


# Molecular Characterization of Carbapenem-Resistant *Acinetobacter baumannii* with Special Reference to Carbapenemases: A Systematic Review

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**Abstract:** Carbapenemases are  $\beta$ -lactamase enzymes that hydrolyze a variety of  $\beta$ -lactams including carbapenem and belong to different Ambler classes (A, B, D). These enzymes can be encoded by plasmid or chromosomal-mediated genes. The major issues associated with carbapenemases-producing organisms are compromising the activity and increasing the resistance to carbapenems which are the last resort antibiotics used in treating serious infections. The global increase of pathogen, carbapenem-resistant *A. baumannii* has significantly threatened public health. Thus, there is a pressing need for a better understanding of this pathogen, to know the various carbapenem resistance encoding genes and dissemination of resistance genes from *A. baumannii* which help in developing strategies to overcome this problem. The horizontal transfer of resistant determinants through mobile genetic elements increases the incidence of multidrug, extensive drug, and Pan-drug resistant *A. baumannii*. Therefore, the current review aims to know the various mechanisms of carbapenem resistance, categorize and discuss carbapenemases encoding genes and various mobile genetic elements, and the prevalence of carbapenemase genes in recent years in *A. baumannii* from various geographical regions.

**Keywords:** carbapenemases, multidrug-resistance, metallo- $\beta$ -lactamases, oxacillinases

## Introduction

Genus *Acinetobacter* is comprised of a group of species that are gram-negative coccobacilli, aerobe, non-fermenting, encapsulated, and present in the environment. Members from the genus *Acinetobacter* are regarded as non-motile, but there are reports which found that this pathogen showed surface swarming and produced channels (“ditches”) in the semisolid agar used usually as a motility medium.<sup>1–3</sup> *Acinetobacter* can invade the body in various ways and lead to fatal infections.<sup>1</sup> Among *Acinetobacter* spp., *A. baumannii* is the bacterial pathogen from the ESKAPE group (*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii* (*A. baumannii*), *Pseudomonas aeruginosa*, and *Enterobacter* species) and has gained major attention in recent years as a nosocomial pathogen, especially in intensive care and burn units.<sup>4</sup> However, community-acquired infections usually occur in people who have preexisting comorbid conditions.<sup>5</sup> *A. baumannii* is part of the *Acinetobacter calcoaceticus-baumannii* complex, which also includes other species like *Acinetobacter pittii*, *Acinetobacter nosocomialis*, *A. dijkshoorniae*, *A. seifertii* which are pathogenic and *Acinetobacter calcoaceticus* which is nonpathogenic.<sup>6</sup> *A. baumannii* shows increased resistance to most antibiotics and the slower pace in the development of newer antibiotics and limited treatment options have resulted in increased mortality following various infections due to this organism.<sup>1,7</sup>

The carbapenem class of drug is commonly used to treat the life-threatening infections caused by MDR *Acinetobacter* species.<sup>1,8</sup> Carbapenems are bactericidal, broad-spectrum, beta-lactam antibiotics and like all beta-lactam antibiotics

inhibit bacterial cell wall synthesis by binding to penicillin-binding proteins (PBPs 1a, 1b, 2, and 3) and inactivating these enzymes. Certain examples of worldwide used carbapenem are imipenem, meropenem, doripenem, ertapenem, panipenem, and biapenem.<sup>9,10</sup> Taking into consideration carbapenem activity against *A. baumannii*, it has been shown that imipenem and doripenem are more potent than meropenem. Multidrug-resistant (MDR) *A. baumannii* including resistance to carbapenem drugs has been reported globally and is an alarming sign for clinicians due to the burden of infections caused by carbapenem-resistant *A. baumannii*. Both the Center for Disease Control (CDC) and the World Health Organization (WHO) have ranked carbapenem-resistant *A. baumannii* (CRAB) as a high-priority antibiotic-resistant pathogen to tackle.<sup>8–12</sup>

The main mechanisms in carbapenem resistant *Acinetobacter* species are, (i) the production of enzymes (eg, carbapenemase) which hydrolyze these drugs and non-enzymatic mechanisms which include modification in the porins expression or alterations in the gene encoding porins, OMP (Caro, OprD) that result in loss or defects in porins and limit the drug entry into periplasmic space where PBPs are located, (ii) new or altered structure of penicillin-binding proteins (PBPs) that decrease the affinity of  $\beta$ -lactam to PBP and, (iii) overexpression of drug efflux pumps.<sup>13–15</sup> Degradation of  $\beta$ -lactam by  $\beta$ -lactamase enzymes is the most prevalent drug resistance mechanism in *A. baumannii*.<sup>16</sup> But the combination of different drug resistance mechanisms can be observed in the same microorganism. It is important to note that this organism undergoes rapid genetic mutation and acquires foreign antibiotic-resistant determinants by mobile genetic elements and thus expands the spectrum of resistance.<sup>17–21</sup> The global spread of resistant organisms because of the exchange of different resistance determinants was possible with the increase of tourism and human migration in the recent era. Therefore, knowing the epidemiology and change in the genetic pattern of the organism helps to understand this organism better.<sup>17–23</sup>

In this review, we performed a systematic search of the literature to discuss the various mechanisms of carbapenem resistance, especially gene encoding carbapenemases in *A. baumannii*, to highlight the various mobile genetic elements in *A. baumannii* and their role in the spread of carbapenemase genes and to review the prevalence of various carbapenemase encoding genes from 2019–2021 in various parts of the world to understand the present situation.

## Materials and Methods

### Search Strategy with Inclusion and Exclusion Criteria

Articles for the incidence and dissemination of various carbapenemase genes in *A. baumannii* were searched for in Pubmed for the years 2019–2021 using the Boolean query “carbapenem-resistant genes and *Acinetobacter baumannii*”. The search of articles was restricted by selecting full and free full text articles for these years.

Review and original articles were also searched for using various word combinations for *Acinetobacter baumannii* carbapenemase genes, their historical perspectives, mobile genetic elements and mechanism of carbapenem resistance from the Google and Google Scholar search engines.

All those articles found relevant to our review were also included in the study. Articles showing the isolation of only one or two carbapenemase genes (OXA-51 and OXA-23), known to be common to *Acinetobacter baumannii*, were excluded from the study.

The presence of various carbapenemase genes was also searched for from website: <https://www.ncbi.nlm.nih.gov/pathogens/isolates#/refgene/BETA-LACTAM>.

### Data Extraction

Information from various searched studies extracted and included in the present study are the prevalence of various carbapenemase genes, presence of mobile genetic elements, geographical location and year of isolation. For historical perspective the type/site of infection in patients and samples from which they were isolated was also added wherever a search was found. Data identification was done by first author of studies and year of publication. Various types and subtypes of carbapenemase genes present in *A. baumannii* were also included from above mention links.

## Data Analysis

Findings from various studies is structured in two tables provided and also summarized under various headings and subheadings below.

## Mechanisms of Carbapenem Resistance

### Non-Enzymatic Mechanisms of Resistance

#### Penicillin-Binding Proteins (PBPs)

Mutations that change the production level or decrease the binding affinity of PBPs lead to resistance but the mechanism is associated with only low-level carbapenem resistance.<sup>24</sup> In a study from Spain, *A. baumannii* isolated from the blood showed the production of oxacillinases and the lack of PBP2 were the most frequently observed mechanisms of resistance to carbapenems.<sup>25</sup> In a study from Germany, the Im R clone displayed a significantly diminished expression of all PBPs except the 24kD protein. There was no saturation of this PBP, even with a higher concentration of imipenem, explaining the low affinity of imipenem to this target protein.<sup>26</sup>

#### Porin Channels and Outer Membrane Proteins (OMPs)

Various studies identify the differential expression of OMPs in antibiotic-resistant *A. baumannii* strains. OmpA imparts drug resistance to *A. baumannii* by allowing the slow diffusion of negatively charged beta-lactam antibiotics. OprD downregulation was observed in multidrug-resistant and pan-drug-resistant *A. baumannii*.<sup>27</sup> Decreased membrane porin density (Omp22–23, Omp43, Omp44, Omp47, Omp33–36, Omp37 and CarO) was associated with pan-drug-resistance in *A. baumannii*.<sup>28</sup> Several other OMPs in *A. baumannii* associated with carbapenem non-susceptibility are CarO or carbapenem associated protein, HMP-AB (heat-modifiable protein in *A. baumannii*) and OmpW.<sup>29</sup> Various examples of the reduced number of porin channels and poor expression of genes resulting in porin loss or efficacy have been described in the review by Bonomo and Szabo.<sup>30</sup>

#### Efflux Pumps

There are various families of efflux pumps; ABC (ATP-binding cassette) transporter family, RND (resistance nodulation-cell division), MATE (multidrug and toxic compound extrusion), MFS (major facilitator superfamily), SMR (small multidrug resistance). The ABC family mainly exists in Gram-positive bacteria. The CraA, AmvA, CmlA, MdfA, and Tet pumps (part of the MFS family) have been identified in *A. baumannii*. In *A. baumannii* for an increase in the MIC of antibiotics, AbeM is the only efflux pump in the MATE family. For some antibiotics, AbeS (part of the SMR family) is a low-level resistance pump in the *A. baumannii*. AdeABC, AdeDE, AdeIJK, AdeXYZ, and AdeFGH efflux pump, which is associated with resistance to carbapenem, belongs to the RND family prevalent in the *Acinetobacter* species. The *adeABC* is the most studied pump gene that has a strong association with carbapenem resistance. It is composed of AdeA — membrane fusion protein; AdeB — inner membrane protein channel; and AdeC — outer membrane protein channel. Overexpression of *adeABC* is managed by genes -sensor kinase, *adeS*, and response regulator *adeR*. Overexpression of *adeABC* occurs due to mutation of *adeRS* or the insertion sequence of IS*Aba1* element upstream of the *adeABC* operon in *A. baumannii*. *adeABC* include  $\beta$ -lactams, [fluoroquinolones](#), [tetracycline](#) (tigecycline), [macrolide](#) (linamides) and [chloramphenicol](#), [aminoglycosides](#).<sup>29–32</sup> Another RND-type efflux pump in *A. baumannii* is AdeIJK, which is regulated by AdeN, a TetR-type regulator. Located upstream from the AdeFGH operon, AdeL, a LysR-type transcriptional regulator transcribed in the opposite direction and found to be responsible for the overproduction of AdeFGH.<sup>33</sup> A study from China showed the overexpression of AdeABC efflux pump genes was closely associated with carbapenem (meropenem) resistance in *A. baumannii*.<sup>34</sup> A study from South Korea also showed that the expression of the *AdeABC* efflux pump is an important resistance determinant in obtaining antibiotic resistance to the carbapenem group in *A. baumannii*.<sup>32</sup>

## Enzymatic Mechanism of Resistance

Beta-lactamase enzymes are categorized into four classes based on sequence motifs and different hydrolytic mechanisms. Carbapenems are hydrolysed by Class A, B and D enzymes. Carbapenemases are classified according to their active sites into two groups, (i) serine carbapenemases and (ii) metallo- $\beta$ -lactamases (MBLs).<sup>35–37</sup>

### Class A Carbapenemases

In these active sites of enzymes contain serine. These serine- $\beta$ -lactamases can be inactivated by  $\beta$ -lactamase inhibitors like [clavulanic acid](#) and [tazobactam](#).<sup>37</sup>

### Class B Carbapenemases

These  $\beta$ -lactamases are MBLs having Zn or another heavy metal in their catalytic site. Metallo  $\beta$ -lactamase enzymes require a water molecule and a zinc ion to trigger and disrupt the Beta-lactam ring of the drug. These enzymes, like serine- $\beta$ -lactamases, are not inhibited by clavulanate, sulbactam, or tazobactam; instead they are inhibited by metal ion chelators like ethylenediamine tetraacetic acid (EDTA), 1,10-o-phenanthroline or dipicolinic acid. Although MBL-type carbapenemases are less common than OXAs, their hydrolytic activity is 100–1000 times more potent.<sup>35–40</sup>

### Class D Carbapenemases

Genes encoding oxacillinase enzymes (OXAs) are the main cause of carbapenem resistance in *Acinetobacter baumannii*. These enzymes are serine-dependent; usually not inhibited by clavulanic acid, sulbactam, and tazobactam whereas in vitro their activities may be inhibited at a concentration of 100 mM by sodium chloride (NaCl).<sup>35,40</sup>

## Genes Encoding Carbapenemases in *A. baumannii*

Increased carbapenem resistance in *Acinetobacter baumannii* has been primarily driven by acquisition of resistance determinants and activation of intrinsic resistance mechanisms such as the chromosomal  $\beta$ -lactamases, *bla*<sub>OXA-51-like</sub>.<sup>41</sup> *A. baumannii* carbapenem resistance is mainly due to the Ambler class D (OXA-type) carbapenemases and Ambler class B (Metallo- $\beta$ -lactamases) carbapenemase and less frequently with Ambler class A.<sup>39,42</sup> As of 5 June 2022, 370 *bla*<sub>OXA-51</sub> variants, 46 *bla*<sub>OXA-23</sub> variants, 24 *bla*<sub>OXA-134</sub> variants, 12 variants of *bla*<sub>OXA-24</sub>, 9 *bla*<sub>OXA-143</sub>, and 7 *bla*<sub>OXA-58</sub> variants of  $\beta$ -lactamases have been identified (<https://www.ncbi.nlm.nih.gov/pathogens/isolates#/refgene/BETA-LACTAM>, <https://www.ncbi.nlm.nih.gov/nuccore/MK682761.1>) In *A. baumannii* class D carbapenemases (oxacillinases), class B (metallo- $\beta$ -lactamases), and class A ( $\beta$ -lactamases) collected from various published studies and in the above link are shown in Table 1. OXA-48 variants are widespread in the Enterobacteriaceae family but reported from *A. baumannii* as well.<sup>43</sup>

## Role of Mobile Genetic Elements (MGEs) in the Spread of Drug Resistance

Genome plasticity mechanisms include mutations and mobile genetic elements such as R Plasmids, insertion sequence, composite [transposons](#), [integrations](#), and resistance islands which result in the dissemination of antimicrobial resistance determinants encoding carbapenemase enzymes.<sup>44,45</sup> The simplest form of mobile genetic elements (MGEs) are insertion sequences (IS) which are present in all domains of life.<sup>46</sup> Same insertion sequences present on both sides of an antibiotic resistance gene form a compound transposon.<sup>39</sup> Intercellular mobility of these MGEs occurs through self-replicative plasmids encoding genes for conjugative transfer and with a conjugative transposon.<sup>31</sup>

## Insertion Sequences

In *A. baumannii*, the genes with resistant determinant encoding carbapenemases enzymes are regulated by the upstream presence of insertion sequences (IS): *ISAbal* (IS4 family), *ISAbal2* (IS3 family), *ISAbal3* (IS1 family), *ISAbal4* (IS982 family), *IS1008*, *ISAbal25* (IS30 family), *ISAbal9*, *ISAbal10* and *IS18* (IS30 family), and *ISAbal825* (IS982 family). Due to the presence of promoter regions in the insertion sequence or after the insertion event the formation of a new promoter region, insertion sequences perform a major role to activate or increase the expression of downstream resistant genes and result in increased resistance to carbapenems.<sup>38,39,42,47</sup>

**Table I** Carbapenemases in *A.baumannii* (Higgins et al, 2010; Lin and Lan, 2014; Cicek et al, 2014; Evans and Amyes, 2014; Cayô et al, 2015; Azizi et al, 2016; Kumar, 2016; Lee et al, 2017; Al-Agamy et al, 2017; Vrancianu et al, 2020; Ramirez et al, 2020)

Class D carbapenemases	
OXA-51 family	OXA-51,OXA-64,OXA-65,OXA-66,OXA-67,OXA-68,OXA-69,OXA-70,OXA-71,OXA-75, OXA-76,OXA-77,OXA-78,OXA-79,OXA-80, OXA-82,OXA-83,OXA-84,OXA-86, OXA-87, OXA-88, OXA-89,OXA-90, OXA-91,OXA-92,OXA-93,OXA-94, OXA-95,OXA-98, OXA-99, OXA-100, OXA-104, OXA-106,OXA-107,OXA-108, OXA-109,OXA-110,OXA-111,OXA-112, OXA-113,OXA-115,OXA-117, OXA-120, OXA-121,OXA-122,OXA-123,OXA-124,OXA-125,OXA-126,OXA-127,OXA-128,OXA-130,OXA-131, OXA-132, OXA-144, OXA-148, OXA-149,OXA-150,OXA-172, OXA-173,OXA-174,OXA-175,OXA-176,OXA-177,OXA-178, OXA-179,OXA-180, OXA-200,OXA-201, OXA-202,OXA-203,OXA-206, OXA-208, OXA-216,OXA-217, OXA-219,OXA-223, OXA-234,OXA-241, OXA-242,OXA-248,OXA-249, OXA-250, OXA-254, OXA-259,OXA-260,OXA-261, OXA-262,OXA-263, OXA-312,OXA-313,OXA-314,OXA-315,OXA-316,OXA-317, OXA-336,OXA-337,OXA-338,OXA-339,OXA-340,OXA-341,OXA-342,OXA-343,OXA-344,OXA-345,OXA-346,OXA-365,OXA-371, OXA-374,OXA-375,OXA-376,OXA-377, OXA-378,OXA-379, OXA-380,OXA-381, OXA-382,OXA-383, OXA-384, OXA-385, OXA-386, OXA-387,OXA-388,OXA-389,OXA-390,OXA-391, OXA-400, OXA-401,OXA-402,OXA-403, OXA-404,OXA-406,OXA-407,OXA-408, OXA-409,OXA-411,OXA-412,OXA-413, OXA-414, OXA-424, OXA-425, OXA-426,OXA-429,OXA-430,OXA-431, OXA-432, OXA-433, OXA-441,OXA-442,OXA-480,OXA-497,OXA-507,OXA-508,OXA-509,OXA-510,OXA-511,OXA-516,OXA-521, OXA-523,OXA-524, OXA-525, OXA-528,OXA-529,OXA-530, OXA-531, OXA-532, OXA-536,OXA-545, OXA-554,OXA-555, OXA-556, OXA-557, OXA-558, OXA-559, OXA-560, OXA-561, OXA-562, OXA-654, OXA-680, OXA-682, OXA-683, OXA-684, OXA-685, OXA-686, OXA-687, OXA-6688, OXA-689, OXA-690, OXA-691, OXA-692, OXA-693, OXA-694, OXA-695, OXA-696, OXA-697, OXA-698, OXA-699, OXA-700, OXA-701, OXA-702, OXA-703, OXA-704, OXA-705, OXA-706, OXA-707, OXA-708, OXA-709, OXA-710, OXA-711, OXA-712, OXA-713, OXA-714, OXA-715, OXA-716, OXA-718, OXA-719, OXA-720, OXA-721, OXA-722, OXA-723, OXA-733, OXA-734, OXA-735, OXA-738, OXA-739, OXA-740, OXA-741, OXA-742, OXA-743, OXA-744, OXA-745, OXA-746, OXA-747, OXA-748, OXA-749, OXA-750, OXA-751, OXA-752, OXA-753, OXA-754, OXA-755, OXA-756, OXA-757, OXA-758, OXA-759, OXA-760, OXA-761, OXA-762, OXA-763, OXA-764, OXA-765, OXA-766, OXA-767, OXA-768, OXA-769, OXA-770, OXA-771, OXA-772, OXA-773, OXA-774, OXA-775, OXA-776, OXA-781, OXA-782, OXA-797, OXA-798, OXA-799, OXA-800, OXA-828, OXA-829, OXA-831, OXA-834, OXA-852, OXA-853, OXA-854, OXA-855, OXA-856, OXA-857, OXA-858, OXA-859, OXA-860, OXA-861, OXA-862, OXA-863, OXA-864, OXA-865, OXA-866, OXA-867, OXA-868, OXA-869, OXA-870, OXA-871, OXA-872, OXA-873, OXA-874, OXA-875, OXA-876, OXA-877, OXA-878, OXA-879, OXA-880, OXA-881, OXA-882, OXA-883, OXA-884, OXA-885, OXA-886, OXA-887, OXA-889, OXA-890, OXA-891, OXA-892, OXA-916, OXA-927, OXA-938, OXA-939, OXA-940, OXA-954, OXA-955, OXA-970, OXA-971, OXA-972, OXA973, OXA-974, OXA-975, OXA-976, OXA977, OXA-1013, OXA-1047, OXA-1048, OXA-1058, OXA-1059, OXA-1060, OXA-1061, OXA-1062, OXA-1063, OXA-1064, OXA-1065, OXA-1066, OXA-1067, OXA-1068, OXA-1069, OXA-1070, OXA-1071, OXA-1072, OXA-1073, OXA-1074, OXA-1075, OXA-1076, OXA-1077, OXA-1078, OXA-1079, OXA-1080, OXA-1092, OXA-1093, OXA-1094, OXA-1096, OXA-1097, OXA-1098, OXA-1117, OXA-1118 Lin and Lan, 2014
OXA-23 family	OXA-23, OXA-27, OXA-49, OXA-134, OXA-146, OXA-165, OXA-166, OXA-167, OXA-168, OXA-169, OXA-170, OXA171, OXA-225, OXA-239, OXA-366, OXA-398, OXA-422, OXA-423, OXA-435, OXA-440, OXA-482, OXA-483, OXA-565, OXA-657, OXA-893, OXA-911
OXA-24 family	OXA-24, OXA-25, OXA-26, OXA-27, OXA-72, OXA-139, OXA-160, OXA-207, OXA-437, 897, OXA-1040,
OXA-58 family	OXA-58, OXA-96, OXA97, OXA-164, OXA-397, OXA-420, OXA-512 )
OXA-143 family	OXA-143, OXA-182, OXA-231, OXA-253, OXA-182, OXA-825
OXA-134 family	OXA-235, OXA-236, OXA-237
Class B metallo-β-lactamases (Lee et al, 2017; Lin and Lan, 2014; Azizi et al, 2016; Cayô et al, 2015; Kumar, 2016; Vrancianu et al, 2020; Ramirez et al, 2020)	
VIM (Verona integron - encoded metallo-β- lactamase)	VIM-1, VIM-2, VIM-3, VIM-4, VIM-6, VIM-11, VIM-25
IMP (Imipenemase)	IMP-1, IMP-2, IMP-4, IMP-5, IMP-6, IMP-8, IMP-10, IMP-11, IMP-14, IMP-19, IMP-55
NDM (New Delhi metallo-β-lactamase)	NDM-1, NDM-2, NDM-3, NDM-5, NDM-6, NDM-40, NDM-42
SIM (Seoul imipenemase)	SIM-1
Class A β-lactamases (Lin and Lan, 2014; Cicek et al, 2014; Lee et al, 2017; Al-Agamy et al, 2017; Vrancianu et al, 2020; Ramirez et al, 2020)	
KPCs (Klebsiella pneumoniae carbapenemases)	KPC-2, KPC-3, KPC-4, KPC-10
GES-type (Guiana extended spectrum)	GES-5, GES-11, GES-12, GES-14, GES-22

IS*Aba1* plays a major role in the [carbapenem](#) resistance gene transfer and expression in *A. baumannii*. This insertion sequence association with *bla*OXA-51-like, *bla*OXA-23-like, and *bla*OXA-58-like is reported in many studies.<sup>38,39,42</sup> In one study the author reported the presence of IS*Aba1* in *A. lwoffii* which demonstrates the mobility of this IS in this genus.<sup>48</sup> In *A. baumannii* isolates, the insertion IS*Aba2*, IS*Aba3*, and IS*Aba4*, IS*18* elements have also been identified upstream to *bla*OXA-58-like and *bla*OXA-23-like genes in many studies. The study described the novel IS*Aba4* element upstream to *bla*OXA-23 gene in *A. baumannii*.<sup>49</sup> In a study from Egypt, insertion sequence IS*Aba1* was detected in all tested isolates, while IS*Aba2* was detected in 2.7% and IS*Aba3* was detected in 4% of isolates.<sup>15</sup> A study done in Tehran, Iran revealed IS*Aba1* (45.1%) and IS*Aba4* (12.9%) were detected upstream of *bla*OXA-23-like genes of isolates.<sup>50</sup> The presence of IS*Aba1* upstream to *bla*OXA-51-like genes was seen in 32.2% of all isolates. In a study from Vietnam, PCR



amplification of upstream and downstream sequences of *bla*<sub>OXA-58</sub> gene revealed the IS*Aba3* presence at both locations in one multidrug-resistant isolate that showed high resistance to imipenem due to overexpression of the *bla*<sub>OXA-58</sub> gene and very high periplasmic  $\beta$ -lactamase activity.<sup>24</sup> In a study of Weiyuan Wu, *S1008-ΔISAba3* was the most common IS upstream of the *bla*<sub>OXA-58-like</sub> gene in *A. baumannii* clinical isolates, followed by IS*Aba3* and IS*Aba1*. All *bla*<sub>OXA-23-like</sub> genes but one had an upstream insertion of IS*Aba1*. The insertion of IS1008 (IS6 family) provided a hybrid promoter and increased the transcription level of the *bla*<sub>OXA-58</sub> gene.<sup>47</sup> The study detected, the IS*Aba825*-IS*Aba3*-like hybrid promoter upstream of *bla*<sub>OXA-58</sub> leading to carbapenem resistance.<sup>51</sup> A study from France identified an IS*Aba10*, 1203 bp novel insertion sequence. This element was found to be inserted into the IS*Aba1* element upstream *bla*<sub>OXA-23</sub> gene in an *A. baumannii* to provide an additional promoter sequence showing high minimum inhibitory concentrations (MICs) to carbapenems.<sup>52</sup> ISs such as IS*Aba1*, IS*Aba10*, IS*Aba825*, and IS*Aba125* elements with the spread of resistance are also involved in the disruption of the *carO* gene that codes for an important outer membrane channel and participates in the influx of carbapenem drug in *A. baumannii*. The absence of this outer membrane protein in isolates has been correlated with reduced carbapenem susceptibility.<sup>52,53</sup>

## Transposon

Composite transposons have resistance genes in their center and are flanked by insertion sequences on both ends.<sup>39</sup> Several studies reported that the *bla*<sub>NDM</sub> gene is located between two copies of the IS*Aba125* element, forming a composite transposon named Tn125.<sup>54,55</sup> In a study from India, two clinical isolates were collected (ACN21 from Sir Ganga Ram Hospital, Delhi, and CIAT758 from Tata Medical Center, Kolkata) and of *bla*<sub>OXA-23</sub>, *bla*<sub>NDM-1</sub> and *bla*<sub>OXA-58</sub> genetic arrangement identified in complete genomes. In the ACN21 genome, the variant of the *bla*<sub>OXA-58</sub> gene, *bla*<sub>OXA-420</sub>, and *bla*<sub>NDM-1</sub> gene was present. The *bla*<sub>OXA-420</sub> gene is bracketed by two elements of IS*Aba3* and forms a composite transposon. *bla*<sub>NDM-1</sub> gene with downstream IS*Aba125* and upstream ble-MBL, bracketed by two copies of IS*Aba125* but additional insertion sequence, IS*Aba14* was identified upstream ATP binding protein and forming a Tn125-like composite transposon. The CIAT758 genome harbors *bla*<sub>OXA-23</sub> on the chromosome and are bracketed by two copies of IS*Aba1* and *bla* OXA-58 gene with two copies of IS*Aba3*. Downstream of IS*Aba3* possesses another insertion element, IS1008.<sup>56,57</sup> A study described how Tn125 composite transposon in NDM-1 producing isolates disrupted by IS26 might potentially mobilize gene *bla*<sub>NDM-1</sub>.<sup>58</sup>

Transposons Tn2006, Tn2007, Tn2008, Tn2008B, and Tn2009 harboring *bla*<sub>OXA-23</sub> have been reported in *A. baumannii*. In Tn2007, IS*Aba4* promoter upstream gene *bla*<sub>OXA-23</sub>. In comparison other transposons carry IS*Aba1*, in Tn2006 and Tn2009, *bla*<sub>OXA-23</sub> genes have been reportedly flanked on both sides by IS*Aba1* and named as compound or class 1 transposons. But in Tn2006, two IS*Aba1* copies inversely oriented compared to the Tn2009 were present in the same direction. Tn2008 and Tn2008B have only one copy of IS*Aba1* upstream to OXA-23 and lack the second copy of IS*Aba1*. These transposons share a common region “*bla*<sub>OXA-23</sub>- ΔATPase”. Tn2006, Tn2008, and Tn2009 all found in the conjugative plasmids. Transposon Tn2007 is immovable and not considered a transposon. Tn2006 and Tn2008 are reported to be globally disseminated.<sup>59,60</sup> One study identified, the *bla*<sub>OXA-23</sub> gene in carbapenem-resistant *A. baumannii* was carried by Tn2009 (54%), Tn2006 (44%), and in Tn2008 (1.6%).<sup>61</sup> A study showed the *bla*<sub>NDM</sub> genes in a novel Tn7 family transposon designated Tn6924 or its variants which indicates the significance of this transposon in spreading resistance genes.<sup>62</sup>

## Integrations

Integrations are immobile but can be transferred through mobile genetic elements e.g. plasmids or transposons. Integrations are composed of an *intI* gene encoding an [integrase](#), proximal primary recombination site *attI*, and a strong promoter gene, where mobile [gene cassettes](#), carriage efflux pump genes, and drug resistance determinants, can be acquired or excised by a site-specific recombination mechanism catalyzed by the integrase. Various gene cassettes in integrations rearrange under antibiotic selective pressure.<sup>44</sup> Classification of integrations based on the amino acid sequence of the *IntI* integrases. Common types of integrations in *A. baumannii* are the transportable class I (Tn402 derivatives) integration, followed by class II (Tn7 family) and class III integrations. Among these, the class I integration has the high prevalence in *A. baumannii* followed by class II.<sup>44,63,64</sup> Resistance to carbapenem by metallo  $\beta$ -lactamases has been reported by

integrons in *A. baumannii* in many studies from parts of the world.<sup>64–66</sup> In one study, Class 1 and 2 integrons were detected in 74.1% and 12.5% of isolates respectively, and Class 3 integrons were not detected among these isolates. Various gene cassettes in Class 1 integron-carrying strains (ampC, aacA4-catB8, IS*Aba*1-blaOXA-23-GES-14, aadA2-cm1A6-GES-14-qacF, VIM-25-GES-24-qacF, dfrA5-IS*Aba*1-blaOXA-51-blaOXA-40 and aadA2-GES-11-IMP-1) and class 2 integron-bearing *A. baumannii* strains (IMP-4, VIM-2-VEB-aacA4 and dfrA2-sat-2-aadA4) were observed.<sup>44</sup> In a study from Korea, MBL gene, blaSIM-1 was detected in class 1 integrons borne gene cassette among seven clinical isolates of *A. baumannii*.<sup>52</sup> In a study from Iran class I integrons and II integrons were detected in 63.9% and 78.2% of *A. baumannii* isolates respectively and 49.6% had both classes of integron genes. In any of the isolates, class III integron was not detected. All of the isolates positive for integron were resistant to the drugs imipenem, meropenem, and ceftriaxone.<sup>67</sup> A study from Iran detected the most prevalent gene cassette arrays class 1 integron carrying isolates were bla<sub>IMP-19</sub>, aacA31, bla<sub>OXA-21</sub>, aadA-1 and bla<sub>VIM-1</sub>, qacED-1.<sup>65</sup> In a study from South India, Class-1 integrase genes were found in all strains of *A. baumannii* whereas class 2 integrase genes were found in 6% of isolates.<sup>68</sup> A study from Uganda found, Class 1 integrons in 62% of CRAB isolates.<sup>69</sup> The importance of integrons in a clinical setting is that frequent use of a single antibiotic lead to overexpression of various antibiotic resistance gene determinants due to the presence of a common promoter.<sup>29</sup>

## AbaR-Type Genomic Resistance Islands

Carbapenem resistance can also be acquired in *A. baumannii* by AbaR-type genomic islands that can harbor multiple antimicrobial resistance determinants. AbaRs are transposons that incorporate themselves into the chromosomal comM genes, encoding an ATPase domain, and play as important vehicles for acquiring antimicrobial resistance genes.<sup>70</sup> In 2006, the first *A. baumannii* resistance island (AbaR1) was described in the multidrug-resistant AYE *A. baumannii* strain from France with a large genomic island of 86kbp in the chromosome in which there was a cluster of 45 resistance genes.<sup>71</sup> In *A. baumannii* strains there have been many resistant islands described so far including AbaR1, AbaR3, AbaR4, AbaR5-Aba19, AbaR25, and others.<sup>72</sup> In *A. baumannii*, different backbones are usually found in different epidemic clones. The AbaR3-type resistant island found in Global Clone 1 (GC1) has been mapped to the Tn6019 backbone and invariably associated with Tn6018 or its elements with multiple antimicrobial resistance regions (MARRs). AbaR4-type islands are mostly found in Global Clone 2 (GC2), Tn6022 is the predominant backbone element and sometimes bears the bla<sub>OXA-23</sub> gene (Bi et al, 2020). Plasmids are also reported to carry AbaRs which can be exchanged both intra- and interspecies.<sup>73</sup> AbGRI1-type islands have been identified in GC2, originate from a plasmid-borne ancestral form -AbGRI1-0, and consist of a Tn6022, a Tn6172, and a plasmid-borne fragment between the two linker transposons as a transposable unit.<sup>74</sup> *Acinetobacter baumannii* strain AbaR25 was linked to an international clone (a variant of AbaR4) that carried bla<sub>OXA-23-like</sub> carbapenemase gene within the resistance island.<sup>72</sup>

## Historical Perspectives

Increasing antibiotic resistance in *Acinetobacter* has been noticed in various surveys since 1975. Before that *Acinetobacter* infections could be easily treated with a single or combination of antibiotics.<sup>75</sup> By the year 1998, the carbapenem-hydrolyzing beta-lactamases were identified throughout the world in clinical isolates of *Acinetobacter* species.<sup>76</sup>

## Class D $\beta$ -Lactamases (OXAs)

The first reported case of the OXA-Beta-lactamase enzyme with potent carbapenemase activity was plasmid-encoded and described by Pantón et al in 1993.<sup>77</sup> The gene was detected from a multidrug-resistant *A. baumannii* isolated from the blood culture of a patient from Edinburgh, Scotland in 1985, and the same year imipenem was approved for its first use.<sup>77</sup> It was named first as ARI-1 (*Acinetobacter* resistant to imipenem) and renamed after sequencing as OXA-23. blaOXA23-like gene was discovered on the chromosome of *Acinetobacter resistans* which was the natural source of this enzyme and was mobilized to *A. baumannii* through IS*Aba*1, insertion sequence provided by *A. baumannii*.<sup>39,43,76,78</sup> The bla<sub>OXA-23</sub> gene can be located either on the chromosome or on plasmids.<sup>76,78</sup> These genes have been found in many species of *Acinetobacter* as well as members of the *Enterobacteriaceae* family.<sup>76</sup> OXA-27 and OXA-49 variants of OXA-23 were identified in CRAB from Singapore and China

respectively.<sup>79,80</sup> OXA-423, a new variant of OXA-23 in *A. baumannii* was reported from China in 2020 from a sputum sample isolate collected in 2013.<sup>81</sup> An extremely drug-resistant (XDR) *A. baumannii* AB030 isolate from the IC5 lineage, isolated in Canada showed resistance to fluoroquinolones, carbapenem, aminoglycosides, and tigecycline. Carbapenem resistance was due to the presence of *bla*<sub>OXA-65</sub> and two copies of *bla*<sub>OXA-23</sub>. In AB030 both copies of *bla*<sub>OXA-23</sub> are flanked by IS*Aba1* insertion sequences.<sup>82</sup> A study identified the strains with co-occurrence of resistance genes on the chromosome and plasmids occurring with *bla*<sub>OXA-23</sub> and showed that the presence of multiple copies and locations had no significant effect on the susceptibility to carbapenems and most antibiotics.<sup>83</sup>

The largest group of OXA beta-lactamases mentioned to date are the OXA-51-like. OXA-51/69-like beta-lactamase is mentioned as intrinsic, a naturally occurring chromosomal enzyme in *A. baumannii*.<sup>43</sup> The study described the emergence of a novel carbapenemase (OXA-51) in genetically distinct carbapenem-resistant clinical isolates of *A. baumannii* from Argentina. OXA-51 presence, in different clones of *A. baumannii*, obtained from three hospitals within Buenos Aires indicates that the horizontal transfer of the encoding gene had occurred.<sup>84</sup> However, plasmids harboring IS*Aba1* – *bla*<sub>OXA-51-like</sub> have been detected in *A. baumannii*, *Acinetobacter nosocomialis* and *Acinetobacter pittii*.<sup>85,86</sup> *bla*<sub>OXA-51-like</sub> genes, which were thought to reside exclusively in *Acinetobacter* species but also found in members of the *Enterobacteriaceae* family.<sup>87</sup> This affects the accuracy of using *bla*<sub>OXA-51-like</sub> detection as a tool for differentiating *A. baumannii* from other *Acinetobacter* species and non-*Acinetobacter* Gram-negative genera.

OXA-24/40 B-lactamase was first identified from the chromosome of *A. baumannii* isolated from a bronchial aspirate of a patient admitted to the Medical Intensive Care Unit in the Ramón y Cajal Hospital, Madrid, Spain in 1997.<sup>88</sup> The first representative to be isolated from this group was OXA-24, subsequently renamed OXA-40 after sequencing which showed that these were identical enzymes.<sup>89</sup> However, now the gene OXA-24 carrying plasmids in carbapenem-resistant *Acinetobacter baumannii* has been identified worldwide. OXA-25 and OXA-26 variants were identified in Spain and in Belgium respectively, from isolates collected between 1995 and 1997.<sup>79</sup> The *bla*<sub>OXA-72</sub> gene was first reported in Thailand from an *Acinetobacter* strain (GenBank accession no. AY739646) in 2004.<sup>90</sup> The OXA-58 gene was identified from the plasmid of a strain isolated from a 24-year-old female with a skin burn infection at the Rangueil University Hospital (Toulouse, France) in August 2003. They cloned and characterized a novel carbapenem-hydrolyzing oxacillinase, OXA-58.<sup>91</sup> The OXA-58 gene is associated with hospital outbreaks in Europe, the USA, South America, Australia, and Africa.<sup>89,92–96</sup> A novel plasmid-borne carbapenemase gene, OXA-143 identified from an *A. baumannii* strain isolated from blood culture in the Brazilian Intensive care unit in 2004.<sup>97</sup> A carbapenem-resistant *A. baumannii* (strain Ac-141) was isolated from the urine culture of a patient admitted to a tertiary teaching hospital located in southern Brazil, 2007 and sequencing of the *bla*<sub>OXA-143-like</sub> gene identified a single mutation. This new OXA-143 variant was named OXA-231.<sup>98</sup> Three novel class D β-lactamase, OXA-235, OXA-236, OXA-237 were reported in 2013, from the plasmids of *A. baumannii* strains isolated from the United States and Mexico between 2005 and 2009.<sup>99</sup> The first report of OXA-48-like producing *A. baumannii* from a nursing home resident with faecal colonization was in northern Portugal.<sup>100</sup>

## Class B β-Lactamases (MBLs)

IMP-1 was described in *Acinetobacter* strains collected between 1998–2001 in the clinical microbiology laboratory of the São Paulo Hospital, Brazil. This study showed the first occurrence of IMP-1 from collected isolates in 1998, when 29% of tested isolates carried the *bla*<sub>IMP</sub> gene but from January 1999 to December 2001 all CRAB strains isolated in the hospital carried IMP-1 showing the emergence of this mechanism of resistance in hospital.<sup>101</sup> The IMP-2 variant after sequencing was first reported in a clinical isolate *Acinetobacter baumannii* AC-54/97 from Italy which was isolated in 1997 from an intensive care unit of a hospital.<sup>102</sup> IMP-4, a novel metallo-beta-lactamase was identified from the isolates collected in Hong Kong between 1994 and 1998.<sup>103</sup> A new variant of *bla*<sub>IMP</sub> (IMP5) inserted in a class 1 integron (named In76) was reported from Portugal from a clinical strain *A. baumannii* 65FFC isolated in 1998 from the urine of the patient.<sup>104</sup> IMP-6's first appearance in *A. baumannii* A3227 isolated from the tracheal secretion of a patient, reported from Brazil.<sup>105</sup> IMP-8 was reported in *A. phenon* 6/ct 13TU, from China.<sup>106</sup> IMP-10 was reported from two *A. baumannii* strains isolated from blood and bronchoalveolar lavage (BAL) samples of two different patients collected in São Paulo, Brazil, in 2000.<sup>107</sup> IMP-11 (accession no. AB074436) in Japan IMP-19 reported in *A. baumannii* from Japan.<sup>108</sup> *A.*



*baumannii* strain 56 recovered from tracheal aspirate sample from an adult ICU, Iran showed MBL activity, and analysis of IMP sequence identified a novel allelic IMP-55 variant.<sup>109</sup> The first reported VIM-2 enzyme found on a Class 1 integron of strains collected in 1998 and 1999 was from respiratory samples in Seoul, Korea.<sup>110</sup> The first report of the VIM-1 determinant in *A. baumannii* in the world was from Greece, from the isolates collected from March 2004 to March 2005.<sup>111</sup> The first VIM-4 MBL determinant was a part of a class 1 integron reported in *Acinetobacter* species isolated from a sputum sample collected between 2001 and 2006 in Greece.<sup>112</sup> First description of the *bla*VIM-11 gene spreading among *A. baumannii* strains in southern Taiwan was recovered between 2002 and 2006. *bla*VIM-11 was associated with a class 1 integron, the study also reported the presence of VIM-3 in *A. baumannii*.<sup>113</sup> SIM-1 is the only variant of the SIM enzyme reported in *A. baumannii* and this new MBL determinant, was reported from isolates collected from 2003–2004 sputum and urine samples in Seoul, Korea. The SIM-1 variant in this study was found encoded by gene cassette associated with a class 1 integron.<sup>114</sup> The *bla*NDM-1 report with the coexistence of the *bla*OXA-23 gene and *armA* gene in *A. baumannii* was reported from patients admitted to intensive care units in Chennai, India.<sup>17</sup> However, the detection of NDM-1 in *A. baumannii* 161/07 in Germany in the year 2007 in transposons structure which was composed of two copies of insertion sequence *IS**Aba*125 suggests that NDM-1 in *A. baumannii* might be disseminated earlier than it was thought.<sup>54</sup> NDMs variant NDM-2 was detected from the isolate from a central venous line catheter reported from Egypt.<sup>115</sup> A new variant *bla*NDM-3 from multidrug-resistant *A. baumannii* isolated from a patient with burn injuries from India was reported.<sup>116</sup> NDM-6 in an *Acinetobacter baumannii* isolated from urine from northern Spain.<sup>117</sup> First report of the existence of *bla*SPM-1 among the clinical isolates of *A. baumannii* was from Iran.<sup>118</sup> Genes, including SPM (São Paulo metallo-β-lactamase) and GIM (German imipenemase), were reported in *A. baumannii* in many studies.<sup>118–120</sup>

## Class A β-Lactamases

KPC-2, KPC-3, KPC-4, and novel variant KPC-10 were reported from the *A. baumannii* isolates collected from January to May 2009 from 17 hospitals in Puerto Rico.<sup>121</sup> GES-11, a new extended-spectrum-lactamase conferring reduced susceptibility to carbapenem was detected as a part of a class 1 integron in *Acinetobacter baumannii* BM4674 isolated from the tibia fracture of a patient, in France in 2008.<sup>122</sup> Plasmid-located *bla*GES-11 and *bla*GES-12 variants and a likely chromosomally located *bla*GES-14 novel variant reported from the isolates of *A. baumannii* collected between January 2008 to December 2009 from the hospitals of Belgium.<sup>123</sup> GES-5 conferring carbapenem resistance in *A. baumannii* was reported from the isolates collected from January to December 2010 from patients admitted to a tertiary hospital in Riyadh, Saudi Arabia.<sup>124</sup> The first report of the existence of *bla*SPM with GES-1 beta-lactamase was from Iran in *A. baumannii*.<sup>118</sup>

## Presence of Various Carbapenemase Genes in Different Countries

From a nationwide surveillance study from Thailand MDR *A. baumannii* harboured *bla*Oxa23 (85.8%), *bla*OXA58(7.9%), *bla*OXA-40(1%), *bla*VIM (2.9%), and *bla*IMP (2%), and in XDR *A. baumannii* detected *bla*OXA23(93%), *bla*OXA 58 (3.9%), *bla*VIM (1.3%), and *bla*IMP(0.8%).<sup>125</sup>

Analysis of three years (2019–2021) of articles from Table 2 showed that after OXA-51-like genes, which are intrinsic to *A. baumannii*, OXA-23 was predominantly seen in most of the studies from various countries which is already known and also seen previously to these studies. Multilocus sequence typing (MLST) data reported that the OXA-23 gene, particularly associated with clone CC92, especially ST75, ST92, ST138 was spreading rapidly in China.<sup>126</sup>

In studies from Egypt and Serbia the percentage of OXA-24-like exceeded the OXA-23-like percentage whereas in other studies OXA-24 percentage was either less than OXA-23 or not detected. In other studies, done in Egypt, China, Turkey, Vietnam, India (Chandigarh), South Africa, and Lahore, OXA-58-like was found in more isolates than OXA-24-like, while in most studies OXA-24-like genes were detected followed by OXA-23 or not detected. The studies where MBLs have been seen predominantly rather than OXA-23-like after OXA-51-like were from Saudi Arabia (IMP and NDM), Uganda (VIM), Brazil (VIM), Washington, DC (VIM), and Egypt (NDM). In a study from Egypt and Uganda, 100% of isolates showed the presence of VIM. In MBLs IMP, VIM, NDM were commonly identified in *A. baumannii*. Other carbapenemases identified were GES-type from the study of Morocco, SIM and SPM from Iran, and GIM, SPM,

**Table 2** Carbapenemase Genes Dissemination in *A. baumannii* from Various Countries in the Last Three Years (2019–2021)

Region	Year of Sample Collection	Isolates with Carbapenemase Genes (% Age)	Isolates with Coexistence of Genes in Isolate (% Age of Isolates)	Presence or Upstream of Insertion Sequence to carbapenemase Genes Transposon and Integrin	Reference
Madagascar	2008–2016	*OXA-51-like (OXA-65, OXA-66, OXA-67 and OXA-69) (100%), OXA-23 (53.3%), OXA-24 (13.3%), OXA-58 (6.7%)		*ISAbal/ OXA-23 (100%) embedded in *Tn2008 and Tn2006	[137]
Egypt	2010 and 2015	*OXA-51 (100%), OXA23 (100%), OXA58 (1.4%) *VIM (100%), NDM-1 (12.1%) *IMP, SIM, SPM, GIM, KPC, OXA40-ND		*ISAbal (100%), ISAb2 (2.7%) and ISAb3 (4%)	[15]
Taif, Saudi Arabia	Dec 2016–May 2017	*OXA-51 (100%), OXA-23 (59.4%), OXA-40 (3.1%) *IMP (87.5%), NDM (62.5%), VIM (9.4%), *KPC, OXA-48, OXA-58, OXA-181-ND			[138]
Morocco	Apr 2015–Jul 2016	*OXA-51-like (100%), OXA23 (69.6%) *NDM (21.7%), GES (65.2%) *OXA58, OXA-24, VIM, OXA48, KPC-ND	GES, NDM and OXA23 (13.3%),		[139]
China	Jan–Dec 2016	*OXA-51-like (100%), OXA-23 (94%), OXA-58 (1.5%) *VIM (80.6%) *OXA-24, NDM, SPM, and IMP-ND	OXA-23 and VIM (74.6%)	*ISAbal/ OXA-51+ ISAbal/ OXA-51 (88.9%) *Tn2008 (79.1%)	[140]
Turkey	2012 (6 months)	*OXA-51 (100%), OXA-23 (96%), OXA-58 (3%), OXA-24 *IMP, KPC, NDM, OXA-48-ND			[141]
India	2015–2017	*OXA-51-like (100%), OXA-23-like (97%) *NDM-like (17%), *OXA-24-like, OXA-58-like, IMP-like, VIM-like, SIM-like, SPM-like, KPC-like, GES-like-ND		*ISAbal/OXA-23 (n=25)	[142]
Turkey	Jan 2014–Jul 2015	*OXA-51 like (100%), OXA23-like (100%) *IMP, VIM, NDM, KPC, GES, OXA-24, OXA-58-ND			[143]
Central China	Jan 2017–Jan 2018	*OXA-51-like (100%), OXA-23-like (100%) *OXA-24, OXA-58, OXA-143, IMP, VIM, NDM-ND		*All isolates except isolate 19 showed ISAbal/ OXA-51/OXA-23	[144]
Southern Vietnam	Sep 2017–Mar 2018	*OXA-51-like (100%), OXA-23-like (78.4%), OXA-58-like (10.3%), *NDM-1 (6.2%)	OXA-51-like and OXA-23-like (67%), OXA-51-like and OXA-58-like (2.1%), OXA-51-like and NDM-1 (1%), OXA-51-like and OXA-23-like and NDM-1 (6.2%), OXA-51-like, OXA-23-like, OXA-58-like and NDM-1 (2.06%)		[145]
Kampala, Uganda	Jan 2015–Jul 2017	*OXA-51 (100%) OXA-23 (29%), OXA-24 (24%) * VIM (100%) *OXA-58, IMP, SPM, NDM, KPC-ND	OXA-23 and OXA-24 (14%)	*Integron-1 (62%)	[69]
Tehran, Iran	2016–2018	*OXA-51-like (100%), OXA-23-like (53.57%), OXA-24-like (41.67%), OXA-58-like (30.95%)	OXA-51, OXA-23 and OXA-24 (3.57%), OXA-51, OXA-23 and OXA-58 (20.23%), OXA-51, OXA-24 and OXA-58 (10.7%) OXA-51, OXA-23 OXA-24 and OXA-58 (1.19%)	* ISAbal/OXA-23-like (71.11%) and ISAbal/ OXA-58-like (15.38%)	[146]
Ahvaz, Iran	Jul 2017–Mar 2018	*IMP (IMP-4 and IMP-19) (12.98%), VIM (VIM-1 VIM-2 and VIM-25) (22.07%), SIM (2.59%), SPM (5.19%) *GIM, DIM and NDM-ND	VIM and IMP (3.89%)	*intl 1 (34/77), intl 2 (10/77), intl 1 and intl 2 (15/77).	[65]
Sao Paulo, Brazil	2008–2014	*OXA-51-like (100%), OXA-23-like (97.2%), OXA-231 (1.9%), OXA-72 (0.9%) *OXA-58-like, KPC, NDM, SPM, IMP, VIM-ND		*ISAbal /OXA-23-like (97.2%)	[147]

(Continued)

Table 2 (Continued).

Region	Year of Sample Collection	Isolates with Carbapenemase Genes (% Age)	Isolates with Coexistence of Genes in Isolate (% Age of Isolates)	Presence or Upstream of Insertion Sequence to carbapenemase Genes Transposon and Integron	Reference
Shahrekord, Southwest Iran	Jun 2013–Jun 2014	*OXA-51 (100%) *VIM-I (23%), IMP-I (3%)			[148]
Iran	Jan 2016–Jul 2018	*OXA-51-like (100%), OXA-23-like (85.1%), OXA-40-like (54.5%), *OXA-58-like, OXA-143-like and OXA-253-like-ND	OXA23 and OXA-40 (54.7%) of XDR <i>A.baumannii</i>	*ISAbal element associated with 25.8% of OXA-51-like and 98.5% of OXA-23-like	[149]
Chandigarh, India	Aug 2013–Jan 2014	*OXA-51 (100%), OXA-23 (98%) OXA-58 (2%), *VIM (49.3%), NDM-I (18.7%) *OXA-24, IMP/KPC, OXA-48-ND	OXA-23 and VIM (45.3%), OXA-23 and NDM-I (15.3%)		[150]
Gorgan, Northern Iran	May 2016–Jun 2017	*OXA-51-like (100%), OXA-23-like (77.27%), OXA-24/40 (43.18%) *OXA-58-like, OXA-143-like-ND			[151]
Egypt	Aug 2017–Oct 2018	*OXA-51 (100%), OXA-24-like (65.2%), OXA-23 (30.4%), OXA-58 (17.4%), *NDM (13%), VIM (43.5%), IMP (60.9%) *KPC, GES-ND			[152]
Malaysia	2011–2016	*OXA-51-like (100%) (OXA-66 (85%), OXA-64 (8%), OXA-91 (8%)), OXA-23-like (100%) *NDM (23.1%), *OXA-24-like, OXA-58-like, IMP/VIM, GIM, SPM-ND		*ISAbal/OXA-23 (100%), ISAbal/OXA-66 (7.7%), ISAbal25/NDM-I (23.1%), *All OXA-23-like genes carried by Tn2006 and Tn2008	[153]
Iran	Sep 2016–Sep 2017	*OXA-51 (91.6%), OXA-23 (76.5%), OXA-24 (65.8%), OXA-40 (22.3%), OXA-48 (15.4%) *NDM-I (9.4%), VIM (2%), IMP (0.3%) *SPM-I, KPC, GES, OXA-58-ND			[154]
Thailand	2016–2017	*OXA-51-like (100%), OXA-23-like (68.31%), OXA-40/24-like (4.92%), OXA-58-like (1.09%)	OXA-51-like, OXA-23-like, and OXA-40/24-like (4.92%), OXA-51-like, OXA-23-like and OXA-58-like (0.54%),		[155]
Pelotas, RS, Brazil	Oct 2014–Jul 2016	*OXA-51 (100%) *VIM (90.9%) *OXA-23, OXA-24, OXA-58-ND		*All isolates ISAbal+	[156]
Egypt	2015–2016	*OXA-51-like (100%), OXA-23-like (82.3%) *NDM-like (23.5%), *GES-like (11.8%) *OXA-58-like, OXA-40-like-ND	OXA-51-like, OXA-23-like and NDM-like (5.9%), OXA-51-like, GES-like and OXA-23-like (11.8%)		[157]
Brazil	Apr 2012–Oct 2017	*OXA-51-like (100%), OXA-23 (72.2%), OXA-72 (27.8%)		*ISAbal/OXA-23 (72.2%)	[158]
Washington DC	2011–2014	*OXA-51-like (100%), OXA-23-like (36%), *VIM (71%) *OXA-24-like, OXA-58-like, IMP/SIM-ND	VIM and blaOXA-23-like +	*All isolates ISAbal+ ISAbal/OXA-23-like (36%), ISAbal/OXA-51-like (96%)	[159]
Ahvaz, South-west, Iran	Jan 2018–Nov 2019	*OXA-51-like (100%), OXA-23-like (68.75%), OXA-24-like (20%), *OXA-143-like-ND	OXA-24-like, OXA-58-like and OXA-23-like (3.75%), OXA-24-like and OXA-23-like (5%) OXA-58-like and OXA-23-like (2.5%)		[160]
India	Jan 2014–Dec 2017	*OXA-51-like (100%), OXA-23 only (29%), OXA-24 only (<1%) *NDM only (<1%)	OXA-23-like and NDM-like (10%), OXA-23 and VIM (<1%), OXA-58 and NDM (<1%), OXA-23-like, NDM-like and VIM (<1%), study also showed the combination of carbapenemases with other $\beta$ -lactamases genes	*ISAbal with OXA-23-like and OXA-51-like +	[57]

(Continued)

Table 2 (Continued).

Region	Year of Sample Collection	Isolates with Carbapenemase Genes (% Age)	Isolates with Coexistence of Genes in Isolate (% Age of Isolates)	Presence or Upstream of Insertion Sequence to carbapenemase Genes Transposon and Integron	Reference
South Africa	Aug–2016–Jul 2017	*OXA-51-like (100%), blaOXA-23-like (70%), OXA-58-like (8%), OXA24-like (5%) *IMP-I (4%), VIM (3%), and NDM-I (2%) *SIM-I-ND	OXA-51-like and OXA-23-like (23%), OXA-51-like and OXA-58-like (4%), OXA-51-like and OXA-24-like (5%) OXA-51-like and IMP-I (1%) OXA-51-like and VIM (3%), OXA-51-like and NDM-I (2%), OXA-51-like, OXA23-like and IMP-I (1%) OXA-51-like, OXA-23-like and OXA-58-like (2%) OXA-51-like, OXA-23-like, OXA-58-like and IMP-I (2%)	*ISAbal/blaOXA-51-like (15%), blaOXA-51-like and ISAbal/blaOXA-23-like (40%), ISAbal/ blaOXA-51-like and ISAbal/blaOXA-23-like (2%) *intI (80%)	[161]
Serbia	Jan 2018–Jun 2018	*OXA-51-like (100%), OXA-24-like (44.2%), OXA-23-like (34.5%) * NDM-I (3.2%), *OXA-58-like, OXA-143-like, IMP, VIM, GIM, SPM, SIM-ND	OXA-23 and OXA-24 (0.9%), OXA-51, OXA-23 and OXA-24 (0.5%), NDM-I and OXA-24 (7%)	*ISAbal (71.8%), ISAbal/OXA-51-like (16.5%), ISAbal/OXA-24-like (28.1%), ISAbal/OXA-23-like (26.7%)	[162]
South India	May 2011–Jan 2012	*OXA-51-like (98%), OXA-23-like (96%) *VIM (64%), NDM (13%), IMP (16%)	OXA-51 and OXA-23 (93%)	*ISAbal with OXA-51-like (94%) ISAbal with OXA-23-like (92%) ISAbal with VIM (62%), ISAbal with IMP (16%) ISAbal with NDM (12%) *Class 1 integrase genes (100%) and Class 2 (6%)	[68]
Iran	2016–2017	*OXA-51 (100%), OXA-23 (91.3%), OXA-24 (61.7%) * IMP-I (27.2%), IMP-2 (3.7%), VIM-I (6.2%), VIM-2 (5%) *OXA-58, SIM-I-ND	OXA-23 AND OXA-24 (55.5%), IMP-I and IMP-2 (3.7%), VIM-I and VIM-2 (1.23%)		[163]
Turkey	2016	*OXA-51-like (100%), OXA-23-like (100%), OXA-58-like (28.2%), *NDM (1.1%) *OXA-24-like, OXA-48-like, IMP, VIM-ND			[164]
Giza, Egypt	Jul 2017–Jan 2018	* OXA-51-like (100%), OXA-23-like (55.9%), OXA 24/40 (26.4%), OXA58 (2.9%) *NDM (67.7%), GIM (38.2%), SPM (29.4%), SIM (8.8%), IMP (5.8%) *KPC (50%), GES (26.4%) VIM -ND	Co-existence of more than one carbapenemase encoding gene (82.3%)	ISAbal/OXA 23-like (5.9%), ISAbal/ OXA24/40-like (5.9%), ISAbal /OXA 51-like (2.9%)	[165]
Egypt	Dec 2018–Dec 2019	*OXA-51-like (100%), OXA-23 (77.7%), OXA-58 (1.9%) *NDM-I (11.7%), SPM (6.3%), VIM (0.5%), SIM-I (0.5%) *KPC (10.7%) *OXA-24/40, IMP, GIM, GES, VEB -ND	Isolates harbour two or more of the tested genes (18.4%)	ISAb1/blaOXA-23 (7.8%)	[166]
European countries	May 2016–Nov 2018	*OXA-23 (67.7%), OXA-72 (30.1%), OXA-58 (2.7%)	OXA-72 and NDM-I (1.8%), OXA-58 and OXA-72 (2.7%)	ISAbal31/ blaOXA-72+	[167]
Mthatha, South Africa	Jul 2017–Aug 2018	*OXA-51-like (100%), OXA-23-like (100%) OXA-58-like (10%), IMP (10%) *OXA-24-like, VIM, NDM-I, SIM-ND	OXA-23-like, OXA-58-like and IMP (10%)	ISAbal /OXA-51-like (55%), ISAbal /blaOXA-23-like (75%)	[168]
Northwest Iran	Oct 2018–Oct 2019	*OXA-51-like (100%), OXA-23-like (82.1%), OXA-24/40-like (36.6%) *NDM (6.2%), IMP (4.4%), * OXA-58-like, OXA-143-like, OXA-235-like, VIM, SIM, GIM and SPM-ND	OXA-23-like, blaOXA-51-like and OXA-24/40-like (25.8%), OXA-23-like, NDM/IMP, (7.1%), OXA-24/40-like, NDM and IMP (6.2%)	ISAbal (95.5%) ISAbal/OXA-23-like (69.5%),	[169]
Thailand	2016–2017	*OXA-51-like gene (100%) OXA-23-like (92.59%), OXA-24-like (14.81%), OXA-58-like (1.48%) *NDM-type (4.44%)			[170]
Lahore, Pakistan	Sep 2020–Dec 2020	*OXA-51 (100%), OXA-23 (49.5%), OXA-58 (19.4%), OXA-24 (8.8%), OXA-143 (2.6%) *NDM-I (24.7%),	OXA-51, NDM-I and OXA 23 (9.7%), OXA-51, OXA-23, OXA-24 and NDM-I (2.6%), OXA-51, OXA-23, OXA-58 and NDM-I (6.2%), OXA-24, OXA-51, OXA-23 and OXA-58 (15%)		[171]

(Continued)

**Table 2** (Continued).

Region	Year of Sample Collection	Isolates with Carbapenemase Genes (% Age)	Isolates with Coexistence of Genes in Isolate (% Age of Isolates)	Presence or Upstream of Insertion Sequence to carbapenemase Genes Transposon and Integron	Reference
Shenzhen, China	Jul 2018–Jun 2019	*OXA-51-like (100%), OXA-23-like (93.4%), OXA-24-like (2.2%) and OXA-58-like (2.2%) *NDM-I (8.8%), *SIM, VIM and IMP-ND		ISAbal/OXA-51-like (27.5%)	[172]
Birjand, South-East Iran	Jan 2018–May 2019	* VIM-I (28.9%), IMP-I (13.3%) *NDM -ND			[173]
Egypt	May 2019–Feb 2021	*OXA-51-like (100%), OXA-23-like (88.9%) *NDM (27.7%) *OXA-24-like, OXA-58-like, IMP, VIM-ND	OXA-23-like and NDM (25.9%)		[174]
China	Jan 2012–Dec 2018	* OXA-51 (93%), OXA-23 (91%), OXA-24 (81%)			[175]
Lucknow, India	Jun 2019–May 2020	*VIM (48.6%), NDM (40.5%), *IMP-ND	VIM and NDM (21.6%)		[176]
Western Maharashtra, India	Nov 2018–Dec 2019	*OXA-51-like (100%), OXA-23-like (94.4%) *OXA-24-like, OXA-58-like-ND		ISAbal/OXA-23-like (94.4%), ISAbal/OXA-51-like (12.9%), ISAbal/OXA-23-like/OXA-51-like (7.4%)	[177]

**Note:** n the table [\*] indicates ““Present””

**Abbreviations:** ND, not detected; +, present.

and SIM from Egypt. This highlights the predominance of OXAs other than OXA-23, MBLs and Class A carbapenemases in different regions also.

## Limitation

The search was restricted to only the PubMed engine and Google for the prevalence of carbapenemase genes. In the present review, details of MLST clones were not included. The remaining search engines would have given more data to analyse and discuss which is not included in PubMed.

## Strategies in Controlling the Dissemination of Resistant Determinants

Active antimicrobial stewardship program in hospitals needs the time to reduce the selective antibiotic pressure and the development of resistance to broad spectrum antibiotics. The use of various care bundles in Infection Control Practices (ICP) is needed to control the spread of these organisms among patients, staff, and patient attendants to become infected or colonized. A colonized individual with a drug resistant organism can further spread the organism to the community and on migration to various geographical regions which can complicate the present situation. Taking into consideration treatment options, in a retrospective (2015–2017) study from Chiang Mai University Hospital, Thailand conducted on critically ill CRAB infected patients, the author concluded that there is a reduction in 30-day mortality on addition of drug meropenem to colistin, high clinical and microbiological responses, and no difference in nephrotoxicity when compared to drug colistin monotherapy.<sup>127</sup> The author also found in one of his studies that a loading dose of colistin methanesulfonate resulted in favourable patient outcomes with a better clinical, microbiological response and survival rate than a non-loading dose. But a loading dose of colistin methanesulfonate found with an increase in nephrotoxicity, therefore rigorous renal function monitoring is required when a loading dose of colistin is administered to the patient.<sup>128</sup> The author also found increased nephrotoxicity when a loading dose of colistin is given in XDR-AB infected cancer patients but in comparison to the above study not resulted in significant better outcome comparing to nonloading dose.<sup>129</sup> One more study conducted by the same author compared the combination of loading dose colistin with imipenem and loading dose colistin with meropenem for treatment of CRAB infected patients. He found that the loading dose of colistin



and meropenem treatment gave a better survival rate, clinical and microbiological response, but no significant difference in nephrotoxicity while comparing the two combination regimens.<sup>130</sup> In one scientific review, the author discussed Infection control precautions including hand hygiene, cohorting, and environmental decontamination, to control MDR *A. baumannii* outbreak and various treatment options.<sup>29</sup> A study from Korea showed the efficacy of various combination regimens including drug colistin, sulbactam, minocycline, and tigecycline in the treatment of CRAB.<sup>131</sup> Before treatment, the important thing to differentiate colonization from infection to avoid misuse of antibiotics and if carbapenem resistance genes are detected, confirming the in-vitro susceptibility need to be performed as many times genes do not express and it helps in treating the patient in case of pan-drug resistant and extensively drug resistant organism. At the same time, knowing the presence of genes in phenotypic carbapenem sensitive organisms, the doctor understands that the failure of a drug can occur during treatment due to some inducer and is able to choose the drug on a case by case basis.<sup>132</sup> As some carbapenemases retain activity against beta-lactamase inhibitors, they can be used in combination with other agents for treatment. So knowing the type, presence and expression of the carbapenemase gene helps in ways to avoid therapy failure.

## Conclusion

*A. baumannii* with various carbapenem resistance encoding genes is widespread worldwide and the rapid spread of resistance due to mobile genetic elements has declared this organism as a high- priority antibiotic-resistant pathogen and global threat in medical care. But as the situation is still not well documented certain parts of the world need to be studied from various regions to know more about the genetics of this drug resistant superbug.

It is observed from various studies that OXA-23 is the most frequently detected carbapenemase in the CRAB worldwide but recent studies have been reported with an increased prevalence of other carbapenemase genes in various regions over OXA-23 and the importance of various mobile genetic elements. There is the need for active surveillance to understand the exact situation in various countries, to track the spread, to start the appropriate controlling measures, to break the chain of this bug and, most importantly, to start timely proper treatment of patients based on the presence of various genes to avoid therapeutic failure and mortality.

Therefore, compiled genotypic systematic data have been prepared for the thorough knowledge of its molecular characterization with its global genetic diversity.

## Disclosure

The authors report no conflicts of interest in this work.

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