.19-7.41)	14.33 (14.10-14.56)	13.67 (13.46-13.88)
Invasive disease/100.000 hospitalization days (95%CI)	2.01 (2.00-2.02)	2.03 (2.02-2.04)	1.03 (1.03-1.03)	2.06 (2.05-2.07)	2.02 (2.01-2.03)

CPE = carbapenemase-producing *Enterobacteriaceae*; NA = not available.

In the 4th quarter of 2013 a specific monitoring and control program of CPE diffusion within IGG was started, according to Italian Ministry of Health recommendations [12]. In particular the program called for a rectal swab for CPE detection (colonization screening) at the admission of patients hospitalized in the previous three months or coming from foreign countries, even if not hospitalized before. Moreover, in patients fulfilling these criteria positive cultures from any site of suspected infection (e.g. blood, CSF, urines, etc.) were also screened for carbapenemase. Pending cultures results these patients were managed with pre-emptive contact isolation precautions until notification of absence of CPE in screening and/or clinically relevant cultures. In the case of CPE identification, contact isolation precautions of the index case were maintained and all patients admitted in the same ward underwent weekly screening rectal swab until one week after discharge of the index patient. Presence of CPE was notified to the clinical team in charge of the patient, as well as to the infectious diseases consultant and to the hospital-infection control team, that promptly started an epidemiological workup in order to find possible in-hospital sources and secondary cases. Meanwhile routine bundles for healthcare-associated infections prevention and patients' isolation procedures were actively stressed [13–15].

Study design and definitions

Data on CPE isolates from blood or CSF (from here on indicated as invasive infections) were prospectively collected since 2013, while data on isolates detected after implementation of the screening program were collected from January 2014. For the present analysis data collection was censored at December 2017. Isolations of CPE were divided in invasive infections or cultures from other sites, including screening rectal swab [3]. To describe the CPE spread within the hospital we adopted the epidemiological staging system implemented by the EuSCAPE working group (Table 1) [5]. Multiple isolations of the same pathogen in the same patient were considered as different episodes in the presence of at least one month of negative weekly cultures in a persistently observed patient (in-hospital or out-patient clinic), or after at least 4 months of stay at home without further hospital admissions (time reported in literature for intestinal decolonization in the majority of patients) [16]. In the case of concomitant isolation of the same pathogen from multiple sites during the same period of hospitalization only one positive culture was recorded for the present study, preferably that from invasive infections.

Data were reported as proportions of CPE over the total number of *Enterobacteriaceae* isolated in invasive infections and as rates of CPE/100,000 hospital discharges per year and 100,000 hospitalization-days per year, with 95% Confidence Interval (95%CI) for both invasive infections and overall isolations. Calculations were performed with SPSS version 22 (IBM-SPSS statistics).

Microbiological methods

As for the colonization screening, each rectal swab (Eswab, Copan, Brescia, Italia) was cultured onto MacConkey agar plates and carbapenemase detection screening was performed according with European Committee on Antimicrobial Susceptibility Testing (EUCAST) published in 2013 [17]. In particular, a 10 mg meropenem

disk (Beckton Dickinson, USA) was placed on the agar. Bacterial colonies grown within a 25 mm zone of inhibition around the disk were further investigated for both identification (Phoenix, BD, USA) and detection of carbapenemase genes, using a real-time PCR (XpertCarba-R, Cepheid USA) which is also able to differentiate between the different blaKPC, blaNDM, blaVIM, blaOXA-48 and blaIMP genes sequences [18]. For CPE isolated from blood, CSF or other usually sterile sites or urine, minimum inhibitory concentration (MIC) values of ertapenem and meropenem were evaluated and results interpreted according to the EUCAST standard published each year [18].

Results

A total of 9 invasive infections (all bacteremias) due to CPE were diagnosed from 2013 to 2017 (2 per year, except 1 in 2015), representing 3.5% (9/253) of all invasive infections due to *Enterobacteriaceae* observed in this period (7/208, 3.4% from January 2014, after implementation of screening program) (Table 2). Overall, mortality was 44% (4/9), and 43% (3/7) from 2014. All patients who died were immunocompromised.

After implementation of the screening program, 73 strains of CPE bringing 77 carbapenemases were detected in 53 patients, with some strain carrying multiple enzymes and some patient multiple CPE. Fig. 1 shows the proportion of CPE and carbapenemases observed from 2014 to 2017. *K. pneumoniae* and *Escherichia coli* (32% each) were the most frequently isolated pathogens, and VIM (51%) was the most common carbapenemase. Noteworthy KPC represented only 12% of all the detected enzymes. Table 2 describes changes in proportions and rates of total CPE isolates (2014–2017) and invasive diseases (2013–2017). The absolute numbers and rates of CPE detection increased during the study period, while the absolute number of invasive infections remained substantially constant as well as their proportions and rates. We observed 2 clusters, each involving 1 index and 2 secondary cases of *Enterobacter cloacae*-VIM colonization, one in 2014 and one in 2015 (epidemiological stages 2a). In 2016 and 2017 there was sporadic CPE occurrence (epidemiological stage 1) with no cluster. As for identified *Enterobacteriaceae* and carbapenemases there were a progressive increase of *K. pneumoniae* and *E. coli* isolation and a rise in New Dely Metallo-beta-lactamase (NDM), Oxacillinase-48 (OXA-48) and KPC (Fig. 2) detection. Altogether, VIM and NDM represented 70% of all carbapenemase identified during the study period, and 59% of those detected in 2017, last year of the survey.

Finally, we also analyzed the geographical distribution of CPE detected during the screening program. Considering the 53 patients with isolation of CPE and excluding the 4 secondary cases originated by intra-hospital transmission, 11 (22%) of the remaining 49 came from outside of Italy (2 from European countries, 7 from Mediterranean countries and 2 from Pakistan) and 38 (78%) from different Italian regions.

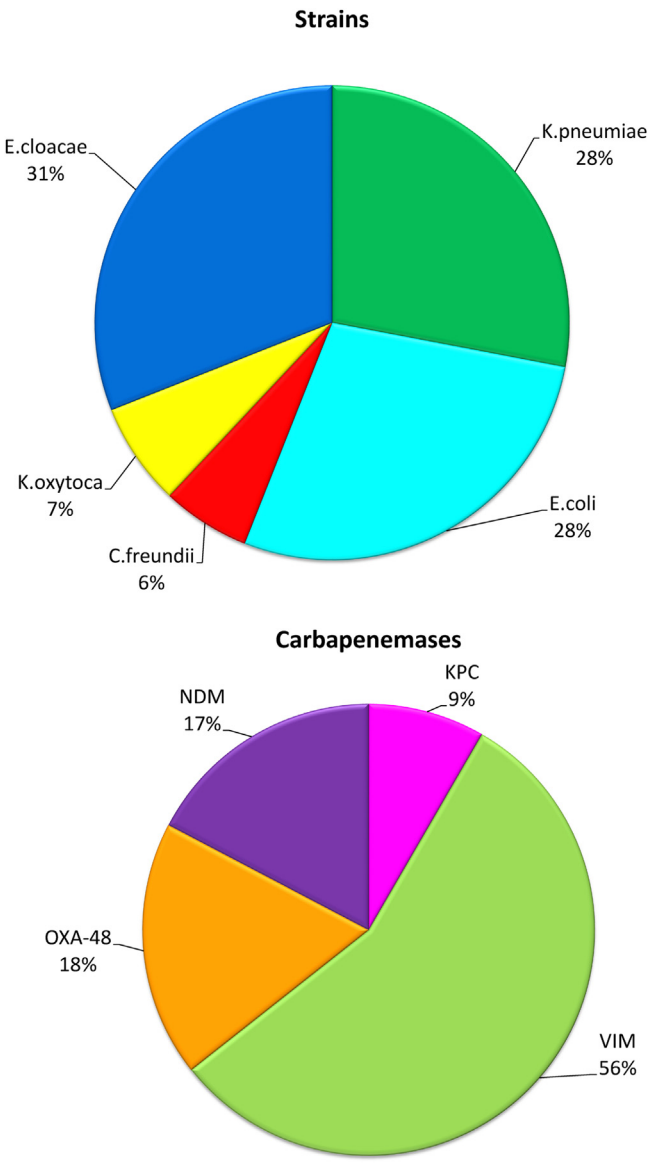

Fig. 1. Proportions of carbapenemase resistant strains and carbapenemases identified during the study period.

Discussion

This study describes CPE epidemiology in a tertiary care pediatric Italian hospital, where patients from areas with high CPE diffusion are commonly admitted.

In our opinion the first interesting point is the peculiar spectrum of *Enterobacteriaceae* detected and their associated enzymes. In our series, *E. coli* and *K. pneumoniae* represented the most frequently isolated CPE and VIM was the most frequently observed carbapenemase. These findings differ from the most recent Italian studies both in children and adults [6–9,11]. It is not clear if these findings are a peculiar characteristics of our center, but it must be noted that VIM has a not negligible diffusion both in Italy [5] and in many of the nations from which the patients admitted to our hospital come [19–22], suggesting only a possible "selection bias" for our observation. VIM has been reported as the most frequently detected carbapenemase in some pediatric American series [23–26] but not in others [23–32], while many other European or American pediatric studies do not clearly specify the type of carbapenemase detected [23–34]. During the study period, we also detected changes in types of isolated pathogens and enzymes, with an increase in *E. coli* and *K. pneumoniae* and a rise of NDM, OXA-48 and KPC. We do not know the reasons for these observations, but this occurrence could be at least partially due to patients coming from geographic areas with poorly known epidemiology of CPE, even if NDM has been reported in North American children without travel history [35]. All these data could therefore suggest also the presence of "pediatric" epidemiological peculiarities, probably with geographical variations. Anyway, these findings are worrisome and worth high attention since the majority of the carbapenemases we identified were metallo-beta-lactamases (VIM and NDM) that are not inhibited by the newest available drugs like avibactam, rele-

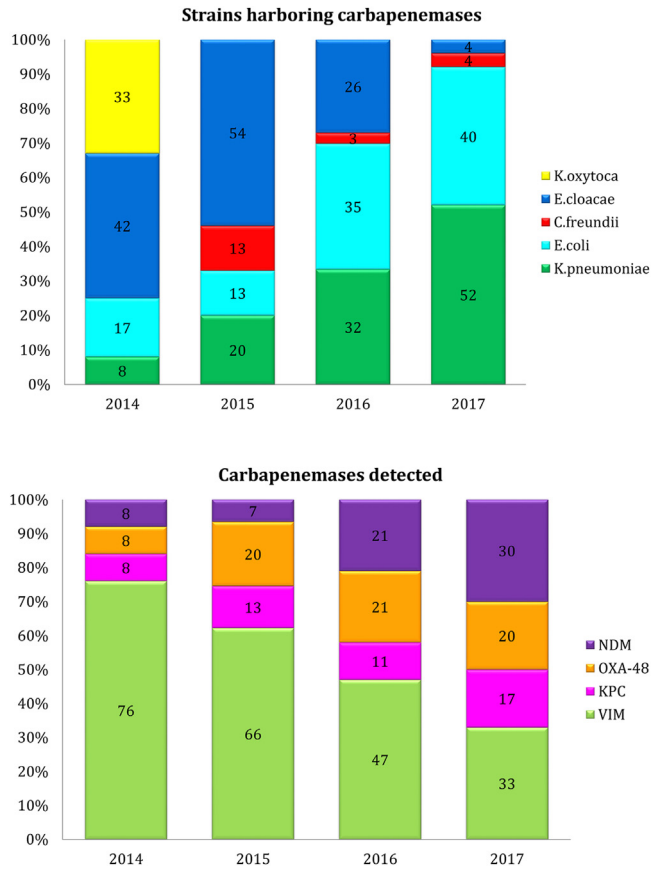

Fig. 2. Changes in proportions of *Enterobacteriaceae* identified as harboring carbapenemase and in type of enzymes identified during the study period.

bactam or vaborbactam, thus making the treatment of possible CPE infections in children very complicated [36,37].

Starting from Autumn 2013 we adopted a proactive strategy with CPE screening and pre-emptive patient's contact isolation pending cultures results, associated with bundles for healthcare associated infections control, to limit CPE intra-hospital diffusion and invasive infections. This approach, which has been recommended in January 2017 to all Italian hospitals by ECDC [38], allowed to maintain intra-hospital spreading of CPE on very low levels [5], in spite of the constant increase of patients carrying CPE admitted in our Center. By the way, we can also speculate that the high proportion of carbapenemase-producing *E. coli* observed in our series might be another factor implicated in the low rate of outbreaks. Indeed, it has been demonstrated that extended-spectrum beta lactamase (ESBL)-producing *E. coli* have a much lower rate of cross-infection than other ESBL-producing Gram negatives, and it could be possible that the same phenomenon applies to carbapenemase-producing *E. coli* [39]. CPE colonization is a known risk factor for subsequent invasive disease and a rise in invasive diseases could be expected in our cohort [40,41], as observed in a multicenter Italian survey on CPE in children with cancer [10], because of the increase in the number of colonized patients admitted. With our proactive approach this risk was very limited. Our results demonstrate that also in pediatrics a CPE screening program associated with proactive measures to control cross transmission and bundles for healthcare-associated infections control are effective in reducing CPE spreading, especially in a non-endemic situation like that present in our hospital [42–44].

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Competing interests

None declared.

Ethical approval

Not required.

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