Quest Journals
Journal of Medical and Dental Science Research
Volume 8~ Issue 3 (2021) pp: 31-34
ISSN(Online) : 2394-076X ISSN (Print):2394-0751
www.questjournals.org

Research Paper

Infections with enterobacteriaceae producing carbapenemase type OXA48

Khayati Siham, Rada Rania, Zahlane Kawtar.
Bacteriology laboratory, Ibn Tofail Hospital, Mohammed VI Marrakech University Hospital, Morocco.

ABSTRACT: *Introduction: Enterobacteriaceae producing carbapenemase, whether or not associated with extended spectrum betalactamase (ESBL), pose a health problem. They are responsible for severe infections with high epidemic potential, leading to limited therapeutic choices and prolonged hospital stay. The phenotypic and genotypic detection of these strains makes it possible to curb this problem. Material and method: Our work is a retrospective study over a period of 3 years. It concerned all enterobacteriaceae resistant to carbapenems isolated from various bacteriological samples in hospitalized patients, all departments combined, at the Ibn Tofail hospital in Marrakech. The search for carbapenemase was done by phenotypic methods (resistance to ertapenem, cloxacillin agar and hodge test). Molecular confirmation was performed by real-time PCR. Results: During our study, we isolated 22 enterobacteria resistant to carbapenems, 45% of which were also ESBL producers. Klebsiella pneumonae accounted for 61% of these strains followed by Enterobacter cloacae 33% and Klebsiella oxytoca in 8%. Co-resistance was noted for all the other bacterial families with the exception of Amikacin, 95% of the strains of which were susceptible. The hodge was positive for all strains. All these strains carried the blaOXA48 gene in addition to the presence of the blaCTXM15 gene in the strains also producing ESBL. Conclusion: The development of new real-time PCR techniques improves the specificity and sensitivity of the detection of multi-resistant bacteria.*

KEYWORDS: *Infection, Enterobacteriaceae, Resistance, Carbapenemase*

Received 01 Mar, 2021; Revised: 12 Mar, 2021; Accepted 14 Mar

I. INTRODUCTION:

Carbapenems belong to the beta-lactam family and have a broad spectrum of activity. These antibiotics are active against a large number of Gram-negative bacilli species including Enterobacteriaceae. Carbapenems are limited to hospital use, prescribed mainly for the treatment of nosocomial infections. Carbapenem-resistant Enterobacteriaceae have been reported worldwide, mainly due to the acquisition of the carbapenemase gene [1]. Carbapenemase-producing Enterobacteriaceae, whether or not associated with extended spectrum betalactamase (ESBL), pose a health problem. They are responsible for severe infections with high epidemic potential, leading to limited therapeutic choices and prolonged hospital stay. The phenotypic and genotypic detection of these strains makes it possible to curb this problem.

II. MATERIAL AND METHOD:

Our work is a retrospective study spanning a period of 3 years, from January 1, 2015 to December 31, 2017. It concerned enterobacteria resistant to carbapenems isolated from various bacteriological samples received at the microbiology laboratory of the Ibn Tofail hospital in Marrakech. Bacterial identification was based on morphology, cultural and biochemical characters using the conventional identification galleries of enterobacteriaceae Api 20 E. The search for carbapenemase was done by phenotypic methods (resistance to ertapenem, cloxacillin agar and hodge test). Molecular confirmation was performed by real-time PCR. We included in our study all enterobacteriaceae resistant to carbapenems isolated in cultures of various bacteriological samples from hospitalized patients, all departments combined. Data entry and statistical analysis were performed using Microsoft Office Excel software.

III. RESULTS:

During our study, we isolated 22 enterobacteriaceae resistant to carbapenems. 45% of these Enterobacteriaceae were also ESBL producers. 62% of the samples came from male patients.

In the cloxacillin medium, no high level cephalosporinase was found. The hodge test was positive for all strains (Figure 1). All these strains carried the blaOXA48 gene in addition to the presence of the blaCTXM15 gene in strains also producing ESBL.

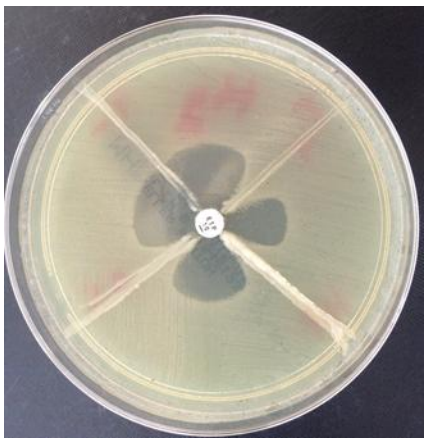

Figure 1: Example of 3 strains showing a positive Hodge test

Klebsiella pneumonae was the most predominant strain. It was found in 61% of cases, followed by Enterobacter cloacae (33%), then *Klebsiella oxytoca* (8%). No strain of *E. coli* was resistant to carbapenems (Figure 2).

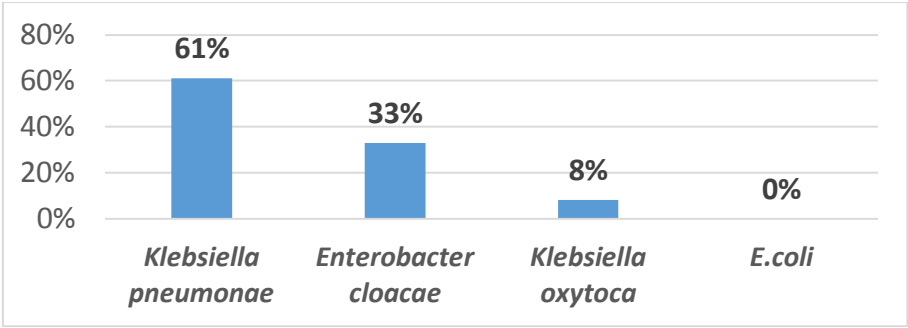

Figure 2: Species resistant to carbapenems

These strains were isolated in the majority of cases from urine, but also from pus, bronchial samples and blood cultures (Figure 3).

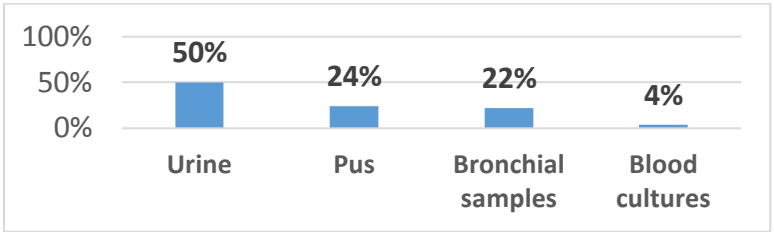

Figure 3: Nature of the sample

The services concerned were mainly the intensive care services in 40% followed mainly by the surgical services (Figure 4).

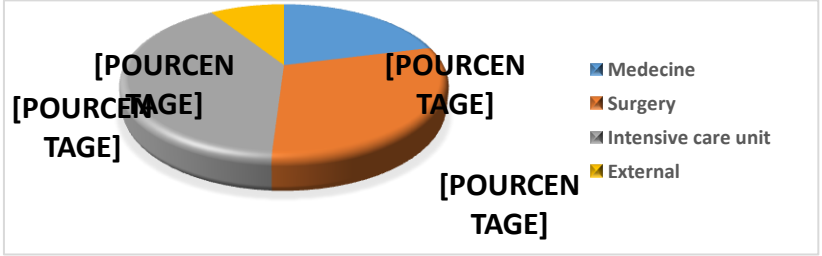

Figure 4: Distribution of isolates by hospital services

Co-resistance has been noted for all other bacterial families except amikacin. 95% of the strains were sensitive to this last. Table 1 shows the antibiotic resistance profile of the isolated strains resistant to carbapenems.

Table 1: Antibiotic resistance profile of isolated strains resistant to carbapenems

Antibiotic	Number	Percentage (%)
fluoroquinolones	22	100
Gentamicin	20	91
Amikacin	0	0
Tombramicin	21	95
Cotrimoxazole	22	100
Nitrofurane	17	97

IV. DISCUSSION

The carbapenemases described in Enterobacteriaceae belong to the known classes of beta-lactamases of the Ambler classification. Three classes of carbapenemase types are described: For class A, the most frequent and the most threatening are the KPC-type carbapenemases (KPC-2 to KPC-8). KPC-2 hydrolyzes all beta-lactams, although cefamycins and ceftazidime are poor substrates [2]. Most often the strains that produce KPC also express other beta-lactamases including many types of ESBLs (TEM, SHV, CTX-M) and have a certain degree of resistance by impermeability [2]. KPC strains therefore appear most often multidrug resistant to beta-lactams, ertapenem being the carbapenem with the highest level of resistance [2]. For class B (or metallobeta-lactamases, MBL), these are the many varieties of beta-lactamases. The best known are of the IMP, VIM and NDM type. These enzymes strongly hydrolyze all beta-lactams except aztreonam. Their activity is not inhibited by clavulanic acid or tazobactam. The levels of resistance to carbapenems are quite variable [1,3]. In many cases, MBL producing strains also produce ESBLs [3]. For class D carbapenemase, this is OXA-48. OXA-48 hydrolyzes carbapenems much more strongly and does not hydrolyze 3rd generation cephalosporins [4]. Its activity is not inhibited by clavulanic acid [4]. OXA-48 is often combined with other beta-lactamases, in particular ESBLs, which contributes to the multidrug resistance of the strains [4,5]. In the absence of other beta-lactamases, strains that produce only OXA-48 may show only a slight decrease in susceptibility to carbapenems [6].

The first strain to produce OXA-48 was isolated in Turkey, and this country is currently considered to be an endemic area for OXA-48 [7]. However, OXA-48-producing strains have now spread widely, especially in North Africa [7]. However, the clinical consequences of OXA-48 are now well established with its distribution in K. pneumoniae in many hospitals in Turkey and in many countries around the Mediterranean (Lebanon, Tunisia, Israel, Egypt, France) in Great Britain, India and Argentina [4,5].

In France, OXA-48 is now the most commonly identified carbapenemase. Probably due to the large flow that this country is experiencing with North Africa [6].

In Morocco, since the first description in 2009 by Benouda et al [8] of the first case of *K. pneumoniae* OXA-48 positive, this mechanism of resistance to carbapenems has experienced significant nosocomial dissemination through various bacterial species, suggesting an endemic state. Indeed, studies report cases of OXA-48 positive enterobacteriaceae in patients transferred to different hospitals in France and Belgium after a hospital stay in Morocco [9, 10].

V. CONCLUSION:

The isolation of strains of Enterobacteriaceae producing carbapenemase is increasing worldwide. *K. Pneumoniae* remains the enterobacteriaceae in which most of these carbapenemas have been identified. These carbapenemases are overwhelmingly identified in nosocomial strains. Community dissemination of these carbapenem resistance would make their control impossible. The development of new real-time PCR techniques can improve the specificity and sensitivity of the detection of multi-resistant bacteria.

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