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REVIEW

# Antimicrobial resistance in *Acinetobacter baumannii*: From bench to bedside

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## Abstract

*Acinetobacter baumannii* (*A. baumannii*) is undoubtedly one of the most successful pathogens in the modern healthcare system. With invasive procedures, antibiotic use and immunocompromised hosts increasing in recent years, *A. baumannii* has become endemic in hospitals due to its versatile genetic machinery, which allows it to quickly evolve resistance factors, and to its remarkable ability to tolerate harsh environments. Infections and outbreaks caused by multidrug-resistant *A. baumannii* (MDRAB) are prevalent and have been reported worldwide over the past twenty or more years. To address this problem effectively, knowledge of species identification, typing methods, clinical manifestations, risk factors, and virulence factors is essential. The global epidemiology of MDRAB is monitored by persistent surveillance programs. Because few effective antibiotics are available, clinicians often face serious challenges when treating patients with MDRAB. Therefore, a deep understanding of the resistance mechanisms used by MDRAB can shed light on two possible strategies to combat the dissemination of antimicrobial resistance: stringent infection control and antibiotic treatments, of which colistin-based combination therapy is the mainstream strategy. However, due to the current unsatisfying therapeutic outcomes, there is a great need to develop and evaluate the efficacy of new antibiotics and to understand the role of other potential alternatives, such as antimicrobial peptides, in the treatment of MDRAB infections.



**Key words:** *Acinetobacter baumannii*; Antibiotic resistance; Epidemiology; Genomics; Infection control

**Core tip:** With the current rapid increase in the numbers of studies on Acinetobacter baumannii (*A. baumannii*), the complexity of the entire picture regarding how this superbug copes with its environment and influences human beings is gradually being understood. By conducting a thorough review of this topic, this paper aims to present the relevant literature regarding the antimicrobial resistance of *A. baumannii* and the currently available treatment options for *A. baumannii* infections to highlight possible future research directions.

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## INTRODUCTION

### Species identification and current taxonomy

*Acinetobacter spp.* are glucose-non-fermentative, non-motile, non-fastidious, catalase-positive, oxidase-negative, aerobic Gram-negative coccobacilli[1]. Since 1986, the taxonomy of the genus *Acinetobacter* has been modified several times. Currently, the original single species clas-

sification of *Acinetobacter calcoaceticus (A. calcoaceticus)* has been abandoned, and at least 34 genomic species can be distinguished within the genus *Acinetobacter*, 23 of which have been assigned species names[2]. The challenge in the taxonomy of *Acinetobacter* is due to the clusters of closely related species that are difficult to distinguish using phenotypic traits and chemotaxonomic methods. The *A. calcoaceticus-Acinetobacter baumannii (A. baumannii)* complex, comprising *A. calcoaceticus*, *A. baumannii*, and the genomic species 3 and 13TU, is the most well-known example[3]. Because the antibiotic susceptibilities and clinical relevance of the different genomic species are significantly different[4-7], genomic methods for *Acinetobacter* species identification are necessary. A number of genomic fingerprinting methods have been proposed, including pulsed-field gel electrophoresis (PFGE); ribotyping; polymerase chain reaction (PCR)-based fingerprinting techniques, such as random amplified polymorphic DNA analysis; repetitive extragenic palindromic sequence-based PCR (rep-PCR); amplified ribosomal DNA restriction analysis; RNA spacer fingerprinting; and amplified fragment length polymorphism analysis[8]. In addition, new methods, such as 16S-23S ribosomal intergenic spacer, 16S rRNA gene, *rpoB* gene and *gyrB* gene sequence analyses, have been developed for *Acinetobacter* species identification[9,10].

### Common typing methods in outbreak investigations

Of all of the *Acinetobacter* species, *A. baumannii* is the most important member associated with infections in clinical practice and causes most of the reported outbreaks. In addition to chart review and statistical epidemiology, some DNA fingerprinting methods are valuable in outbreak investigations and strain discrimination. Rep-PCR, PFGE, and multilocus sequence typing (MLST) have all been used in previous studies. Rep-PCR has been proven to be a useful and expedient method for the epidemiological characterization of *A. baumannii* nosocomial outbreaks[11]. Rep-PCR has also been used as a tool for determining species lineages of *A. baumannii* in a hospital[12] and for differentiating pan-European, multi-resistant *A. baumannii* clone Ⅲ from clones Ⅰ and Ⅱ[13]. Despite the inter-laboratory variability of rep-PCR, this method has the advantage of being faster to perform than PFGE and MLST. The intra-laboratory clustering of *A. baumannii* has been shown to be well conserved[14] and to correlate well with PFGE[15] or MLST results[16], demonstrating the robustness of rep-PCR. We have found one rep-PCR major cluster (84%) of *A. baumannii* carrying a class I integron that spread among four regional hospitals in northern Taiwan[17]. However, PFGE is still considered the gold standard for typing outbreak-related isolates of *A. baumannii*[18-21], whereas MLST provides a high level of resolution and is an excellent tool for studying the population structure and long-term epidemiology of *A. baumannii*[22]. Recently, the *A. baumannii* MLST database (http://pubmlst.org/abaumannii/) was developed for the BIGSdb genomics platform[23] to assist the broader community in elucidating the structure and function of this microorganism.

### Clinical manifestations

*A. baumannii,* named after Paul Baumann, is ubiquitous in soil and water[24]. Previously, *A. baumannii* was regarded as a low-virulence commensal bacterium. However, it has become a successful pathogen[25] and has emerged as a major cause of healthcare-associated infections, most of which have occurred in critically ill patients in the intensive care unit (ICU) setting[26]. In recent decades, infections caused by *A. baumannii* have also occurred outside the ICU or in trauma patients after natural disasters, and they have even affected patients with co-morbidities in the community[27]. Reports of community-acquired *Acinetobacter* infections have increased over the past decade[28]. Several different types of infections, including pneumonia, urinary tract infections, bacteremia, wound infections and even meningitis, are caused by this organism[29]. These infections often occur in older patients, many of whom have chronic underlying diseases and have previously received antimicrobial treatment[30,31]. The mortality of patients with *A. baumannii* infections in hospitals and in the ICU has ranged from 7.8% to 23% and from 10% to 43%, respectively[32].

### Risk factors

In recent years, many studies have reported the risk factors for acquiring *A. baumannii* infections and have particularly focused on those caused by multidrug-resistant strains. The acquisition of MDRAB is related to multiple factors, including environmental contamination and contact with transiently colonized healthcare providers[33]. The independent risk factors for the acquisition of imipenem-resistant *A. baumannii* (IRAB) include a hospital size of > 500 beds, previous antimicrobial treatment, a urinary catheter, surgery[34], previous ICU stay, and prior exposure to imipenem or third-generation cephalosporins[35]. The only significant independent risk factor for the appearance of imipenem-resistant multidrug-resistant *A. baumannii* (MDRAB) in patients formerly infected with imipenem-susceptible MDRAB is imipenem or meropenem exposure[36]. For extensively drug-resistant *A. baumannii* (XDRAB) infections, the prior use of imipenem, meropenem, piperacillin/tazobactam or fourth-generation cephalosporins and > 30 d of being bedridden have been found to be independent risk factors[37]. A systematic review concluded that the acquisition and spread of *A. baumannii* appeared to be related to a large number of variables, the most important of which were deficiencies in the implementation of infection control guidelines and the use of broad-spectrum antibiotics[38].

The risk factors that are associated with *A. baumannii* bacteremia are immunosuppression, unscheduled hospital admission, respiratory failure at ICU admission, previous antimicrobial therapy, previous sepsis in the ICU, and the invasive procedures index[39]. Resistance to carbapenems, mechanical ventilation, and the presence of malignancy have also been found to be associated with high mortality rates in patients with *A. baumannii* bacteremia[40].

Regarding ventilator-associated pneumonia caused by *A. baumannii*, the risk factors include neurosurgery, adult respiratory distress syndrome, head trauma, and large-volume pulmonary aspiration[41]. Because various studies showed certain differences in the risk factors of acquiring drug-resistant *A. baumannii* bacteremia or pneumonia[42-46], a separate investigation should be performed in each hospital setting to limit the spread of this pathogen[38].

### Virulence factors

Previously, *A. baumannii* was regarded as a low-grade pathogen; however, it contains virulence factors that enhance its bacterial toxicity and pathogenicity. A combined approach of genomic and phenotypic analyses led to the identification of several virulence factors, including extracellular components with hemolytic, phospholipase, protease and iron-chelating activities, biofilm formation, surface motility, and stress resistance[47]. The biofilm formation of *A. baumannii* facilitates its attachment to abiotic and biotic surfaces[48], including those of medical devices and host tissues. The initiation and maturation of biofilms are related to pilus assembly and the production of the biofilm-associated protein (Bap), which is regulated by the two-component system BfmRS[49]. The Bap protein plays a role in adhesion to human epithelial cells[50], and the inhibition of this protein can prevent *A. baumannii* infection[51]. In fact, in a multicenter cohort study, all catheter-related urinary or blood stream infections due to *A. baumannii* were caused by biofilm-forming strains[52]. A 2D proteomic analysis of pellicle-forming *A. baumannii* isolates showed that overexpression of CarO, which is an OprD-homolog, siderophore iron uptake, and pili systems are involved in the development of biofilms[53].

Iron uptake systems are essential to the survival and pathogenicity of bacteria, especially in the low-iron environment of the human host. *A. baumannii* grown under iron-limited conditions undergo major transcriptional changes of not only many iron acquisition-related genes but also of genes involved in motility[54]. *A. baumannii* is well-equipped with metal homeostatic systems that are required for the colonization of a diverse array of tissues[55]. Genome investigations have revealed wide distributions of endogenous siderophores in clinical *A. baumannii* isolates, arguing for their role in pathogenic capabilities[47]. The zinc acquisition system has also been found in *A. baumannii,* which is required for efficient zinc uptake *in vitro* and full pathogenesis *in vivo*[56].

*A. baumannii* adheres to human bronchial epithelial cells *in vitro*, and its prevalent European clone Ⅱ has a relatively high capacity for adhering to these cells[57]. Additionally, the K1 capsular polysaccharide has been shown to prevent *A. baumannii* from being phagocytized by macrophages, to optimize its growth in human ascites fluid and serum, and to enhance its survival in a rat soft tissue infection model[58]. Moreover, several proteins have been implicated as possible virulence factors in *A. baumannii*. Omp38 induces the apoptosis of host cells[59], the absence of the RecA protein decreases survival in response to both heat shock and desiccation[60], and the inactivation of phospholipase D diminishes *A. baumannii* pathogenesis[61]. Importantly, the outer membrane protein A of *A. baumannii* (AbOmpA) is the most abundant surface protein that has been associated with the apoptosis of epithelial cells through mitochondrial targeting[62]. AbOmpA is also the major nonspecific channel in *A. baumannii* and appears to be essential for this organism's high levels of intrinsic resistance to a number of antibiotics[63]. *A. baumannii* can rapidly develop resistance to polymyxin antibiotics through the loss of the lipid A component of lipopolysaccharide[64], which subsequently alters the expression of critical transport and biosynthesis systems associated with modulating the composition and structure of the bacterial surface[65].

## GLOBAL EPIDEMIOLOGY

Two key factors contributing to the significant and ubiquitous dissemination of *A. baumannii* in hospitals are the extent of its antimicrobial resistance and its environmental resilience[66]. The extent of antimicrobial resistance is more severe in *A. baumannii* isolates from patients in Asian and European ICUs than from patients in American ICUs[27], and significant increases in antimicrobial resistance were noted worldwide from 2004 to 2009. The highest resistance rates in 2009 were for ceftriaxone (83.6%), piperacillin-tazobactam (82.0%), and ceftazidime (80.3%) in the Middle East. Increases in resistance were noted for all antimicrobials in isolates collected from the Asia-Pacific Rim, ranging from a 19.1% increase in ceftazidime resistance to a 38.9% increase in levofloxacin resistance. Resistance also increased significantly in Africa (including piperacillin-tazobactam, ceftriaxone, cefepime, amikacin, meropenem, and levofloxacin resistance) and Europe (including piperacillin-tazobactam, ceftriaxone, ceftazidime, levofloxacin, amikacin, minocycline, meropenem, and cefepime resistance)[67].

The first MDRAB isolate resistant to almost all available antibiotics in Taiwan was discovered in 1998[68]. Since then, many MDRAB outbreaks have been reported in Taiwan[69-72]. A Taiwanese surveillance report of antimicrobial resistance in 2000 found that 73% of *A. baumannii* isolates collected from 21 medical centers and regional hospitals were ceftazidime-resistant[73]. Another study conducted during the same year at five major teaching hospitals in Taiwan showed that as many as 22% of *A. baumannii* isolates were not susceptible to imipenem[74]. In 2012, the Taiwan Surveillance of Antimicrobial Resistance program showed that the prevalence of the IRAB complex increased from 3.4% in 2002 to 58.7% in 2010 and that of the XDRAB complex increased from 1.3% in 2002 to 41.0% in 2010[75]. In addition, the proportion of healthcare-associated infections caused by carbapenem-resistant *A. baumannii* (CRAB) significantly increased, compared to infections by all *A. baumannii*, from 14% in 2003 to 46% in 2008 in Taiwan[76]. The local spread of MDRAB has been demonstrated in five proximal hospitals in northern Taiwan, with resistance determinants

distributed widely in clonal and non-clonal isolates[77].

In addition to its prevalence in Taiwan, MDRAB is also prevalent in hospitals in many areas of the world, including Korea[78], Belgium[79], Italy[80], Iraq[81], Israel[82], Greece[83] and America[84]. Furthermore, a one-year study demonstrated that three clones of MDRAB had spread in hospitals in Brazil[85]. In a single institution in Queensland, Australia, sequence type 92 (ST92) was the dominant sequence type and was present for 9 years[86]. Additionally, clonal dissemination among three hospitals located in two different cities has been documented in China, indicating the epidemic potential of MDRAB[87]. Both inter-institutional and intra-institutional transmission of a strain of *A. baumannii* is possible[15]. Several multidrug-resistant clones can coexist endemically in one hospital for several years[31,88], and the same clones often spread on a small scale within a short period of time[31] or can be detected during an outbreak by a close survey of epidemic sources[88]. Furthermore, such outbreaks can occur across national boundaries. For example, Wybo *et al*[89] reported a MDRAB nosocomial infection involving approximately 20 patients in a university hospital in Belgium that was the result of a transfer of two patients from Greece.

In addition to the increasing importance of MDRAB in nosocomial infections, the increasing reports of outbreaks caused by CRAB in recent years have become another frightening reality. The imipenem resistance rate of *A. baumannii* from a worldwide collection between 2005 and 2009 reached resistance rates of greater than 50%[90]. In Brooklyn, New York, citywide surveillance revealed that about 2 of every 3 isolates were resistant to carbapenem antibiotics[91]. One predominant strain type of CRAB has established predominance after being introduced in a university hospital in Chicago in 2005[21]. In addition, molecular epidemiological investigations of sequential outbreaks of *A. baumannii* in an ICU showed the emergence of carbapenem resistance in Italy from 1999 to 2002[19]. The clonal spread of imipenem-resistant *Acinetobacter* spp. accompanied by the wide dissemination of the OXA-23 carbapenemase has been noted in China[92]. The first CRAB outbreak was reported in America in 1991, followed by global CRAB dissemination[93]. Most outbreaks caused by CRAB have occurred in ICU settings[29,94] throughout many countries. An outbreak caused by pandrug-resistant *A. baumannii* (PDRAB) was also reported in a pediatric ICU in a Taiwanese hospital[95].

## COMPARATIVE GENOMICS

In recent years, whole-genome sequencing and comparative genomics have been performed to elucidate the genetic basis of *A. baumannii* resistance, especially regarding the extent of variability and the acquisition and transfer of resistance determinants among different strains. The *A. baumannii* strain AYE, an endemic strain in France, exhibits an 86-kb resistance island in which 45 resistance genes are clustered[96]. Sequence similarities and phylogenetic analyses confirm that most of the resistance genes found in the *A. baumannii* AYE strain have been acquired from bacteria of the genera *Pseudomonas*, *Salmonella*, or *Escherichia*. Using pyrosequencing and transposon mutagenesis, the assembled genome of *A. baumannii* ATCC 17978 has been shown to consist of 3976746 base pairs (bp) and 3830 open reading frames (ORFs), a significant fraction (17.2%) of which are located in 28 putative alien islands[97]. A remarkable number of the islands contain genes implicated in virulence. *A. baumannii* ACICU has a single chromosome of 3904116 bp and two plasmids, pACICU1 and pACICU2, of 28279 and 64366 bp, respectively[98]. As many as 36 putative alien islands (pAs), 15 of which encode genes related to drug resistance, have been detected in the *ACICU* genome. One investigation involving MDRAB strains from hospitals of 10 European countries showed that AbaR3 is the original structure from which the AbaRs, the genomic islands containing many resistance genes, have been derived in European clone I, thus providing the strains of this lineage with a selective advantage[99]. All of these findings indicate that the genome of *A. baumannii* has acquired a large amount of foreign DNA, which has an important role in pathogenesis and antimicrobial resistance.

Currently, the whole-genome sequencing of the widely spread MDRAB strain MDR-ZJ06[100]; an MDR-TJ[101] strain in China; and two other multidrug-resistant strains (TCDC-AB0715, harboring both *bla*$_{\text{OXA-23}}$ and *bla*$_{\text{OXA-66}}$[102], and TYTH-1[103] from Taiwan) has been completed. A comparative genomics analysis has revealed a common strain lineage between the Taiwanese strains (TYTH-1 and TCDCAB0715) and the Chinese strains (MDR-TJ and MDR-ZJ06)[104]. Phylogenetic studies and GC profiles showed that the genome of TYTH-1 was the closest to the genome of MDR-ZJ06, which implies that the dissemination of *bla*$_{\text{OXA-23}}$-carrying CRAB in Taiwan may have been mediated by the transfer of people between Taiwan and China.

Adams *et al*[105] found that the entire multidrug-resistance phenotype of *A. baumannii* can be explained by the acquisition of discrete resistance determinants distributed throughout the genome. A comparison of closely related multidrug-resistant and drug-susceptible isolates suggests that drug efflux may contribute less to the resistance to certain classes of antibiotics than inactivation of enzymes. A resistance island with a variable composition of resistance determinants interspersed with transposons, integrons, and other mobile genetic elements is a significant contributor to the multidrug-resistant phenotype. A whole-genome sequencing analysis of six closely related clinical isolates of *A. baumannii*, including four from one hospital, revealed an extensive divergence of the resistance genotype that correlated with the observed differences in antimicrobial susceptibility[106]. Resistance genes associated with insertion sequences, plasmids, and a chromosomal resistance gene island all showed certain degrees of variability. The dynamic resistance gene pool suggests the rapid evolution of drug resistance in *A. baumannii*. The whole-genome sequencing of three dominant *A. baumannii* strains in an outbreak concluded that

much of their diversification was mediated by homologous recombination across 20% of their genomes[107]. The differences in genomic contents among different *Acinetobacter* spp. are partly shaped by their distinct ecological niches[108]. This notion is further supported by the variable presence of some genes encoding transcription factors and transporters among clinical isolates and their environmental *Acinetobacter* spp.[105].

## RESISTANCE MECHANISMS

### Overview

Currently, centain strains of *A. baumannii* is highly resistant to most antibiotics available in clinical practice. A number of resistance mechanisms to many classes of antibiotics are known to exist in *A. baumannii*, including β-lactamases, multidrug efflux pumps, aminoglycoside-modifying enzymes, permeability defects, and the alteration of target sites[109-111]. Most of these resistance mechanisms can target different classes of antibiotics. However, several different mechanisms can work together to contribute to the resistance to a single class of antibiotics. For example, the resistance mechanisms in CRAB are diverse[112]. In addition to β-lactamases with carbapenem-hydrolyzing activity as a major carbapenem resistance mechanism, which include carbapenem-hydrolyzing class D β-lactamases (CHDLs) and metallo-β-lactamases (MBLs), porins such as CarO[66] and penicillin-binding protein modifications might also be involved in carbapenem resistance[113]. The spread of multidrug-resistance determinants in *A. baumannii* is mostly through plasmid conjugation, transposon acquisition or integron mobilization to gain clusters of genes encoding resistance to several antibiotic families[110]. Furthermore, the functional insertion sequences are important in amplifying antimicrobial resistance and gene plasticity[114-118]. Table 1 shows the various antimicrobial resistance mechanisms of *A. baumannii*. The details are further discussed below.

### β-lactamase

Inactivation of β-lactams constitutes an important part of multidrug resistance in *A. baumannii*, especially for β-lactam antibiotic resistance. All four Ambler classes of β-lactamases (*i.e.*, classes A, B, C and D) can be identified in this organism[66]. Although a wide range of class A β-lactamases, including those of temoneira (TEM)[119-121], sulfhydryl variable (SHV)[122], cefotaxime hydrolyzing capabilities (CTX-M)[123,124], guiana extended-spectrum (GES)[115,125], self-transferable plasmid from *E. coli* (SCO)[126], *Pseudomonas* extended resistant (PER)[127-130], vietnam extended-spectrum β-lactamase (VEB)[96,131-133], carbenicillin hydrolyzing β-lactamase (CARB)[134,135] and *K. pneumoniae* carbapenemase (KPC)[136], have been reported in *A. baumannii* (Table 1), they are generally regarded to play a minor role in its resistance phenotype, especially in carbapenem resistance. Some of these enzymes are narrow-spectrum β-lactamases, *e.g.*, TEM-1[119-121], SCO-1[126] and CARB-4[135]; however, a number of these enzymes are still responsible for the hydrolysis of extended-spectrum β-lactams (ESBL). PER-1 was the first ESBL enzyme identified in *A. baumannii*[137], whereas TEM-92 and CARB-10 were the first reported TEM-type[120] and CARB-type[134] ESBLs, respectively. Later, the chromosomally encoded ESBLs SHV-5[122], PER-2[132] and PER-7[129,130] were also described. *A. baumannii* strains carrying the extended spectrum VEB-1 enzyme were first reported in an outbreak in France[131]. GES-11, an integron-associated GES variant, can even confer reduced susceptibility to carbapenems[115,125]. In addition, CTX-M enzymes are transmitted by integrons or plasmids, indicating the potential dissemination in outbreaks between different strains[123, 124]. Finally, KPC-10 was the first KPC β-lactamase to be identified[136].

Class B β-lactamases can confer resistance to the majority of β-lactams because of their broad range, potent carbapenemase activity and resistance to inhibitors[138]. Although MBLs are not the predominant carbapenemases in *A. baumannii*, verona integron-encoded metallo-β-lactamase (VIM), imipenemase (IMP) and seoul imipenemase (SIM) MBLs have been found contribute to the high-level resistance to carbapenems. The first VIM enzyme was described by Yum in 2002[139]. Thereafter, several other VIM variants, including VIM-1[140-142], VIM-3[143], VIM-4[141,142], and VIM-11[143], were identified in *A. baumannii*. IMP enzymes have also been reported in several Gram-negative bacteria worldwide, including *A. baumannii*. At least nine variants of IMP enzymes have been identified in *A. baumannii*: IMP-1[144], IMP-2[145], IMP-4[146,147], IMP-5[148], IMP-6[149], IMP-8[143], IMP-11[150], IMP-19[150] and IMP-24[143]. SIM-1 is the only SIM enzyme that has been reported in *A. baumannii*[151]. More recently, NDM (new Deli metallo-β-lactamase)-1[152-154] and NDM-2[155] were observed in *A. baumannii*. *bla*$_{NDM-1}$ is integrated in the chromosome within a new transposon structure with two copies of the insertion sequence IS*Aba125* in one clinical strain of *A. baumannii*. Such variability of the genetic environment of *bla*$_{NDM-1}$ likely facilitates its rapid dissemination[153].

The nucleotide sequence of the chromosomal cephalosporinase gene, which encodes an AmpC β-lactamase, in *A. baumannii* was first characterized in a clinical isolate from Spain in 2000[156]. Different isolates of *A. baumannii* have been shown to have almost identical AmpC sequences (no more than two amino-acid substitutions)[157]. A phylogenetic analysis showed that *Acinetobacter ampC* genes are descended from a common ancestor and are more closely related to each other than the *ampC* genes found in other species of bacteria[158]. The class C chromosomal β-lactamase AmpC in *A. baumannii* has a typical cephalosporinase substrate profile[156]. The presence of AmpC β-lactamase plays an important role in β-lactam resistance in *A. baumannii*, and in fact, a high percentage of drug-resistant *A. baumannii* possess *bla*$_{ampc}$[119]. In a study of 23 MDRAB clinical isolates from five proximal hospitals in Taiwan, all isolates had AmpC-type *bla*[77]. The presence of an insertion sequence with a strong promoter upstream of *ampC* in *A. baumannii* clinical isolates has the potential to overexpress AmpC, resulting in high-

**Table 1 Antimicrobial resistance mechanisms in *Acinetobacter baumannii***

| Resistance mechanism | Class/family | Protein | Ref. |
|---|---|---|---|
| β-lactamases | Class A | TEM-1 | [105,119,121] |
| | | TEM-92 | [120] |
| | | SHV-5 | [122] |
| | | CTX-M-2 | [123] |
| | | CTX-M-15 | [124] |
| | | GES-11 | [115,125] |
| | | GES-12 | [115] |
| | | GES-14 | [115] |
| | | SCO-1 | [126] |
| | | PER-1 | [127,128] |
| | | PER-2 | [132] |
| | | PER-7 | [129,130] |
| | | VEB-1 | [96,105,131-133] |
| | | CARB-4 | [135] |
| | | CARB-10 | [134] |
| | | KPC-10 | [136] |
| | Class B | VIM-1 | [140-142] |
| | | VIM-2 | [139,143] |
| | | VIM-3 | [143] |
| | | VIM-4 | [141,142] |
| | | VIM-11 | [143] |
| | | IMP-1 | [144] |
| | | IMP-2 | [145] |
| | | IMP-4 | [146,147] |
| | | IMP-5 | [148] |
| | | IMP-6 | [149] |
| | | IMP-8 | [143] |
| | | IMP-11 | [150] |
| | | IMP-19 | [150] |
| | | IMP-24 | [143] |
| | | SIM-1 | [151] |
| | | NDM-1 | [152-154] |
| | | NDM-2 | [155] |
| | Class C | AmpC | [156-160] |
| | Class D | | |
| | Narrow-spectrum | | |
| | OXA-3 group | OXA-21 | [163] |
| | OXA-20 group | OXA-37 | [164] |
| | OXA-10 group | OXA-128 | [387] |
| | CHDLs | | |
| | OXA-23 group | OXA-23 | [66,92,105,147,167-183] |
| | | OXA-133 | [185] |
| | OXA-24 group | OXA-40/24 | [197,201,204] |
| | | OXA-40 | [188,200, 202,203] |
| | | OXA-72 | [92,205,206] |
| | | OXA-25, OXA-26, OXA-27 | [198] |
| | OXA-51 group | OXA-51 | [105,187-190] |
| | | OXA64, OXA-65, OXA-66, OXA-68, OXA-70, OXA-71 | [191] |
| | | OXA-69, OXA-75, OXA-76, OXA-77 | [186] |
| | | OXA-79, OXA80, OXA-104, OXA106~OXA-112 | [194] |
| | | OXA-82, OXA-83, OXA-84 | [192,194] |
| | | OXA-86, OXA-87 | [193] |
| | | OXA-88, OXA-91, OXA-93, OXA-94, OXA-95, OXA-96 | [147] |
| | | OXA-92 | [195] |
| | | OXA-113 | [122] |
| | OXA-58 group | OXA-58 | [116,118,207,210,211, 21,5,219] |
| | | OXA-96 | [147] |
| | | OXA-97 | [220] |
| | Novel groups | OXA-143 | [196] |
| | | OXA-182 | [221] |
| | | OXA-235 | [222] |
| Efflux pumps | RND | AdeABC | [235,238] |
| | | AdeFGH | [243] |
| | | AdeIJK | [244] |
| | MFS | TetA | [248] |
| | | CmlA | [225] |
| | | MdfA | [233] |
| | | CraA | [249] |
| | | AmvA | [250] |
| | MATE | AbeM | [251] |
| | SMR | AbeS | [252] |
| AME | AAC | AAC3 (aacC1, aacC2) | [256] |
| | | AAC (6′) (*aacA4*) | [17,253,257-259,261] |
| | ANT | ANT (2″) (*aadB*) | [256] |
| | | ANT (3″) (*aadA1*) | [17,253,261] |
| | APH | APH (3′) (*aphA1*) | [255] |
| | | APH (3″) | [253] |
| Permeability defects | | CarO | [263-267] |
| | | 47-kDa OMP | [91] |
| | | 44-kDa OMP | [91] |
| | | 37-kDa OMP | [91] |
| | | 33-36-kDa OMP | [269] |
| | | 22-33-kDa OMP | [268] |
| | | 43-kDa OMP | [271] |
| | | Lipopolysaccharide | [64] |
| | | OmpA | [274] |
| Alteration of target sites | Change of PBP | PBP2 | [276] |
| | DNA gyrase | GyrA/ParC | [237] |
| | Ribosomal protection | TetM | [280] |
| | Dihydrofolate reductase | Dfr or Dhfr | [17,281] |
| | | FolA | [281] |
| | 16S rRNA methylation | ArmA | [253,258,282-286] |

TEM: Temoneira; SHV: Sulfhydryl variable; CTX-M: Cefotaxime hydrolyzing capabilities; GES: Guiana extended-spectrum; SCO: Self-transferable plasmid from *E. coli*; PER: *Pseudomonas* extended resistant; VEB: Vietnam extended-spectrum β-lactamase; CARB: Carbenicillin hydrolyzing β-lactamase; KPC: *K. pneumoniae* carbapenemase; VIM: Verona integron-encoded metallo-β-lactamase; IMP: Imipenemase; SIM: Seoul imipenemase; NDM: New Deli metallo-β-lactamase; AmpC: Ampicillin class C β-lactamase; CHDL: Carbapenem-hydrolyzing class D β-lactamase; OXA: Oxacillinase; RND: Resistance-nodulation-division; MFS: Major facilitator superfamily; MATE: Multidrug and toxic compound extrusion; SMR: Small multidrug resistance; Ade: *A. baumannii* multidrug-resistant efflux pump; TetA: Tetracycline resistant *Acinetobacter*; CmlA: Chloramphenicol resistance *Acinetobacter*; MdfA: Multidrug facilitator; CraA: Chloramphenicol resistance *Acinetobacter*; Amva: *A. baumannii* Methyl Viologen and antimicrobial resistance protein; AbeM: *A. baumannii* efflux pump of MATE family; AbeS: *A. baumannii* efflux pump of SMR family; AME: Aminoglycoside-modifying enzyme; AAC: Aminoglycoside acetyltransferases; ANT: Aminoglycoside adenyltransferases; APH: Aminoglycoside phosphotransferases; CarO: Carbapenem-associated outer membrane protein; OMP: Outer membrane protein; PBP: Penicillin binding protein; GyrA/ParC: DNA Gyrase/partitioning of the nucleoid partition; Dhfr: Dihydrofolate reductase; FolA: Folate; ArmA: Armillaria mellea.

level ceftazidime resistance[159,160]. IS*Aba1*-like sequences have been identified immediately upstream of the *bla*$_{ampC}$ gene in ceftazidime-resistant *A. baumannii* isolates but have been shown to be absent in ceftazidime-susceptible *A. baumannii* isolates[157].

Class D β-lactamases were designated OXAs in reference to their preferred substrate oxacillin[161]. Some OXAs are also able to hydrolyze extended-spectrum cephalosporins, and some can even inactivate carbapenems by acting as carbapenemases[66]. At least 121 different variants of class D β-lactamases have been identified at the protein level, and in contrast to other class D β-lactamases, 45 of these variants exhibit carbapenem-hydrolyzing activities[162]. The *bla*$_{oxa}$ genes can be located either on a chromosome or a plasmid and can sometimes be found in integrons[163,164]. Among the four classes of β-lactamases, MBLs and CHDLs are the two main groups of carbapenemases in *A. baumannii*, the latter of which is responsible for the most common type of carbapenem resistance *via* enzymatic degradation[165]. Currently, nine major subgroups of OXA carbapenemases have been identified based on amino acid homologies[166]. Four subgroups of OXA with carbapenemase activity, including the OXA-23, OXA-40/24, OXA-51 and OXA-58 clusters, are prevalent in *A. baumannii*[162,166].

New OXA-type carbapenemases have been frequently discovered since the first clinical isolate of *A. baumannii* with OXA-23 was characterized[66]. The *bla*$_{OXA-23}$ carbapenemase gene has also been disseminated worldwide[167]. The countries that have reported *A. baumannii* with OXA-23 carbapenemase include France[168-170], Germany[171], Bulgaria[172], Romania[173], the United States[105], Colombia[174], Brazil[175], Australia[176], Taiwan[177,178], China[92,179], Korea[180], Singapore[147,181], Italy[182] and Spain[183]. *A. radioresistens* has been proposed as a silent source of *bla*$_{OXA-23}$ for *A. baumannii*[184], and a novel variant, named *bla*$_{OXA-133}$, has been reported by the Asia-Pacific SENTRY surveillance program[185].

OXA-51/69-like β-lactamases are intrinsic chromosomal enzymes in *A. baumannii*[166,186] that emerged as a new subgroup of carbapenemases in MDRAB in 2004[187] and that show increased carbapenemase activity when IS*Aba1* is upstream of the promoter region[188,189]. However, drug export by an efflux pump might be more important in some clinical isolates[190]. A comparative genomics study by Adams *et al*[105] showed that the studied *A. baumannii* strains, including wild-type strains and clinical isolates of MDRAB, all possessed genes belonging to the OXA-51 group. The recently identified OXA-51 group of β-lactamases comprises a novel cluster among the OXA-type carbapenemases, and the cluster includes many variant oxacillinases that have been reported in several studies, including those by Heriter in 2005[186], Brown in 2005[191], Turton in 2006[192], Vahaboglu in 2006[193], Koh in 2007[147], Evans in 2007[194], Naas in 2007[122], Tsakris in 2007[195] and Higgins in 2009[196]. The CHDLs that have been found are listed in Table 1.

The OXA-40/OXA-24 CHDL group is made up of OXA-25, OXA-26, OXA-40, and OXA-72 (an original sequencing error occurred in sequencing OXA-24; it is now known as OXA-40)[166]. These enzymes only differ by a few amino acid substitutions. OXA-40/OXA-24 was originally identified as chromosomally encoded in a carbapenem-resistant *A. baumannii* isolate recovered from Spain[197]. OXA-25, OXA-26, and OXA-27 were later characterized to be associated with carbapenem resistance in clinical isolates of *A. baumannii* from Spain, Belgium and Singapore[198]. Thereafter, the OXA-40/OXA-24 gene in *A. baumannii* was reported in several areas[199], including Spain[188,200,201], Portugal[202] and the United States[203]. The plasmid-mediated *bla*$_{OXA-24}$ gene was noted in the isolates from an outbreak in Spain[204]. Additionally, OXA-72 has been identified in *A. baumannii* isolates from Taiwan[205], China[92] and Croatia[206].

OXA-58 was first identified from an isolate of MDRAB in France[207]. The *bla*$_{OXA-58}$ gene was found to be plasmid borne. Many OXA-58-producing *A. baumannii* isolates were reported worldwide in subsequent years, including isolates in Europe[208-211], Argentina[208], Kuwait[208], the United Kingdom[208], Australia[212], Taiwan[116], the United States[213,214] and China[215]. A number of outbreaks have also been reported in many countries, including Italy[216], Belgium[79], France[217], Turkey[193], Greece[218,219], and the United States[214]. OXA58 can lead to high-level carbapenem resistance in *A. baumannii via* the upstream IS*1008* insertion[116] or the presence of the ISAba825-ISAba3-like hybrid promoter[118]. OXA-97 is a point mutation variant of OXA-58 that shares the same hydrolytic properties and has been recently identified in *A. baumannii* isolates from Tunisia[220]. Another point mutation derivative is OXA-96, which was identified in *A. baumannii* from Singapore[147].

In 2009, a novel CHDL, OXA-143, was identified that shares 88% amino acid identity with OXA-40, 63% identity with OXA-23, and 52% identity with OXA-58[196]. Another novel oxacillinase, OXA-182, was identified in imipenem-nonsusceptible *Acinetobacter* isolates in Korea[221] and showed 93% identity with OXA-143 and 89% identity with OXA-40 based on amino acid sequence alignment. OXA-235, and the amino acid variants OXA-236 and OXA-237, were identified from *A. baumannii* isolates from the United States and Mexico[222]. The deduced amino acid sequences shared an 85% identity with OXA-134, 54 to 57% identities with the acquired OXA-23, OXA-24, OXA-58, and OXA-143, and a 56% identity with the intrinsic OXA-51. Thus, OXA-235, OXA-236 and OXA-237 represent a novel subclass of OXAs. The expression of OXA-235 in *A. baumannii* leads to reduced carbapenem susceptibility, while the cephalosporin minimal inhibition concentrations (MICs) are unaffected.

### Multidrug efflux pumps

While multidrug-resistant efflux pumps have been shown to have roles in bacterial pathogenicity[223], the contribution of efflux pumps to bacterial multidrug resistance is often reported[224,225]. Efflux-based mechanisms are responsible for resistance against many different classes of antibiotics, including tigecycline resistance[226,227] or imipenem resistance[190] in *A. baumannii*. Furthermore, the

linear relationship between the log-transformed expression values of the AdeABC efflux pump genes and the log-transformed MIC values is statistically significant, indicating that overexpression of the AdeABC efflux pump is a prevalent mechanism for decreased susceptibility to tigecycline[228]. The importance of efflux pumps in multidrug resistance in *A. baumannii* is supported by the fact that the presence of efflux pump inhibitors, such as 1-(1-naphthylmethyl)-piperazine[229,230], phenyl-arginine-β-naphthylamide[231,232], or carbonyl cyanide 3-chlorophenylhydrazone[232], can reverse the resistance pattern.

Four categories of efflux pumps, including the resistance-nodulation-division (RND) superfamily, the major facilitator superfamily (MFS), the multidrug and toxic compound extrusion (MATE) family and the small multidrug resistance (SMR) family transporters, have been reported to be related to antimicrobial resistance in *A. baumannii*[233,234]. Of these different pumps, the RND and MFS transporters are mentioned most often. AdeABC, a RND-type efflux pump with a three-component structure, is not only associated with aminoglycoside resistance[235] but is also associated with decreasing susceptibility to several antimicrobials, including tigecycline[226]. Differences in the expression of *adeABC* were shown to contribute to both inter- and intra-clone variation in tigecycline MICs in a study of *A. baumannii* epidemic clones[236]. Both the increase in tigecycline resistance during therapy[236] and the decrease in susceptibility to non-fluoroquinolone antibiotics during an outbreak[237] are mediated by the up-regulation of AdeABC in *A. baumannii*. The AdeABC pump in wild *A. baumannii* is cryptic due to stringent control by the AdeRS two-component system[238]. Point mutations in AdeS and AdeR or a truncation of AdeS due to an IS*Aba1* insertion may be related to the overexpression of AdeABC, which leads to multidrug resistance[238,239]. However, the existence of tigecycline-nonsusceptible and *adeB*-overexpressing *A. baumannii* clinical isolates without known *adeRS* mutations[240] and the low expression of *adeABC* in a clinical strain of *A. baumannii* with the IS*Aba1* insertion in the *adeRS* operon[239] suggest that the regulation of *adeABC* gene expression is complex. Additionally, the cell density-dependent expression of *adeB* suggests the presence of global regulatory mechanisms for the expression of this gene in *A. baumannii*[241]. BaeSR, which functions as an envelope stress response system to external stimuli, is proposed to influence the transcription of *adeAB* and thus tigecycline susceptibility in *A. baumannii* by functioning as a regulator of global transcription[242].

In addition to the AdeABC efflux pump, the inactivation of other RND-type efflux pumps, including AdeFGH[243] and AdeIJK[232,244,245], demonstrates their contribution to multidrug resistance in *A. baumannii*. The AdeABC and AdeIJK efflux systems can contribute synergistically to tigecycline resistance[244]. An open reading frame encoding a LysR-type transcriptional regulator, named *adeL*, is located upstream of the *adeFGH* operon and is responsible for the overexpression of AdeFGH[243], whereas the expression of AdeIJK in *Acinetobacter baumannii* is regulated by AdeN, a TetR-Type regulator[246]. Although the RND efflux pump AdeDE was initially identified in *Acinetobacter* genomic group 3[247], *adeE* was later found to coexist with *adeB* in some clinical isolates of *A. baumannii*[245].

A number of MFS efflux pumps, including TetA[248], CmlA[225], MdfA[233], CraA[249] and AmvA[250], that mediate resistance to different types of antibiotics in *A. baumannii* have been characterized. AbeM, a H-coupled pump that belongs to the MATE family[251], was reported to be present in the clinical isolates of *A. baumannii* in several studies[77,232,245] and to confer resistance to fluoroquinolones or imipenem in *A. baumannii*. *A. baumannii* with a mutant AbeS SMR pump exhibits erythromycin and chloramphenicol resistance[252].

### Aminoglycoside-modifying enzymes

Aminoglycoside-modifying enzymes (AMEs) are the principal mode of resistance to aminoglycosides. This resistance is primarily mediated by three classes of enzymes, including acetyltransferases, adenyltransferases and phosphotransferases, that typically reside on transposable elements; these enzymes chemically modify aminoglycosides[253]. The coding genes for these enzymes can be transferred among different bacterial types through plasmids, transposons, integrons, and natural transformation or transduction[254]. A phenotypic analysis of aminoglycoside resistance profiles indicated that many isolates could produce a combination of aminoglycoside-modifying enzymes[255,256]. The co-carrying of four AME genes, including a novel AME gene *aac(6')-Ib*, was reported in a PDRAB strain from China[257]. The identification of MDRAB isolates harboring genes for the *bla*$_{\text{OXA-23}}$-like genes, AME (*aac(6')-Ib*) and the 16S rRNA methylase (*armA*) implicates AMEs in multidrug resistance[258].

Different types of AMEs have been reported in *A. baumannii*. Amikacin resistance has been reported to be associated with a gene encoding APH(3')-VI phosphotransferase[255]. Furthermore, AME *aac(6')-Iad* plays an important role in amikacin resistance in *Acinetobacter spp.* in Japan[259]. Of the 106 MDRAB isolates identified in one study, 95% possessed at least one type of AME, including *aacA4*, *aacC1*, *aacC2*, *aadB*, *aadA1*, *aphA1* and *aphA6*[256]. In another study in Greece, all of the collected *A. baumannii* strains contained AMEs, which were either *aac(6')-Ib* or *aac(6')-Ih*[260]. Class I integrons containing the gene cassettes *aacA4-catB8-aadA1*, *dhfrXII-orfF-aadA2*, or *aacC1-orfP-orfP-orfQ-aadA1* have been proposed to be associated with the horizontal transfer of diversified aminoglycoside-resistant genes among clinical isolates of *A. baumannii*[17,256,261].

### Permeability defects

Porins, which perform multiple functions in membranes, are proteins that can form channels to allow the transport of molecules across lipid bilayer membranes[233]. These outer membrane proteins not only influence the virulence of *A. baumannii*, *e.g.*, through Omp38-induced epithelial cell apoptosis[59], biofilm formation related to OmpA[262],

OmpA-dependent host cell death[263], and attenuated virulence by the decreased expression of genes encoding CarO- and OprD-like proteins[263], but also play a significant role in the mechanisms of resistance. For example, the loss of a 29 kDa outer-membrane protein, which was later shown to be CarO, contributes to imipenem resistance[263-267]. Several other studies have also identified a number of OMPs involved in the carbapenem resistance of *A. baumannii*. A reduction in the expression of two porins of 22 and 33 kDa was involved in the carbapenem resistance of *A. baumannii* strains in an outbreak in Spain[268]. In one study, CRAB isolates found in New York had reduced expression of the 47-, 44-, and 37-kDa outer-membrane proteins[91], while in other studies, a 33- to 36-kDa OMP was also shown to be associated with carbapenem resistance in *A. baumannii*[269,270]. A 43-kDa OMP, belonging to the OprD family, has been identified as a basic amino acid and imipenem porin through electrophoresis and MALDI-MS analyses[271].

In the presence of OXA carbapenemases, including OXA-51-like or OXA-23-like enzymes, the loss of the 29-kDa outer-membrane protein is associated with a higher imipenem MIC in *A. baumannii*[272,273]. Moreover, a novel insertion sequence, IS*Aba10*, inserted into IS*Aba1* adjacent to the *bla*$_{\text{OXA-23}}$ gene, can disrupt the outer-membrane protein gene *carO* in *A. baumannii*[180]. The loss of lipopolysaccharide (LPS) from the outer membrane, resulting in a decrease in membrane integrity, occurred in a colistin-resistant clinical isolate of *A. baumannii* in Australia[64]. Disruption of the *ompA* gene can lead to decreases in the MICs of chloramphenicol, aztreonam, and nalidixic acid[274].

### Alteration of target sites

Changes in penicillin-binding proteins (PBPs), mutations of DNA gyrase, ribosomal protection by the TetM protein and the involvement of dihydrofolate reductase in trimethoprim resistance all occur *via* mechanisms that alter the target sites for antibiotics[275]. Imipenem resistance has been associated with the overexpression of certain PBPs with a low affinity for imipenem in the absence of other known resistance mechanisms[276]. While an insertion sequence disrupting the gene encoding PBP6b has been identified in an endemic carbapenem-resistant clone, its role must be further evaluated[277]. Furthermore, mutations in DNA gyrase gene *gyrA* and *parC*, which encode topoisomerase Ⅳ, have been reported in an *A. baumannii* outbreak investigation[237]. The *gyrA* mutation at Ser-83 was shown to be associated with quinolone resistance in epidemiologically unrelated isolates of *A. baumannii*[278]. While *tetA* and *tetB* genes are well recognized for their role in tetracycline resistance in *A. baumannii* through efflux pumps[225,279], *tetM* is proposed to be another resistance mechanism that acts through ribosomal protection[280]. Trimethoprim resistance through dihydrofolate reductase in *A. baumannii* is similar to that of other bacteria. Plasmids containing *folA* genes and integrons harboring *dfr* or *dhfr* genes in *A. baumannii* have been found[17,279,281]. Recently, the coexistence of the 16S rRNA methylase *armA* gene and genes encoding OXA carbapenemases were reported in many countries, including China[282], South Korea[253,283], India[284], Italy[285], Japan[286], and Yemen[258], indicating the contribution of the *armA* gene to the multidrug resistance of MDRAB.

### Roles of integrons

The horizontal transfer of resistance genes is a successful mechanism for the transmission and dissemination of multiple drug resistance determinants among bacterial pathogens[287]. Integrons, which are located on either bacterial chromosomes or plasmids, are assembly platforms that incorporate exogenous ORFs by site-specific recombination and convert them to functional genes by ensuring their correct expression[288]. Integrons share common features: a gene encoding an integrase, a specific recombination site that is recognized by the integrase and into which the cassettes are inserted, and a promoter that directs the transcription of the cassette-encoded genes. Currently, there are four classes of integrons, and class 1 integrons are the most common in bacteria[289].

The role of integrons in the development of multidrug resistance relies on their unique capacity to cluster and express drug resistance genes[287]. Many studies regarding integrons harboring different types of resistance genes have been reported worldwide in recent decades. Class I integrons were detected in 52.8% of *A. baumannii* strains in the Nanjing area of China in 2007[290], whereas an epidemic, class 1 integron-carrying MDRAB clone was found to be widespread in Taiwan in the same year[291]. Four different integron structures were detected in 84% of all collected isolates of *A. baumannii* in a Spanish study[255]. However, while no clear antibiogram differences could be associated with the presence or absence of integron structures in the Spanish study, other reports have suggested that integrons play a major role in multidrug resistance in *A. baumannii*[261,291,292]. Additionally, epidemic strains of *A. baumannii* have been found to contain significantly more integrons than non-epidemic strains[293]. Therefore, integrons are regarded as useful markers for epidemic strains of *A. baumannii*, and their typing can provide valuable information for epidemiological studies[294,295].

A study performed in Italy found that 44% of the epidemiologically unrelated *A. baumannii* isolates collected over an 11-year period were integron-positive[296]. Most integron-positive strains carried the same array of cassettes, despite their notable genetic diversity that was identified through a ribotyping analysis, implying that horizontal transfer of the entire integron structure or an ancient acquisition occurred. Additionally, while the same integron can be present in unrelated strains[17], related strains can also have different integrons[297].

Although different relationships exist among different classes of antibiotics and integrons[298,299], most studies have emphasized the association of integrons with cassette genes and aminoglycoside resistance[261]. The diversity of the genes encoding AMEs and their association with class 1 integrons was observed in a study involving

three pan-European clones of *A. baumannii*[256]. Six different class 1 integron variable regions were detected in 74% of the collected strains. Furthermore, Huang *et al*[291] collected 283 MDRAB isolates from three medical centers in Taiwan from 1996 to 2004 and found seven types of gene cassettes, most of which contained AMEs, including *aacA4*, *aacC1*, *aac(6')-II*, *aadA1*, *aadA2*, *aadA4* and *aadDA1*.

Variable CHDL genes, including *bla*$_{OXA-3}$[292], *bla*$_{OXA-10}$[96,290], *bla*$_{OXA-20}$[19,292,296], *bla*$_{OXA-21}$[297], and *bla*$_{OXA-37}$, have been reported in integrons[164,297]. Integron-associated imipenem resistance in *A. baumannii* has also been documented[300]. Genes encoding carbapenemases, such as MBLs *bla*$_{VIM}$, *bla*$_{IMP}$ and *bla*$_{SIM}$, have been found in integrons. *bla*$_{VIM-1}$-carrying integrons[140] and *bla*$_{VIM-2}$-carrying integrons[139] have been noted in Greece and Korea, respectively. In Taiwan, integron-mediated gene spreading has been demonstrated hospitals[301], especially in a unit with high antibiotic selective pressure[302]. *bla*$_{VIM-11}$-carrying integrons have also been identified in MDRAB isolates, and this MBL gene has been postulated to spread among *Pseudomonas aeruginosa* and *A. baumannii* strains[143,291]. Other reported MBLs include *bla*$_{IMP-1}$[303], *bla*$_{IMP-2}$[145], *bla*$_{IMP-4}$[146,147], *bla*$_{IMP-5}$[148], *bla*$_{IMP-8}$[291] and *bla*$_{SIM-1}$[151]. The genes for chloramphenicol resistance in the integrons of *A. baumannii* are *catB2*[135], *catB3*[146,147,151] and *catB8*[294,304].

## CLINICAL IMPACT OF ANTIMICROBIAL RESISTANCE

The clinical impact of *A. baumannii* infections has been a matter of debate[2]. A high mortality rate in immunocompromised hosts with *A. baumannii* infections had been attributed to the patients' underlying diseases rather than to the infections. One Spanish study concluded that there were no differences in mortality among patients with ventilator-associated pneumonia (VAP) caused by imipenem-resistant or imipenem-susceptible *A. baumannii* or by other pathogens[305]. However, other related studies suggest that *A. baumannii* infection itself has a profound influence on high mortality or prolonged length of stay (LOS)[306]. Falagas suggested that the mortality attributed to *A. baumannii* infections should no longer be a controversial issue[307] based on six relevant case-control studies[308-313].

Several previous surveillance[314-317] studies have demonstrated that increasing antimicrobial resistance, especially multidrug resistance, has become a major issue in *A. baumannii* strains in recent years. Whether multidrug resistance is a risk factor for high mortality in *A. baumannii* infections has been a controversial issue. A few studies suggested that MDRAB-related pneumonia or bacteremia is a signal of disease severity and is not related to prolonged LOS or increased mortality[318,319], but more recent studies have shown that MDRAB infections lead to higher mortality. The acquisition of MDRAB was shown to be an independent risk factor for mortality in a burn center in Singapore[320]. A multicenter retrospective study in Taiwan also showed that patients with CRAB infections have a higher mortality rate than those with carbapenem-susceptible *A. baumannii* infections[321], which is consistent with the results of several previous studies[309-311,313,322]. The high impact of imipenem resistance on the mortality rate of patients with *Acinetobacter* bacteremia is chiefly attributable to discordant antimicrobial therapy[311]. Moreover, patients with MDRAB infections have increased hospital and ICU LOS compared to patients with susceptible *A. baumannii* infections and uninfected patients[308]. A mini review of this issue indicated that blood stream infections and nosocomial ICU infections caused by carbapenem-resistant *Acinetobacter* spp. are associated with increased rates of mortality, whereas other types of infections have not clearly been shown to be associated with higher mortality rates but are associated with increased LOSs and hospital costs[323].

## STRATEGIES TO COMBAT THE DISSEMINATION OF ANTIMICROBIAL RESISTANCE

The development of new antibiotics against MDRAB and the implementation of infection control measures are regarded as two methods to aid in controlling the increasing problem of *A. baumannii* infections[307]. When GlaxoSmithKline shared the challenges and difficulties in screening for new classes of antimicrobial agents over a 7-year period, the authors concluded that the pipeline of novel-mechanism antibacterials is still empty and will remain so for a considerable period[324]. Therefore, the importance of following the Association of Professionals in Infection Control and Epidemiology's (APIC) 2010 guide to the elimination of MDRAB transmission in health care settings cannot be overemphasized[325]. This guide includes MDRAB risk assessment and infection surveillance, strict adherence to hand hygiene protocols, implementation of standard and transmission-based precautions, environmental decontamination, outbreak recognition and control, and antibiotic stewardship.

Gastrointestinal or skin colonization of *A. baumannii* develops soon after the pathogen is first isolated from a clinical site[326]. The finding of multidrug-resistant colonized strains compared with susceptible clinical strains without apparent relation to antibiotic use implies that a new onset of MDRAB colonization may not be identified without surveillance. Additionally, the increasing occurrence of multidrug-resistant strains among seriously ill patients emphasizes the importance of continued surveillance as a critical component of any program aimed at preventing and controlling antimicrobial resistance[315]. Environmental contamination, airborne transmission, patient transfer, and cross-contamination are regarded as key factors in causing *A. baumannii* epidemics[327], and clonal expansion has been shown to play a major role in the increase of MDRAB in hospitals[328]. Therefore, barrier infection control measures are necessary to prevent the nosocomial spread of MDRAB[326]. One outbreak

**Table 2 Antimicrobial treatment for MDRAB infections**

| Regimen | Pathogen | Diseases | Outcome[1] | Comparator | Ref. |
|---|---|---|---|---|---|
| CST + RIF | XDRAB | HAP<br>VAP<br>BSI<br>cIAI | The same in<br>CR (mortality) Better in MR | CST | [367] |
| CST + RIF | CRAB | VAP | The same in CR + MR | CST | [366] |
| CST + IPM<br>CST + SAM<br>CST + others | XDRAB | BSI | Better in CR (mortality) + MR | CST | [369] |
| CST + SUL | MDRAB | VAP | The same in CR + MR | CST | [341] |
| TGC based | MDRAB | Pneumonia | Higher mortality | CST based | [349] |
| TGC based | MDRAB | HAIs | The same in mortality[2] Better in MR | IPM + SAM | [352] |
| CT | MDRAB | Infections | The same in mortality | MT | [374] |

[1]"The same" means no significant difference between comparator groups, and "Better" means a significant difference exists between comparator groups; [2]Has a statistically significant favorable outcome. MDRAB: Multidrug-resistant *A. baumannii*; CST: Colistin; IPM: Imipenem; RIF: Rifampicin; SUL: Sulbactam; SAM: Ampicillin/sulbactam; TGC: Tigecycline; HAP: Hospital-associated pneumonia; VAP: Ventilator-associated pneumonia; BSI: Blood stream infection; cIAI: Complicated intra-abdominal infection; HAIs: Healthcare-associated infections; CR: Clinical response; MR: Microbiological response; CT: Combination therapy; MT: Monotherapy.

reported in an ICU in a Greek hospital ceased after the implementation of hygienic measures, complete cleaning and complete disinfection in the ICU[329]. However, cross-infection with *A. baumannii* among patients still occurred, despite the implementation of stringent infection control measures, in a previously reported outbreak; thus, temporary closure of the surgical ward for disinfection was necessary to control the outbreak[330].

Environmental contamination plays an important role in the transmission of MDRAB. One outbreak investigation found that the affected patients had a higher risk of harboring *A. baumannii* after blood transfusion, hydrotherapy or extended use of a respirator, which was possible through the contamination of healthcare personnel and the environment. Another *A. baumannii* outbreak investigation in a surgical ICU at a teaching hospital in Taiwan showed extensive amounts of environmental contamination, including the contamination of bed rails, bedside tables, sinks, ventilator and infusion pump surfaces, and water for nasogastric feeding and ventilator rinsing. Hence, intensified infection prevention control (IPC) measures are needed to terminate an outbreak. The IPC measures include: (1) implementation of enhanced contact isolation precautions; (2) active surveillance cultures; (3) daily environmental cleaning with detergents and phenolic agents; (4) an up-to-date education program for all healthcare workers; and (5) delivery of real-time feedback to healthcare workers regarding IPC compliance[331], which has minimized the spread of colistin-resistant *A. baumannii*. Furthermore, the infection control bundle resulted in a significant reduction in the incidence of nosocomial *A. baumannii* in one burn unit and prevented further outbreaks of this organism, with an 88.8% decrease during the intervention period[332].

Imipenem has been proven to be a strong inducer of multidrug resistance in *A. baumannii*[333]. Many *A. baumannii* isolates exhibit imipenem resistance, which is strongly associated with the prior use of carbapenems[334]. Because of the high mortality rate associated with *A. baumannii* infection, strategies to slow down the emergence of MDRAB in clinical practice by optimizing antimicrobial therapy are necessary. Therefore, antimicrobial stewardship is mandatory in an infection prevention program to prevent the emergence and transmission of MDRAB in health care facilities[325].

## ANTIMICROBIAL THERAPY

Carbapenems, including imipenem or meropenem, have been regarded as effective antimicrobial agents to treat *A. baumannii* infections[314,335]. With many studies reporting increasingly high rates of CRAB in clinical isolates[75,76,90], other classes of antibiotics or combination therapies are urgently needed. Because the choices of antimicrobial treatment for MDRAB are severely limited by resistance, there are only a few effective options available, including polymyxins and tigecyclines[336]. Furthermore, the appearance of PDRAB, which is resistant to all available antibiotics, including polymyxin, implies that more efforts should be devoted to investigating the treatment options for this superbug[27]. Combination therapies with imipenem/sulbactam, colistin/rifampicin, colistin/sulbactam, colistin/tigecycline, colistin/imipenem or meropenem and colistin/teicoplanin have been studied and proposed as possible choices. The recently published reports on the treatment of MDRAB are summarized in Table 2.

### *Sulbactam*

While ampicillin/sulbactam has been shown to be effective in treating blood stream infections caused by MDRAB[337], a later meta-analysis revealed that sulbactam-based therapy is not superior to other therapeutic approaches, including colistin, cephalosporins, antipseudomonas penicillins, fluoroquinolones, minocycline/doxycycline, aminoglycosides, tigecycline, polymyxin, imipenem/cilastatin, and combination therapies[338]. Although sulbactam-based therapy failed to prove its superiority to other regimens for the treatment of *A. baumannii* in-

fections, a case of skin and soft tissue infection caused by CRAB that was treated successfully with ampicillin/sulbactam and meropenem combination[339] raises the possibility of ampicillin/sulbactam as a component of combination therapy against CRAB. The combination of ampicillin/sulbactam with a carbapenem for treating MDRAB bacteremia has been shown to be associated with a better outcome[340], but such beneficial effects were not observed for MDRAB VAP[341].

### Tigecycline-based therapy

In 2004, tigecycline was reported to have a good *in vitro* bacteriostatic effect against *A. baumannii*, including strains resistant to imipenem[342]. Another *in vitro* study using a time-kill assay demonstrated the potential role of tigecycline in the treatment of *A. baumannii* and proposed that doxycycline could be a suitable and cost-effective option in some instances[343]. Tigecycline efficacy was shown to correlate well with the free concentration-time curve of MIC in a murine *Acinetobacter* spp. model[344]. Additionally, several cases affiliated with severe infections by MDRAB were successfully treated with tigecycline in terms of their clinical and microbiological outcomes[345].

With its increasing use, the limitations and adverse aspects of tigecycline in treating MDRAB infections have begun to be realized. Tigecycline was less effective than imipenem in the treatment of pneumonia caused by non-IRAB strains in a murine pneumonia model[346]. In a study consisting of 34 patients with MDRAB infections, the mortality rate reached up to 41%. The authors found that the correlation of clinical and microbiological outcomes was poor and concluded that tigecycline had excellent *in vitro* activity against MDRAB, but its clinical efficacy was still uncertain[336]. One of the possible causes for the discrepancy of treatment outcomes may be variable tigecycline MICs. MIC determination for tigecycline before treatment, with the broth dilution method being favored[347], might increase clinical success[345]. *A. baumannii* isolates with tigecycline MICs of $\geqslant$ 2 mg/L were associated with higher mortality rates; thus, treatment with β-lactams or carbapenems instead of with tigecycline is preferred[348]. This notion was further supported in a matched cohort study in Taiwan that dealt with the effectiveness of tigecycline-based versus colistin-based therapy for the treatment of pneumonia caused by MDRAB[349]. The excess mortality rate of 16.7% in the tigecycline-based group compared with the colistin-based group was mostly attributed to subjects with MIC > 2 μg/mL.

In a meta-analysis of the efficacy and safety of tigecycline, clinical failure, superinfection and adverse events were more frequent with the use of tigecycline[350]. The authors suggested that physicians should avoid tigecycline monotherapy for the treatment of severe infections caused by MDRAB and that they should use it as a last-resort antibiotic. There was no antagonism found when tigecycline was used with other antimicrobials possessing activities against Gram-negative bacteria[351]. However, tigecycline-based therapy for MDRAB infections is not satisfactory. In a study of 266 patients with healthcare-associated MDRAB infections, the mortality rate was not significantly different between those receiving tigecycline-based therapy and those receiving non-tigecycline therapy[352].

While tigecycline has an expanded spectrum of antibacterial activity and a synergic effect with some classes of antibiotics, such as amikacin[353], earlier studies have shown that tigecycline resistance in *A. baumannii* has emerged[354] and is associated with multidrug efflux systems, especially overexpression of the *adeABC* pump[226,227]. The increased expression of the *adeABC* operon can be found in clinical isolates of *A. baumannii* post-tigecycline therapy[236,355]. High resistance rates and high MICs of tigecycline in multiple clones of MDRAB were noted in a medical center in Israel[356]. This phenomenon led to concern regarding the use of tigecycline as one of the few treatment choices for infections caused by MDRAB.

### Colistin-based therapy

Colistin has been described as a last resort for the treatment of MDRAB[357], and this drug is often used in combination therapy. In a report on the clonal spread of MDRAB in eastern Taiwan, antibiotic susceptibility testing showed that 10.4%, 47.8% and 45.5% of MDRAB isolates were resistant to colistin, rifampicin, and tigecycline, respectively, implying that colistin was the only effective antimicrobial agent in that area for treating MDRAB[358]. In addition to its intravenous injection for MDRAB infections, colistin can be given *via* intraventricular and intrathecal routes for meningitis[359] and *via* nebulization for pneumonia[360,361].

Unfortunately, colistin-resistant *A. baumannii* strains have been reported all over the world[357] and are attributed to the loss of lipopolysaccharide[64] or/and phosphoethanolamine modification of lipid A mediated by the PmrAB two-component system[362,363]. Because colistin monotherapy is unable to curb the appearance of resistance, colistin-based combination therapy might be the optimal antimicrobial strategy. Colistin combined with different classes of antibiotics, including tigecycline, cefoperazone/sulbactam or piperacillin/tazobactam, revealed synergistic effects in some CRAB strains[364]. Time-kill assays have also shown that colistin/meropenem, colistin/rifampicin, and colistin/minocycline are synergistic *in vitro* against XDRAB strains[365]. The beneficial effects of colistin and rifampicin combination for patients with VAP caused by CRAB have been documented in terms of clinical and microbiological outcomes[366]. However, another multi-center, randomized clinical trial concluded that 30-d mortality was not reduced by the addition of rifampicin to colistin in serious XDRAB infections[367]. Additionally, such a regimen might be hindered by a high level of rifampicin resistance in *A. baumannii*[368]. Treatment with combination therapy, including colistin/carbapenem and colistin/sulbactam, for XDRAB blood stream infections led to higher microbiological eradication and lower mortality rates in comparison with the colistin monotherapy group[369]. The combination therapy

of colistin and tigecycline has also been proposed as a reasonable treatment of choice for XDRAB pneumonia, especially in the first 48 h, in a rat lung model[370]. Interestingly, a significant synergy has been observed for the combination of colistin and teicoplanin against MDRAB *in vitro*[371]. Telavancin, a similar lipoglycopeptide of teicoplanin, has been shown to be efficacious *in vivo* when used in colistin combination therapy in a *Galleria mellonella* model of *A. baumannii* infection[372].

### Other antimicrobial therapies

Doripenem, a novel broad-spectrum carbapenem, has displayed *in vitro* synergistic activity with tigecycline, colistin and amikacin against MDRAB strains with doripenem resistance[373]. One recent prospective, observational Spanish study did not support an association of combination therapy with reduced mortality in MDRAB infections[374]. Overall, the choice of combination therapy should take several key factors into consideration, including the antimicrobial resistance phenotype, resistance mechanisms, and MIC[375].

## FUTURE PERSPECTIVES

One of the difficulties encountered in understanding the antimicrobial resistance mechanisms of *A. baumannii* lies in the complexity of the involved genes. A DNA microarray, the Check-MDR CT102 microarray, has proven useful in detecting TEM, SHV and CTX-M extended-spectrum β-lactamases and KPC, OXA-48, VIM, IMP, and NDM-1 carbapenemases in some *Enterobacteriaceae* and glucose non-fermentative bacteria, including *A. baumannii*, with 100% sensitivity and specificity for most of the tested genes[376]. The detection of plasmid-mediated cephalosporinases, including CMY-2-like, DHA, FOX, ACC-1, ACT/MIR and CMY-1-like/MOX, was also possible using this assay, suggesting that this DNA array is a powerful high-throughput tool for most common resistance gene identifications and provides a platform for epidemiological or infection-control studies[377].

Bacteria develop resistance to new classes of antibiotics very quickly, and bacteria may even be resistant to new classes of antibiotics before they are introduced to clinical use[378]. Hence, antimicrobial peptides (AMPs) may be another option due to the rare appearance of resistance to AMPs in addition to their antimicrobial and anti-inflammatory effects[379]. AMPs are an important component of host defenses against invading pathogens[380]. They are small, cationic and amphipathic peptides of variable length, sequence and structure. Thus far, more than 750 different AMPs have been identified in various organisms ranging from plants to animals, including humans, most of which exhibit broad-spectrum activity against a wide range of microorganisms by disrupting the plasma membrane and causing cell lysis. Three classes of AMPs, including defensins, cathelicidins, and histatins, have been found in humans[379]. The cathelicidin family is currently limited to a single gene, CAMP. LL-37, which begins with two leucine residues and consists of 37 amino acids, was the first mature peptide isolated from *CAMP* gene products[381].

While only a few studies regarding the use of AMPs in *A. baumannii* have been reported, AMPs might be a potential therapeutic alternative to antibiotics. This hypothesis is supported by the conclusion reached from a study of an LPS-deficient, colistin-resistant *A. baumannii* strain, which showed reduced viability even at a low concentration of LL-37[382]. The human antimicrobial peptide LL-37 and its fragments KS-30 and KR-20 have been shown to have significant antimicrobial activity against clinical isolates of MDRAB, of which the KS-30 fragment exhibits the highest bactericidal ability[383]. Moreover, the prevention of biofilm formation *in vitro* by LL-37, KS-30 and KR-20 adds significance to their efficacy. We predict that AMPs, specifically LL-37, will be promising targets in future research on therapeutics against MDRAB infections.

Because marketing a new antimicrobial is extremely difficult and because bacteria quickly adapt to so-called magic bullets, understanding the interplay between a pathogen such as *A. baumannii* and its hosts may provide another possible solution in the war against bacteria. The microbes that exist in the human body are collectively known as the human microbiota, and this remarkably complex and poorly understood group of communities has an enormous impact on humans[384]. The Human Microbiome Project, funded by the National Institutes of Health, aims to develop tools and databases for the research community to study the role of these microbes in human health and disease. One of the tasks the NIH has set itself is to develop a catalog of the microbial genome sequences of reference strains[385]. For example, the microbiome diversity in the bronchial tracts of patients with chronic obstructive pulmonary disease has been documented[386]. More advances in understanding the pathogenesis of *A. baumannii* using the databases of the Human Microbiome Project can be anticipated.

In conclusion, we hope that this review will aid in understanding the relevant studies regarding the antimicrobial resistance of *A. baumannii* as well as the currently available treatment options for the infections that this pathogen cause, thereby leading to new strategies to combat *A. baumannii*.

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