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Case report

Healthcare-associated infections due to carbapenemase-producing Enterobacteriaceae: Bacteriological profile and risk factors

Infections liées aux soins dues à des entérobactéries productrices de carbapénèmases : profil bactériologique et facteurs de risque

M. Chabah [a,*], M. Chemsi [a], K. Zerouali [b], O. Alloula [c], M. Lehlimi [a], A. Habzi [a], S. Benomar [a]

[a] *Service de néonatologie et de réanimation néonatale, hôpital d'enfants Abderrahim Harouchi, faculté de médecine et de pharmacie de Casablanca, centre hospitalier universitaire Ibn Rochd, Casablanca, Morocco*
[b] *Service de laboratoire de microbiologie, faculté de médecine et de pharmacie de Casablanca, centre hospitalier universitaire Ibn Rochd, Casablanca, Morocco*
[c] *Comité de lutte contre les infections nosocomiales (CLIN), hôpital Ibn Rochd, faculté de médecine et de pharmacie de Casablanca, centre hospitalier universitaire Ibn Rochd, Casablanca, Morocco*

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1. Introduction

Carbapenemase-producing Enterobacteriaceae (CPE) healthcare-associated infections have been a major health problem since the first ever reported case in 1996 (North Carolina, United States) [1–3]. CPEs are also frequently observed in pediatric settings [4]. An increased prevalence of CPEs has been reported worldwide. CPE infections are responsible for hospital epidemics that are not easily controlled and associated with a very high morbidity and case fatality [5]. This is mainly due to the excessive use of broad-spectrum antibiotics.

Some highly pathogenic Enterobacteriaceae (*Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter cloacae*, *Enterobacter aerogenes*) are now resistant to every betalactam antibiotic. These bacteria are even resistant to carbapenems, backbone of Enterobacteriaceae infection antibiotic treatment [6,7].

Carbapenemases are betalactamases with a strong hydrolytic activity towards carbapenems. On the basis of Ambler's classification, one may distinguish three classes of betalactamases: class A (KPC-, IMI-, and GES-type enzymes), class B (VIM-, IMP-, and NDM-1-type metallo-betalactamases), and class D (OXA-type enzymes such as OXA-48, OXA-163, OXA-181) [1].

In our ward, first-line carbapenems are administered to patients presenting with healthcare-associated infections as we are mainly confronted with Gram-negative bacilli [8]. We aimed to measure the prevalence of CPE healthcare-associated infections in the neonatal ward and intensive care unit (ICU). We also aimed to identify associated risk factors.

2. Patients and methods

We conducted a retrospective study over a 24-month period (January 1st, 2012–December 31st, 2013) in the neonatal ward and ICU of the Abderrahim El Harrouchi Children hospital (Casablanca, Morocco). The ward consists of 13 rooms (22 beds: 16 incubators and 6 cradles): nine neonatal wards and four neonatal ICUs. Patients are mainly hospitalized for medical and sometimes for surgical reasons. All patients presenting with an infection are placed in an airborne infection isolation room and the infection must be formally notified. Nursing staff consists of five nurses working the morning shift, three working the afternoon shift, and two working the night shift. Medical staff consists of 12 physicians (four senior physicians and eight residents).

* Corresponding author.
E-mail address: meryemchabah@gmail.com (M. Chabah).

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We included all newborns aged between 0 and 28 days who had been hospitalized in the ward for more than 48 hours and who presented with an Enterobacteriaceae infection, either resistant to or with a reduced susceptibility to carbapenems (drug susceptibility testing performed for imipenem and ertapenem).

We did not include asymptomatic patients with a positive bacteriological result. They did not receive any treatment and samples were considered contaminated.

We measured prevalence as follows: number of CPE case patients compared with the overall number of patients hospitalized for more than 48 hours during the study period.

Study's variables were the patient's age and weight on admission, sex, gestational age, type and place of delivery, reason for hospitalization, length of hospital stay in the ward, antibiotic therapies received, feeding mode (breast, bottle, or nasogastric tube), and initial inflammatory and bacteriological findings on admission and after suspicion of a healthcare-associated infection: C-reactive protein (CRP), procalcitonin (PCT) level, blood culture, cerebrospinal fluid (CSF) testing, urine cytobacteriological examination, rectal swab, invasive devices and duration of use (umbilical vein catheter, intubation, bladder catheter, chest drain, exchange transfusion, and surgical procedures). We also analyzed healthcare-associated infection onset compared with the hospitalization date, the involved bacterium and its susceptibility to antibiotics with a special attention paid to carbapenemase secretion, antibiotic therapy received, and outcome after treatment completion.

We conducted a comparative case-control study to identify the clinical risk factors for CPE infections. Case patients presented with CPE infections and control patients presented with carbapenem-susceptible Enterobacteriaceae infections.

We jointly conducted the study with the microbiology laboratory team of the Ibn Rochd university hospital of Casablanca.

Bacteria were isolated and identified using standard bacteriological tests (culture, morphology, and biochemistry using analytical profile index [BioMérieux]).

Antibiotic susceptibility was assessed by agar diffusion test (Mueller-Hinton agar) according to the Clinical and laboratory standards institute (CLSI) guidelines. Tested antibiotics included amoxicillin, ampicillin, cefpodoxime, cefotaxime, ceftazidime, ertapenem, imipenem, gentamicin, tobramycin, netilmicin, amikacin, trimethoprim-sulfamethoxazole, ciprofloxacin, norfloxacin, cefoxitin, tazobactam-piperacillin.

Extended-spectrum-betalactamase (ESBL) detection was performed with a conventional phenotypic drug susceptibility testing using double disc synergy for amoxicillin-clavulanic acid and third-generation cephalosporins.

Carbapenemase detection was performed with a conventional phenotypic drug susceptibility testing to assess the reduced susceptibility to ertapenem and/or imipenem using disc method. We also performed a Hodge test.

Carbapenemase typing was performed on a few strains by Multiplex PCR to look for OXA-48, NDM-1, VIM, and KPC genes.

We did not take into consideration any duplicated result.

Data collection was performed using a predefined form for each newborn baby included in the study. The form was designed on the basis of medical chart data.

We only performed a univariate analysis using the Epi Info software. A P-value ≤ 0.05 was considered statistically significant. We used the 95% confidence interval (CI).

3. Results

A total of 1287 newborns were hospitalized in the neonatal ward and ICU during the study period: 288 healthcare-associated infections, including 157 Enterobacteriaceae infections (34 CPEs). The prevalence of Enterobacteriaceae infections was 12.2% and that of CPE infections was 2.6%.

We included 34 patients presenting with carbapenem-resistant Enterobacteriaceae infection or infection due to Enterobacteriaceae with a reduced susceptibility to carbapenems (ertapenem and/or imipenem). Each infection was confirmed by Hodge test and/or PCR.

Median age was 29 hours (range: 1 hour–24 days). Sex-ratio was 0.9 (16 boys/18 girls). A total of 19 newborns were full term babies (55.9%) and 15 (44.1%) were born prematurely. Mean weight on admission was 2430.8 g $\pm$ 848.7 g (range: 950 g–4600 g). Mean hospital stay was 20.24 $\pm$ 9.4 days (range: 5 days–42 days). Most patients had been hospitalized for neonatal respiratory distress syndrome ($n = 18$; 52.9%) or neurological distress ($n = 5$). An empirical antibiotic therapy combination was initiated in all patients because of suspected mother-to-fetus infection: third-generation cephalosporin + aminoglycoside ($n = 33$; 97.1%) and amoxicillin + aminoglycoside ($n = 1$). Mean time to healthcare-associated infection onset was 5.7 $\pm$ 3.2 days (range: 48 hours–16 days). Six patients presented with healthcare-associated infection onset within 72 hours. Clinical symptoms of infection included skin complexion change (septic or icteric) ($n = 25$), mechanical ventilation failure ($n = 8$), hemodynamic

Table 1
Bacteriological profile and sites of healthcare-associated bacterial infections.
Profil bactériologique et sites des infections bactériennes liées aux soins.

Pathogenic bacteria	Blood culture	Urine cytobacteriological examination	Umbilical catheter	CSF	Other	Total
Klebsiella pneumoniae	18	2	3	1	1	25
Enterobacter cloacae	6	1	1	0	0	8
Escherichia coli	0	1	0	0	0	1
Total	24	4	4	1	1	34

CSF: cerebrospinal fluid.