Review Article

OXA-type carbapenemases in *Acinetobacter baumannii* in South America

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Abstract
Acinetobacter baumannii is an opportunistic pathogen that is frequently involved in outbreaks of infection, occurring mostly in intensive care units. The increasing incidence of carbapenem resistance in *A. baumannii* worldwide is a concern since it limits drastically the range of therapeutic alternatives. The most important mechanism of carbapenem resistance is the enzymatic hydrolysis mediated by carbapenemases. In *A. baumannii* these enzymes are usually OXA-type carbapenemases, and belong to class D according to the classification of Ambler. The OXA-type carbapenemases are divided into five subgroups, four of which correspond to acquired carbapenemases, which accounts for the distribution of genes bla_{OXA} in different geographic areas. In this work we review the different types of OXA-type carbapenemases present in *A. baumannii,* emphasizing the current situation in South America with special mention to the findings in Chile.

Key words: *Acinetobacter baumannii*; carbapenem-resistance; OXA-type carbapenemases; South America; Chile

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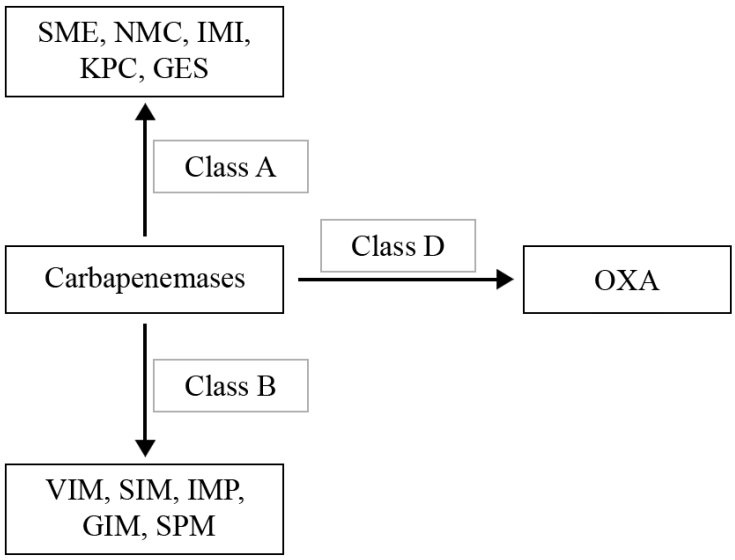
Introduction

Acinetobacter baumannii is a glucose non-fermentative Gram-negative bacillus classified as an opportunistic pathogen and is usually involved in infectious outbreaks originating in intensive care units [1]. The infections caused by *A. baumannii* include bloodstream infections and ventilator-associated pneumonia [2]. The beta-lactam antibiotics are an important group of antibiotics used to treat infections caused by various microorganisms, including *A. baumannii*, due to their efficacy and safety, and because their activity can be increased by chemical modification [3,4]. Until the 1970s, most clinical isolates of *Acinetobacter* spp. were susceptible to most groups of antibiotics available, including beta-lactams; however, the species *A. baumannii* has a great ability to develop resistance against antibiotics [3], which has generated, over the last decade, an increase in the number of multidrug resistant (MDR) isolates of *A. baumannii* [5]. Due to the increased rate of resistance to other antibiotics, the use of carbapenem antibiotics has become necessary in *A. baumannii* infections. This class of antibiotics exhibits a broad-spectrum activity against Gram-negative and Gram-positive organisms, including anaerobic bacteria; and is therefore used to treat serious infections [4]. Carbapenems, except for ertapenem, are active against *A. baumannii* and have become the drugs of choice for infections caused by this bacterium. Carbapenems are generally more active and more resistant to beta-lactamases, including extended spectrum beta-lactamases and derepressed chromosomal AmpC beta-lactamases due mainly to the characteristics of the lateral chains present in its chemical structure [6]. The resistance to these compounds is not due to the presence of a single mechanism, but to a combination of different mechanisms classified as enzymatic and non-enzymatic with most important mechanism of resistance to this class of antibiotics the enzymatic hydrolysis, mediated by enzymes called carbapenemases [7]. These enzymes belong to any of three molecular classes according to the Ambler classification [8] (Figure 1). Class A includes beta-lactamases that possess serine in their active site and are inhibited by clavulanic acid. These carbapenemases are part of the Bush functional group 2f [9], and have been detected mainly in

Figure 1. Classification of carbapenemases



Enterobacteriaceae; however, KPC-like enzymes and GES-like enzymes have been detected in carbapenem-resistant *A. baumannii* strains isolated in Puerto Rico and Paris, respectively [10,11]. Class B includes zinc dependant beta-lactamases named metallo-beta-lactamases (MBL), which are part of the functional group 3 [7,9]. To date, the presence of IMP, VIM, and SIM-1 groups of MBL has been identified in *A. baumannii* [5,12]. Finally, the third molecular class corresponds to class D serine-carbapenemases, called OXA-type carbapenemases (OTC), which belongs to the functional group 2d [7,9]. Although OTC have a lower catalytic efficiency to hydrolyse carbapenems in comparison with MBL (100 to 1000 fold lower), it is important to consider them as potentially dangerous because their expression can be regulated by the upstream insertion of IS elements such as IS*Aba1* [13,14]. This can be intensified when other mechanisms of resistance are present, such as increased expression of efflux pumps and loss of porins [15,16,17]. The most prevalent carbapenemases in *A. baumannii* are the OXA-type-beta-lactamases [12] and, for this reason, this review analyses molecular and epidemiological aspects of OTC in *A. baumannii* emphasizing the current situation in South America, and the latest finding in Chilean strains of *A. baumannii.*

General properties of OXA-type beta-lactamases

Originally, the denomination OXA was due to the capacity of this group of carbapenemases to hydrolyze isoxazolylpenicillin oxacillin faster than classical penicillins and the fact that they are not inhibited by clavulanic acid and EDTA [7,9]. However, today this definition is not valid because since enzymes have been recently described that inactivate cloxacillin and oxacillin weakly, but all OXA beta-lactamases are active against amino- and carboxipenicillins [18]. Multiple alignment analysis of the sequences of these enzymes identifies three highly conserved active-site elements [18,19]. The first corresponds to a tetrad, composed of Ser^{70}-X-X-Lys, in which X corresponds to any amino acid, and the serine in position 70 corresponds to the amino acid of the active site. The second element corresponds to Ser^{118}-X-Val/Ile. The third element is represented by the Tyr/Phe^{144}-Gly-Asn triad plus the Trp^{232}-X-X-Gly tetrad, which have no analogues in class A or AmpC enzymes [19].

During the last four years descriptions of new OXA-type beta-lactamases have increased considerably. Thus Queenan and Bush reported in 2007 [7] that 102 unique OXA sequences had been assigned to this group, 9 of which were recognized as extended spectrum beta-lactamases and 37 as carbapenemases. Later, in 2010, Poirel *et al.*

reported 147 OXA enzymes [18], 19 of which were expanded-spectrum beta-lactamases and 64 were carbapenem-hydrolyzing class D beta-lactamases. Today this number has reached 227 OXA-type beta-lactamases [20].

OXA-type carbapenemases in *A. baumannii*

The OTC contain between 243 and 260 amino acids residues, with a molecular mass ranging from 23.0 to 35.5 kDa and pI values varying between 5.1 and 9.0 [19]. The first OTC found in *A. baumannii* was obtained from a strain isolated in 1985 in a Scottish hospital, named ARI-1 (*Acinetobacter* Resistant to Imipenem) [21] and now designated as OXA-23 [22]. The $bla_{\text{OXA-23}}$ gene was located on a plasmid (45 kb) that was transferred to *Acinetobacter junii* [23]. However, today five main phylogenetic subgroups of OTC have been recognised in *A. baumannii*: OXA-23-like, OXA-40-like, OXA-51-like, OXA-58-like and OXA-143-like [1,24,25].

By far the largest subgroup is the OXA-51-like, which corresponds to chromosomal encoded enzymes and therefore naturally occurring OTC in *A. baumannii*. The enzymes included in this subgroup differ by 1 to 15 amino acids [19,26]. The OXA-23-like subgroup includes the following derivates in *A. baumannii*: OXA-27 and -49 [12,18], which have been identified mainly to be plasmid-mediated.

Although the OXA-23-like carbapenemase subgroup has been mainly reported in *A. baumannii*, in 2002 it was detected in a carbapenem-resistant isolate of *Proteus mirabilis* [27]. Importantly, OXA-23-like enzymes have been detected in strains of *A. radioresistens* [28], which might be the natural reservoir of these enzymes.

Enzymes belonging to OXA-58-like subgroup can be located on plasmids, which may explain their wide distribution [1]. Two variants within this subgroup have been described: OXA-96 and OXA-97 [29,30].

The fourth subgroup corresponds to the OXA-40-like, originally called OXA-24, with three variants, OXA-25, OXA-26 and OXA-72, which have been identified in plasmids [31,32]. Enzymes of this group have not been described to be associated with insertion sequences [1].

In 2009, Higgins *et al.* reported a new OTC, the OXA-143, which was described in a carbapenem-resistant *A. baumannii* strain isolated in Brazil in 2004. This enzyme was located on a *ca* 30 kb plasmid and has 88% amino acid sequence homology with OXA-40, 63% with OXA-23, and 52% with OXA-58 [24], representing a new subgroup of OTC.

The bla_{OXA} genes have been related to a variety of different genetic structures, emphasizing the insertion sequences, which have an important role in the expression of these genes, specifically IS*Aba1*, IS*Aba2*, IS*Aba3* or IS*18* in the case of *A. baumannii* [13,14,33]. Insertion sequences may result in hybrid promoter sequences associated with increased expression rates, which represents a real mechanism of resistance to carbapenems, or at least one of reduced susceptibility [13]. Many oxacillinases genes present in isolates of *A. baumannii* have been detected as gene cassettes in integrons. However, most of the OTC genes were identified in plasmids, but not in the form of genetic cassettes within integrons [19].

Epidemiology

OXA-type carbapenemases have been described around the world [25], including South America (Table 1). Strains of *A. baumannii* harbouring OXA-23-like enzymes have been identified in Brazil, Argentina and Colombia [25,34,35,36,37]. Moreover, carbapenemases belonging to OXA-23-like subgroup have been detected in Europe, Australia, Tahiti, China, Korea, Singapore, Vietnam, USA, Libya and Pakistan [1].

With respect to the subgroup OXA-58-like, which was first detected in France [33], strains of *A. baumannii* carrying $bla_{\text{OXA-58}}$ have been identified in South America, specifically in Argentina, Colombia, Bolivia and Venezuela [25,34,35,38,39]. Additionally, a total of 38 strains of *A. baumannii* carrying the $bla_{\text{OXA-58}}$ gene have been detected in Chile; these were isolated from three different hospitals in Santiago, Chile, between the years 2007 and 2008 [Opazo *et al.*, unpublished results, 2010]. The strains were clonally intra-hospital related, sharing more than 85% similarity among their pulsed-field gel electrophoresis (PFGE) profiles, but they were not inter-hospital related, suggesting the occurrence of a non-clonal dissemination of carbapenem-resistant *A. baumannii* strains harbouring $bla_{\text{OXA-58}}$.

Moreover, strains of *A. baumannii* resistant to carbapenems carrying the $bla_{\text{OXA-58}}$ gene have been reported in European countries such as Spain, Turkey, Romania, United Kingdom, Italy, Poland, Switzerland, Germany, Ireland, Portugal, Hungary,

Table 1. Presence of OXA-type carbapenemases in South America

OTC subgroup	Countries	Genetic location	References
OXA-51	Argentina, Bolivia, Brazil, Chile*, Colombia, Venezuela	Chromosome	25, 38, 46
OXA-23	Argentina, Colombia, Brazil	Chromosome, Plasmid	25, 34, 35, 36
OXA-40	Brazil, Chile	Plasmid	42,45
OXA-58	Argentina, Bolivia, Chile*, Colombia, Bolivia, Venezuela	Plasmid	25, 35, 38, 39
OXA-143	Brazil	Plasmid	24

OTC: OXA-type carbapenemase; * Unpublished data (Opazo, 2010)

Bulgaria, and Greece as well as in the USA, Oceania, and Asia [1,5,25]. Additionally, the $bla_{\text{OXA-58}}$ gene was identified in strains of *A. junii* isolated in Romania and Australia [1,40] and in a clinical isolate of *Acinetobacter* genospecies 3 in Spain [41].

The OXA-40-like enzymes are the less widespread OTC [12]. In 2007, the occurrence of a plasmid OXA-40-like enzyme, OXA-72, was described in a carbapenem-resistant *A. baumannii* strain isolated in Brazil [42], that was also detected in Taiwan [32], France [43] and Croatia [44]. In Chile, two clonally unrelated strains of *A. baumannii* resistant to carbapenems isolated in 2008 were positive for OXA-40-like carbapenemases; this was the first report of the detection of this enzyme in Chile [45]. Moreover, this subgroup has been found in strains isolated in Europe (principally in Spain, Belgium, and the Czech Republic), the United States, and parts of Asia, including Iran [12].

Carbapenemases that belong to the OXA-51-like subgroup have been identified globally, due to their chromosomal location and the fact that every *A. baumannii* isolate carries an OXA-51-like gene [1]. They were first discovered in strains isolated from hospitals in Buenos Aires, Argentina, between 1993 and 1994, when the incidence of carbapenem resistance even at that time was around 35% [46]. Today, carbapenem-resistant strains of *A. baumannii* carrying an OXA-51-like enzyme have been described in various countries in South America (Table 1). Within the OXA-51-like enzymes, there are clusters of enzymes that are associated with certain epidemic lineages [26]. The cluster related to OXA-66 has been associated with an *A. baumannii* lineage including a European clone (often now called Worldwide 2), being also associated with strains from South America and Asia [26,47], whereas those clustered around OXA-69 enzyme are found in another lineage encompassing European clone 1. Finally, OXA-71 enzyme is associated with European clone 3 [26].

Conclusions

The OXA-type carbapenemases have a global distribution. Mobilization of the bla_{OXA} genes is, in some cases, determined by the presence of insertion sequences and transposons, and therefore has a high potential to spread. OXA-23-like and OXA-58-like enzymes have been detected in Brazil, Venezuela, Colombia, Chile, Bolivia and Argentina; however, OXA-58-like enzymes are most frequently identified in South America. More recently, the presence of OXA-72, from the OXA-40-like subgroup, has been reported in Brazil. This group is mostly detected in some European countries, Asia and the United States, which may indicate the spread of resistant clones from these countries to South America, and in the long term, it can mean lower effectiveness of treatment of infections caused by MDR *A. baumannii*.

Recently the first member of a novel subgroup of OXA-carbapenemases in Brazil, OXA-143, has been described and its prevalence remains to be determined. This discovery opens the possibility to find new variants in South America, which could be

present in several countries of the continent. Therefore, it is important to note that the first emergences of the OXA-51, [48] and now the OXA-143 [24], as well as the second independent emergence of OXA-23 [49] carbapenemases, progenitors of three of the five types of OXA carbapenemases, were all identified in strains from South American countries in the last 20 years. It is thus very important to focus on the MDR *A. baumannii* strains from this continent, especially in countries where information is currently not available. On the other hand, the spread of bla_{OXA} genes can occur intra- and inter-hospital; therefore, it is necessary to implement rigorous control programs on infections caused by *A. baumannii* resistant to carbapenems. Furthermore, it is essential to conduct molecular genotyping studies of these strains as well as fully characterize the carbapenemases found in specific geographic areas, to prevent the spread of both genes and resistant clones.

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