Drug-resistant *Acinetobacter baumannii*: From molecular mechanisms to potential therapeutics (Review)

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Abstract. Bacterial drug resistance is increasingly becoming an important problem that needs to be solved urgently in modern clinical practices. Infection caused by *Acinetobacter baumannii* is a serious threat to the life and health of patients. The drug resistance rate of *Acinetobacter baumannii* strains is increasing, thus research on the drug resistance of *Acinetobacter baumannii* has also seen an increase. When patients are infected with drug-resistant *Acinetobacter baumannii*, the availability of suitable antibiotics commonly used in clinical practices is becoming increasingly limited and the prognosis of patients is worsening. Studying the molecular mechanism of the drug resistance of *Acinetobacter baumannii* is fundamental to solving the problem of drug-resistant *Acinetobacter baumannii* and potentially other 'super bacteria'. Drug resistance mechanisms primarily include enzymes, membrane proteins, efflux pumps and beneficial mutations. Research on the underlying mechanisms provides a theoretical basis for the use and development of antibiotics and the development of novel treatment methods.

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Contents

1. Introduction

The problem of bacterial resistance is ever increasingly becoming a serious threat to humans, and superbugs now account for >540,000 infections and nearly 14,000 deaths each year in the United States alone (1). The discovery of penicillin and the synthesis and application of antibacterial sulfonamides in the 20th century have greatly eased the suffering of patients, but the uncontrolled abuse of antibiotics in the past 50 years has made 'ESKAPE' (*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa* and *Enterobacter species*) increasingly resistant and treatment of these bacterial infections has become increasingly difficult (2). Amongst these superbugs, drug-resistant *Acinetobacter baumannii* infections are notably serious with the increasing number of its infections (3). The purpose of this review is to highlight the molecular mechanisms underlying drug resistance in *Acinetobacter baumannii* and to summarize novel ideas for solving the problem of drug resistance.

2. Epidemiology of *Acinetobacter baumannii*

The history of Acinetobacter can be traced back to 1991 when the Danish microbiologist Martinus Willem Beijerinck discovered *Micrococcus calcoaceticus* (4). The first identification analysis of Acinetobacter species was based on their biochemical characterization, while the use of molecular

methods, in particular DNA-DNA hybridization, identified at least 33 genetically distinct species of *Acinetobacter* (5). In the majority of laboratories, *Acinetobacter baumannii*, *Acinetobacter pittii* and *Acinetobacter nosocomialis* are difficult to distinguish (6), as they possess closely related microbiological characteristics. Hence, this review will use *Acinetobacter baumannii* in the comprehensive sense to refer to these three species collectively. The identification of *Acinetobacter baumannii* can be distinguished by multilocus sequence typing, as it utilizes 16s ribosomal RNA as well as conserved regions of seven housekeeping genes: gltA, gyrB, gdhB, recA, cpn60, gpi and rpoD (7).

Acinetobacter baumannii, once even considered benign, is now considered a global threat in healthcare settings, and it is gaining resistance at an unforeseen rate (8). In early 2019, the World Health Organization stated that *Acinetobacter baumannii* is considered the most dangerous multidrug-resistant bacteria (9). Until the early 1970s, *Acinetobacter* strains showed susceptibility to most antibiotics (10). Extensive resistance to carbapenem antibiotics is considered to be a sign of extensively drug-resistant bacteria, and carbapenem-resistant *Acinetobacter baumannii* is now causing serious problems in Asia and the Americas. In Southern Europe, Middle East and Asia and North Africa ~90% of clinical isolates of *Acinetobacter baumannii* are resistant to carbapenems (11). Globally, ~45% of *Acinetobacter baumannii* isolates are multi-drug resistant, with >70% of isolates in Latin America and the Middle East exhibiting multi-drug resistance (12).

3. Features of *Acinetobacter baumannii*

Acinetobacter baumannii was considered a low-virulence bacterium in the past, and its severity was not taken seriously until the mid-1990s (13). In recent years, following the continual increase in its virulence and the difficulty in treating infections due to drug resistance has resulted in increased attention from public health bodies (14). *Acinetobacter baumannii* is a Gram-negative bacterium that is a strictly aerobic, catalase-positive, oxidase-negative and non-lactose-fermentative opportunistic pathogen (6). *Acinetobacter baumannii* is almost everywhere such as waterbodies, soil, mines, crude oil, sewage, sludge, solid surfaces, human skin and wild animals (11), it is not only difficult to treat but also difficult to eliminate. This is due to its excellent anti-starvation (15), anti-desiccating (16), seasonal adaptation and high-temperature resistance properties (17), in addition to reduced sensitivity to disinfectants (18) and biofilm protection (19). Drug-resistant *Acinetobacter baumannii* is one of the most common pathogens of nosocomial infections, especially in immunocompromised patients and in ICU wards (20). In addition, prolonged use of antibiotics, major surgery, severe burns and immunosuppression increase the risk of *Acinetobacter baumannii* infections (21). *Acinetobacter baumannii* infections can lead to ventilator-associated pneumonia, bacteremia, urinary tract infection and meningitis (22). The overall prevalence of multidrug-resistant strains of *Acinetobacter baumannii* in patients with hospital-acquired pneumonia and ventilator-associated pneumonia is estimated at 79.9%, with an overall mortality rate that can be as high as 56.2% (23).

4. Mechanisms of drug resistance and their clinical implications

With improvements in research equipment and methods in the fields of modern medicine and microorganisms, the mechanisms underlying *Acinetobacter baumannii* drug resistance have become increasingly understood. The known mechanisms of *Acinetobacter baumannii* drug resistance and potential developmental directions are summarized in Table I and Fig. 1, with treatment options being listed in Table II. Below, an in-depth summary of the known body of knowledge on *Acinetobacter baumannii* drug resistance is provided.

β-lactams. Since the first β-lactam antibiotic was discovered (penicillin), they have become incorporated as a core part of clinical practice as treatments for various bacterial infections; β-lactam antibiotics are chosen as the antibacterial drug of choice (16). β-lactam antibiotics act on the peptidoglycan in the cell walls of fungi and bacteria, and they work by suppressing bacterial cell division or inducing bacterial rupture (24). However, bacteria can produce β-lactamase to enzymatically break down β-lactam antibiotics, which is the most prevalent mechanism of drug resistance. In the Ambler classification, β-lactamases can be grouped into one of four classes (A-D) according to the sequences of the amino acids that make up the enzyme (25).

Ambler class A enzymes. The serine β-lactamases of molecular class A are the most important enzymatic source of both natural and acquired resistance to β-lactams, particularly in *Acinetobacter baumannii* (26). TEM, SHV, CTX-M and KPC are the primary Ambler class A enzymes (27). TEM, CTX-M and KPC can hydrolyze penicillin, cephalosporin and carbapenem. Additionally, the use of antibiotics allows these enzymes to evolve and develop stronger drug resistance (28).

Ambler class B enzymes. Zinc-dependent metallo-β-lactamases (MBLs) are typically associated with gene cassettes of integrons and thus spread easily amongst bacteria (29). MBLs are classified into 3 subclasses. B1 and B3 are catalytically inactivated by two Zn^{2+} ions, and B2 is catalytically inactivated by one Zn^{2+} ion (14). NDM, VIM, SPM and IMP are the primary Ambler class B enzymes. The presence of the plasmid enables the rapid spread of the MBL gene, and the spread of NDM-1 is closely associated with drug resistance in *Acinetobacter baumannii* (30,31). Since the discovery of NDM-1 in India, over 24 NDM variants have been identified (32). NDM enzymes, composed of 270 amino acids, hydrolyze most β-lactams (including carbapenems) but not monobactams. However, NDM enzymes cannot be countered by clinically available β-lactamase inhibitors, including avibactam, clavulanate, sulbactam and tazobactam (33). Studies have shown that the percentage of NDM-1-positive isolates tends to be the highest, and *Acinetobacter baumannii* with the NDM gene show resistance to ampicillin (34). The acquisition of the NDM-1 gene is likely facilitated by the action of Tn125 (35).

Ambler class C enzymes. Acinetobacter-derived cephalosporinases (ADCs) are responsible for resistance to cephalosporin antibiotics. ADC is the primary Ambler class C enzyme (27). ADC-mediated drug resistance is achieved through overexpression of ADC, and this overexpression

Table I. Mechanisms of resistance employed by *Acinetobacter baumannii*.

Antibiotic	Resistance mechanism	Enzyme or target	Key point	(Refs.)
β-lactams	β-lactamases	Ambler class A	TEM, SHV, CTX-M, KPC	(26-28)
		Ambler class B	NDM, VIM, SIM, IMP	(30,31)
		Ambler class C	AmpC, ADC	(27,36,37)
		Ambler class D	OXA	(7,39-41,43,44)
	Permeability lesions	Outer membrane porin	CarO	(46)
			OmpA	(46-48)
	Efflux pump overactivity	RND pump	AdeABC	(49,50)
Tetracyclines	Efflux pump overactivity	RND pump	AdeABC, AdeIJK	(79,80)
		Tet pump	TetA, TetG	(81)
Quinolones	Target mutation	DNA gyrase	GyrA	(88)
		DNA topoisomerase IV	ParC	(88)
	Efflux pump overactivity	RND pump	AdeABC	(89)
Aminoglycosides	Drug inactivating enzymes	Aminoglycoside modifying enzymes	aadB, apa6, aadA, aacc1	(92)
	Target mutation	16s RNA methylase genes	armA	(93)
	Efflux pump overactivity	RND pumps	AdeABC	(94)
Polymyxins	Target mutation	Abnormalities of lipid A and LPS	PmrC, PmrB, lpx gene	(68-71)

itself is achieved through an ISAba1 insertion sequence, which is located in close proximity to the genes which confer resistance (36). The production of AmpC β-lactamases may be either chromosomally mediated or plasmid-mediated. AmpC β-lactamases are not inhibited by clavulanic acid, but are inhibited by cloxacillin or boronic acid (37). *Acinetobacter baumannii* can rapidly develop drug resistance due to the chemical similarity of the molecules between β-lactamase inhibitors and β-lactams, thus β-lactamase inhibitors, such as sulbactam and clavulanic acid, eventually become ineffective against *Acinetobacter baumannii* (38).

Ambler class D enzymes. Amongst the D-type β-lactamases, oxacillinase (OXA) is associated with resistance to carbapenems (39). The primary reason for carbapenem resistance is the presence of oxacillinase, which belongs to class D Ambler β-lactamases. To date, >400 OXA enzymes encoded by chromosomal or plasmid-localized genes have been characterized (40). The hydrolytic activity of OXA-type groups is more potent for oxacillin than benzylpenicillin; however, OXA-type enzymes are not considered extended-spectrum β-lactamases (ESBLs) as they do not hydrolyze broad-spectrum cephalosporins (7). The OXA-23 enzyme is encoded by a chromosomal gene or located on a plasmid, and it confers resistance to several antibiotics including ticarcillin, meropenem, amoxicillin and imipenem. The OXA-40 enzyme can hydrolyze penicillin; however, its ability to hydrolyze cephalosporins and carbapenems is weak, and it is resistant to inhibitors such as tazobactam, sulbactam, clavulanic acid and NaCl. The OXA-51 gene is generally non-transferable, encoded by chromosomal DNA. Clavulanic acid, tazobactam, or NaCl effectively blocks the activity of OXA-51. OXA-58 is found on a non-transferable 30k plasmid. When this plasmid is incorporated into the gene chain of *Acinetobacter baumannii*, carbapenem susceptibility is reduced (7). Because of certain insertion sequences, such as ISAbaI, ISAba125 and ISAba825, the overproduction ADC and OXA-51 confer high-level resistance to third- and fourth-generation cephalosporins (41). Carbapenem antibiotics, as the most commonly used antibiotics for nosocomial infections in the world, have successfully led to the enhancement of drug resistance in microorganisms such as *Acinetobacter baumannii* (16). The prevalence of carbapenem-resistant *Acinetobacter Baumannii* (CRAB) is increasing rapidly in many countries and regions, and this has complicated treatment choices (42). Carbapenem resistance is primarily mediated by B-type and D-type. The most common OXA-type carbapenemases include OXA-23, OXA-24, OXA-48, OXA-51 and OXA-58. Among them, OXA-23, OXA-24, OXA-48 and OXA-58 are acquired carbapenemases, whereas OXA-51 is intrinsic to *Acinetobacter baumannii* (43). The genes encoding these enzymes are regulated by upstream insertion sequences (IS), specifically ISAba1, ISAba2, ISAba3, ISAba9 and IS18. They lead to increased resistance to carbapenems through the expression of the blaOXA gene. In addition to OXA

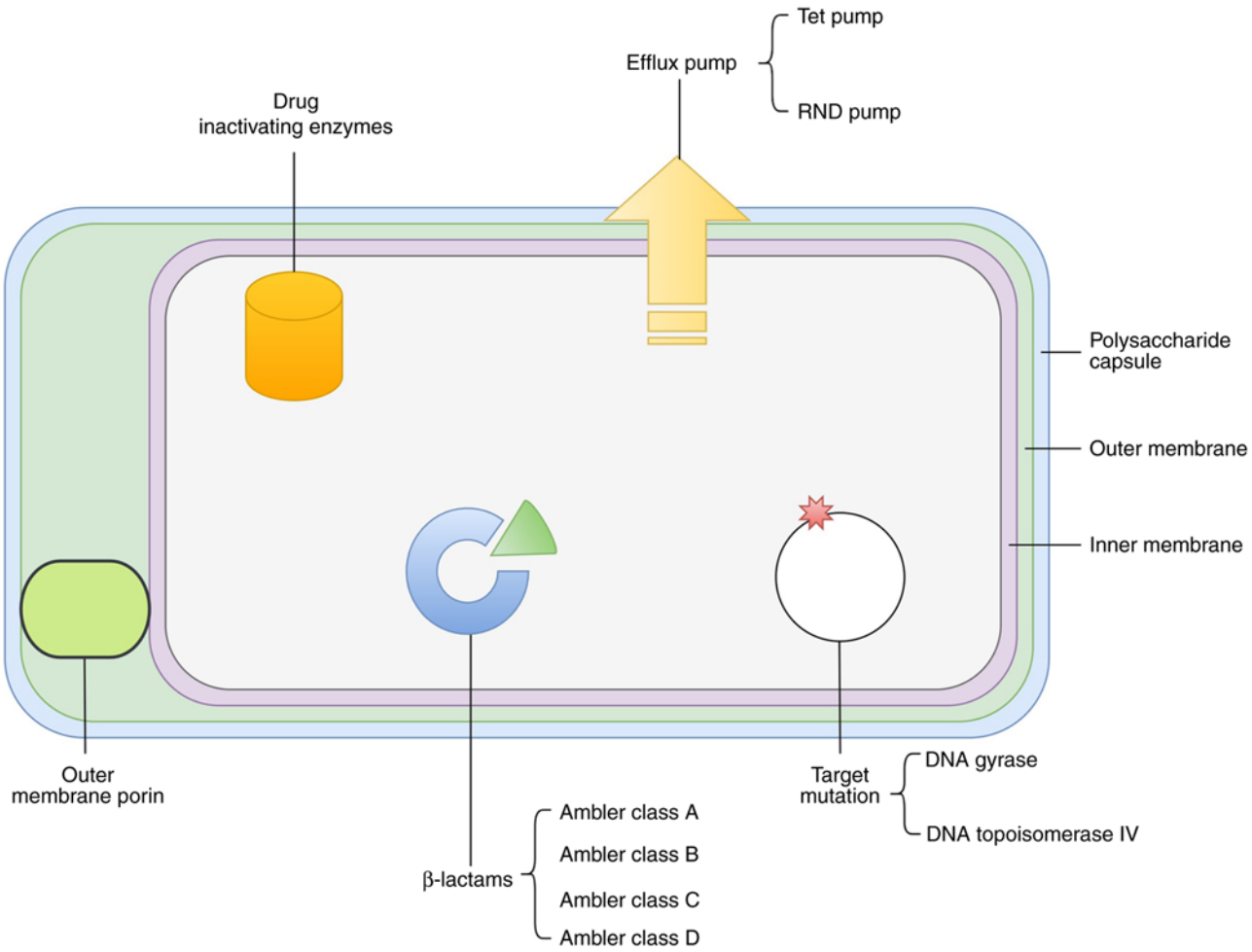

Figure 1. Schematic diagram of the resistance mechanisms employed by *Acinetobacter Baumannii*. Common resistance mechanisms include β-lactamase hydrolysis, mutations in target genes, overexpression of efflux pumps, drug inactivation of enzymes, and permeability impairment caused by outer membrane porins.

carbapenemases, the transferable MBL family, including VIM, IMP, GIM, SIM and NDM enzymes are also associated with the drug-resistant phenotype of *Acinetobacter baumannii* (44).

Other aspects aside from enzymes. Outer membrane proteins (OMPs) in general are β-barrel-shaped monomeric or trimeric porins that allow the diffusion of small molecules into and out of the periplasmic space of Gram-negative bacteria (45). The outer membrane of *Acinetobacter baumannii* contains several OMPs, including OmpA, CarO, OprD-like OMPs, Omp 33-36 kDa, AbuO, TolB, DcaP, Oma87/BamA, NmRmpM, CadF and OprF, amongst others. OMP has multiple functions, which confers bacterial resistance to threats such as harsh environments and antibiotics (46). OmpA is the most abundant outer membrane porin in *Acinetobacter baumannii*, and it functions by binding to efflux pumps and expelling antimicrobial compounds from the periplasm (47). OmpA increases the sensitivity of *Acinetobacter baumannii* to nalidixic acid, chloramphenicol, aztreonam, imipenem and meropenem, this feature is inseparable from its C-terminal region and *Acinetobacter baumannii* peptidoglycan (PG) coupling regulates outer membrane vesicle (OMV) stability (48). In addition, OmpA also actively siphons extracellular drugs to mediate antibiotic resistance and isogenic mutants, which in turn leads to a loss of cell wall integrity that sensitizes bacteria to colistin and also confers virulence (46). The outer membrane protein CarO is a carbapenem drug resistance-related OMP encoded by the CarO gene. CarO is divided into two subgroups, namely CarOa and CarOb. Facing different environments and hosts, the rapid adaptation of *Acinetobacter baumannii* results in alterations of the CarO gene (46). The resistance-nodulation-cell division (RND) efflux pump system is also associated with resistance in *Acinetobacter baumannii*. The efflux pump can extrude a variety of antibacterial agents, reducing the accumulation of antibiotics (49). The overexpression of adeABC plays an important role in acquired resistance to antibiotics. Cefepime, cefpirome and cefotaxime are the β-lactams most affected by the adeABC efflux system (50). Moreover, penicillin-binding protein 7/8 increases susceptibility to complement and contributes either directly or indirectly to serum resistance (51).

Novel options for resistance against β-lactam-based antibiotics. In recent years, researchers have found that the amino acid sequence of OmpA is highly conserved (>89%) in various clinical isolates, and OmpA mediates the adhesion and invasion of *Acinetobacter baumannii* to epithelial cells. OmpA can stimulate the innate immune response and induce biofilm formation, thus OmpA is a potential therapeutic target, although it has been shown that OmpA is not necessary for bacterial survival (22). It has been

Table II. Treatment options for drug-resistant *Acinetobacter baumannii* infections.

Resistance to antibiotics	Treatment (for reference only)	(Refs.)
β-lactams	Cefiderocol	(53-55)
	CCCP and imipenem/cefepime	(56)
	Quercetin and imipenem	(57)
	DBOs and sulbactam	(59)
	QPX7728 and meropenem/ceflorazone/piperacillin/cefepime	(60)
	Ampicillin and sulbactam	(61)
	Berberine hydrochloride and sulbactam	(63)
	Piper betle and antibiotics	(65)
	Vaccines (preventative)	(58,62)
	Iron control	(52)
	Cilantro oil combined with piperacillin or cefoperazone	(64)
Tetracyclines	KBP-7072 and omadacycline	(83)
	Omadacycline and sulbactam	(84)
	Tetracycline and D-LANA-14	(85)
Quinolones	Ciprofloxacin/imipenem and Mentha longifolia/Menthol	(90)
	Ciprofloxacin and Na-3DH-DCA/Na-3DH-CDCA	(91)
Aminoglycosides	Tobramycin and colistin	(97)
	Aminoglycosides and L-lysine	(96)
	Colistin and Silver nanoparticles	(74)
	Macolacin	(75)
	Polymyxin B and rifampicin/imipenem/meropenem/tigecycline	(76)
	Scutellaria barbata	(77)
Biofilm	Myrtenol and antibiotics	(102)
	Polymyxin B/E and azithromycin	(103)
	Illicium verum Hook	(104)
	Phage	(105)
	Antimicrobial photodynamic therapy	(106)
	Antimicrobial peptides	(107)

shown that increased iron content enhances OmpA protein expression in *Acinetobacter baumannii*, and strains with high OmpA protein expression are more aggressive, thus iron control strategies can be used in the management of *Acinetobacter baumannii* to reduce drug resistance (52). Cefiderocol, a member of the β-lactam antibiotics family, inhibits the synthesis of Gram-negative bacterial cell walls by binding to penicillin-binding proteins. However, due to its siderophore-like properties, it can enter the periplasmic space in bacteria and exhibits high stability to various β-lactamases such as AmpC and ESBLs (53,54). In an *in vitro* study, Cefiderocol was shown to be effective against OXA-23, OXA-40 and OXA-58. as well as NDM and IMP-producing *Acinetobacter baumannii* isolates (55). Efflux pumps are an important part of drug resistance. The efflux pump inhibitor carbonyl cyanide m-chlorophenylhydrazone can enhance the susceptibility of *Acinetobacter baumannii* to imipenem and cefepime (56). Equally effective efflux pump inhibitors include Quercetin, particularly when combined with imipenem, and it has a significant inhibitory effect on NDM and mexB/adeB (57). *Acinetobacter baumannii* vaccine studies has shown that the most effective vaccines tend to be multiplexed (consisting of outer membrane vesicles, bacterial ghosts, or multi-subunits) and are usually composed of antigens from OmpA, OmpW, OmpK and Omp22 (58). For resistance to carbapenem antibiotics, the development of β-lactamase inhibitors has shown favorable results. β-lactamase inhibitor diazabicyclooctanes combined with sulbactam restored the sensitivity of sulbactam to carbapenem-resistant Acinetobacter (59). QPX7728 is a boric acid-lactamase inhibitor, which was shown to inhibit class A ESBLs, class B carbapenemases (NDM, VIM and IMP), class C and class D (OXA-23), and it enhanced its action against carbapenem-resistant *Acinetobacter baumannii* when combined with meropenem, ceflorazone, piperacillin and cefepime (60). Additionally, the combination of ampicillin and sulbactam (18 g per day) is an effective regimen for reducing the mortality of patients with CRAB (61). In addition, in terms of vaccine development, vaccines against BauA and OmpA that are vital virulence factors in pathogenicity of *Acinetobacter baumannii* play a certain role and combination of these antigens that can bind BauA and OmpA enhanced clearance of bacteria in liver and spleen (62). TCM ingredients can also be used to treat drug-resistant *Acinetobacter baumannii*. Possibly due to the synergistic action with antibiotics on efflux pump AdeB, Berberine

hydrochloride combined with sulbactam can improve the antibacterial efficiency against *Acinetobacter baumannii* (63). Cilantro oil combined with piperacillin or cefoperazone can enhance the efficacy of the latter (64); however, the mechanism underlying the improved efficacy when combined needs to be determined. Other TCMs such as Piper betle combined with antibiotics are also worthy of research (65).

Polymyxins. The resistance of *Acinetobacter baumannii* to Polymyxins include: i) modification of the lipid A structure, ii) complete loss of Lipopolysaccharide (LPS) via mutations in the genes that synthesize lipid A, iii) reduction in the expression of cofactors involved in LPS synthesis, and iv) downregulation of proteins that participate in the export and/or stabilization of outer membrane precursors (66). LPS is part of the outer membrane of bacteria. Polymyxins inhibit bacterial membranes after binding to LPS, interact with lipid A of the bacterial outer membrane, and cause cell permeability and death by destroying membrane phospholipids. However, polymyxins antibiotics take a long time to work, and the use of colistin may increase the probability of nephrotoxic and neurotoxic complications (67). Colistin resistance in *Acinetobacter baumannii* is primarily caused by mutations in the PmrBTCS sensor kinase resulting in overexpression of PmrC. It has been shown that by knocking out the colistin PmrA mutant, its MICs is reduced by 64 to 1,024-fold, thereby restoring sensitivity to polymyxins (68). In *Acinetobacter baumannii*, various mutations and small fragments in the PmrB region are the primary cause of colistin resistance, and the most common PmrB mutation is A138T (69). The mutation of PmrA and PmrB of *Acinetobacter baumannii* can lead to resistance to polymyxins, and its virulence and fitness are also reduced. In addition, impaired virulence and fitness are also related to the lpx gene (70). Mutations in lpxA, lpxC and lpx affect lipid A synthesis. These spontaneous mutations include single-base changes, large deletions, and insertions of IS elements, all of which contribute to the high resistance exhibited by *Acinetobacter baumannii* (71). In addition, the induction of endogenous production of reactive oxygen species (ROS) by polymyxins, thus leading to oxidative killing of bacteria via hydroxyl radicals. *Acinetobacter baumannii* via inhibiting the formation of hydroxyl radicals attenuates polymyxin killing (72).

In the face of increasing drug resistance, it is a novel direction to identify new targets for use in combination with multiple drugs, such as the development of inhibitors against the targets of the modified bacterial outer membrane LPS two-component signal transduction system (73). Solving the problem of drug resistance should not only rely on antibiotics, instead, it may be favorable to combine current therapeutics with silver nanoparticles. Silver nanoparticles can penetrate microbial cell walls and alter cell membrane structure; this may reduce the MIC by 8-32X when used in combination with colistin (74). In addition, macolacin, a chemically synthesized substance that targets the plasmid-borne polymyxin resistance gene mcr-1, is also effective for Gram-negative pathogens expressing mcr-1 including *Acinetobacter baumannii* (75). The combination of polymyxin B with imipenem, meropenem, tigecycline and rifampicin in the treatment of *Acinetobacter baumannii* was superior to any of these alone, and the combination with rifampicin had the best effect (76). In terms of TCMs, the extract of *Scutellaria barbata* was shown to exhibit a good inhibitory effect on *Acinetobacter baumannii*, and the mechanism may be related to ROS (77), and the combination of *Scutellaria barbata* and polymyxin may have unexpected effects.

Tetracyclines. Tigecycline, a unique semi-synthetic antibacterial agent of the glycylcycline class, is derived from tetracycline and designed to overcome common resistance mechanisms to tetracycline (78). Its mechanism of action is to inhibit bacterial growth by binding to the bacterial 30S ribosome and blocking the entry of tRNA, ultimately preventing protein synthesis. Although tigecycline circumvents resistance mechanisms of tetracycline, *Acinetobacter baumannii* can acquire tigecycline resistance through overexpression of efflux pumps, particularly AdeABC, and modification of the tigecycline-binding site in the ribosome through rpsJ mutations (79). Likewise, the adeIJK of the RND efflux pump confers *Acinetobacter baumannii* resistance against tetracycline antibiotics (80). It has been shown that *Acinetobacter baumannii* expressing tetracycline transporter gene (tet)A have significantly increased MICs for tetracycline and tigecycline. *Acinetobacter baumannii* that express tetG also show resistance to these tetracyclines in addition to drug resistance to tigecycline (81). Although there are also genetic studies showing that the increased resistance of strains induced by tigecycline can be recovered, this also indicates that the use of tigecycline therapy may increase the risk of multidrug-resistant gaining additional resistance (82).

It has been shown that third-generation tetracyclines (aminomethylcycline) KBP-7072 and omadacycline overcome efflux and ribosomal protection resistance mechanisms observed during tetracycline resistance, highlighting a novel direction for the development of tetracycline-based antibiotics (83). In addition, Omadacycline in combination with sulbactam was shown to be synergistic and bactericidal against 80% of isolates (84). A study showed that D-lysine conjugated aliphatic norspermidine analogue bearing tetradecanoyl chain (also known as D-LANA-14) increased the permeability of cell membranes. When D-LANA-14 was combined with tetracycline and other inactive antibiotics, it exhibited synergistic activity against *Acinetobacter baumannii* (85).

Quinolones. Through gene knockout studies, it has been shown that the transporter AbaQ is primarily involved in the extrusion of quinolones from *Acinetobacter baumannii* (86). Resistance to quinolones has also been attributed to spontaneous mutations in genes, including DNA gyrase and topoisomerase IV. This leads to high levels of resistance to quinolones in *Acinetobacter baumannii* (87). Changes in antibiotic target sites are an important mechanism of bacterial resistance, that manifests through random point mutations with a minimal impact on bacterial cell homeostasis. In *Acinetobacter baumannii*, the most common mechanism of resistance is fluoroquinolone resistance, which is acquired by spontaneous mutations in the gyrA, gyrB and parC genes which encode gyrase and topoisomerase IV (88). The existence

of the efflux pump adeABC is still an important cause of drug resistance in *Acinetobacter baumannii* (89).

A newer study shows that *Mentha longifolia* and Menthol can facilitate the entry of material into the cell membrane of bacteria and mitochondria, thereby facilitating the inhibition of the adeABC efflux pump in *Acinetobacter baumannii*. When Mentha longifolia and Menthol are combined with ciprofloxacin and imipenem, it can significantly reduce the MIC for *Acinetobacter baumannii* (90). Bile salt derivatives, Na-3DH-DCA and Na-3DH-CDCA, have synergistic effects on certain strains of *Acinetobacter baumannii* when used in combination with ciprofloxacin, highlighting a potential future direction (91).

Aminoglycosides. The most common aminoglycoside resistance gene in *Acinetobacter baumannii* is aadB (42%), followed by apa6 (26%), while aadA1 (18%), with aacc1 (12%) being rare (92). The armA gene is an effective factor for the resistance of *Acinetobacter baumannii* to aminoglycosides; the gene encodes 16S rRNA methylase, which leads to the limited access of aminoglycosides into the bacterial ribosomes, and furthermore leads to high-level aminoglycoside resistance (HLAR) to gentamicin, bruomycin, amikacin and kanamycin (93). In addition, AdeABC has a restrictive effect in reducing the susceptibility of *Acinetobacter baumannii* to aminoglycoside antibiotics (94).

It has been shown that strains with a single well-defined resistance mechanism lack cross-resistance to gentamicin, amikacin, tobramycin and prazomycin (95). Thus, the cross-use of aminoglycosides is a temporary solution. Additionally, L-lysine combats drug-resistant *Acinetobacter baumannii* by increasing the transmembrane DpH difference which in-turn increases the bacterial proton motive force and stimulates the uptake of aminoglycoside antibiotics (96). The combination of antibiotics is another method of treatment. Tobramycin and colistin can be used to treat or eradicate *Acinetobacter baumannii* by reducing the expression of the universal stress protein (uspA) (97).

Biofilm. Several pathogens, including *Acinetobacter Baumannii*, produce biofilms in response to dry conditions, nutrient shortages, resistance to antibiotics, and other challenges (98). The formation of *Acinetobacter Baumannii* is associated with the Quorum sensing pathway, two-component system signal transduction pathway, cyclic-di-GMP signaling and the capsular polysaccharide synthesis pathway. Biofilm-associated proteins such as Bap in *Acinetobacter Baumannii* also serve a vital role in biofilm (99). Several studies have shown that csuE, pgaB, epsA, ptk, bfmS and the ompA biofilm-related genes are involved in biofilm formation (99,100). However, resistance due to biofilms is specific and these genes are not direct factors for the resistance of *Acinetobacter Baumannii* (101). Thus, additional research is required to clarify the specific mechanisms involved.

Myrtenol is an important dicyclic monoterpene alcohol, which inhibits the growth of biofilms by affecting the adhesion factors associated with biofilms and improves the sensitivity of certain antibiotics to *Acinetobacter baumannii*. Myrtenol has the potential to be used in combination with antibiotics (102). The combination of polymyxin B or E with azithromycin can inhibit biofilm formation (103). These studies suggest that the combination of antibiotics is still a valuable method for the treatment of multiple drug resistant infections. The extract of star anise (*Illicium verum Hook*.) has a significant inhibitory effect on biofilm, which does not affect the growth of cells. The underlying mechanism may involve the disruption of the cell membrane of bacteria due to the lipophilic nature of the extract (104). In addition, phage (105), antimicrobial photodynamic therapy (106) and antimicrobial peptides (107) are seen as non-antibiotic therapies with significant potential for the future.

5. Conclusions and future perspectives

Bacterial infections are the cause of several diseases and can aggravate already present diseases as well. The development of drug resistance caused by its unique physiological characteristics makes infections caused by drug-resistant *Acinetobacter baumannii* considerably more difficult to treat. Therefore, a deeper understanding on the drug resistance mechanisms is required to improve our armamentarium against said infections. At present, differing combinations of antibiotics is the easiest and most effective way to manage infections. However, novel therapeutics will likely be required going forward as drug resistance increases. Thus, robust clinical trials will also be required for any novel therapeutics. That is, to manage the ever-increasing drug resistance, improved drugs, newer treatment technologies and alternative treatment methods are required.

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Authors' contributions

HJW and ZGX designed the subject of review. HFL revised the article. HJW, ZGX, XJL, HTH, CYH, CL, YX and HFL participated in writing and reviewing the manuscript. All

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Competing interests

The authors declare that they have no competing interests.

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