Journal of Progressive Medical Sciences
ISSN: 3052-8518
DOI: https://doi.org/10.63939/0h70qx09
J.P.M.S

Vol. 1 , No 4 , February 2026

RESEARCH Open Access

Carbapenem Hydrolysing Oxacillinase in *Acinetobacter baumannii*

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ABSTRACT

The global rise in carbapenem resistance in *Acinetobacter baumannii* is alarming, as it severely restricts available therapeutic options. Among the resistance mechanisms identified in this species, carbapenem-hydrolyzing class D β-lactamases (CHDLs) represent the most prevalent β-lactamases and are largely specific to *A. baumannii*. This review focuses on the different clusters of oxacillinases that have been reported in *Acinetobacter baumannii* worldwide.

Keywords: *Acinetobacter baumannii*, CHDLs, carbapenem-hydrolyzing, β-lactamases.

1. INTRODUCTION

Acinetobacter baumannii, a Gram-negative non-fermentative strictly aerobic, non-motile, non-pigmented, catalase-positive and oxidase-negative coccobacillus belonging to the family Moraxellaceae, has in recent years gained increasing notoriety as a nosocomial pathogen. First described in 1911 by Beijerinck, the genus Acinetobacter has expanded to contain 32 taxonomically distinct species, most of which are environmental organisms not associated with human disease. However, in the past decade strains of *A. baumannii* often exhibiting multidrug resistance have emerged as a significant clinical problem worldwide. *Acinetobacter spp*. has emerged in recent years as a major cause of nosocomial infections associated with significant morbidity

and mortality. They can be associated with a wide range of clinical complications, such as pneumonia, septicemia, urinary tract infections, wound infections and meningitis, especially in immunocompromised patients and are a particular problem in intensive care units where numerous outbreaks have been extremely difficult to control (1,2,3,4)

The rapid emergence and global dissemination of *A. baumannii* as a major nosocomial pathogen is remarkable and demonstrates its successful adaptation to the 21st century hospital environment. The growing prevalence of carbapenem-resistant *A. baumannii* (CRAB) restricts available treatment options and is associated with elevated mortality rates (5).

2. TAXONOMY

The genus *Acinetobacter* was previously classified under at least 15 different names including *Bacterium anitratum*, *Heralleavaginicola*, *Mimapolymorpha*, *Achromobacter*, *Alcaligenes*, *Micrococcus calcoaceticus*, B5W, *Moraxella glucidolytica*, and *Moraxella lwoffii*. In 1954, Brisou and Prévot identified the genus as *Acinetobacter*, which was then divided into 2 species: *A. calcoaceticus* and *A. lwoffii*. Based on recent genetic studies, 19 different species have been identified, but only 7 have been given names (*calcoaceticus*, *baumannii*, *haemolyticus*, *junii*, *johnsonii*, *lwoffii*, *radioresistens*) (6). Outbreaks of nosocomial infections have most commonly been associated with *A. baumannii*. Other *Acinetobacter* spp. cause infections, but less frequently. The genus Acinetobacter has a long and convoluted taxonomic history.

3. MECHANISMS OF CARBAPENEMS RESISTANCE

The majority of clinical *A. baumannii* isolates are highly resistant to a variety of antibiotics, including carbapenems, which are currently the drugs of choice in the treatment of the severe infections caused by this organism. Carbapenem resistance in *A. baumannii*is associated with a variety of combined mechanisms, including the acquisition of β-lactamases, AmpC stable derepression, decreased permeability, altered penicillin-binding proteins (PBPs), and to a small extent, efflux pump overexpression. In particular, Ambler class B enzymes (also referred to as metallo- β-lactamases, MBLs) and carbapenem hydrolyzing class D- β-lactamases (CHDLs) have been identified worldwide from carbapenem-resistant *A. baumannii*strains. (7,8).

Although carbapenems generally represent the last resort in treating life-threatening infections caused by *A. baumannii*, carbapenem resistance due to OXA-

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type (class D) carbapenemasesis increasing. The most problematic recent occurrence of antimicrobial resistance in *A. baumannii*is the emergence of numerous OXA enzymes that confer β-lactam resistance.

3-ACQUISITION OF CARBAPENEM HYDROLYSING OXACILLINASE GENES: CHDLs.

Oxacillinases are unusual β-lactamases that forma heterogeneous group with respect to their structural or biochemical properties (9). Class D β-lactamases, also known as oxacillinases or OXA type β-lactamases (OXAs), are active-serine-site enzymes like Ambler class A and class C β-lactamases, differing from class A and C enzymes in amino acid structure, whereas class B β-lactamases are metalloenzymes with a Zn^{2+} ion(s) in the active site. Phenotypically, many class D β-lactamases belong to the Bush subgroup 2d β-lactamases. (10)

These enzymes usually hydrolyse oxacillin more efficiently than benzylpenicillin. Some acquired class D β-lactamases may also hydrolyze carbapenems. None of these carbapenem-hydrolyzing class D β-lactamases (CHDLs) significantly hydrolyze expanded- spectrum cephalosporins, therefore indicating that currently known class D β-lactamases are unable to combine extended-spectrum and carbapenem-hydrolyzing properties. (11,12,13). The vast majority of OXA carbapenemases have been discovered in the opportunistic gram-negative pathogen *Acinetobacter baumannii*. Based on their amino acid sequence, three main acquired carbapenem-hydrolysing class D oxacillinase (CHDL) gene clusters have been identified in *Acinetobacter baumannii*.

Identification of a CHDL-encoding gene was first reported in *A. baumannii* in 1995. This enzyme was obtained from a clinical isolate found in Scotland in 1985 before the introduction of carbapenems. Since then, this plasmid-encoded enzyme, initially named ARI-1 (Acinetobacter Resistant to Imipenem). This enzyme hydrolyses imipenem and also confers resistance to penicillins, but not to second and third-generation cephalosporins. Biochemical characterization revealed a β-lactamase with a pI value of 6.65 that was poorly inhibited by clavulanic acid and EDTA (14,15,16,17). OXA-23 is a representative of a CHDL subgroup that also includes OXA-27.

The corresponding *bla*OXA-27 gene, identified in a carbapenem resistant *A. baumannii* isolate from Singapore, was likely chromosomally located (18). Recent data indicate that OXA-23-positive *A. baumannii* strains have spread throughout the world,

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to locations including Senegal, Spain, Iran, Bulgaria, Greece, France, Bulgaria, Iran, the United Arab Emirates, Tunisia, Brazil, and Australia. In addition, OXA-23 producers have been at the origin of hospital outbreaks in French Polynesia, Colombia, the United Kingdom, Turkey, China, and Korea and very recently in Algeria (13,19,20). A second group of CHDLs is made up of OXA-25, OXA-26, OXA-40, and OXA-72. These enzymes differ by a few amino acid substitutions only. An original sequencing error in OXA-24 makes it now OXA-40.

OXA-40, that differed by one or two amino acid changes from OXA -25, and -26 and an AmpC-type cephalosporinase. The OXA-40 β-lactamase had a mainly narrow spectrum hydrolytic profile, but it included ceftazidime and imipenem. Its activity was resistant to inhibition by clavulanic acid, tazobactam, sulbactam, and, like most of the other carbapenem-hydrolyzing oxacillinases, NaCl. The $bla_{\text{OXA-40}}$ gene has since been identified in different areas, especially in Portugal and Spain (21,22,23,24). OXA -160 a novel variant of OXA-4O was recently identified in *A. Baumannii* isolates from Pennsylvania (25). OXA-25 and OXA-26, had >98% amino acid homology with each other and have been identified in carbapenem-resistant *A. baumannii* isolates recovered from Spain and Belgium, respectively (18).

OXA-72 has been identified in *A. baumannii* isolates from China, South Korea, Taiwan, and Bahrain and recently in Brazil, Croatia and Colombia (26,27,28,29,30,31,32). A third group of CHDLs contains OXA-58. The OXA-58 enzyme hydrolyzes penicillin and carbapenemmsat low levels. Whereas weak hydrolysis of cefpirome was detected, hydrolysis of cefepime, ceftazidime, and cefotaxime was not. The rate of hydrolysis of imipenem was 10-fold lower, and that of meropenem was 100-fold lower, than that of benzylpenicillin. The OXA-58 confers reduced susceptibility to carbapenems, but in vitro experiments suggest that it can produce a high level of resistance when additional efflux mechanisms are expressed. The *bla*OXA-58 gene was found to be plasmid located, and the activity of OXA-58 was inhibited by NaCl, as opposed to the other oxacillinases possessing some carbapenemase activity(33; 34 ; 13).The OXA-58 was 1st identified in France in 2003(35); at present, it has been found worldwide in *A. baumannii* including France, Italy, Belgium, the United Kingdom, Austria, Turkey, Greece, Kuwait, Brazil, Argentina, and Australia (13).

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Recently, the OXA-58 was founded in *Acinetobacter baumannii* isolates respectively from Algeria, Bolivia and Brazil (19,36,37). OXA-97 is a point mutation variant of OXA-58 that shares the same hydrolytic properties.OXA-97, which differed from OXA-58 by a single amino acid substitution and conferred the same β-lactam resistance profile as OXA-58. The *bla*OXA-97 gene was located on plasmids in a clonal isolate collected at the Sahloul Hospital in Sousse, Tunisia (38). Very recently, the novel CHDL OXA-143 was identified in a clinical *A. baumannii* isolate that had been recovered in Brazil. OXA-143 showed 88% amino acid sequence identity with OXA-40, 63% identity with OXA-23, and 52% identity with OXA-58. It hydrolyzed penicillin, oxacillin, meropenem, and imipenem but not expanded-spectrum cephalosporins. Recently an OXA-231, a new variant of OXA-143 was detected in a Brazilian isolate of *Acinetobacter baumannii* (39,40).

Acinetobacter baumannii possesses an intrinsic class D oxacillinase, the ubiquitous nature of OXA-51-like genes. The OXA-51 subgroup of enzymes exhibits relatively weak hydrolytic activities, compared with other carbapenemases but has been associated with carbapenem resistance in isolates with the insertion sequence ISAba1 upstream of the oxacillinase gene. bla$OXA_{-51\text{-like}}$ alleles are chromosomally located and it has been confirmed that these sequences are intrinsic in most or all *A. baumannii* strains. β-Lactamase OXA-69 shared 97% amino acid identity with the recently described OXA-51 enzyme of *A. baumannii* and 62 and 56% amino acid identity with the carbapenem-hydrolyzing oxacillinases OXA-24 andOXA-23, respectively. Biochemical characterization of the purified OXA-69 revealed a narrow-spectrum hydrolysis profile but including, at a low level, imipenem and meropenem (41,42). The commonest enzymatic mode of carbapenem resistance is the production of oxacillinases encoded by genes of the bla_{OXA-23}, bla_{OXA-40} and $bla_{OXA-58\text{-like}}$ lineage. These may be plasmid or chromosomally located (1).

4- CONCLUSION

Carbapenems remain drugs of choice for the treatment of *A. Baumannii* infection, but their efficacy can be compromised by the spread of novel class D carbapenemases. As a result, carbapenem-intermediate or -resistant *A. baumannii* isolates are becoming increasingly prevalent in several countries. Colistin, an old antibiotic from the polymyxin group, is very effective against multidrug-resistant (MDR) *A. baumannii* isolates, but the emergence of resistance has occasionally been

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experienced. Tigecycline, has provided hope for the treatment of *A. baumannii* infections, including carbapenem- resistant isolates. Because therapeutic options are limited for multidrug-resistant *Acinetobacter* infection, the development or discovery of new therapies, well-controlled clinical trials of existing antimicrobial regimens and combinations, and greater emphasis on the prevention of health care–associated transmission of multidrug-resistant *Acinetobacter* infection are essential.

ACKNOWLEDGEMENT

This work was funded by grants from the Tunisian Ministry of Scientific Research and Technology.

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