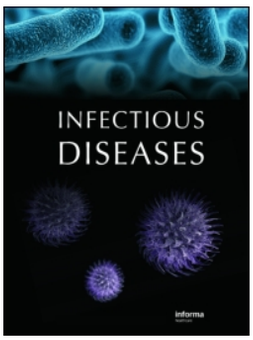

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BRIEF REPORT

Incidence of colonization and bloodstream infection with carbapenem-resistant *Enterobacteriaceae* in children receiving antineoplastic chemotherapy in Italy

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ABSTRACT

Few data are available on the incidence of carbapenemase-producing *Enterobacteriaceae* (CPE) infection or colonization in children receiving anticancer chemotherapy. We performed a nationwide survey among centers participating in the pediatric hematology-oncology cooperative study group (Associazione Italiana Ematologia Oncologia Pediatrica, AIEOP). During a 2-year observation period, we observed a threefold increase in the colonization rate, and a fourfold increase of bloodstream infection episodes, caused by CPE, with a 90-day mortality of 14%. This first nationwide Italian pediatric survey shows that the circulation of CPE strains in the pediatric hematology-oncology environment is increasing. Given the mortality rate, which is higher than for other bacterial strains, specific monitoring should be applied and the results should have implications for health-care practice in pediatric hematology-oncology.

KEYWORDS

Carbapenemase-producing Enterobacteriaceae, Klebsiella pneumoniae carbapenemase, cancer, immunosuppression, children

HISTORY

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Introduction

Bacteria resistant to most antibiotic classes, including carbapenemase-producing *Enterobacteriaceae* (CPE), are emerging throughout the world [1]. CPE were identified in 1993; thereafter, a large variety of carbapenemases have been identified in *Enterobacteriaceae* belonging to the three Ambler classes (A, B, and D) of β-lactamases [2]. The single most frequent CPE is the *Klebsiella pneumoniae* carbapenemase-producing strain (KPC+). After the initial report in 1996, it rapidly spread in many countries [3] to become a major public health concern [4,5]. In Italy, KPC + was initially isolated in 2008 in Florence [6], then rapidly spread across the country. The proportion of resistant strains increased from 2% in 2009 to 19% in 2012 [7], and they are currently considered endemic [8].

Adult patients with CPE infection are frequently elderly and debilitated by multiple co-morbidities, including diabetes mellitus and immunosuppression, causing repeated hospitalizations and invasive procedures. Patients infected with KPC + are more likely to have undergone organ or stem cell transplantation (SCT) or mechanical ventilation, and to have had a longer hospital stay before infection, than those infected with non-KPC strains [9].

Infections with resistant strains have a high mortality rate, ranging from 30% in patients with non-bloodstream infection (BSI) to 72% in patients with liver transplants or BSI [10–12].

KPC + strain infections in children have been reported in very young and critically ill patients. Mortality in children ranged from 4.6% to 21% in recent reports [13,14]. Specific risk factors are co-morbidities, presence of indwelling devices, history of surgery, and immunosuppressive and antibiotic therapies [15]. In the subset of patients with fever during neutropenia, limited reports are available [16,17], although the proportion of multidrug-resistant bacterial infections in children treated for cancer, or with transplants, accounts for 30–73% [12–19]. In children treated for hematological diseases, resistance rates seem much lower than in adults [16]. A recent Italian survey in pediatric patients undergoing SCT reported an incidence of *K. pneumoniae* of 0.3% during autologous transplant and 1.8% in allogeneic transplant. The mortality rate is as high as 70% in allogeneic SCT [17].

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Knowledge of the epidemiology of a communicable infection is the first step of its management strategy. Yet, nationwide programs of infection control interventions are scarce in Italy [4]. The emergence of carbapenem resistance in *Enterobacteriaceae* prompted us to evaluate the carbapenem susceptibility patterns in strains isolated in children with cancer. We implemented a survey among centers participating in the pediatric hematology-oncology cooperative study group (Associazione Italiana Ematologia Oncologia Pediatrica; AIEOP) to assess the incidence of CPE infection. This study focuses on (i) the trend of carbapenem susceptibility in *Enterobacteriaceae* causing BSI and colonization in children treated with chemotherapy, over a 2-year period; (ii) the rate of BSI or colonization related to duration of hospital stay; and (iii) infection-related mortality.

Material and Methods

Study design

The study was designed as a retrospective (from January 2012 to December 2012) and prospective (from January 1, 2013 to December 31, 2013) data collection. The total observation time was 24 months.

Definitions

An infection case is defined as a patient with BSI caused by CPE. A colonization case is defined as a patient with the presence of bacteria on a body surface (such as on the skin, mouth, intestines or airway) that did not cause any modification or sign and symptom of any type of disease. A bacterial isolate was considered non-susceptible when it tested resistant, intermediate or non-susceptible according to the interpretative criteria used by the individual centers, comprising the following: European Committee on Antimicrobial Susceptibility Testing (EUCAST); Clinical and Laboratory Standards Institute (CLSI); US Food and Drug Administration (FDA). It should be noted that the CLSI criteria have recently undergone substantial changes, with the breakpoints for many β-lactams made considerably more conservative

Study population and items collected

All of the AIEOP (www.aieop.org) centers were invited to participate in a survey by reporting, for the observation period, the following information: total number of children (0–18 years) newly diagnosed and on treatment, type of tumor (leukemia/lymphoma or solid tumors), number of days of hospital admission, ongoing surveillance culture for CPE, number of patients with BSI, number of patients colonized including those with other sites of infection (e.g. the urinary tract), number of patients with polymicrobial infection including CPE, and number of patients who died. Data were collected on a specific form by a web survey and pooled.

Statistical analysis

Incidences of BSI or colonization were calculated as rates (episodes per 1000 days of hospital admission) during each year of observation. Mortality in patients with BSI was evaluated at 90 days after the first positive blood culture. All the analyses were performed with STATA version 10 software.

Since this was an observational, non-interventional study, according to local regulations, IRB approval was not mandatory at that time. Informed consent for collection of the data on treatment, toxicity, and complications was collected, together with consent to the therapeutic program. Information on individual patients remained blinded after data pooling.

Results

Fifteen centers participated in the survey; their geographic distribution within the country homogenous. During the period, they enrolled a total of 3248 children: 1610 treated for solid tumor (49%) and 1638 for leukemia/lymphoma (51%). The mean number of patients followed by each center was 216 (range 44–426). The study population accounted for 49% of the entire population of patients treated in the AIEOP centers during the study period.

Of the 15 centers, 4 (27%) reported no isolation of CPE, while 8 reported BSI by CPE, and 3 reported episodes of colonization only. In one center an epidemic cluster of CPE occurred. Overall, 44 episodes of CPE BSI were reported. The incidence of BSI was 0.16 (0.07–0.31)/1000 days of hospital stay (Table I) in 2012, and increased to 0.67 (0.47–0.93) in 2013. Seven of the 44 patients with BSI died (15.9%); the crude mortality rate was 0.22 in the year 2012 (5 of 23 BSI subjects), and a lower rate of 0.05 (2 of 36) in 2013. None of the patients with CPE isolation was reported with polymicrobial infection.

A screening program for CPE was applied in 25% of the centers by the end of 2012, and in 60% (9/15) by the end of 2013.

Discussion

The expansion of CPE strains in the centers of pediatric hematology-oncology in our country is well documented by the rate of infection, which rose from 0.16/1000 patient-days in 2012 to 0.67/1000 patient-days in 2013. Although calculated from small numbers, this shows a fourfold increase of the phenomenon. The increased circulation of CPE strains is shared by all but one center. This increase remained significant even if the data from the single center in which a cluster occurred in 2012 were excluded (from 0.09 in 2012 to 0.73 in 2013), showing a relative risk (RR) of 8.04 (95% confidence interval, CI = 2.852–22.65) in 2013, compared with 2012 ($p = 0.000$).

The mortality rate of infections with CPE is exceedingly high in adults from similar settings, with percentages as high as 67% [20–23]. The 15.9% mortality rate in children is definitely lower than in adults, and our results do not offer an explanation for this difference, which might depend on the patients' degree of immune suppression, co-morbidities, or duration of neutropenia. The mortality rate was lower in the second part of the observation period (i.e. in 2013). This might depend on a higher level of attention and awareness of the problem, due to previous and recent adverse outcomes, resulting in some learning effect. Although a single center observation cannot be

Table I. Epidemiology of CPE bacteremia and colonization in 15 Italian pediatric hematology-oncology centers during the years 2012–2013.

Characteristic	2012	2013	Total	2013/2012 rate of incidence (95% CI; *p* value)
Bacteremia (*n*)	8	36	44	–
Colonization (*n*)	15	35	50	–
Days of hospitalization	50.513	53.431	103.944	–
Rate of bacteremia/1000 days of hospitalization (95% CI)	0.16 (0.07–0.31)	0.67 (0.47–0.93)	0.42 (0.31–0.57)	4.25 (1.98–9.15; $p = 0.000$)
Rate of colonization/1000 days of hospitalization (95% CI)	0.30 (0.17–0.49)	0.65 (0.49–0.61)	0.48 (0.36–0.63)	2.21 (1.20–4.04; $p = 0.004$)
Mortality rate × 100 (95% CI)	22.73 (9.71–43.85)	3.08 (0.22–11.17)	8.04 (3.59–15.27)	0.13 (0.03–0.65; $p = 0.005$)

CI, confidence interval; CPE, carbapenemase-producing *Enterobacteriaceae*.

considered significant, the center in which a cluster was observed in 2012 had no cases in the following year, 2013. The observation of fatalities in patients with CPE infection may induce a reduction of the intensity of cancer-directed therapy. If so, although the risk of infection-associated mortality may indeed be reduced, the risk of treatment failure – because the malignant disease becomes refractory or recurs – should be considered. The current study was not tailored to address this question.

The incidence of colonization doubled in 1 year (from 0.30 to 0.65 per 1000 hospital days). This figure may have been affected by progressive introduction of screening. Yet, despite a specific recommendation released by the Italian Ministry of Health, only 60% of centers had a screening policy in place.

This study has limitations. First, only 15 of the 55 centers in the AIEOP network (27%) participated in the data collection. Yet, the population enrolled accounts for 49% of the total pediatric population treated in the network. Limited participation might result from underestimation of the problem, although shortage of resources available for research cannot be excluded, since the study was not specifically funded and thus was performed using internal resources. Second, although a separate analysis of patients diagnosed by a screening process could have provided additional information, the study was not designed to address this issue. Finally, the exact contribution of CPE infection to mortality cannot be detected with this study design.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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