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Oxacillinase (OXA)-producing Acinetobacter baumannii in Brazil: clinical and environmental impact and therapeutic options

Acinetobacter baumannii produtor de oxacilinases (OXA) no Brasil: impacto clínico, epidemiológico e opções terapêuticas

Micheli Medeiros[1]; Nilton Lincopan[2]

ABSTRACT

Following a worldwide trend, infections caused by MDR OXA-type (Ambler class D) carbapenemase-producing *Acinetobacter baumannii* are currently regarded as a clinical and epidemiological emergency in Brazil. OXA-producing *A. baumannii* strains have been identified in the states of Alagoas, Amazonas, Bahia, Distrito Federal, Espírito Santo, Goiás, Mato Grosso, Mato Grosso do Sul, Minas Gerais, Paraná, Pernambuco, Rio de Janeiro, Rio Grande do Norte, Rio Grande do Sul, Santa Catarina and São Paulo. In some settings, the presence of OXA-23- and/or OXA-143 -producing *A. baumannii* (so far restricted to Brazil) has been endemic and *A. baumannii* strains carrying blaOXA-23 genes have been detected in hospital wastewater effluents, hence a potential risk to the community and the environment. Although molecular typing by *multilocus sequence typing* (MLST - Bartual scheme, University of Oxford, http://pubmlst.org/abaumannii/) has revealed the international spread of a clonal complex (CC) denominated CC92, in Brazil most OXA-23-producing *A. baumannii* belong to CC113, CC109 or CC104 clonal complexes. Finally, from a clinical point of view, the main problem of *A. baumannii* infections is the limited use of antibacterial agents with *in vitro* activity, often restricted to ampicillin/sulbactam, polymyxin B and/or colistin (polymyxin E)..

Key words: huHAIs; multidrug-resistant; carbapenems; oxacilinases; OXA-23; OXA-143; MLST.

INTRODUCTION

Acinetobacter baumannii is a non-fermentative Gram-negative bacillus widely recognized as an opportunistic nosocomial pathogen. It has assumed high clinical importance in the last two decades due to its frequent association with healthcare infections (healthcare- associated infections -HAI), most of which with unfavorable prognosis and expression of comprehensive antimicrobial resistance mechanisms to antibiotics (ATBs)[11, 25, 101, 116, 118, 121].

In Latin America, *A. baumannii* has accounted for 6.6% of the cases of HAI[36]. The main sites reported by multicenter studies are lower respiratory tract (17.7%), bloodstream (7.2%) , skin and soft tissues - including burns and surgical sites - (9.9%) and urinary tract (1.6 %)[36, 117].

The risk factors comprise invasive procedures such as mechanical ventilation, central venous catheter or urinary catheter as well as the prior use of broad-spectrum ATBs[14, 29, 42, 76, 85, 101, 117, 118].

In many cases, recurrent outbreaks of nosocomial infection are favored by the intrinsic factors of the species such as the following: i) tolerance to desiccation ; ii) viability and growth in a wide temperature and pH range; iii) the multidrug resistance, which contributes to the spread of these isolates among patients

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at hospital environment[8, 25, 53, 85]. Furthermore, the epidemiology of the infection by *A. baumannii* is often complex and the coexistence of epidemic and endemic infections in a given unit promotes the widespread use of broad-spectrum antibiotics for prolonged periods, hence promoting selective pressure on hospital microbiota and selecting resistant bacterial strains[10, 29, 82, 86, 90, 98, 118].

One of the most striking features of *Acinetobacter* species is its extraordinary ability to develop multiple resistance mechanisms against major classes of commercially available antibiotics. In fact, *A. baumannii* can easily express resistance to the broad spectrum beta-lactam (third generation cephalosporins, carboxypenicillins and carbapenems) and to aminoglycosides by the production of a variety of hydrolytic enzymes, namely beta-lactamases and transferases, which inactivate this class of antibacterial agents. Additionally, most strains can express high levels of resistance to fluoroquinolones[29, 118] (**Figure 1**).

In general, the expression of multiple resistance mechanisms provides phenotypes categorized as multidrug -resistant (MDR- resistance to ≥ 1 antibacterial agent in ≥ 3 categories), extensively drug resistant (XDR- resistance to ≥ 1 antibacterial agent in all except to ≤ 2 categories) and pan -resistant (resistant to all tested antibiotics)[75]. Among the ATB categories used in this definition, the following ones are recommended for *A. baumannii*: aminoglycosides (gentamicin, tobramycin , amikacin and netilmicin), carbapenems (imipenem, meropenem and doripenem), fluoroquinolones (ciprofloxacin and levofloxacin), antipseudomonal penicillin / beta-lactamase inhibitor (piperacillin/tazobactam and ticarcillin/clavulanate), extended-spectrum cephalosporins (cefotaxime, ceftriaxone, ceftazidime and cefepime), inhibitors of folic acid synthesis (trimethoprim-sulfamethoxazole), penicillin / beta-lactamase inhibitor (ampicillin/ sulbactam), polymyxins (polymyxin B and colistin) and tetracyclines (tetracycline, doxycycline and minocycline)[75].

The widespread use of ATBs has contributed to the emergence of multi-resistant bacteria which are associated with nosocomial infections and high morbidity and mortality rates[82, 98]. This problem is exacerbated by the failure to develop new antibiotics[7, 148].

The multiple resistance mechanisms in *A. baumannii* may have an intrinsic and/or acquired origin, including the following: i) loss of membrane permeability; ii) ATB efflux; iii) change in the target binding site; iv) production of enzymes (beta-lactamases, methylases and transferases); vi) alternative metabolic routes[39, 86, 101].

Currently, in Brazil, the main problem in the treatment of infections caused by MR bacteria, including *A. baumannii*, is the expression of beta-lactamases that hydrolyze carbapenems (imipenem , meropenem, ertapenem and doripenem) and third

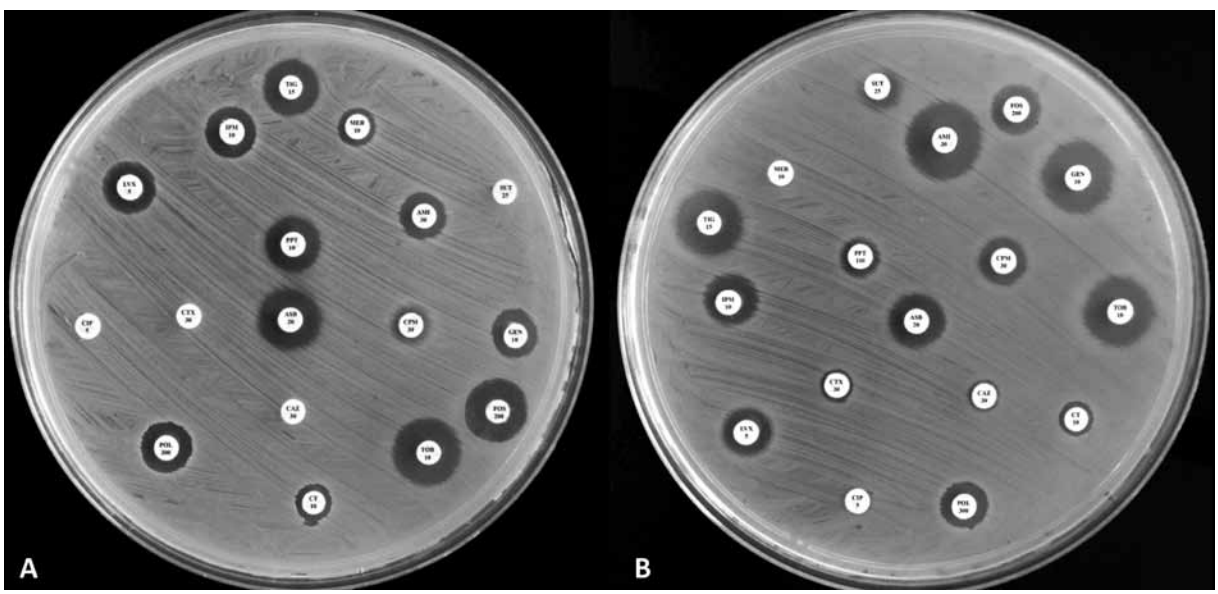

FIGURE – *Antibiogram (Kirby-Bauer) of MR* Acinetobacter baumannii *strain*

A) OXA -23 – producing Acinetobacter baumannii , *sensitive only to TOB, ASB and FOS; B) OXA -143 – producing* Acinetobacter baumannii *sensitive only to GEN, AMI and TOB.*

The tested antibiotics correspond to TIG - 15 µg; MER - 10 µg; IPM - 10 µg; PPT -10 µg; AMI - 30 µg; SUT - 25 µg; ASB - 20 µg; CPM - 30 µg; GEN - 10 µg; FOS - 200 µg; TOB - 10 µg; CAZ : 30 µg; CT - 10 µg; CIP - 5 µg, CTX - 30 µg; LVX - 5 µg.

MR: multi-resistant; OXA: oxacillinase; TIG: tigecycline; MER: meropenem; IPM: imipenem; PPT: piperacillin / tazobactam; AMI: amikacin; SUT: sulfamethoxazole; ASB: ampicillin/sulbactam; WITH: cefepime; GEN: gentamicin; FOS: fosfomycin; TOB: tobramycin; CAZ: ceftazidime, CT: colistin, CIP: ciprofloxacin; CTX: cefotaxime; LVX: levofloxacin.

generation (ceftazidime) and fourth generation (cefepime) cephalosporins, which are considered the latest therapeutic choices[59, 95, 134].

Carbapenems have been regarded as drugs of choice for the treatment of infection by MR *A. baumannii*. In this regard , the Antimicrobial Surveillance Program (SENTRY), Meropenem Yearly Susceptibility Test Information Collection (MYSTIC) and Surveillance and Control of Pathogens of Epidemiological Importance (SCOPE) have reported that carbapenem resistance in *A. baumannii* has increased considerably in Latin America, mainly in Brazil, Argentina and Chile (**Table**) .

Acinetobacter baumannii and production of oxacilinase type carbapenemase: clinical and environmental significance

Oxacillinase type carbapenemases (OXA) belonging to Class D (Ambler classification) have been reported in *Acinetobacter* species worldwide, particularly in hospital environment. In Brazil, OXA-producing strains have been associated with outbreaks of nosocomial infection[4, 22, 24, 86].

Class D differs from other classes of enzymes due to the fact that it contains serine in the active site. Initially, the main species belonging to the *Pseudomonadaceae* family, particularly the *Pseudomonas aeruginosa* species, showed resistance to some types of non-carbapenem beta-lactams, mediated by the action of these enzymes. However, the first OXA-type carbapenemase was characterized from a clinical strain of MR *A. baumannii* isolated from a patient in Edinburgh, Scotland, in 1985[126, 138].

In *A. baumannii* , oxacilinases (class D) are subdivided into 6 groups: OXA-23 -like (OXA-23, OXA-27 and OXA-49), OXA-24/40-like (OXA- 24, OXA-25, OXA-26, OXA-40, OXA-72 and OXA-160), OXA-58-like (OXA-96 and OXA-97), OXA-51-like[28, 147] and OXA -182, which is restricted to South Korea[61]. A new variant has been recently identified in Brazil (OXA-143), which is restricted to the country with rapid spread in major urban centers[6, 51, 52, 88, 97, 156].

Unfortunately, OXA-23-producing *A. baumannii* isolates have been detected in hospital sewage in large cities such as Porto Alegre[27] and in urban rivers from the state of São Paulo[109], which entails the possibility of spread of hospital strains to the environment, hence a serious public health problem.

Acinetobacter baumannii and production of OXA-23-type carbapenemase

The first description of OXA-23 – producing *A. baumannii* was reported in Scotland in 1985[138]. Since the last decade this enzyme has been detected in several countries such as Tunisia[78], the United Arab Emirates[99], Bulgaria[143], Afghanistan and Iraq[16], Turkey[48],Thailand[104], South Korea[54, 151], Italy[3],France[37], China[31, 55], Portugal[77], Poland[106], Greece[69] and Brazil[4, 5, 18, 19, 24, 84, 85, 97].

In Brazil, the emergence and spread of OXA-23 seemingly began in Curitiba, state of Paraná, in 2003. After 2003, this enzyme has been found in other states such as São Paulo[4, 5, 97], Rio de Janeiro[18, 19], Rio Grande do Sul[84-86], Espírito Santo, Alagoas, Amazonas, Bahia, Distrito Federal, Goiás, Minas Gerais, Rio Grande do Norte, Santa Catarina, Mato Grosso do Sul[19] and Mato Grosso (research in progress) (**Figure 2**).

In Brazil, the high rate of resistance to imipenem in *A. baumannii* was initially attributed to the production of

TABLE – Antimicrobial resistance indexes in *A. baumannii* isolates reported by SENTRY, MYSTIC and SCOPE

% resistance/ year of study /total number of isolates

Antimicrobial	Brazil					Latin America			Global	
	SENTRY 1997-1999[134] *n* = 252	SENTRY 2001[135] *n* = 90	SENTRY 2008-2010[36] *n* = 355	MYSTIC 2009[59] *n* = 137	SCOPE 2007-2010[83] *n* = 282	SENTRY 1997-2001[149] *n* = 826	SENTRY 2008-2010[36] *n* = 845	MYSTIC 1998-2004[150] *n* = 452	MYSTIC 2002-2004[150] *n n* = 2.253	SENTRY 2008-2010[36] *n* = 4.686
Imipenem	11.9%	2.2%	73.0%	2.9%	55.9%	13.1%	67.8%	28.1%	25.3%	40.3%
ceftazidime	73.4%	71.1%	87.0%	59.1%	70.0%	71.5%	81.7%	72.1%	61.9%	57.6%
Gentamicin	50.4%	61.1%	52.4%	27.7%	51.8%	67.1%	53.3%	52.0%	48.1%	NR
Ciprofloxacin	64.7%	66.7%	86.5%	65.7%	73.4%	69.5%	87.2%	64.6%	59.5%	66.9%
Amikacin	68.3%	64.4%	59.1%	57.7%	NR	66.0%	62.6%	NR	NR	51.4%

SENTRY: Antimicrobial Surveillance Program; MYSTIC: Meropenem Yearly Susceptibility Test Information Collection; SCOPE: Surveillance and Control of Pathogens of Epidemiological Importance;
NR: no resistance

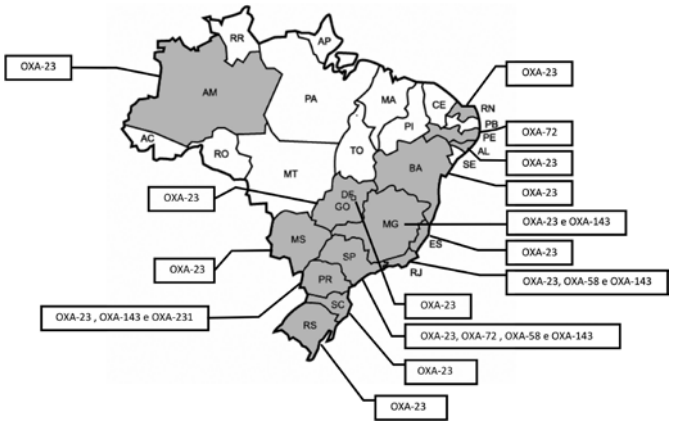

FIGURE 2 – *Current overview of the spread of OXA -type carbapenemase producing A. baumannii isolates in Brazilian states* [4-6, 18, 19, 24, 28, 40, 41, 52, 84-87, 96, 97, 139, 155, 156]

States filled in gray indicate the occurrence of OXA- producing strains.

OXA: oxacillinase.

metallo-beta-lactamase (imipenemase type - IMP -1)[33, 131]. However, following a global trend , the production of OXA -23 began to be reported in several medical centers, contributing to the endemicity of multiple clones[85, 139], which are commonly associated with outbreaks of nosocomial infection[4, 18, 24, 84, 85, 96, 139].

The hydrolysis of carbapenems by OXA-23 enzyme contributes greatly to the emergence of resistant strains[63]. The contamination is associated with risk factors such as previous antibiotic treatment, ICU admission, immunosuppression and severe underlying diseases[14, 15, 29, 42, 76, 117, 118].

The treatment of infection by carbapenem resistant *A. baumannii* is hampered by the lack of therapeutic options. An additional feature of OXA-23 positive strains has been the resistance expression to other classes of antibiotics such as aminoglycosides and fluoroquinolones[153] (Figure 1).

ATB agents exhibiting activity against OXA-23 producing *A. baumannii* are restricted to the use of polymyxin and ampicillin/sulbactam[67, 107, 161]. Nevertheless, strains resistant to both antibiotics have already been identified[129], corroborating the emergence of MDR phenotypes and/or XDR[75].

Acinetobacter baumannii and production of OXA-58 carbapenemase

The production of OXA-58 carbapenemase has been reported sporadically in comparison with OXA-23 and OXA-24. Moreover, its hydrolytic spectrum is wider[23, 49, 50].

The first case of OXA-58- producing *A. baumannii* occurred in France in 2003, where it spread rapidly[50, 80, 122]. Subsequently, OXA -58 positive strains were described in Australia[116], United Kingdom[23], Argentina[91], Greece[69, 113, 124], China[73, 160], Italy[3, 12, 20], Turkey[48, 64], Brazil[5, 28, 86].

OXA-58 enzyme confers resistance to carbapenems, cephalosporins and monobactams of third and fourth generations. OXA-58 producing isolates have shown a MR profile for aminoglycosides, fluoroquinolones and sulfonamides as well as intermediate resistance to tigecycline. Moreover, they are only sensitive to rifampicin, tetracycline, colistin, polymyxin B and , in some cases, ampicillin/sulbactam[12, 20, 49, 122].

The first cases of infection by OXA-58- producing *A. baumannii* have been recently identified in the states of São Paulo and Rio de Janeiro, Brazil[5, 28, 87].

Acinetobacter baumannii and production of OXA-72 carbapenemase

OXA-72 enzyme belongs to OXA-24/40-like family together with OXA-24, OXA-25, OXA-26 and OXA-40[73, 116].

The first report of OXA-72 occurred in Thailand in 2004 (GenBank Accession no. AY739646). In 2004, it was subsequently identified in Taiwan[72, 73] and other Asian countries such as China[153] and Korea South[65]. In Europe, OXA-72 isolates have been found in France[8], Spain[17] and Croatia[30]. In Brazil, this type of isolate has been recently reported in sporadic cases in the states of São Paulo and Rio de Janeiro[5, 86, 155] and more recently in Recife (personal communication , Professor Marcia Maria Camargo de Morais, *Instituto de Ciências Biológicas*, Universidade de Pernambuco) .

This OXA confers resistance to third and fourth generation cephalosporins as well as carbapenems. Nonetheless, OXA-72 isolates have shown a MR profile to fluoroquinolones and aminoglycosides. In most cases, they are only sensitive to polymyxin B and colistin[17, 73, 155].

Acinetobacter baumannii and production of OXA-143 and 231: new genetic event emerging in Brazil

A new OXA denominated OXA-143 was announced by Higgins *et al.* in 2009. The $bla_{OXA-143}$ gene was identified in a clinical isolate of MR *A. baumannii* recovered in Brazil and collected in an unspecified hospital during a multicenter study[51]. The $bla_{OXA-143}$ gene relates to other OXA enzymes from the group OXA-24/40-like and OXA-182, accounting for over 80% similarity[61, 117, 123].

This new genetic event so far has referred exclusively to *A. baumannii* in Brazil. As there are no studies assessing the

impact of this new genetic resistance determinant, our group has conducted a multicenter study in public hospitals from the state of São Paulo and Minas Gerais, describing a high prevalence of OXA -143 producing *A. baumannii* isolates, which could reflect a new phenomenon with endemic features [6, 87, 88]. These data were corroborated in another study by Mostachio et al. [97]. During the year 2011, a case of OXA-143 producing *A. baumannii* appeared in the state of Rio de Janeiro and a new allelic variant of the $bla_{OXA-143}$ gene was found in the state of Paraná[40, 41, 156]. In the 51st Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC), held in Chicago, USA , in September 2011, Cayo *et al.* claimed that the presence of OXA-143 producing *A. baumannii* in Brazil dates from 1995[21]. Recently, OXA-143 producing *A. baumannii* strains have been isolated in Juiz de Fora, Minas Gerais[108].

Identification of bla_{OXA} genotypes and molecular epidemiology

Unlike other carbapenemases identified in Gram-negative bacteria, which can be screened by phenotypic methods using enzyme inhibitors such as ethylenediaminetetraacetic acid (EDTA), phenyl boronic acid and thiol derivatives , the detection of OXA-type carbapenemase in *A. baumannii* samples is made by molecular biology. Initially, Woodford *et al.* developed a polymerase chain reaction (PCR) multiplex for the identification of genes encoding the major OXAs (bla_{OXA-51}-, bla_{OXA-23}-, bla_{OXA-40}-ebla_{OXA-58}-*like*)[158]. Subsequently, Higgins *et al.* published a paper in which the inclusion of primers for the identification of new variant $bla_{OXA-143}$ was standardized in the multiplex PCR reaction[52]. More recently, Mostachio *et al.* published a multiplex PCR method for the screening of genotypes associated with the production of OXA type carbapenemase and metallo-beta-lactamases in A. *baumannii*[96].

To facilitate the epidemiological study of OXA-producing *A. baumannii*, there is a consensus for the identification of endemic clones spread internationally, which is given by the MLST typing. There are two MLST schemes available for *A. baumannii*, which contain information about primers, PCR conditions, sequencing and a sequence database (SD) for comparative analysis and identification of SDs and CCs. One of the schemes was described by Bartual[9], whose software was developed by Keith Jolley and is hosted at the University of Oxford, UK (http://pubmlst.org/abaumannii/) . This scheme includes alleles *gltA*, *gyrB*, *gdhB*, *recA*, *cpn60*, *gpi* e *rpoD*[56]. A second scheme has a database hosted at the Pasteur Institute (www.pasteur.fr / mlst) and includes alleles *cpn60*, *fusA*, *gltA*, *pyrG*, recA, *rplB* e *rpoB*[45].

Using the software eburst (http://eburst.mlst.net/), the current database comprises 38 different STs of *A. baumannii* isolates in Brazil, which reflects the genetic diversity of strains with bla_{OXA} genes[45].

The worldwide spread of bla_{OXA}-$_{23}$ gene has been linked with specific clones, mainly clonal complex CC92, currently the largest clonal complex at the University of Oxford multilocus sequence typing scheme (MLST-UO) (http://pubmlst.org/abaumannii/), which to date comprises 207 strains and 46 different STs. OXA-23 producing strains belonging to CC92 have been identified in different countries, including Australia, USA, China, Italy, France, Tahiti, Vietnam, South Korea, Thailand and South Africa[1, 3, 31, 66, 100, 103, 133]. Additionally, bla_{OXA-58} *A. baumannii* strains belonging to CC92 -58 have been found in Italy[3].

Interestingly, in Latin America, MLST allelic profiles for OXA-producing *A. baumannii* has been linked to CC92[45, 86, 142]. Conversely, most OXA-23 producing strains belong to CC113 from MLST-UO[45, 86, 127, 142]. Less frequently, in Brazil, strains of OXA-23 positive *A. baumannii* have been identified as belonging to another international clonal complex denominated CC109[85]. Finally , another CC identified in Argentina and Brazil is CC104 (MLST-UO)[86, 127], which has been sparse in European countries such as Norway, Portugal, Czech Republic, Netherlands, Turkey, Spain and Greece[58, 86, 127].

Therapeutic options for the treatment of infections caused by *Acinetobacter baumannii*

ampicillin – sulbactam

This compound is a combination of a beta-lactam and a beta-lactamase inhibitor (**Figure 3).** Betalactamase inhibitors are beta-lactam analogues with limited antibacterial activity and act competitively inhibiting the activity of the beta-lactamase enzyme[68]. Generally, these inhibitors are used in association with beta-lactams, promoting the restoration of their activity[44]. The ampicillin sulbactam is associated with ampicillin in a fixed ratio 1:2, optimizing its activity spectrum.

Currently, some studies have demonstrated synergistic activity of ampicillin - sulbactam with tigecycline[119], amikacin[81, 89, 137], tobramycin[146] and imipenem[114, 140] for treating MDR *A. baumannii.*

Imipenem

Imipenem is an ATB that belongs to the class of beta-lactams, more specifically the carbapenem subclass (Figure 3). This

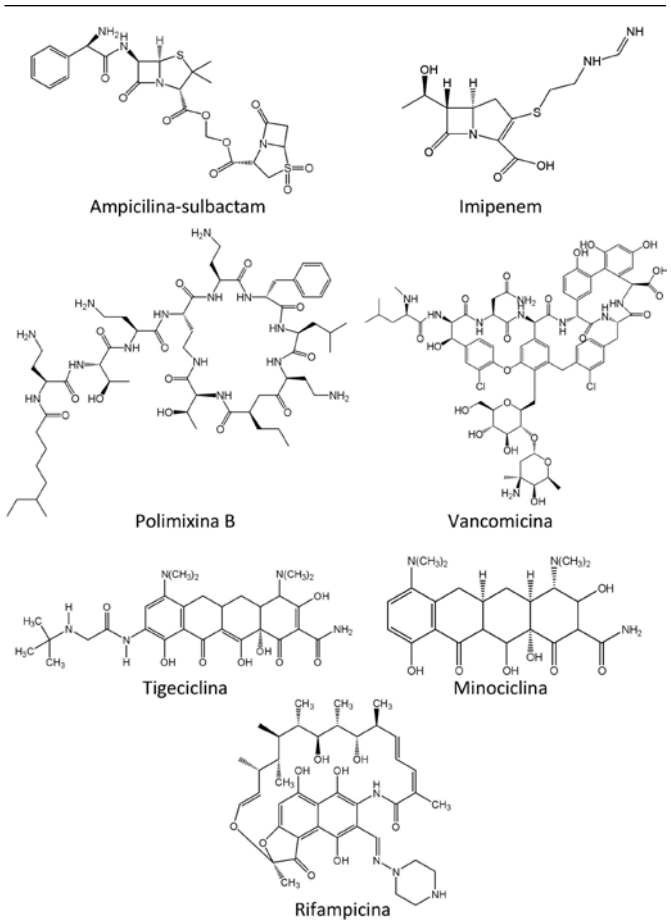

FIGURE 3 – *Chemical structures of the major antimicrobial compounds applied in the clinical treatment of Acinetobacter baumannii*

drug inhibits cell wall synthesis by binding beta-lactam with penicillin-binding proteins(PBPs), which catalyze the synthesis of peptidoglycan present in the bacterial cell wall by means of a transglycosylation and transpeptidation reaction[74, 136].

Carbapenems, conversely, are more efficient and stable to degradation by a broad spectrum of beta-lactamases, exhibiting high antimicrobial activity against almost all Gram-negative bacteria, including MR fermenters[44].

Studies on the synergistic effect against MR *A. baumannii* have been conducted with the use of imipenem in combination with lipopeptides, glycylcyclines , aminoglycosides, aztreonam, rifampicin, and even beta-lactams such as ampicillin - sulbactam[62, 81, 89, 114, 119, 125, 132, 140, 141, 152, 154].

Polymyxin B

Polymyxin B (PB) is an ATB belonging to the class of lipopeptides (Figure 3), which act primarily on the cell wall of Gram-negative bacteria, leading to a rapid change in the permeability of the cytoplasmic membrane, which may ultimate cause cell death[32]. This drug has demonstrated significant in vitro antimicrobial activity against Gram-negative bacteria such as *Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter spp*., *Acinetobacter spp*. and *Pseudomonas aeruginosa*[34, 35, 92]. Currently, it is an important ATB option against MR microorganisms[34, 35, 159], including OXA producing *A. baumannii*.

In recent years, a few studies have confirmed that polymyxin B has a synergistic potential when used in combination with carbapenems[89, 112, 152, 154] and vancomycin[89] as well as partially synergistic potential with rifampicin[89, 154].

Vancomycin

Vancomycin belongs to the glycopeptide class (Figure 3), whose action mechanism is the inhibition of peptidoglycan synthesis in the bacteria cell wall in the late phase, preventing the incorporation of peptidoglycans into the growing cell wall by binding the end portion of D-Alanyl-D-Alanine with the pentapeptide side chain[57, 130].

This drug is widely applied in the treatment of infections caused by methicillin resistant *Staphylococcus aureus* (MRSA) and serious infections by Gram-positive microorganisms in patients who are hypersensitive to penicillin[44, 57, 93, 120].

Gordon and Wareham tested a combination of antimicrobials that are not conventionally applied in the treatment of infections by *Acinetobacter baumannii*, a glycopeptide (vancomycin), which is used for the treatment of Gram-positive, and one lipopeptide (colistin), used to treat Gram – negative infections. Therefore, this combination showed synergism when tested in MR *A. baumannii* strains[42, 89], which is clinically remarkable insofar as many nosocomial patients suffer from polymicrobial infections by Gram-positive bacteria such as *Enterococcus spp*. and coagulase-negative *staphylococcus* (157) as well as Gram-negative bacteria such as *A. baumannii*, *Klebsiella pneumoniae* and *Escherichia coli*[47, 101].

Tigecycline

Tigecycline is a broad-spectrum antimicrobial drug from the Glycylcycline class, semisynthetic derivative of minocycline (Figure 3), representing the first ATB from this class available for clinical use[105, 111]. It inhibits the bacterial protein synthesis by binding to the 30s subunit of the ribosome[26]. Due to its broad spectrum, it has good performance for both Gram - positive and gram- negative (*S. aureus*, *Enterococcus spp*., *S. pneumoniae,*

Haemophilus influenzae, Moraxella catarrhalis, Neisseria gonorrhoeae, Peptostreptococcus and *Clostridium spp*.), including enterobacteria and *Bacteroides spp*.[105, 111]. Some studies have assessed the use of tigecycline in vitro against MR *A. baumannii*, thus revealing a bacteriostatic activity[79, 110].

Other studies have described a synergistic effect on the clinical use against *A. baumannii*, which is due to the combination of tigecycline with other ATBs such as carbapenems, aminoglycosides, minocycline, lipopeptides, quinolones and beta-lactamase inhibitors[71, 94, 119, 125, 140, 141, 145].

Rifampicin

Rifampicin is an ATB belonging to the ansamycin class that was introduced in clinical practice in the 1970s[2] (Figure 3). The action mechanism of this drug consists in the inhibition of ribonucleic acid (RNA) synthesis by attacking the β subunit of RNA polymerase. This drug has a broad spectrum and is applied in the treatment for tuberculosis, which is caused by *M. tuberculosis* microorganism[2, 74, 128].

Some studies indicate a synergistic effect against *A. baumannii* by associating colistin and rifampicin[132] as well as a partially synergistic effect by combining PB[89, 154], tigecycline[26, 119, 123] or colistin[70].

Minocycline

Minocycline belongs to the tetracycline class (Figure 3), broad-spectrum bacteriostatic ATBS, including anaerobic, Gram- positive and Gram -negative bacteria as well as other microorganisms such as *Rickettsia*, *Chlamydia*, *Plasmodium spp*. and *Mycoplasma pneumoniae*[39, 102].

The action mechanism of this drug is associated with the inhibition of protein synthesis by binding to the 30S subunit of the bacterial ribosome preventing aminoacyl -tRNA binding[13, 39].

The drug minocycline has not been closely related to the study of the synergistic effect on the treatment of *A. baumannii*. Tan *et al.* demonstrated that the association of deminocycline and colistin offers synergistic potential[144] as well as minocycline/ meropenem[70] and minocycline/ cefoperazone -sulbactam[115].

Assessment of synergistic effect in Brazil

Few studies have evaluated the synergistic potential of antibiotic combinations against endemic *A. baumannii* strains in Brazil. A study carried out by Kiffer *et al*. and another investigation by Guelfi *et al.* indicated that approximately 50% of the isolates tested in vitro responded partially to the synergistic effect obtained by the combined use of meropenem/polymyxin B and meropenem/sulbactam. It is particularly worth noting that these investigations did not identify carbapenemase producing strains[47, 61].

A study developed by Medeiros *et al* . successfully assessed the synergistic effect of in vitro associations of polymyxin B/imipenem, amikacin/ampicillin-sulbactam, polymyxin B/vancomycin, polymyxin B/rifampicine against OXA-23, OXA-58, OXA-72 , OXA-143 producing strains. Furthermore, the combination polymyxin B/imipenem confirmed both *in vitro* and *in vivo* results[89].

CONCLUSION

The spread of MR OXA producing *Acinetobacter baumannii* in Brazil is a serious public health problem. The emergence of these strains is associated with high rates of resistance to ATBs commonly used in clinical practice, which increasingly hinders the choice of drugs with in vitro activity employed in the treatment of HAIs. The identification of OXA phenotype and genotype is of utmost importance for a suitable patient management, preventing the introduction and spread of outbreaks and establishing a differential therapeutic approach that preferably includes the combined use of antibacterial agents.

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RESUMO

Seguindo uma tendência mundial, no Brasil, infecções por cepas de Acinetobacter baumannii multirresistentes (MRs) produtoras de carbapenemases do tipo oxacilinases (OXA) classe D de Ambler são atualmente consideradas uma emergência clínica e

epidemiológica. Cepas de A. baumannii *produtoras de OXA têm sido reportadas nos estados de Alagoas, Amazonas, Bahia, Distrito Federal, Espírito Santo, Goiás, Mato Grosso, Mato Grosso do Sul, Minas Gerais, Paraná, Pernambuco, Rio de Janeiro, Rio Grande do Norte, Rio Grande do Sul, Santa Catarina e São Paulo. Em algumas unidades, a presença de* A. baumannii *produtor de OXA-23 e/ou OXA-143 (até agora restrita ao Brasil) tem adquirido um caráter de endemicidade, sendo as cepas de A. baumannii carregando genes blaOXA-23 identificadas em efluentes hospitalares, constituindo um risco potencial para a comunidade e o meio ambiente. Embora, a tipagem molecular por* multilocus sequence typing *(MLST) (esquema proposto por Bartual, Universidade de Oxford, http://pubmlst.org/abaumannii/) tem caracterizado a disseminação internacional de um complexo clonal (CC) denominado CC92, no Brasil, a maioria das cepas produtoras de OXA-23 pertencem ao complexo clonal CC113, CC109 ou CC104. Finalmente, do ponto de vista clínico, o principal problema das infecções por* A. baumannii *é o uso limitado de antibacterianos com atividade in vitro, muitas vezes restrito ao uso de ampicilina/sulbactam, polimixina B e/ou colistina (polimixina E).*

Unitermos: *IRAS; multirresistência; carbapenêmicos; oxacilinases; OXA-23; OXA-143; MLST.*

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