BACTEREMIA BY CARBAPENEMASE PRODUCING ENTEROBACTERIACEAE CAN BE REDUCED BY MEASURES OF HOSPITAL INFECTION CONTROL

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Abstract

Carbapenemase-producing Enterobacteriaceae (CPE) , multidrug resistant (MDR) threatens children undergoing chemotherapy. A previous survey reported increase of bloodstream infections and colonization in a 2 year-observation time. To test the efficacy of the measures put in place , a second survey was performed. Data were collected from 13 Italian pediatric cancer centers of AIEOP network. The colonization rate per 1000 hospitalizations days was 0.5 (0.37-0.65) not different from the 0.48 rate (0.36-0.63) observed previously .Yet the 0.12 rate of bacteriemia (0.07-0.21) compared favorably with the 0.42 (0.31-0.57) observed. The awareness of colonization status allowed reducing CPE related morbidity and mortality.

ABSTRACT

The spread of carbapenemase-producing *Enterobacteriaceae* (CPE) is an emerging problem in children undergoing cancer-directed chemotherapy. A previous Italian survey reported a threefold increase of CPE colonization rate, and a fourfold increase of CPE bloodstream infections in a 2 year-observation time interval. To assess the efficacy of the measures put in place to control this emergency, a second survey was performed on the years 2016-2017. The results showed that the number of patients colonized by CPE remained stable, while the number of bloodstream infections decreased, as well as the resulting mortality. We conclude that children undergoing chemotherapy are at risk for CPE colonization/infection, but the awareness of their colonization status may allow reducing CPE morbidity and mortality.

INTRODUCTION

The rapid spread of carbapenemase-producing *Enterobacteriaceae*(CPE), multidrug resistant (MDR), became a serious threat for patients receiving antineoplastic chemotherapy. In 2015, we reported the results of a nationwide survey among centers participating in the Italian network of pediatric hematology-oncology (*Associazione Italiana Ematologia Oncologia Pediatrica;* AIEOP). During a 2-year observation period (2012-2013), a threefold increase in the colonization rate, and a fourfold increase of bloodstream infectious episodes caused by CPE were observed, with a 90-day mortality of 14%. As a result, all centers implemented measures of hospital infection control, including the screening for intestinal MDR strains by rectal swab in every inpatient, on admission.(1) In order to monitor the epidemiological trend of MDR/CPE infectious episodes, we performed a second survey and the results are here reported.

PATIENTS AND METHODS

The study was a retrospective data collection on a 24-month period (from January 2016 to December 2017); 13 of the 40 Italian pediatric cancer centers of the AIEOP network participated in the study. Of them, eight were also included in the previous study.

The following data were collected: total number of children cared per year, either newly diagnosed or on treatment; type of tumor (leukemia/lymphoma or solid tumor); total number of days of hospital admission; routine monitoring of MDR/CPE strains on rectal swab; number of patients colonized by MDR/CPE; number of patients with bacteremia; cause of bacteremia, and number of patients who died following bacteremia. Strains were considered as "non-susceptible" to carbapenems when they tested resistant or non-susceptible according to the interpretative criteria recommended by European Committee on Antimicrobial Susceptibility Testing (EUCAST) (2), or by the Clinical and Laboratory Standards Institute (CLSI)(3). Incidence of colonization and bacteremia were calculated as rates (episodes/1,000 days of hospital admission) during each year of observation. Mortality of bacteremic patients was evaluated at day 90 after the first positive blood culture. All the analyses were performed with SAS vers. 9.4 (SAS Institute Inc., Cary, NC, USA).

RESULTS

During the study period the total number of episodes of admission was 8,257: 3,361 (41%) for patients with solid tumor, and 4,896 (59%) for patients with leukemia or lymphoma. The median number of patients cared by each center was 396 (range, 109 to 1,824). A screening program for detection of MDR/CPE carrier was in place in 12 of the 13 (92%) participating centers during the study period. Table 1 reports data on colonization and bacteremia. Overall, in 53 of the 8,257 episodes (0.64%) the patient was found to be carrier of MDR/CPE. This finding accounted for an overall rate of colonization of 0.5/1,000 days of hospitalization (95% CI, 0.37-0.65). The comparison of the results of the current survey with those of the previous study (table 1) shows that the rate of colonization was comparable between the two study periods: 0.50% (2016-2017) vs. 0.48% (2012-2013). MDR/CPE bacteremia was reported in 13 children from six centers. The rate of MDR/CPE bacteremia was 0.12 for 1,000 days of hospitalization (95% CI, 0.07-0.21) and compared favorably with that observed in the previous survey (0.42 for 1,000 days of hospitalization; 95% CI, 0.31-0.57; $p<0.0001$).

The number of centers participating in the study was similar: 15 in 2012-2013 vs. 13 in 2016-2017. When the comparison between the two eras (2012-2013 vs. 2016-2017) was restricted to the eight centers participating

in both surveys, no difference was observed.

The strains responsible for bacteremia were *Klebsiella pneumoniae*in 9/13 children, *Escherichia coli* in 2/13, *Citrobacter spp. and Stenotrophomonas maltophilia* in one case each. The antibiotic susceptibility was available for 10 MDR/CPE strains. All strains were resistant to third-fourth generation cephalosporin, piperacillin/tazobactam, and carbapenems; they were susceptible to amikacin in seven of nine tested, colistin in five of five, fosfomycin in six of seven and tigecycline in five of eight. Death from any cause occurred in two of the 13 patients with bacteremia (15%). Both patients, a 6-year old female with severe aplastic anemia, undergoing allogeneic hemopoietic stem cell transplant from a matched unrelated donor, and a 10-year old female with acute myeloid leukemia, had a septic shock by MDR *Klebsiella pneumoniae* and died. Death occurred after 11 and 15 days from the first positive blood culture, respectively.

DISCUSSION

The fast and wide spreading of CPE/MDR infections among immune compromised patients, observed in the last years, represented an excess of "preventable deaths" on which much attention was paid. The results of a survey performed in the period 2012-2013 had showed a threatening number of MDR/CPE episodes of bacteremia in children treated for cancer (4,5). This prompted the centers to enforce measures of hospital infection control. They included early identification of MDR/CPE colonized patients by rectal swab screening; adoption of hospital contact precautions by caregivers of colonized patients; single room or cohort isolation for colonized patients; empirical antibiotic therapy guided by the antibiotic susceptibility of colonizing germ; rapid identification of the causative germ of febrile episodes during neutropenia.

To assess the efficacy of such measures, we performed a second, follow-up survey on the years 2016-2017. The differences between the study populations in the two surveys were limited. About one-half of the participating centers were the same in the two studies. All Italian geographical macro-areas were represented in the 2016-2017 survey, with six centers from Northern Italy, three from the center of Italy, and three centers from Southern Italy and islands.

By the time of the follow-up survey, routine screening for colonization of patients was in place in all but one participating centers (92%), while it had been progressively introduced during the years of the initial survey (one quarter of the centers in 2012, 60% in 2013) (1). Overall, the colonization rate observed by routine screening was 0.5/1,000 days of hospitalization, which was not different from what observed in 2012-2013 survey, although on lower numbers of patients. Interestingly, the MDR/CPE bacteremia rate was significantly lower in 2016-2017 than in 2012-2013, with 0.12 vs. 0.48/1,000 days of hospitalization ($p<0.0001$). This difference was confirmed when the analysis was focused on the eight centers which participated in both surveys. Mortality by MDR/CPE remained in the range of 15% in both studies.

In conclusion, circulation of MDR/CPE strains remained stable in children admitted for cancer chemotherapy in the Italian centers between 2012-2013 and 2016-2017, suggesting that the "epidemic" of MDR/CPE, observed at the beginning of the present decade, remained then under control. Furthermore, this was associated with a lower number of bacteremia episodes, thus suggesting that higher awareness of this problem may have resulted in a closer application of preventive measures. The spectrum of antibiotic susceptibility of isolates from blood cultures showed that amikacin maintains a good susceptibility as well as colistin, fosfomycin and tigecyclin (6).

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`Table 1 Caselli.docx` available at https://authorea.com/users/332680/articles/459090-bacteremia-by-carbapenemase-producing-enterobacteriaceae-can-be-reduced-by-measures-of-hospital-infection-control