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Biology of *Acinetobacter baumannii*: Pathogenesis, Antibiotic Resistance Mechanisms, and Prospective Treatment Options

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Acinetobacter baumannii is undoubtedly one of the most successful pathogens responsible for hospital-acquired nosocomial infections in the modern healthcare system. Due to the prevalence of infections and outbreaks caused by multi-drug resistant *A. baumannii*, few antibiotics are effective for treating infections caused by this pathogen. To overcome this problem, knowledge of the pathogenesis and antibiotic resistance mechanisms of *A. baumannii* is important. In this review, we summarize current studies on the virulence factors that contribute to *A. baumannii* pathogenesis, including porins, capsular polysaccharides, lipopolysaccharides, phospholipases, outer membrane vesicles, metal acquisition systems, and protein secretion systems. Mechanisms of antibiotic resistance of this organism, including acquirement of β-lactamases, up-regulation of multidrug efflux pumps, modification of aminoglycosides, permeability defects, and alteration of target sites, are also discussed. Lastly, novel prospective treatment options for infections caused by multi-drug resistant *A. baumannii* are summarized.

Keywords: antimicrobial resistance, *Acinetobacter baumannii*, treatment option, resistance mechanism, virulence factor

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INTRODUCTION

Acinetobacter spp. are glucose-non-fermentative, non-motile, non-fastidious, catalase-positive, oxidative-negative, aerobic Gram-negative coccobacilli (Lin and Lan, 2014). Due to clusters of closely related species, it is difficult to distinguish *Acinetobacter* taxonomy using phenotypic traits and chemotaxonomic methods. Because antibiotic susceptibility and clinical relevance are significantly different between different genomic species, exact identification of *Acinetobacter* species are required (Bergogne-Berezin and Towner, 1996; Dijkshoorn et al., 1996; Houang et al., 2003; Lee et al., 2007). Many genomic fingerprinting methods have been developed, including repetitive extragenic palindromic sequence-based polymerase chain reaction (rep-PCR), pulsed-field gel electrophoresis (PFGE), matrix-assisted laser desorption ionization time-of-flight (MALDI-TOF) mass spectrometry, ribotyping, amplified ribosomal DNA restriction analysis,

random amplified polymorphic DNA analysis, multilocus sequence typing (MLST), RNA spacer fingerprinting, amplified fragment length polymorphism analysis, and sequence analysis of 16S-23S rRNA intergene spacer regions or the *rpoB* and *gyrB* genes (Koeleman et al., 1998; Chang et al., 2005; La Scola et al., 2006; Croxatto et al., 2012; Higgins et al., 2012; Lee C. R. et al., 2015; Li X. M. et al., 2016).

Among *Acinetobacter* species, *Acinetobacter baumannii* is the most important member associated with hospital-acquired infections worldwide (Lin and Lan, 2014). This aerobic Gram-negative coccobacillus had been regarded as a low-grade pathogen, but it is a successful pathogen responsible for opportunistic infections of the skin, bloodstream, urinary tract, and other soft tissues (Peleg et al., 2008). Because many *A. baumannii* infections have suddenly been reported among veterans and soldiers who served in Iraq and Afghanistan (Centers for Disease and Prevention, 2004), *A. baumannii* is referred to as "Iraqibacter." Multidrug-resistant (MDR) *A. baumannii* has spread to civilian hospitals in part by cross-infection of injured military patients repatriated from war zones (Peleg et al., 2008). Most *A. baumannii* infections occur in critically ill patients in the intensive care unit (ICU) setting (Fournier and Richet, 2006) and account for up to 20% of infections in ICUs worldwide (Vincent et al., 2009). Furthermore, the frequency of community-acquired *A. baumannii* infections has been increasing gradually (Lin and Lan, 2014). Several virulence factors have been identified by genomic and phenotypic analyses, including outer membrane porins, phospholipases, proteases, lipopolysaccharides (LPS), capsular polysaccharides, protein secretion systems, and iron-chelating systems (Antunes et al., 2011; McConnell et al., 2013; Lin and Lan, 2014).

Many reports have shown that *A. baumannii* rapidly develops resistance to antimicrobials, and multidrug-resistant strains have been isolated (McConnell et al., 2013). The WHO declared that *A. baumannii* is one of the most serious ESKAPE organisms (*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *A. baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter* species) that effectively escape the effects of antibacterial drugs (Boucher et al., 2009). A number of *A. baumannii* resistance mechanisms are known, including enzymatic degradation of drugs, target modifications, multidrug efflux pumps, and permeability defects (Gordon and Wareham, 2010; Kim et al., 2012; Lin and Lan, 2014). In this review, we summarize the virulence factors of *A. baumannii*, antibiotic resistance mechanisms, and the therapeutic options available for treating *A. baumannii* infections. **Figure 1** depicts all the features described in this review.

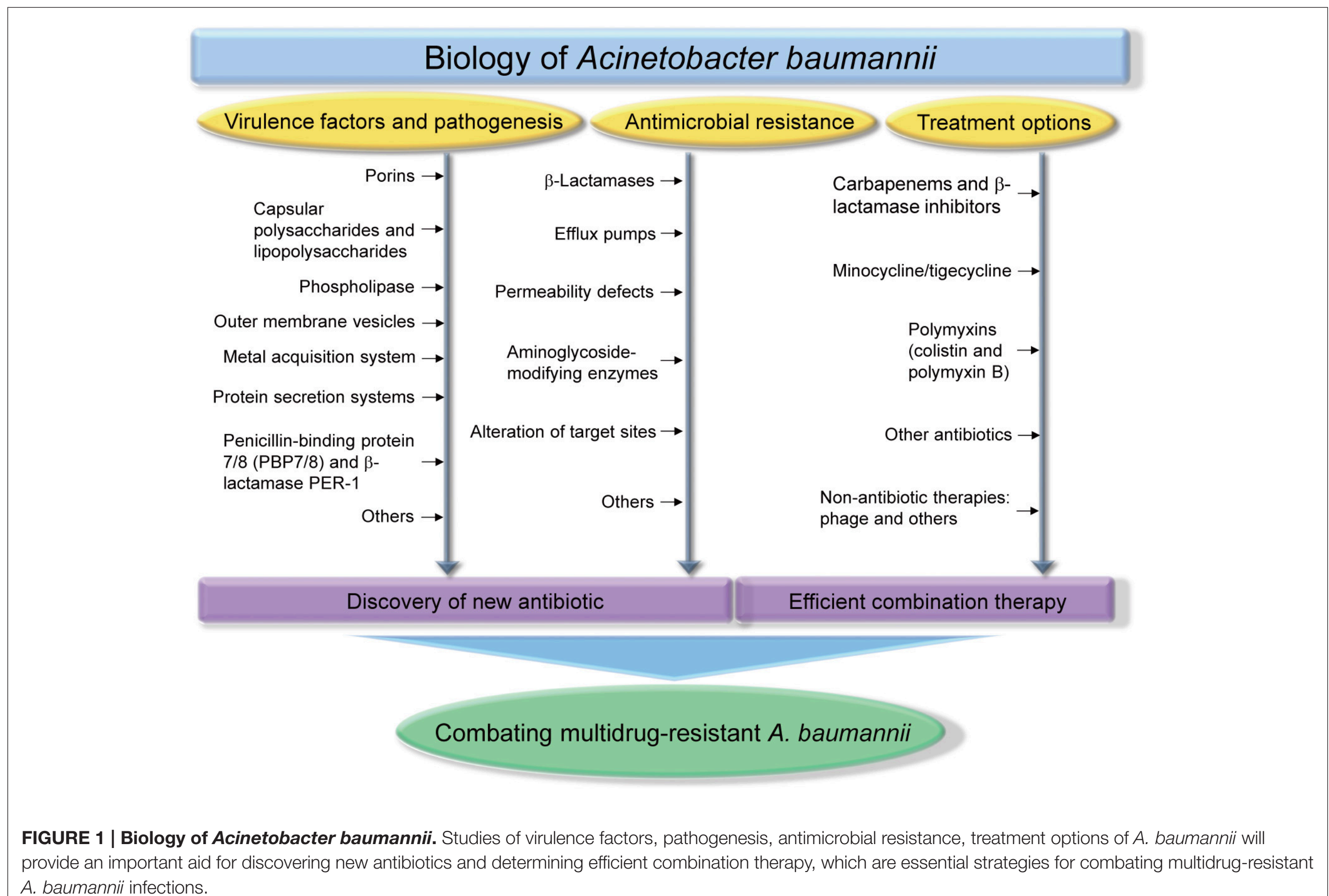

FIGURE 1 | Biology of *Acinetobacter baumannii*. Studies of virulence factors, pathogenesis, antimicrobial resistance, treatment options of *A. baumannii* will provide an important aid for discovering new antibiotics and determining efficient combination therapy, which are essential strategies for combating multidrug-resistant *A. baumannii* infections.

ACINETOBACTER BAUMANNII VIRULENCE FACTORS AND PATHOGENESIS

Although recent genomic and phenotypic analyses of *A. baumannii* have identified several virulence factors responsible for its pathogenicity, relatively few virulence factors have been identified in *A. baumannii*, compared to those in other Gram-negative pathogens (McConnell et al., 2013). The proposed *A. baumannii* virulence factors are summarized in **Table 1**.

Porins

Porins are outer membrane proteins associated with modulating cellular permeability. OmpA is a β-barrel porin and one of the most abundant porins in the outer membrane. In *A. baumannii*, OmpA is the very well-characterized virulence factor with a variety of interesting biological properties identified in *in vitro* model systems (Smith et al., 2007; McConnell et al., 2013). A random mutagenesis screen showed that the *A. baumannii ompA* mutant is defective in inducing apoptosis in human epithelial cells (Choi et al., 2005). Purified OmpA binds host epithelial cells, targets mitochondria, and induces apoptosis by releasing proapoptotic molecules, such as cytochrome c and apoptosis-inducing factor (Choi et al., 2005; Lee et al., 2010). Another study showed that OmpA translocates to the nucleus by a novel monopartite nuclear localization signal and induces cell death (Choi et al., 2008a). OmpA also plays a major role in adherence and invasion of epithelial cells by interacting with fibronectin (Choi et al., 2008b; Gaddy et al., 2009; Smani et al., 2012), and binds to factor H in human serum (Kim et al., 2009), which may allow *A. baumannii* to avoid complement-mediated killing. The

TABLE 1 | Identified virulence factors of *Acinetobacter baumannii.*

Virulence factor	Proposed role in pathogenesis	References
Porin (OmpA, Omp33-36, Omp22, CarO, OprD-like)	Adherence and invasion, induction of apoptosis, serum resistance, biofilm formation, persistence	Choi et al., 2005, 2008b; Gaddy et al., 2009; Kim et al., 2009; Lee et al., 2010; Fernandez-Cuenca et al., 2011; Smani et al., 2012, 2013; Rumbo et al., 2014; Wang et al., 2014; Huang et al., 2016
Capsular polysaccharide	Growth in serum, survival in tissue infection, biofilm formation	Russo et al., 2010; Iwashkiw et al., 2012; Lees-Miller et al., 2013
Lipopolysaccharide (LPS)	Serum resistance, survival in tissue infection, evasion of the host immune response	Luke et al., 2010; Lin et al., 2012; McQueary et al., 2012; McConnell et al., 2013
Phospholipase (PLC and PLD)	Serum resistance, invasion, *in vivo* survival	Camarena et al., 2010; Jacobs et al., 2010; Stahl et al., 2015; Fiester et al., 2016
Outer membrane vesicle (OMV)	Delivery of virulence factors, horizontal transfer of antibiotic resistance gene	Kwon et al., 2009; Jin et al., 2011; Rumbo et al., 2011; Moon et al., 2012; Jun et al., 2013; Li Z. T. et al., 2015
Iron acquisition system (acinetobactin and NfuA)	*In vivo* survival, persistence, killing of host cells	Gaddy et al., 2012; Penwell et al., 2012; Zimbler et al., 2012; Fiester et al., 2016; Megeed et al., 2016
Zinc acquisition system (ZnuABC and ZigA)	*In vivo* survival	Hood et al., 2012; Nairn et al., 2016
Manganese acquisition system (MumC and MumT)	*In vivo* survival	Juttukonda et al., 2016
Type II protein secretion system	*In vivo* survival	Johnson et al., 2015; Elhosseiny et al., 2016; Harding et al., 2016
Type VI protein secretion system	Killing of competing bacteria, host colonization	Carruthers et al., 2013; Wright et al., 2014; Jones et al., 2015; Repizo et al., 2015; Ruiz et al., 2015
Type V protein secretion system	Biofilm formation, adherence	Bentancor et al., 2012b
Penicillin-binding protein 7/8 and β-lactamase PER-1	Serum resistance, *in vivo* survival, adherence	Sechi et al., 2004; Russo et al., 2009
CipA	Serum resistance, invasion	Koenigs et al., 2016
Tuf	Serum resistance	Koenigs et al., 2015
RecA	*In vivo* survival	Aranda et al., 2011
SurA1	Serum resistance, *in vivo* survival	Liu D. et al., 2016
GigABCD	*In vivo* survival, killing of host cells	Gebhardt et al., 2015
UspA	*In vivo* survival, killing of host cells	Elhosseiny et al., 2015; Gebhardt et al., 2015
GacS and PaaE	Neutrophil influx	Cerqueira et al., 2014; Gebhardt et al., 2015; Bhuiyan et al., 2016
Pili	Adherence, biofilm formation	Tomaras et al., 2003, 2008
OmpR/EnvZ	Killing of host cells	Tipton and Rather, 2016
FhaBC	Adherence, killing of host cells	Perez et al., 2016
AbeD	Killing of host cells	Srinivasan et al., 2015

ompA gene is necessary for persistence of *A. baumannii* in the mouse lung (Wang et al., 2014).

Furthermore, OmpA is also involved in antimicrobial resistance of *A. baumannii* (Sugawara and Nikaido, 2012; Smani et al., 2014). The major *A. baumannii* porin is OmpA, which has 70-fold lower pore-forming activity than that of OmpF (Sugawara and Nikaido, 2012). Furthermore, disrupting the *ompA* gene significantly decreases the minimal inhibitory concentrations (MICs) of several antibiotics (chloramphenicol, aztreonam, and nalidixic acid), suggesting that OmpA participates in the extrusion of antibiotics from the periplasmic space through the outer membrane and couples with inner membrane efflux systems (Smani et al., 2014). OmpA enhances survival and persistence of *A. baumannii* by facilitating surface motility and biofilm formation (Gaddy et al., 2009; Clemmer et al., 2011; McConnell et al., 2013). OmpA also regulates biogenesis of outer membrane vesicles (Moon et al., 2012). These results suggest that the OmpA protein is an attractive target for developing novel antibiotics and prevention strategies. Two recent reports based on immuno-proteomics and reverse vaccinology suggested that OmpA is a potential vaccine candidate against *A. baumannii* (Fajardo Bonin et al., 2014; Hassan et al., 2016). Actually, the OmpA protein is immunogenic in healthy individuals and patients with *A. baumannii* invasive infections (Zhang et al., 2016). In a mouse model of *A. baumannii* infection, mice immunized with OmpA had a significantly higher survival rate than that of control mice (Luo et al., 2012; Lin L. et al., 2013; Zhang et al., 2016).

The 33- to 36-kDa Omp protein (Omp33-36), which acts as a water passage channel, is another outer membrane porin associated with *A. baumannii* cytotoxicity (Smani et al., 2013; Rumbo et al., 2014). The *omp33-36* deletion strain significantly reduces adherence and invasion of human lung epithelial cells and cytotoxicity to these cells (Smani et al., 2013). Deletion of the *omp33-36* gene in a murine sepsis model attenuates lethality and reduces bacterial concentrations in the spleen and lungs (Smani et al., 2013). One study showed that purified Omp33-36 induces apoptosis in several different cell types, including immune and connective tissue cells, by activating caspases and modulating autophagy (Rumbo et al., 2014). Omp33-36 is also involved in antibiotic resistance. *A. baumannii* strain JC10/01 resistant to carbapenem antibiotics (imipenem and meropenem) exhibits loss of Omp33-36 and episomal expression of Omp33-36 in this strain clearly reduces the MICs of imipenem and meropenem (del Mar Tomas et al., 2005).

Omp22 has also been identified as a novel, conserved, and safe antigen for developing effective vaccines to control *A. baumannii* infections (Huang et al., 2016), although the contribution of Omp22 to *A. baumannii* pathogenicity has not been determined. Both active and passive immunizations with Omp22 increase the survival rates of mice, suppress bacterial burdens in the organs and peripheral blood, and reduce serum levels of inflammatory cytokines and chemokines (Huang et al., 2016). Other porins, such as carbapenem-associated outer membrane protein (CarO) and OprD-like, are also virulence-related factors associated with attenuated virulence in a mouse model (Fernandez-Cuenca et al., 2011).

Capsular Polysaccharides and Lipopolysaccharides (LPS)

Beyond OmpA, the *A. baumannii* envelope is associated with many factors that contribute to pathogenicity. Among these, capsular exopolysaccharides and LPS are *A. baumannii* pathogenicity factors. Notably, many isolates from patients with *A. baumannii* infections express surface capsular polysaccharides and contain a conserved gene cluster, called the K locus, which may determine production of capsular polysaccharides (Koeleman et al., 2001; Hu et al., 2013; Kenyon and Hall, 2013; Geisinger and Isberg, 2015). A random transposon screening to identify genes essential for growth in an inflammatory exudative fluid lead to the identification of the *ptk* and *epsA* genes, which are predicted to be required for capsule polymerization and assembly (Russo et al., 2010). The *ptk* and *epsA* mutants are deficient in capsule production and have a growth defect in human serum, resulting in a highly significant decrease in survival in soft tissue infection sites (Russo et al., 2010). Mutation in the *pglC* or *pglL* gene, which is responsible for synthesis of the *O*-pentasaccharide found on glycoproteins and capsular polysaccharides, also attenuate lethality in a mouse septicemia model and form abnormal biofilm structures (Iwashkiw et al., 2012; Lees-Miller et al., 2013). Therefore, capsular polysaccharides have been proposed to be a target for protective antibody-based interventions (passive immunization; Russo et al., 2013).

One study showed that capsular polysaccharides are involved in antimicrobial resistance of *A. baumannii* (Geisinger and Isberg, 2015). Mutants deficient in capsular polysaccharides have lower intrinsic resistance to peptide antibiotics. In addition, the presence of antibiotics induces hyperproduction of capsular polysaccharides (Geisinger and Isberg, 2015). Antibiotic-induced production of capsular polysaccharides increases resistance to killing by host complement and increases virulence in a mouse model of systemic infection (Geisinger and Isberg, 2015). That study also demonstrated that increased capsule production after exposure to an antibiotic depends on transcriptional increases in K locus gene expression, and that expression of K locus genes is regulated by the *bfmRS* two-component regulatory system (Geisinger and Isberg, 2015). *bfmR* is a gene essential for growth in human ascites, which is an *ex vivo* medium that reflects the infection environment (Umland et al., 2012), and is important for persistence in the lung in a murine pneumonia model (Wang et al., 2014). BfmS is also a virulence factor that plays an important role in biofilm formation, adherence to eukaryotic cells, and resistance to human serum (Liou et al., 2014). On report showed BfmR-mediated resistance to complement-mediated bactericidal activity and resistance to the clinically important antimicrobials (meropenem and colistin; Russo et al., 2016). However, that study suggested that BfmR effects are independent of capsular polysaccharide production. Therefore, the relationship between BfmRS and capsular polysaccharides must be described in more detail.

LPS is the major component of the outer leaflet of the outer membrane in most Gram-negative bacteria and is an immunoreactive molecule that induces release of tumor necrosis factor and interleukin 8 from macrophages in a Toll-like receptor 4 (TLR4)-dependent manner (Erridge et al., 2007). LPS is composed of an endotoxic lipid A moiety, an oligosaccharide core, and a repetitive O-antigen (Lee et al., 2013b). In *A. baumannii*, LPS plays a major role in virulence and survival of *A. baumannii* (Luke et al., 2010; Lin et al., 2012; McQueary et al., 2012). Mutant cell lacking LpsB glycotransferase have a highly truncated LPS glycoform containing only two carbohydrate residues bound to lipid A, resulting in decreased resistance to human serum and decreased survival in a rat model of soft tissue infection (Luke et al., 2010; McConnell et al., 2013). Inhibiting LpxC, an enzyme involved in the lipid A biosynthesis, dose not inhibit growth of the bacterium, but suppresses *A. baumannii* LPS-mediated activation of TLR4 (Lin et al., 2012). Inhibition of LpxC in mouse model enhances clearance of *A. baumannii* by enhancing opsonophagocytic killing and reduces serum LPS concentration and inflammation, which completely protects mice from lethal infection (Lin et al., 2012; Lee et al., 2013b). These results indicate that blocking LPS synthesis is a powerful strategy for discovering novel antibiotics. Modification of LPS contributes to resistance to antimicrobials. Many studies have shown that modifications in LPS decrease the susceptibility of *A. baumannii* to many clinical important antibiotics, such as colistin (Moffatt et al., 2010; Arroyo et al., 2011; Beceiro et al., 2011; Pelletier et al., 2013; Boll et al., 2015; Chin et al., 2015).

Phospholipase

Phospholipase is a lipolytic enzyme essential for phospholipid metabolism and is a virulence factor in many bacteria, such as *P. aeruginosa*, *Legionella monocytogenes*, and *Clostridium perfringens* (Camarena et al., 2010; Flores-Diaz et al., 2016). Three classes of phospholipases, such as phospholipase A (PLA), phospholipase C (PLC), and phospholipase D (PLD) have been defined based on the cleavage site. PLA hydrolyzes fatty acids from the glycerol backbone, whereas PLC cleaves the phosphorylated head group from the phospholipid. PLD is a transphosphatidylase that only cleaves off the head group. Degradation of phospholipids affects the stability of host cell membranes, and the cleaved head group can interfere with cellular signaling, resulting in changes in the host immune response (Songer, 1997; Flores-Diaz et al., 2016). PLC and PLD have been identified as virulence factors in *A. baumannii* (Camarena et al., 2010; Jacobs et al., 2010; Stahl et al., 2015). *Acinetobacter baumannii* ATCC17978 has two PLCs (A1S_0043 and A1S_2055) and inactivation of the A1S_0043 gene leads to a modest reduction in the cytotoxic effect of *A. baumannii* on epithelial cells compared to that of the parental strain (Camarena et al., 2010; Fiester et al., 2016). Disrupting one (A1S_2989) of the two PLD genes present in *A. baumannii* strain 98-37-09 results in reduced resistance to human serum, decreased capacity for invading epithelial cells, and decreased virulence in a murine model of pneumonia (Jacobs et al., 2010). Another report showed that *A. baumannii* ATCC 19606 has three PLD genes and all three play important roles in virulence and host cell invasion in a concerted manner (Stahl et al., 2015). These results suggest that phospholipase enzymes are important virulence factors in *A. baumannii* pathogenesis.

Outer Membrane Vesicles (OMVs)

OMVs are spherical, 20–200 nm diameter vesicles secreted by the outer membranes of various Gram-negative pathogenic bacteria (Kulp and Kuehn, 2010). They are composed of LPS, outer membrane and periplasmic proteins, phospholipids, and DNA or RNA, and are recognized as delivery vehicles for bacterial effectors to host cells (Ellis and Kuehn, 2010). OMVs deliver diverse virulence factors to the interior of host cells simultaneously and allow the pathogens to interact with the host without close contact between bacteria and host cells (Jun et al., 2013). Many *A. baumannii* strains secrete OMVs containing various virulence factors, including OmpA (Kwon et al., 2009; Jin et al., 2011; Moon et al., 2012), proteases (Kwon et al., 2009), and phospholipases (Kwon et al., 2009). OMVs derived from *A. baumannii* interact with host cells and deliver bacterial effectors to host cells via lipid rafts, resulting in cytotoxicity (Jin et al., 2011). Purified OMVs of *A. baumannii* ATCC 19606 induce expression of pro-inflammatory cytokine genes in epithelial cells in a dose-dependent manner (Jun et al., 2013). Notably, OMVs treated with proteinase do not induce a significant increase in the expression of pro-inflammatory cytokine genes, suggesting that the membrane proteins in OMVs are responsible for eliciting a potent innate immune response (Jun et al., 2013). One study supports the role of OMVs in *A. baumannii* pathogenesis. An *A. baumannii* strain that produces abundant OMVs with more virulence factors induces a stronger innate immune response and is more cytotoxic compared with those of a strain producing fewer OMVs (Li Z. T. et al., 2015).

Due to the importance of OMVs in *A. baumannii* virulence, several reports have shown that *A. baumannii* OMVs could be used as an acellular vaccine to elevate protective immunity (McConnell et al., 2011; Huang et al., 2014). In a mouse model of disseminated sepsis, vaccination with *A. baumannii* ATCC 19606 strain OMVs protects mice from challenge with homologous bacteria and provides protection against other clinical isolates (McConnell et al., 2011). Similar results were obtained in a pneumonia mouse model. Bacterial burden, inflammatory cell infiltration, and inflammatory cytokine accumulation in the pneumonia model were significantly suppressed by both active and passive immunization with OMVs (Huang et al., 2014). These results indicate that *A. baumannii* OMVs can be used as an acellular vaccine to effectively control *A. baumannii* infections. Interestingly, *A. baumannii* OMVs are also related with the spread of antibiotic resistance and induce the horizontal transfer of the OXA-24 carbapenemase gene (Rumbo et al., 2011).

Metal Acquisition System

Although iron is one of the most abundant elements in environmental and biological systems, ferric iron is relatively unavailable to bacteria in the preferred state, because of its poor solubility (10^{-17} M solubility limit for ferric iron) under aerobic and neutral pH conditions as well as due to chelation by low-molecular-weight compounds, such as heme, or high-affinity

iron-binding compounds, such as lactoferrin and transferrin (Rakin et al., 2012; Saha et al., 2013). To overcome this iron limitation, most aerobic bacteria produce a high-affinity iron chelator known as a siderophore (Saha et al., 2013). Siderophores are low molecular weight compounds (400–1,000 kDa) with high affinity for iron. The range of Fe^{3+}-siderophore association constants is 10^{12}–10^{52} (Saha et al., 2013). Siderophores have been classified into catecholates, hydroxymates, and a mixed type based on the moiety that donates oxygen ligands to coordinate Fe^{3+} (Saha et al., 2013). *Acinetobacter baumannii* also has iron siderophores and acinetobactin, the best-characterized *A. baumannii* siderophore, is a mixed type siderophore with an oxazoline ring derived from threonine (McConnell et al., 2013). Acinetobactin is an *A. baumannii* virulence factor (Gaddy et al., 2012; Penwell et al., 2012; Megeed et al., 2016). Impaired acinetobactin biosynthesis and transport functions significantly reduce the ability of *A. baumannii* ATCC 19606 cells to persist within epithelial cells and cause cell damage and animal death (Gaddy et al., 2012). Mutation in the *entA* gene, which is essential for biosynthesis of the acinetobactin precursor 2,3-dihydroxybenzoic acid, also significantly reduces the capacity of *A. baumannii* ATCC 19606 cells to persist within human alveolar epithelial cells and diminishes the ability to infect and kill *Galleria mellonella* larvae (Penwell et al., 2012). One study showed that acinetobactin production occurs significantly more frequently in MDR *A. baumannii* isolates than that in avirulent isolates (Megeed et al., 2016).

The *A. baumannii* NfuA Fe-S scaffold protein, that participates in the formation of Fe-S clusters and plays a role in cell responses to iron chelation and oxidative stress, has also been identified as a virulence factor (Zimbler et al., 2012). The *nfuA* mutant is more sensitive to reactive oxygen species (ROS), such as hydrogen peroxide and cumene hydroperoxide, and shows significantly reduced growth in human epithelial cells. In addition, a *G. mellonella* infection model showed that more than 50% of injected *G. mellonella* larvae die 6 days after infection with the parental strain, whereas less than 30% of the larvae die when infected with the *nfuA* mutant (Zimbler et al., 2012). One report showed that iron starvation increases production of PLCs, which increase hemolytic activity of *A. baumannii* (Fiester et al., 2016). These reports indicate that iron acquisition functions play a critical role in *A. baumannii* virulence.

The innate immune metal-chelating protein calprotectin inhibits bacterial growth by host-mediated chelation of metals, such as zinc (Zn^{2+} and Zn) and manganese (Mn^{2+} and Mn) (Corbin et al., 2008). However, *A. baumannii* can cause disease in the presence of this nutritional immune protein *in vivo* (Juttukonda et al., 2016). To combat the zinc limitation, *A. baumannii* uses a zinc acquisition system (ZnuABC), which is up-regulated under Zn-limiting conditions, and the *znuB* mutant strain experiences Zn starvation at higher Zn concentrations than that of the wild-type (Hood et al., 2012). ZnuB contributes to the pathogenesis of *A. baumannii* pulmonary infections. Notably, a zinc limitation reduces the imipenem MIC of MDR *A. baumannii* to below the clinical breakpoint for imipenem resistance in *A. baumannii* (Hood et al., 2012), possibly because many carbapenemases are metalloenzymes that require Zn for their hydrolyzing activity. Besides the ZnuABC system, the novel Zn metallochaperone ZigA has been characterized in *A. baumannii* (Nairn et al., 2016). ZigA tightly interacts with Zn, which is required for bacterial growth under Zn starvation conditions and for disseminated infection in mice (Nairn et al., 2016).

The mechanism employed by *A. baumannii* to overcome a Mn limitation has been identified. Calprotectin induces Mn starvation in *A. baumannii*, which increases transcription of an NRAMP (Natural Resistance-Associated Macrophage Proteins) family Mn transporter and a urea carboxylase to resist the antimicrobial activities of calprotectin (Juttukonda et al., 2016). A urea carboxylase enzyme (MumC) is important for growth of *A. baumannii* in the presence of calprotectin and an NRAMP family transporter (MumT) contributes to the fitness of *A. baumannii* in a murine pneumonia model (Juttukonda et al., 2016), suggesting that the two proteins are virulence factors. *Acinetobacter baumannii* can utilize urea as a sole nitrogen source, and this urea utilization is required for MumC (Juttukonda et al., 2016). Based on the contribution of MumC to *A. baumannii* resistance to calprotectin, the authors suggest a connection between metal starvation and metabolic stress, such as nitrogen starvation.

Protein Secretion Systems

Several protein secretion systems have been identified in *A. baumannii* (Weber et al., 2015a). The most recently described *A. baumannii* secretion system is a type II secretion system (T2SS) (Johnson et al., 2015). The T2SS is a multi-protein complex that is structurally very similar to type IV pili systems, which is an appendage that is commonly found in Gram-negative bacteria (Korotkov et al., 2012). T2SS translocates a wide range of proteins from the periplasmic space to the extracellular milieu out of the cell or the outer membrane surface. The T2SS is composed of 12–15 proteins comprised of four sub-assemblies: a pseudopilus, a cytoplasmic secretion ATPase, an inner-membrane platform assembly, and a dodecameric outer-membrane complex (Korotkov et al., 2012; Harding et al., 2016). Secretion by T2SS is a two-step process. The target proteins are first translocated to the periplasm by the general secretory (Sec) system or the twin arginine transport (Tat) system, where the target proteins are then secreted out of the cell through the T2SS (Korotkov et al., 2012). Deleting *A. baumannii* genes for the T2SS components, *gspD* or *gspE*, results in loss of LipA secretion, indicating that LipA is a T2SS substrate (Johnson et al., 2015). Because LipA is a lipase that breaks down long-chain fatty acids, *lipA*, *gspD*, and *gspE* mutant strains are incapable of growing on long-chain fatty acids as a sole carbon source and are defective in *in vivo* growth in a neutropenic murine model of bacteremia (Johnson et al., 2015). The role of a functional T2SS for full virulence of *A. baumannii* has been shown in *G. mellonella* and murine pulmonary infection models (Harding et al., 2016). Lipases (LipA, LipH, and LipAN) and the metallopeptidase CpaA have been identified as T2SS substrates (Elhosseiny et al., 2016; Harding et al., 2016). Notably, two proteins (LipA and CpaA) among these secreted proteins require specific chaperones for

secretion. These chaperones are encoded adjacently to their cognate effector, and their inactivation abolishes secretion of LipA and CpaA (Harding et al., 2016).

Acinetobacter baumannii also has a type VI secretion system (T6SS). The T6SS was first identified in *Vibrio cholera* and *P. aeruginosa* (Mougous et al., 2006; Pukatzki et al., 2006). Many bacteria use the T6SS to inject effector proteins, providing a colonization advantage during infection of eukaryotic hosts (Mougous et al., 2006) or to kill competing bacteria (Basler et al., 2013). The T6SS leads to DNA release and horizontal gene transfer in *V. cholera*, which may contribute to spread of antibiotic resistance (Borgeaud et al., 2015). The T6SS is composed of many conserved structural proteins and accessory factors, and bears a contractile bacteriophage sheath-like structure forming a needle or spike structure used to penetrate the target cell (Shneider et al., 2013). Hcp is a structural protein forming a polymerized tubular structure that is secreted out of the cell, and VgrGs are involved in attaching effector domains to the spike, and a proline-alanine-alanine-arginine (PAAR) repeat protein forms the sharp tip of the distinctive needle-like structure (Shneider et al., 2013; Zoued et al., 2014).

The presence of T6SS in *A. baumannii* was initially predicted by bioinformatic analysis (Weber et al., 2013). Although the role of T6SS in *A. baumannii* ATCC 17978 has not been determined (Weber et al., 2013), research on *A. baumannii* strain M2 showed that this strain produces a functional T6SS and that the T6SS mediates killing of competing bacteria (Carruthers et al., 2013). Another study showed that the T6SS is active in six pathogenic strains of *A. baumannii* (Ruiz et al., 2015). However, the T6SS seems to play an important role in *A. baumannii* virulence in a strain-specific manner (Repizo et al., 2015). They compared T6SS functionality of several *A. baumannii* strains, including ATCC17978 (a type strain), various MDR strains implicated in hospital outbreaks (Ab242, Ab244, and Ab825), and DSM30011 (a non-clinical isolate). Although the T6SS genomic locus is present in all of these strains, only DSM30011 has a fully active T6SS that mediates *E. coli* killing (Repizo et al., 2015). In addition, the T6SS of DSM30011 is required for host colonization of the *G. mellonella* model organism (Repizo et al., 2015). Similar results were obtained from a comparative analysis of the genomes of MDR *A. baumannii* clinical strains (Wright et al., 2014; Jones et al., 2015). *A. baumannii* isolates of a particular clade exhibit complete loss of the T6SS genomic locus. Therefore, these results suggest that more extensive investigations are required to analyze the role of T6SS in *A. baumannii* virulence, even though this system seems to play an important role in *A. baumannii* virulence in some strains. Notably, one study showed that several MDR *A. baumannii* strains have a large, self-transmissible plasmid that carries negative regulators for T6SS (Weber et al., 2015b). The T6SS is silenced in plasmid-containing, antibiotic-resistant cells, whereas plasmid-losing cells have an active T6SS. Although plasmid-losing cells are capable of T6SS-mediated killing of competing bacteria, they become susceptible to antibiotics (Weber et al., 2015b). This result suggests a molecular switch between T6SS and antibiotic resistance.

The type V system autotransporter Ata has also been characterized in *A. baumannii* (Bentancor et al., 2012a). This is a trimeric membrane protein that mediates biofilm formation, adherence to extracellular matrix components such as collagen I, III, and IV, and virulence in a murine systemic model of *Acinetobacter* infection (Bentancor et al., 2012a). Another experiment using a pneumonia model of infection in immunocompetent and immunocompromised mice showed that Ata is a vaccine candidate against *A. baumannii* infections (Bentancor et al., 2012b). A type IV secretion system present in the plasmid was bioinformatically identified in *A. baumannii* (Liu C. C. et al., 2014), but no experimental evidence describing its function has been presented.

Penicillin-Binding Protein 7/8 (PBP7/8) and β-Lactamase PER-1

Although PBPs are commonly involved in resistance to β-lactam antibiotics, PBP7/8 encoded by the *pbpG* gene is a virulence factor in *A. baumannii*. The *pbpG* mutant strain grows similar to its wild-type strain in Luria-Bertani medium, but the mutant shows reduced growth in human serum and its survival significantly decreases in rat soft-tissue infection and pneumonia models (Russo et al., 2009). An investigation of bacterial morphology using electron microscopy suggested that loss of PBP7/8 may have affected peptidoglycan structure, which may affect susceptibility to host defense factors (Russo et al., 2009).

Interestingly, β-lactamase PER-1 has been suggested to be an *A. baumannii* virulence factor. PER-1 is an extended-spectrum-β-lactamase (ESBL), but this gene is associated with cell adhesion (Sechi et al., 2004). Nine PER-1-producing strains adhere to the Caco2 cell lines, whereas all PER-1-negative strains are negative for cell adhesion (Sechi et al., 2004). Notably, many β-lactamases are associated with virulence in various pathogenic bacteria, such as *E. coli* (Dubois et al., 2009), *P. aeruginosa* (Moya et al., 2008), and *K. pneumoniae* (Sahly et al., 2008). However, no general mechanisms have been proposed (Beceiro et al., 2013).

Others

Acinetobacter baumannii CipA is a novel plasminogen binding and complement inhibitory protein that mediates serum resistance (Koenigs et al., 2016). CipA-binding plasminogen is converted to active plasmin that degrades fibrinogen and complement C3b, which contributes to serum resistance of *A. baumannii*. Therefore, the *cipA* mutant strain is efficiently killed by human serum and also shows a defect in the penetration of endothelial monolayers (Koenigs et al., 2016). Similar to CipA, the *A. baumannii* translation elongation factor Tuf is also a plasminogen-binding protein. Tuf-binding plasminogen can be converted to active plasmin, which proteolytically degrades fibrinogen as well as component C3b (Koenigs et al., 2015). RecA, which is involved in homologous recombination and the SOS response, has been identified as an *A. baumannii* virulence factor. The *recA* mutant shows significantly reduced survival within macrophages and decreases lethality in a mouse model of systemic infection (Aranda et al., 2011). The surface antigen protein 1 (SurA1) plays an important role in fitness and virulence of *A. baumannii* (Liu D. et al., 2016). Serum resistance of the *surA1* mutant significantly decreases compared with that of

the wild-type strain CCGGD201101. In the *G. mellonella* insect model, a *surA1* mutant strain exhibits a lower survival rate and decreased dissemination (Liu D. et al., 2016).

A growth analysis of 250,000 *A. baumannii* transposon mutants within *G. mellonella* larvae identified 300 genes required for survival or growth of *A. baumannii* inside *G. mellonella* larvae (Gebhardt et al., 2015). The 300 genes were classified into six categories of micronutrient acquisition, cysteine metabolism/sulfur assimilation, aromatic hydrocarbon metabolism, cell envelope/membrane/wall, stress response genes, antibiotic resistance, and transcriptional regulation. Among them, four transcriptional regulators required for growth in *G. mellonella* larvae were called the *gig* (growth in *Galleria*) genes. Loss of these genes (*gigA-D*) led to a significant defect in both growth within and killing of *G. mellonella* larvae (Gebhardt et al., 2015). This study identified stress proteins, such as UspA, as factors required for growth in *G. mellonella*. Another study showed that UspA is essential for pneumonia and sepsis pathogenesis of *A. baumannii* (Elhosseiny et al., 2015). Among the 300 genes, several genes are involved in aromatic hydrocarbon metabolism (Gebhardt et al., 2015). Another study showed that GacS, which is a transcriptional factor that regulates expression of genes, such as *paaE*, and is responsible for the phenylacetic acid catabolic pathway, affects *A. baumannii* virulence (Cerqueira et al., 2014). Experiments using a *paaE* deletion mutant confirmed the role of aromatic hydrocarbon metabolism in *A. baumannii* virulence (Cerqueira et al., 2014), but its molecular mechanism remains unknown. Interestingly, a recent report showed that accumulation of phenylacetate in *A. baumannii* induces rapid neutrophil influx to a localized site of infection and increases bacterial clearance (Bhuiyan et al., 2016). They suggested that phenylacetate is a neutrophil chemoattractant inducing bacterial-guided neutrophil chemotaxis. This report may reveal a novel molecular mechanism about the role of the phenylacetic acid catabolic pathway in *A. baumannii* virulence.

Biofilm formation plays an important role in immune evasion by *A. baumannii* (de Breij et al., 2010), and pili are essential for *A. baumannii* adherence to and biofilm formation on abiotic surfaces as well as virulence (Tomaras et al., 2003, 2008). Notably, imipenem treatment of the imipenem-resistant *A. baumannii* isolate induces expression of important genes responsible for synthesis of type IV pili (Dhabaan et al., 2015), suggesting that the ability to overproduce pili confers a biological advantage to *A. baumannii*.

Other virulence-related proteins have been identified, including OmpR/EnvZ (Tipton and Rather, 2016), FhaBC (Perez et al., 2016), and the resistance-nodulation-division-type membrane transporter AbeD (Srinivasan et al., 2015), but their molecular mechanisms remain unknown.

ANTIMICROBIAL RESISTANCE OF *A. BAUMANNII*

Acinetobacter baumannii has become one of the most successful pathogens in modern healthcare because of its amazing ability to acquire antimicrobial resistance. Several strains of *A. baumannii* are highly resistant to most clinically available antibiotics (Lin and Lan, 2014). *A. baumannii* has a number of resistance mechanisms, including β-lactamases, aminoglycoside-modifying enzymes, efflux pumps, permeability defects, and modifications of target sites. The accumulation of several resistance mechanisms in *A. baumannii* has gradually decreased the number of antibiotic classes available to treat *A. baumannii* infections in clinical practice. **Table 2** shows the antibiotic resistance mechanisms found in *A. baumannii*. We will discuss the details below.

β-Lactamases

Inactivation of β-lactams by β-lactamases is a major antibiotic resistance mechanism in *A. baumannii*. Based on sequence homology, β-lactamases are grouped into molecular classes, A, B, C, and D (Jeon et al., 2015). All four classes of β-lactamases were identified in *A. baumannii*. Recent studies have shown that *A. baumannii* has natural competence to incorporate exogenous DNA and its genome has foreign DNA at high frequencies, implying frequent horizontal gene transfer in this pathogen (Ramirez et al., 2010a; Touchon et al., 2014; Traglia et al., 2014). Additionally, albumin, a main protein in blood, enhances natural competence of *A. baumannii* (Traglia et al., 2016). Therefore, natural competence of *A. baumannii* may contribute to identification of a large number of β-lactamases in this threatening human pathogen.

Class A β-lactamases inhibited by clavulanate hydrolyze penicillins and cephalosporins more efficiently than carbapenems, except for some KPC type enzymes (Jeon et al., 2015). A number of class A β-lactamases, including TEM, SHV, GES, CTX-M, SCO, PER, VEB, KPC, and CARB, have been identified in *A. baumannii* (**Table 2**). Some of these enzymes, such as TEM-1, CARB-4, and SCO-1, are narrow-spectrum β-lactamases, whereas other enzymes (e.g., PER-1, TEM-92, CARB-10, SHV-5, PER-2, CTX-M-2, CTX-M-15, VEB-1, GES-14, and PER-7) are ESBLs. Some carbapenemases, such as GES-14 and KPC-2, have been detected in *A. baumannii* (Moubareck et al., 2009; Bogaerts et al., 2010).

Unlike the serine-dependent β-lactamases (classes A, C, and D), class B β-lactamases are metallo-β-lactamases (MBLs) that require zinc or another heavy metal for catalysis (Jeon et al., 2015). Due to a broad substrate spectrum, MBLs catalyze the hydrolysis of virtually all β-lactam antibiotics including carbapenems, but not monobactams (Jeon et al., 2015). A variety of class B β-lactamases have been identified in *A. baumannii* (**Table 2**).

Class C β-lactamases pose therapeutic problems because they can confer resistance to cephamycins (cefoxitin and cefotetan), penicillins, cephalosporins, and β-lactamase inhibitor combinations, but are not significantly inhibited by clinically used β-lactamase inhibitors, such as clavulanic acid (Jeon et al., 2015). *Acinetobacter baumannii* has an intrinsic AmpC cephalosporinase (Gordon and Wareham, 2010). An analysis of 23 MDR *A. baumannii* clinical isolates in Taiwan showed that all isolates had AmpC-type β-lactamases (Lin et al., 2011a). Several clinical isolates of *A. baumannii* have the *ampC* gene transcribed

TABLE 2 | Resistance mechanisms in *Acinetobacter baumannii.*

Resistance mechanism	Class/subgroup	Protein	References
β-Lactamases	Class A	TEM-1	Chen et al., 2006; Adams et al., 2008; Krizova et al., 2013
		TEM-92	Endimiani et al., 2007
		GES-1	Al-Agamy et al., 2016
		GES-5	Al-Agamy et al., 2016
		GES-11	Moubareck et al., 2009; Bogaerts et al., 2010; Chihi et al., 2016
		GES-12	Bogaerts et al., 2010
		GES-14	Bogaerts et al., 2010
		PER-1	Jeong et al., 2005; Poirel et al., 2005a; Aly et al., 2016
		PER-2	Pasteran et al., 2006
		PER-7	Bonnin et al., 2011b
		CTX-M-2	Nagano et al., 2004
		CTX-M-15	Potron et al., 2011
		SCO-1	Poirel et al., 2007
		VEB-1	Fournier et al., 2006; Naas et al., 2006; Pasteran et al., 2006; Adams et al., 2008; Poirel et al., 2009
		KPC-2	Martinez et al., 2016
		KPC-10	Robledo et al., 2010
		CARB-4	Ramirez et al., 2010b
		CARB-10	Potron et al., 2009
	Class B	IMP-1	Tognim et al., 2006
		IMP-2	Riccio et al., 2000
		IMP-4	Chu et al., 2001
		IMP-5	Koh et al., 2007
		IMP-6	Gales et al., 2003
		IMP-8	Lee M. F. et al., 2008
		IMP-11	Yamamoto et al., 2011
		IMP-19	Yamamoto et al., 2011
		IMP-24	Lee M. F. et al., 2008
		VIM-1	Tsakris et al., 2006, 2008; Papa et al., 2009
		VIM-2	Yum et al., 2002; Lee M. F. et al., 2008
		VIM-3	Lee M. F. et al., 2008
		VIM-4	Tsakris et al., 2008; Papa et al., 2009
		VIM-11	Lee M. F. et al., 2008
		NDM-1	Chen et al., 2011; Pfeifer et al., 2011; Bonnin et al., 2012; Voulgari et al., 2016
		NDM-2	Espinal et al., 2011
		NDM-3	Kumar, 2016
		SIM-1	Lee et al., 2005
	Class C	AmpC	Bou and Martinez-Beltran, 2000; Corvec et al., 2003; Segal et al., 2004; Hujer et al., 2005; Heritier et al., 2006; Liu and Liu, 2015
	Class D		
	OXA-2 subgroup	OXA-21	Vila et al., 1997
	OXA-10 subgroup	OXA-128	Giannouli et al., 2009
	OXA-20 subgroup	OXA-37	Navia et al., 2002
	OXA-23 subgroup	OXA-23	Heritier et al., 2005b; Naas et al., 2005; Corvec et al., 2007; Koh et al., 2007; Perez et al., 2007; Valenzuela et al., 2007; Wang et al., 2007; Adams et al., 2008; Stoeva et al., 2008; Kohlenberg et al., 2009; Kuo et al., 2010; Mugnier et al., 2010; Bonnin et al., 2011a; Lee et al., 2011; Lin et al., 2011b; Koh et al., 2012; Mosqueda et al., 2013; Chagas et al., 2014; Principe et al., 2014; Li Y. et al., 2015

(Continued)

TABLE 2 | Continued

Resistance mechanism	Class/subgroup	Protein	References
		OXA-133	Mendes et al., 2009
		OXA-239	Gonzalez-Villoria et al., 2016
	OXA-24 subgroup	OXA-24	Bou et al., 2000b; Merino et al., 2010; Acosta et al., 2011; Pailhories et al., 2016
		OXA-25, OXA-26, OXA-27	Afzal-Shah et al., 2001
		OXA-40	Heritier et al., 2003; Lolans et al., 2006; Quinteira et al., 2007; Ruiz et al., 2007
		OXA-72	Wang et al., 2007; Lu et al., 2009; Goic-Barisic et al., 2011; Dortet et al., 2016; Kuo et al., 2016
		OXA-143	Higgins et al., 2009
		OXA-182	Kim et al., 2010
	OXA-51 subgroup	OXA-51	Brown et al., 2005; Hu et al., 2007; Ruiz et al., 2007; Adams et al., 2008; Chen et al., 2010; Fang et al., 2016
		OXA-64, OXA-65, OXA-66, OXA-68, OXA-70, OXA-71	Hamouda et al., 2010; Biglari et al., 2016
		OXA-69, OXA-75, OXA-76, OXA-77	Heritier et al., 2005a
		OXA-79, OXA-80, OXA-104, OXA-106∼ OXA-112	Evans et al., 2007
		OXA-82, OXA-83, OXA-83, OXA-84	Turton et al., 2006b; Evans et al., 2007
		OXA-86, OXA-87	Vahaboglu et al., 2006
		OXA-88, OXA-91, OXA-93, OXA-94, OXA-95, OXA-96	Koh et al., 2007
		OXA-92	Tsakris et al., 2007
		OXA-113	Naas et al., 2007
	OXA-58 subgroup	OXA-58	Dijkshoorn et al., 1996; Poirel et al., 2005b; Pournaras et al., 2006; Chen et al., 2008; Qi et al., 2008; Donnarumma et al., 2010; Gogou et al., 2011; Ravasi et al., 2011; Hou and Yang, 2015
		OXA-96	Koh et al., 2007
		OXA-97	Poirel et al., 2008
	OXA-143 subgroup	OXA-253	de Sa Cavalcanti et al., 2016
	OXA-235 subgroup	OXA-235	Higgins et al., 2013
Efflux pumps	Resistance-nodulation-division superfamily	AdeABC	Magnet et al., 2001; Marchand et al., 2004; Peleg et al., 2007; Ruzin et al., 2007; Lin et al., 2015; Sun et al., 2016
		AdeFGH	Coyne et al., 2010; He X. et al., 2015
		AdeIJK	Damier-Piolle et al., 2008
	Major facilitator superfamily	TetA	Ribera et al., 2003a
		TetB	Vilacoba et al., 2013
		CmlA	Coyne et al., 2011
		CraA	Roca et al., 2009
		AmvA	Rajamohan et al., 2010
		AbaF	Sharma et al., 2016
	Multidrug and toxic compound extrusion family	AbeM	Su et al., 2005
	Small multidrug resistance family	AbeS	Srinivasan et al., 2009
	Other efflux pumps	EmrAB-TolC	Nowak-Zaleska et al., 2016
		A1S_1535, A1S_2795, and ABAYE_0913	Li L. et al., 2016
Permeability defects	Porin	OmpA	Smani et al., 2014; Wu et al., 2016
		CarO	Mussi et al., 2005, 2007; Siroy et al., 2005; Catel-Ferreira et al., 2011; Jin et al., 2011

(Continued)

TABLE 2 | Continued

Resistance mechanism	Class/subgroup	Protein	References
		Omp22-33	Bou et al., 2000a
		Omp33-36	del Mar Tomas et al., 2005
		Omp37	Quale et al., 2003
		Omp43	Dupont et al., 2005
		Omp44	Quale et al., 2003
		Omp47	Quale et al., 2003
Aminoglycoside-modifying enzymes	Aminoglycoside acetyltransferases	AAC3 (*aacC1*, *aacC2*)	Nemec et al., 2004
		AAC(6′) (*aacA4*)	Doi et al., 2004; Cho et al., 2009; Zhu et al., 2009; Lin et al., 2010; Lin M. F. et al., 2013; Bakour et al., 2014
	Aminoglycoside adenyltransferases	ANT(2′′) (*aadB*)	Nemec et al., 2004
		ANT(3′′) (*aadA1*)	Cho et al., 2009; Lin et al., 2010; Lin M. F. et al., 2013
	Aminoglycoside phosphotransferases	APH(3′) (*aphA1*)	Gallego and Towner, 2001
		APH(3′′)	Cho et al., 2009
Alteration of target sites	Change of penicillin binding protein(PBP)	PBP2	Gehrlein et al., 1991
	16S rRNA methylation	ArmA	Yu et al., 2007; Cho et al., 2009; Karthikeyan et al., 2010; Brigante et al., 2012; Hong et al., 2013; Bakour et al., 2014; Tada et al., 2014
	Ribosomal protection	TetM	Ribera et al., 2003b
	DNA gyrase	GyrA/ParC	Higgins et al., 2004
	Dihydrofolate reductase	DHFR	Mak et al., 2009; Lin M. F. et al., 2013
		FolA	Mak et al., 2009
	Lipopolysaccharide	PmrC, LpxA, LpxC, LpxD	Adams et al., 2009; Moffatt et al., 2010; Arroyo et al., 2011
Other mechanisms	S-adenosyl-L-methionine-dependent methyltransferase	Trm	Chen et al., 2014; Trebosc et al., 2016
	1-Acyl-sn-3-phosphate acyltransferase	PlsC	Li X. et al., 2015
	Peptidase C13 family	Abrp	Li X. et al., 2016
	Cell division proteins	BlhA, ZipA, ZapA, and FtsK	Knight et al., 2016
	SOS response	RecA	Aranda et al., 2011, 2014; Norton et al., 2013

from a strong promoter contained within a putative insertion sequence element (IS*Aba1*-like sequence), which results in high resistance to ceftazidime (Corvec et al., 2003; Segal et al., 2004). This sequence has been identified in ceftazidime-resistant *A. baumannii* isolates, but is absent in ceftazidime-susceptible *A. baumannii* isolates (Heritier et al., 2006).

Class D β-lactamases are called OXAs (oxacillinases), because they commonly hydrolyze isoxazolylpenicillin oxacillin much faster than benzylpenicillin (Jeon et al., 2015). More than 400 OXA-type enzymes have been identified and many variants actually possess carbapenemase activity. The presence of carbapenem-hydrolyzing class D β-lactamases or MBLs is one of the major carbapenem resistance mechanisms in *A. baumannii* (Lin and Lan, 2014). The subgroups of carbapenem-hydrolyzing OXAs, such as the OXA-23, OXA-24, OXA-51, and OXA-58 subgroups, are prevalent in *A. baumannii* (**Table 2**). The OXA-23 enzyme was first identified in an *A. baumannii* isolate in the United Kingdom in 1985 (Perez et al., 2007). The $bla_{\text{OXA-23}}$ gene has been disseminated worldwide, and the frequency of OXA-23-producing *A. baumannii* strains is significantly high (Mugnier et al., 2010; Al-Agamy et al., 2016). One recent report from Lebanon showed 76.5% of 119 *A. baumannii* isolates are resistant to carbapenems, and OXA-23 β-lactamases have been found in 82 isolates (Al Atrouni et al., 2016). Insertion of IS*Aba1* in the $bla_{\text{OXA-23}}$ promoter sequence has been reported to be associated with overexpression of $bla_{\text{OXA-23}}$, $bla_{\text{OXA-51}}$, or $bla_{\text{OXA-58}}$ in *A. baumannii* (Turton et al., 2006a). One report from India showed that $bla_{\text{OXA-51}}$ and $bla_{\text{OXA-23}}$ were present in all 103 carbapenem-resistant *A. baumannii* isolates and almost 80% of the isolates had IS*Aba1* upstream of the $bla_{\text{OXA-23}}$ gene, indicating the prevalence of the IS*Aba1* insertion (Vijayakumar et al., 2016).

Efflux Pumps

Efflux pumps are associated with resistance against many different classes of antibiotics, such as imipenem (Hu et al., 2007) and tigecycline (Peleg et al., 2007; Ruzin et al., 2007), in *A. baumannii*. Reversal of antibiotic resistance by

efflux pump inhibitors, such as 1-(1-naphthylmethyl)-piperazine and carbonyl cyanide 3-chlorophenyl-hydrazone, supports the importance of efflux pumps in *A. baumannii* antibiotic resistance (Pannek et al., 2006; Deng et al., 2014). Four categories of efflux pumps, such as the resistance-nodulation-division superfamily, the multidrug and toxic compound extrusion family, the major facilitator superfamily, and the small multidrug resistance family transporters, are related to antimicrobial resistance in *A. baumannii* (**Table 2**; Lin and Lan, 2014).

AdeABC in the resistance-nodulation-division superfamily is associated with aminoglycoside resistance (Magnet et al., 2001) and with decreasing susceptibility to tigecycline (Ruzin et al., 2007) and non-fluoroquinolone antibiotics (Higgins et al., 2004). AdeABC seems to be cryptic in wild-type *A. baumannii* because of stringent control by the AdeRS two-component system (Marchand et al., 2004), but point mutations or insertion of the IS*Aba1* sequence in the *adeS* gene leads to overexpression of AdeABC (Marchand et al., 2004; Sun et al., 2012, 2016; Hammerstrom et al., 2015). Cell density (Fernando and Kumar, 2012) and the BaeSR two-component system (Lin et al., 2014, 2015), which is involved in an envelope stress response, also seem to regulate transcription of the *adeA* gene and thus affect tigecycline susceptibility. Other resistance-nodulation-division type efflux pumps, such as AdeFGH and AdeIJK, are synergistically associated with tigecycline resistance (Damier-Piolle et al., 2008). AdeFGH and AdeIJK expression is regulated by the LysR-type transcriptional regulator AdeL and the TetR-type transcriptional regulator AdeN (Coyne et al., 2010; Rosenfeld et al., 2012).

Acinetobacter baumannii clinical isolates possess a strong ability to form biofilms (Rodriguez-Bano et al., 2008). Notably, the subinhibitory concentrations of antibiotics encountered by low-dose therapy seem to strongly induce biofilm formation (Kaplan, 2011). A recent result revealed the mechanism. Overexpression of the AdeFGH efflux pump by low-dose antimicrobial therapy increases the synthesis and transport of autoinducer molecules, which induce biofilm formation (He X. et al., 2015). These results suggest a link between low-dose antimicrobial therapy and a high risk for biofilm infections caused by *A. baumannii*.

CmlA and CraA are major facilitator superfamily efflux pumps related with chloramphenicol (Fournier et al., 2006; Roca et al., 2009), and TetA is associated with tetracycline resistance (Ribera et al., 2003a). The novel efflux pump AmvA mediates resistance to different classes of antibiotics, disinfectants, detergents, and dyes, such as erythromycin, acriflavine, benzalkonium chloride, and methyl viologen (Rajamohan et al., 2010). AbaF was recently identified as a novel efflux pump associated with fosfomycin resistance (Sharma et al., 2016).

AbeM is in the multidrug and toxic compound extrusion family and confers resistance to imipenem and fluoroquinolones (Su et al., 2005). AbeS is the small multidrug resistance family transporter and affects resistance to various antimicrobial compounds. Deletion of the *abeS* gene results in increased susceptibility to various antimicrobial compounds, such as chloramphenicol, nalidixic acid, and erythromycin (Srinivasan et al., 2009).

Some other efflux pumps, such as MacAB-TolC (Kobayashi et al., 2001) and EmrAB-TolC (Lomovskaya and Lewis, 1992), have been well described in *E. coli*, but their role in *A. baumannii* has been recently explored. The EmrAB-TolC efflux pump is also present in *A. baumannii* where it conferred resistance to netilmicin, tobramycin, and imipenem (Nowak-Zaleska et al., 2016). Another report identified three novel efflux pumps (A1S_1535, A1S_2795, and ABAYE_0913) in *A. baumannii* using multiplexed phenotypic screening (Li L. et al., 2016). A1S_1535 confers resistance to various antibiotics, including gentamicin, kanamycin, chloroxylenol, oxytetracycline, 1,10-phenanthroline, and chloramphenicol (Li L. et al., 2016). A1S_2795 is the first major facilitator superfamily efflux pump found to confer resistance to the sulphonamide sulfathiazole, and ABAYE_0913 is associated with resistance to chloramphenicol and fusidic acid (Li L. et al., 2016).

Permeability Defects

A change in envelope permeability can influence antibiotic resistance. For example, porins form channels that allow transport of molecules across the outer membrane and play a significant role in *A. baumannii* virulence (**Table 1**). Because porins affect membrane permeability, they also play a significant role in the mechanism of resistance. Reduced expression of some porins, including CarO (Mussi et al., 2005, 2007; Siroy et al., 2005; Catel-Ferreira et al., 2011; Jin et al., 2011), Omp22-33 (Bou et al., 2000a), Omp33-36 (del Mar Tomas et al., 2005; Hood et al., 2010), Omp37 (Quale et al., 2003), Omp43 (Dupont et al., 2005), Omp44 (Quale et al., 2003), and Omp47 (Quale et al., 2003), is associated with carbapenem resistance in *A. baumannii*. Loss of Omp29 in *A. baumannii* producing OXA-51-like or OXA-23-like carbapenemases results in increased imipenem resistance (Jeong et al., 2009; Fonseca et al., 2013). OmpA is also related with resistance to aztreonam, chloramphenicol, and nalidixic acid (Smani et al., 2014). One study showed that OmpA and CarO physically interact with OXA-23 carbapenemase, and these interactions are associated with antibiotic resistance (Wu et al., 2016). These results provide a novel view to increase understanding of bacterial antibiotic resistance mechanisms.

Besides outer membrane proteins, envelope components, such as LPS and peptidoglycans, also affects antibiotic resistance of *A. baumannii*. Loss or modification of LPS decreases membrane integrity and increases colistin resistance in *A. baumannii* (Adams et al., 2009; Moffatt et al., 2010).

Aminoglycoside-Modifying Enzymes

Aminoglycoside-modifying enzymes are the major mechanism by which *A. baumannii* confers resistance to aminoglycosides. Aminoglycoside-modifying enzymes can be classified into acetyltransferases, adenyltransferases, and phosphotransferases. These enzymes are typically present on transposable elements and are transferred among pathogenic bacteria (Lin and Lan, 2014). Several reports show that many MDR *A. baumannii* isolates produce a combination of aminoglycoside-modifying enzymes (Gallego and Towner, 2001; Nemec et al., 2004). A study from China identified a MDR *A. baumannii* strain carrying four aminoglycoside-modifying enzymes (Zhu et al., 2009). Another

study from Greece reported that all *A. baumannii* strains contain aminoglycoside-modifying enzymes (Ploy et al., 1994), indicating the high prevalence of these enzymes in *A. baumannii*.

Alteration of Target Sites

Modifications in antibiotic target sites for antibiotics can induce antibiotic resistance in *A. baumannii*. In the absence of other known resistance mechanisms, only overexpression of altered PBPs with a low affinity for imipenem induce imipenem resistance (Gehrlein et al., 1991). Quinolone resistance is associated with modifications in GyrA (one subunit of DNA gyrase) and ParC (one subunit of topoisomerase IV) in epidemiologically unrelated *A. baumannii* isolates (Vila et al., 1995). *Acinetobacter baumannii* TetM, which has 100% homology with *S. aureus* TetM, has been proposed to be associated with tetracycline resistance through ribosomal protection (Ribera et al., 2003b). Similar to other pathogenic bacteria, dihydrofolate reductases (DHFR and FolA) responsible for trimethoprim resistance have been found in nosocomial MDR *A. baumannii* isolates (Mak et al., 2009; Lin M. F. et al., 2013; Taitt et al., 2014). The 16S rRNA methylase ArmA responsible for aminoglycoside resistance is also found in many *A. baumannii* strains and always coexists with OXA type carbapenemases such as OXA-23 (Yu et al., 2007; Cho et al., 2009; Karthikeyan et al., 2010; Brigante et al., 2012; Hong et al., 2013; Bakour et al., 2014; Tada et al., 2014; Hasani et al., 2016). As described above, many studies have shown that modifications or/and loss of LPS decrease the susceptibility of *A. baumannii* to many clinical important antibiotics, such as colistin.

Others

AdeABC is associated with decreased susceptibility to tigecycline (Ruzin et al., 2007). However, some clinical isolates without overexpressed AdeABC, AdeFGH, and AdeIJK have decreased susceptibility to tigecycline. Several reports have suggested the mechanism. One study analyzed eight *A. baumannii* clinical isolates and revealed that the deletion mutation in the *trm* gene, which encodes S-adenosyl-L-methionine-dependent methyltransferase, decreases susceptibility to tigecycline (Chen et al., 2014). The same result was reported using a highly efficient and versatile genome-editing platform enabling markerless modification of the *A. baumannii* genome. Deletion of AdeR, a transcription factor that regulates AdeABC efflux pump expression in tigecycline-resistant *A. baumannii*, reduces the MIC of tigecycline. However, 60% of the clinical isolates remained nonsusceptible to tigecycline after the *adeR* deletion according to a highly efficient and versatile genome-editing platform (Trebosc et al., 2016). Whole-genome sequencing in two tigecycline-resistant *adeR* deletion strains revealed that a mutation in the *trm* gene makes the *adeR* mutant resistant to tigecycline. In addition, a *trm* disruption was identified in most tigecycline-resistant clinical isolates (Trebosc et al., 2016). However, its exact mechanism was not determined. Another study revealed that a frameshift mutation in *plsC*, encoding 1-acyl-*sn*-glycerol-3-phosphate acyltransferase, is associated with decreased susceptibility to tigecycline (Li X. et al., 2015).

The *abrp* gene, which encodes the peptidase C13 family, is associated with decreased susceptibility to tetracycline, minocycline, doxycycline, tigecycline, chloramphenicol, and fosfomycin (Li X. et al., 2016). Deletion of *abrp* increases cell membrane permeability, displays slower cell growth rate, and confers reduced susceptibility to these antibiotics (Liu X. et al., 2016). However, its exact mechanism was not determined. Some genes involved in cell division, including *blhA*, *zipA*, *zapA*, and *ftsK*, are associated with intrinsic β-lactam resistance in *A. baumannii* (Knight et al., 2016).

Increased expression of mutagenesis-related genes, such as the SOS response genes, is a well-understood mechanism of *E. coli* and other bacteria to obtain antibiotic resistance (Cirz and Romesberg, 2007). *Acinetobacter baumannii* also seems to have an inducible DNA damage response in which RecA plays a major regulatory role and seems to acquire antibiotic resistances under clinically relevant DNA-damaging conditions (Aranda et al., 2011, 2014; Norton et al., 2013). Furthermore, RecA is involved in the *A. baumannii* pathogenicity (Aranda et al., 2011).

PROSPECTIVE TREATMENT OPTIONS

Although carbapenems are effective antibiotics to treat *A. baumannii* infections (Cisneros and Rodríguez-Baño, 2002; Turner et al., 2003), the rate of carbapenem-resistant *A. baumannii* isolates has been increasing gradually (Mendes et al., 2010; Kuo et al., 2012; Su et al., 2012). Only a few effective antibiotic options are available to treat MDR *A. baumannii* infections (Gordon and Wareham, 2009; Lee J. H. et al., 2015, 2016). To combat MDR or pandrug-resistant (PDR) *A. baumannii*, which are resistant to all available antibiotics, combination therapies, including colistin/imipenem, colistin/meropenem, colistin/rifampicin, colistin/tigecycline, colistin/sulbactam, colistin/teicoplanin, and imipenem/sulbactam, have been extensively studied. Prospective treatment options of *Acinetobacter baumannii* infections are summarized in **Table 3**. We will discuss the most recent published reports.

Carbapenems and β-Lactamase Inhibitors

Carbapenems, including imipenem, meropenem, and doripenem, have generally been considered the agents to treat *A. baumannii* infections, due to their effective activity against this organism and their favorable safety (Doi et al., 2015). However, the decreased susceptibility of *A. baumannii* to carbapenems has forced clinicians and researchers to explore alternative therapeutic approaches (Doi et al., 2015). Because carbapenem-resistant *A. baumannii* strains are often resistant to all other commonly used antibiotics as well, these strains remain susceptible to only limited antibiotics, such as minocycline/tigecycline and polymyxins (colistin and polymyxin B; Lin and Lan, 2014; Doi et al., 2015). Carbapenem therapies combined with a few effective antibiotics was extensively tested and many cases showed a synergistic effect against *A. baumannii* infections (**Table 3**). However, recent increase of tigecycline- or colistin-resistant *A. baumannii* increasingly poses a serious

TABLE 3 | Prospective treatment options of *Acinetobacter baumannii* infections.

Drugs	Type of research	Type of *A. baumannii*	Findings	References
Carbapenem +ampicillin+sulbactam+	*In vivo*	Carbapenem-resistant	Combination therapy with ampicillin-sulbactam and meropenem is effective against skin and soft tissue infection	Hiraki et al., 2013
	In vivo	Multidrug-resistant	The combination of a carbapenem and ampicillin/sulbactam was associated with a better outcome than the combination of a carbapenem and amikacin, or a carbapenem alone	Kuo et al., 2007
Carbapenem +minocycline	*In vitro*	Multidrug-resistant	Minocycline in combination with rifampicin, imipenem, and colistin showed bactericidal synergy in most of the isolates which did not harbor the *tetB* gene, but the combinations were not synergistic in *tetB*-positive isolates	Rodriguez et al., 2015
Carbapenem +tigecycline+colistin	Case report	Multidrug-resistant, colistin-susceptible	A patient with bacteremia had a favorable clinical outcome by a meropenem/colistin/tigecycline combination therapy	Candel et al., 2010
Carbapenem +colistin	*In vitro*/case report	Extensively drug-resistant, colistin-susceptible	Effective; 80% of patients were treated successfully	Ozbek and Senturk, 2010
	In vitro	Multidrug-resistant, colistin-susceptible	Imipenem/colistin showed best synergy effects	Pongpech et al., 2010
	In vitro/case report	Multidrug-resistant, colistin-susceptible	Meropenem/colistin can inhibit bacterial regrowth at 24 h	Lee C. H. et al., 2008
	In vitro	Colistin-susceptible and colistin-resistant	Subinhibitory meropenem/colistin showed synergy against 49 of 52 strains at 24 h	Pankuch et al., 2008
	In vitro	Extensively drug-resistant, colistin-susceptible	Combinations of colistin/rifampicin, colistin/meropenem, colistin/minocycline and minocycline/meropenem are synergistic	Liang et al., 2011
	A retrospective study	Extensively drug-resistant, colistin-susceptible	Colistin/carbapenem and colistin/sulbactam resulted in significantly higher microbiological eradication rates, relatively higher cure and 14-day survival rates, and lower in-hospital mortality compared to colistin monotherapy in patients with bloodstream infections	Batirel et al., 2014
	In vitro	Carbapenem-resistant, colistin-susceptible	Synergistic effects against all 12 isolates	Liu X. et al., 2016
	In vivo	Extensively drug-resistant, colistin-susceptible and colistin-resistant	Colistin/fusidic acid and colistin/rifampicin were synergistic in a murine thigh-infection model; The colistin-meropenem combination was also effective when the colistin MIC is $\leq$32 mg/L.	Fan et al., 2016
	In vitro	Extensively drug-resistant	The daptomycin-colistin combination was the most effective; the colistin/imipenem combination was also effective	Cordoba et al., 2015
Carbapenem +colistin+rifampicin	Case report	Multidrug-resistant, colistin-susceptible	Successful treatment by a meropenem/colistin/rifampicin combination therapy in a case of multifocal infection	Biancofiore et al., 2007
Carbapenem+plazomicin	*In vitro*	Carbapenem-resistant	Synergistic activity	Garcia-Salguero et al., 2015
Imipenem+polymyxin B	*In vitro*	Carbapenem-resistant	Doripenem, meropenem, or imipenem displayed similar pharmacodynamics in combination with polymyxin B	Lenhard et al., 2016b
Meropenem+ polymyxin B	*In vitro*	Multidrug-resistant	Combinations of polymyxin B/meropenem and polymyxin B/meropenem/fosfomycin showed high synergistic activity	Menegucci et al., 2016

(Continued)

TABLE 3 | Continued

Drugs	Type of research	Type of *A. baumannii*	Findings	References
	In vitro/in vivo	Carbapenem-resistant	Intensified meropenem dosing in combination with polymyxin B synergistically killed carbapenem-resistant strains, irrespective of the meropenem MIC	Lenhard et al., 2016a
	In vitro	Carbapenem-resistant	Doripenem, meropenem, or imipenem displayed similar pharmacodynamics in combination with polymyxin B	Lenhard et al., 2016b
Doripenem+tigecycline	*In vitro*	Multidrug-resistant, doripenem-resistant	Synergistic activity	Principe et al., 2013
Doripenem+colistin	*In vitro*	Multidrug-resistant, doripenem-resistant	Synergistic activity	Principe et al., 2013
Doripenem+polymyxin B	*In vitro*	Carbapenem-resistant	Doripenem, meropenem, or imipenem displayed similar pharmacodynamics in combination with polymyxin B	Lenhard et al., 2016b
	In vitro	Polymyxin-heteroresistant	The polymyxin B/doripenem combination resulted in rapid and extensive initial killing within 24 h, which was sustained over 10 days	Rao et al., 2016a
Doripenem+amikacin	*In vitro*	Multidrug-resistant, doripenem-resistant	Synergistic activity	Principe et al., 2013
Ampicillin+sulbactam	*In vitro/in vivo*	Multi-drug resistant	Ampicillin/sulbactam therapy significantly decreased the risk of death in patients with bloodstream infections	Smolyakov et al., 2003
Sulbactam+colistin	A retrospective study	Extensively drug-resistant, colistin-susceptible	Colistin/carbapenem and colistin/sulbactam resulted in significantly higher microbiological eradication rates, relatively higher cure and 14-day survival rates, and lower in-hospital mortality compared to colistin monotherapy in patients with bloodstream infections	Batirel et al., 2014
	A retrospective study	Multidrug-resistant	The colistin/sulbactam combination therapy is promising in patients with ventilator-associated pneumonia	Kalin et al., 2014
Tazobactam+colistin	*In vivo*	Colistin-susceptible	Tazobactam plus colistin showed synergy	Sakoulas et al., 2016
Minocycline+colistin	*In vitro*	Extensively drug-resistant	Combinations of colistin/rifampicin, colistin/meropenem, colistin/minocycline and minocycline/meropenem are synergistic	Liang et al., 2011
	In vitro/in vivo	Minocycline-resistant	Minocycline/colistin synergistically killed minocycline-resistant isolates; minocycline/colistin also significantly improved the survival of mice and reduced the number of bacteria present in the lungs of mice	Yang et al., 2016
	In vitro	Multidrug-resistant	Minocycline in combination with rifampicin, imipenem, and colistin showed bactericidal synergy in most of the isolates which did not harbor the *tetB* gene, but the combinations were not synergistic in *tetB*-positive isolates	Rodriguez et al., 2015
Minocycline+rifampicin	*In vivo*	Multidrug-resistant	Synergistic effect of minocycline/rifampicin and minocycline/amikacin combinations in a mouse lung infection model	He S. et al., 2015
	In vitro	Multidrug-resistant	Minocycline in combination with rifampicin, imipenem, and colistin showed bactericidal synergy in most of the isolates which did not harbor the *tetB* gene, but the combinations were not synergistic in *tetB*-positive isolates	Rodriguez et al., 2015

(Continued)

TABLE 3 | Continued

Drugs	Type of research	Type of *A. baumannii*	Findings	References
Minocycline+amikacin	*In vivo*	Multidrug-resistant	Synergistic effect of minocycline/rifampicin and minocycline/amikacin combinations in a mouse lung infection model	He S. et al., 2015
Tigecycline+colistin	*In vitro*	Carbapenem-resistant, colistin-susceptible	Good synergy	Ozbek and Senturk, 2010; Sheng et al., 2011
	In vitro	Extensively drug-resistant, colistin-susceptible	Good synergy	Dizbay et al., 2010
	In vitro	Tigecycline-non-susceptible	Good synergy	Principe et al., 2009
	In vitro	Carbapenem-resistant, colistin-susceptible and colistin-resistant	Good synergy	Peck et al., 2012
	In vitro/in vivo	Extensively drug-resistant	*In vitro* synergistic activity; no statistically significant differences were found between colistin, tigecycline, and combination treatments in terms of efficacy on bacterial counts in lung tissue of a rat pneumonia model	Mutlu Yilmaz et al., 2012
Tigecycline+polymyxin B	*In vitro*	Carbapenem-resistant, polymyxin-heteroresistant	Combination of polymyxin B-with higher tigecycline concentrations result in sustained bactericidal activity	Rao et al., 2016b
	In vitro	Carbapenem-resistant	Synergistic effects in combination therapy with simulated exposures of polymyxin B and tigecycline at an aggressive dose	Hagihara et al., 2014
Tigecycline+amikacin	*In vitro*	Multidrug-resistant	Synergistic bactericidal activities	Moland et al., 2008
Colistin+rifampicin	*In vitro/in vivo*	Multidrug-resistant, colistin-susceptible	Efficacy *in vitro* and in experimental models of pneumonia and meningitis	Pachon-Ibanez et al., 2010
	Case report	Carbapenem-resistant, colistin-susceptible	Efficacy in 7 of 10 patients with ventilator-associated pneumonia	Song et al., 2008
	Case report	Multidrug-resistant, colistin-susceptible	Efficacy in 22 of 29 critically ill patients with pneumonia and bacteremia	Bassetti et al., 2008
	In vivo	Multidrug-resistant, colistin-susceptible	Synergistic effect in prolonging survival	Pantopoulou et al., 2007
	Clinical trial	Multidrug-resistant, colistin-susceptible	Favorable for all 26 nosocomial infection patients	Motaouakkil et al., 2006
	In vitro	Carbapenem-resistant, colistin-susceptible	Effective for strains highly resistant to imipenem and moderately resistant to rifampicin	Montero et al., 2004
	In vitro	Multidrug-resistant, colistin-susceptible	Synergistic effect against 11 of 13 isolates	Hogg et al., 1998
	In vitro	Extensively drug-resistant	Combinations of colistin/rifampicin, colistin/meropenem, colistin/minocycline and minocycline/meropenem are synergistic	Liang et al., 2011
	In vitro	Multidrug-resistant, colistin-susceptible	Colistin/rifampicin was fully synergistic against 4 of 5 isolates; colistin/meropenem and colistin/azithromycin were synergistic against 3 of 5 isolates; colistin/doxycycline was partially synergistic or additive against 5 isolates	Timurkaynak et al., 2006
	Case report	Carbapenem-resistant, colistin-susceptible	Rifampicin/colistin and ampicillin/sulbactam resulted in microbiological clearance in 9 of 14 critically ill patients	Petrosillo et al., 2005
	In vitro	Carbapenem-resistant, colistin-heteroresistant	Rifampicin/colistin and imipenem/colistin were synergistic against heteroresistant isolates and prevented the development of colistin-resistant strains	Rodriguez et al., 2010
	Case report	Carbapenem-resistant, colistin-susceptible	Synergistic effect in patients with ventilator-associated pneumonia	Aydemir et al., 2013

(Continued)

TABLE 3 | Continued

Drugs	Type of research	Type of *A. baumannii*	Findings	References
	In vivo	Extensively drug-resistant, colistin-susceptible and colistin-resistant	Colistin/fusidic acid and colistin/rifampicin were synergistic in a murine thigh-infection model; The colistin-meropenem combination was also effective when the colistin MIC is $\leq$32 mg/L.	Fan et al., 2016
	In vitro	Colistin-resistant	The most effective combinations were colistin-rifampin and colistin-teicoplanin; both combinations showed synergistic effect against 8 of 9 colistin-resistant strains	Bae et al., 2016
Colistin+teicoplanin	*In vitro/in vivo*	Multidrug-resistant, colistin-susceptible	Synergistic effect of colistin/daptomycin and colistin/teicoplanin in a mouse model	Cirioni et al., 2016
	In vitro	Multidrug-resistant, colistin-susceptible	Significant synergy	Wareham et al., 2011
	In vitro	Colistin-resistant	The most effective combinations were colistin-rifampin and colistin-teicoplanin; both combinations showed synergistic effect against 8 of 9 colistin-resistant strains	Bae et al., 2016
Colistin+daptomycin	*In vitro/in vivo*	Multidrug-resistant, colistin-susceptible	Synergistic effect of colistin/daptomycin and colistin/teicoplanin in a mouse model	Cirioni et al., 2016
	In vitro	Extensively drug-resistant	The daptomycin-colistin combination was the most effective; the colistin/imipenem combination was also effective	Cordoba et al., 2015
Colistin+vancomycin	*In vitro/in vivo*	Multidrug-resistant, colistin-susceptible	Highly active both in vitro and in an animal model of *Galleria mellonella*	Hornsey and Wareham, 2011
Colistin+fosfomycin	*In vitro*	Carbapenem-resistant, colistin-susceptible	Good synergy; no synergy between colistin and sulbactam, colistin and imipenem	Santimaleeworagun et al., 2011
Colistin+fusidic acid	*In vitro*	Carbapenem-resistant, colistin-susceptible and colistin-resistant	*In vitro* synergy between colistin and fusidic acid that is comparable to the synergy between colistin and vancomycin; the synergy with fusidic acid is strain-dependent and applicable to strains for which the colistin MICs are relatively low	Bowler et al., 2016
	In vitro	Carbapenem-resistant, colistin-susceptible and colistin-resistant	Robust synergy between fusidic acid and colistin against multidrug-resistant clinical strains, including some colistin-resistant strains	Phee et al., 2015
	In vivo	Extensively drug-resistant, colistin-susceptible and colistin-resistant	Colistin/fusidic acid and colistin/rifampicin were synergistic in a murine thigh-infection model; The colistin-meropenem combination was also effective when the colistin MIC is $\leq$32 mg/L.	Fan et al., 2016
Colistin+amikacin	Case report	Multidrug-resistant, colistin-susceptible	Successful clinical and microbiological outcomes	Fulnecky et al., 2005
Colistin+trimethoprim-sulfamethoxazole	*In vitro*	Carbapenem-resistant	Colistin/trimethoprim-sulfamethoxazole killed effectively all carbapenem-resistant strains	Nepka et al., 2016
Polymyxin B+netropsin	*In vitro/in vivo*	Colistin-resistant	The survival of infected *Galleria mellonella* was significantly higher when treated with polymyxin B and netropsin in combination than when treated with polymyxin B or netropsin alone	Chung et al., 2016

(Continued)

TABLE 3 | Continued

Drugs	Type of research	Type of *A. baumannii*	Findings	References
Trimethoprim-sulfamethoxazole	*In vitro*	Carbapenem-resistant	Trimethoprim-sulfamethoxazole killed effectively all carbapenem-resistant strains	Nepka et al., 2016
Novobiocin	*In vitro*	Carbapenem-susceptible	Inhibition of frequency of the occurrence of rifampin resistance mutants	Jara et al., 2015
Bacteriophages	*In vitro/in vivo*	Carbapenem-resistant, carbapenem-susceptible	Strong lytic activities and the improvement of survival rates	Jeon et al., 2016; Kusradze et al., 2016
Endolysin (LysABP-01)+colistin	*In vitro*	Multidrug-resistant	Synergistic activity	Thummeepak et al., 2016
Artilysins	*In vitro*	Carbapenem-resistant, carbapenem-susceptible	Artilysins are effective *in vitro* and *in vivo*	Briers et al., 2014; Yang et al., 2015; Defraine et al., 2016; Thandar et al., 2016
Antimicrobial peptides	*In vitro*	Multidrug-resistant	Good antimicrobial activities	Pires et al., 2015; Barksdale et al., 2016
Rose bengal+ carbapenem	*In vitro*	Carbapenem-resistant	Imipenem or meropenem with rose bengal showed synergistic effects	Chiu et al., 2016
β-Aminoketone (MD3)+colistin	*In vitro*	Colistin-susceptible, colistin-resistant	Synergistic effect targeting to strains with specific colistin resistance mechanisms; synergy against both colistin-susceptible strains and colistin-resistant strains with mutations in *pmrB* and phosphoethanolamine modification of lipid A, but not against colistin-resistant strains with loss of lipopolysaccharide	Martinez-Guitian et al., 2016
Bulgecin A+ carbapenem	*In vitro*	Carbapenem-resistant	Synergistic activity	Skalweit and Li, 2016
Farnesol+colistin	*In vitro*	Colistin-resistant	Farnesol increased sensitivity to colistin for colistin-resistant strains	Kostoulias et al., 2015
Oleanolic acid+gentamicin or kanamycin	*In vitro*	Carbapenem-susceptible	Synergistic activity	Shin and Park, 2015
Cyanide 3-chlorophenylhydrazone (CCCP)+colistin	*In vitro*	Colistin-resistant	CCCP reversed colistin resistance and inhibited the regrowth of the resistant subpopulation	Ni et al., 2016
	In vitro	Colistin-resistant	Synergistic activity	Park and Ko, 2015
ABEPI1 or ABEPI2+minocycline	*In vitro*	Carbapenem-susceptible	Synergistic activity	Blanchard et al., 2014
Gallium nitrate	*In vitro/in vivo*	Multidrug-resistant	Good antimicrobial activities; protection of *Galleria mellonella* larvae from lethal *A. baumannii* infection; synergistic activity with colistin	Antunes et al., 2012
Gallium protoporphyrin IX	*In vitro/in vivo*	Multidrug-resistant	Good antimicrobial activities	Arivett et al., 2015
Gallium nitrate+colistin	*In vitro/in vivo*	Multidrug-resistant	Good antimicrobial activities; protection of *Galleria mellonella* larvae from lethal *A. baumannii* infection; synergistic activity with colistin	Antunes et al., 2012

(Continued)

TABLE 3 | Continued

Drugs	Type of research	Type of *A. baumannii*	Findings	References
D-amino acids	*In vitro/in vivo*	Carbapenem-susceptible	Some D-amino acids (D-histidine and D-cysteine) can inhibit bacterial growth, biofilm formation and adherence to eukaryotic cells	Rumbo et al., 2016
Bifidobacterium breve strain Yakult	*In vivo*	Multidrug-resistant	Protection against fatal intestinal infection in a murine infection model	Asahara et al., 2016
Clarithromycin	*In vivo*	Multidrug-resistant	Inhibition of bacterial growth and biofilm formation; immunomodulator	Konstantinidis et al., 2016
Lysophosphatidylcholine +carbapenem	*In vivo*	Multidrug-resistant strain	Lysophosphatidylcholine in combination with colistin, tigecycline, or imipenem markedly enhanced the bacterial clearance from the spleen and lungs and reduced bacteremia and mouse mortality rates	Parra Millan et al., 2016
Lysophosphatidylcholine +tigecycline	*In vivo*	Multidrug-resistant strain	Lysophosphatidylcholine in combination with colistin, tigecycline, or imipenem markedly enhanced the bacterial clearance from the spleen and lungs and reduced bacteremia and mouse mortality rates	Parra Millan et al., 2016
Lysophosphatidylcholine +colistin	*In vivo*	Multidrug-resistant strain	Lysophosphatidylcholine in combination with colistin, tigecycline, or imipenem markedly enhanced the bacterial clearance from the spleen and lungs and reduced bacteremia and mouse mortality rates	Parra Millan et al., 2016

threat to public health worldwide (Peleg et al., 2007; Hornsey et al., 2010; Cai et al., 2012).

Sulbactam is a β-lactamase inhibitor and also has affinity for penicillin-binding proteins of *A. baumannii* (Rafailidis et al., 2007; Doi et al., 2015). Combined therapy of ampicillin with sulbactam is effective for treating bloodstream infections due to MDR *A. baumannii* (Smolyakov et al., 2003). Ampicillin/sulbactam/carbapenem combination therapy is also effective for treating MDR *A. baumannii* bacteremia (Kuo et al., 2007) and skin and soft tissue infection of carbapenem-resistant *A. baumannii* (Hiraki et al., 2013), but not in ventilator-associated pneumonia (Kalin et al., 2014). The population pharmacokinetics and pharmacodynamics of sulbactam were determined in critically ill patients with severe sepsis caused by *A. baumannii* (Jaruratanasirikul et al., 2016) and in patients with impaired renal function (Yokoyama et al., 2015). Another β-lactamase inhibitor tazobactam increases the activity of peptide antibiotics, such as colistin and daptomycin, in a murine model of *A. baumannii* pneumonia (Sakoulas et al., 2016). The authors suggested that β-lactamase inhibitors may exert similar effects in potentiating peptide antibiotics, because of structural similarities between β-lactamase inhibitors and peptide antibiotics (Sakoulas et al., 2016).

Minocycline/Tigecycline

Minocycline, is a broad-spectrum tetracycline antibiotic that has been proposed for treating drug-resistant *A. baumannii* based on its high degree of susceptibility to this drug and its favorable pharmacokinetic profile (Ritchie and Garavaglia-Wilson, 2014). The mean susceptibility rate of *A. baumannii* to minocycline is approximately 80% worldwide (Castanheira et al., 2014). Therefore, minocycline therapy has high treatment success rates and good tolerability (Ritchie and Garavaglia-Wilson, 2014). However, since the introduction of minocycline, approximately 20% of *A. baumannii* isolates are not susceptible to minocycline. The TetB efflux pump is the main determinants of minocycline resistance (Vilacoba et al., 2013). Minocycline therapy combined with colistin is effective for treating minocycline-resistant *A. baumannii* infections (Yang et al., 2016), and minocycline therapy combined with rifampicin, colistin, or imipenem has a synergistic effect in most of isolates without the *tetB* gene, but combined therapies are not synergistic in isolates with the *tetB* gene (Rodriguez et al., 2015).

Tigecycline is the first glycylcycline class antibiotic that exhibits bacteriostatic activity by binding to the 30S ribosomal subunit, and is active against *A. baumannii* infections (Pachon-Ibanez et al., 2004; Anthony et al., 2008; Koomanachai et al., 2009). Tigecycline shows a synergistic effect with some classes of antibiotics, such as amikacin (Moland et al., 2008) and colistin (Mutlu Yilmaz et al., 2012). However, limitations of tigecycline use have emerged with its increasing use. Tigecycline is less effective than imipenem to treat pneumonia in a murine pneumonia model (Pichardo et al., 2010). β-Lactam or carbapenem instead of tigecycline was recommended for *A. baumannii* infections with tigecycline MIC of more than 2 mg/L, due to high mortality from the tigecycline treatment (Curcio and Fernandez, 2008). In a study of 266 patients with MDR

A. baumannii infections, tigecycline-based therapy was not more effective than non-tigecycline-based therapies (Lee Y. T. et al., 2013). Tigecycline resistance associated with overexpression of efflux pumps, such as AdeABC, has been reported in clinical isolates of *A. baumannii* (Peleg et al., 2007; Ruzin et al., 2007; Hornsey et al., 2010, 2011). Multiple MDR *A baumannii* clones resistant to tigecycline have been reported in many medical centers (Navon-Venezia et al., 2007). Therefore, tigecycline can only be used in limited cases for treating *A. baumannii* infections.

Polymyxins (Colistin and Polymyxin B)

Polymyxins are a group of polycationic peptide antibiotics that were discovered more than 60 years ago and exhibit potent efficacy against most Gram-negative bacteria (Liu Q. et al., 2014; Lee C. R. et al., 2016). Among all five polymyxins (A–E), only polymyxin B and E (colistin) with a one amino acid difference are used clinically. Colistin is a key component of combination therapies used to treat MDR *A. baumannii* infections (Cai et al., 2012). The rate of colistin resistance (10.4%) in MDR *A. baumannii* isolates is lower than that of rifampicin (47.8%) or tigecycline (45.5%) resistance (Chang et al., 2012). Similar results were reported in another study (Muthusamy et al., 2016). Therefore, colistin seems to be the only effective antimicrobial agent against MDR *A. baumannii* infections. Many colistin-based combined therapies, including colistin/rifampicin (Liang et al., 2011; Aydemir et al., 2013), colistin/minocycline (Liang et al., 2011), colistin/carbapenem (Liang et al., 2011; Batirel et al., 2014; Liu X. et al., 2016), colistin/sulbactam (Batirel et al., 2014), colistin/tigecycline (Principe et al., 2009; Ozbek and Senturk, 2010; Sheng et al., 2011; Peck et al., 2012), colistin/daptomycin (Cirioni et al., 2016), colistin/fusidic acid (Bowler et al., 2016; Fan et al., 2016), and colistin/teicoplanin (Wareham et al., 2011; Cirioni et al., 2016), are synergistic *in vivo* or *in vitro* against *A. baumannii* infections. Colistin therapy combined with rifampin or fusidic acid seems to be the most effective for treating a MDR *A. baumannii* in a murine thigh-infection model (Fan et al., 2016). Another report comparing colistin/daptomycin, colistin/imipenem, and imipenem/ertapenem showed that the daptomycin-colistin combination was the most effective (Cordoba et al., 2015).

Unfortunately, the emergence of colistin-resistant *A. baumannii* strains has increased worldwide (Cai et al., 2012). The mechanisms of colistin resistance include loss of LPS (Moffatt et al., 2010) and the addition of phosphoethanolamine to LPS by the PmrAB two-component system (Adams et al., 2009). Mutations in *pmrA* and *pmrB* activate *pmrC*, which adds phosphoethanolamine to the hepta-acylated form of lipid A (Beceiro et al., 2011). Interestingly, an investigation of the *in vitro* activities of various antimicrobial combinations against colistin-resistant *A. baumannii* showed that the most effective combinations against colistin-resistant *A. baumannii* are colistin-rifampin and colistin-teicoplanin, indicating that colistin is the most common constituent of antimicrobial combinations even against colistin-resistant *A. baumannii* (Bae et al., 2016). Similarly, minocycline therapy in combination with colistin is effective to treat infections caused by minocycline-resistant *A. baumannii*. Minocycline/colistin therapy significantly improves survival of mice infected with minocycline-resistant *A. baumannii* and reduces the number of bacteria present in the lungs of mice (Yang et al., 2016).

A urinary tract *Enterococcus faecalis* isolate that apparently requires vancomycin to grow was reported in 1994, and this phenomenon is called "antimicrobial agent dependence." Colistin dependence was reported in an *A. baumannii–A. calcoaceticus* complex (Hawley et al., 2007). Partial colistin dependence has been detected in several LPS-deficient strains with mutations in *lpxA*, *lpxC*, and *lpxD* (Garcia-Quintanilla et al., 2015). Many colistin-susceptible *A. baumannii* isolates develop colistin dependence *in vitro* after exposure to colistin (Hong et al., 2016). Although the clinical implication of colistin dependence and its molecular mechanism remain unclear, it is interesting that patients with colistin-dependent *A. baumannii* isolates show a high rate of treatment failure (Hong et al., 2016).

Unlike colistin, polymyxin B is not converted from a prodrug form into an active form; thus, plasma concentrations of polymyxin B more quickly reach target levels (Sandri et al., 2013). In addition, polymyxin B is available for direct parenteral administration (Zavascki et al., 2007). Despite the favorable pharmacokinetics of polymyxin B, dose-related nephrotoxicity limits the concentration of polymyxin B used in combination therapy (Dubrovskaya et al., 2015). Therefore, almost all studies on polymyxins are carried out for colistin. However, because some carbapenems have comparatively safer dose modulation to optimize killing during combination therapy (Cannon et al., 2014), several studies have analyzing the pharmacodynamics of carbapenems in combination with polymyxin B (Lenhard et al., 2016a,b; Rao et al., 2016a). One study showed that intensified meropenem dosing combined with polymyxin B is a good strategy to treat carbapenem-resistant *A. baumannii*, regardless of the meropenem MIC (Lenhard et al., 2016a). Combination therapy with doripenem and polymyxin B also showed similar results. Early aggressive dosing of doripenem combined with polymyxin B is effective for treating heteroresistant *A. baumannii* infections (Rao et al., 2016a). A combined pharmacodynamics analysis of four different carbapenems with polymyxin B showed that doripenem, meropenem, or imipenem display similar pharmacodynamics in combination, and the decision to use carbapenem in combination with polymyxin B is usually based on toxicodynamic profiles (Lenhard et al., 2016b). Polymyxin B also shows good bactericidal activity in combination with high tigecycline concentrations (Hagihara et al., 2014; Rao et al., 2016b). Therefore, polymyxin B combination therapies seem to be one of the most promising options for minimizing the emergence of polymyxin resistance. Increasing the dose intensity of polymyxin B amplifies polymyxin B resistance in *A. baumannii* (Cheah et al., 2016; Tsuji et al., 2016). In conclusion, although polymyxin B displays dose-related nephrotoxicity, it is a potential therapeutic alternative to colistin when use together with intensified doses of other antibiotics. Large-scale screening of *Streptomyces* secondary metabolites was performed to develop a novel combination therapy using minimal concentrations of polymyxin B, and the reliable polymyxin synergist netropsin was identified (Chung et al., 2016). Survival of *G. mellonella*

infected with colistin-resistant clinical *A. baumannii* isolates is significantly higher when treated with polymyxin B combined with netropsin than when treated with polymyxin B or netropsin alone (Chung et al., 2016).

Other Antibiotics

Trimethoprim-sulfamethoxazole is a two antibiotics combination that exerts a synergistic effect by inhibiting successive steps in the folate synthesis pathway against a number of bacteria (Wormser et al., 1982). The *in vitro* killing activity of trimethoprim-sulfamethoxazole against carbapenem-resistant *A. baumannii* was recently studied. Trimethoprim-sulfamethoxazole alone effectively kills all carbapenem-resistant *A. baumannii* strains and trimethoprim-sulfamethoxazole combined with colistin also rapidly kills all strains for up to 24 h (Nepka et al., 2016). These results suggest that trimethoprim-sulfamethoxazole might be an effective therapy for severe carbapenem-resistant *A. baumannii* infections. Plazomicin is a next-generation aminoglycoside synthetically derived from sisomicin that enhances activity against many MDR Gram-negative bacteria (Garcia-Salguero et al., 2015). A synergistic effect was observed with carbapenems along with plazomicin during treatment of *A. baumannii* infections (Garcia-Salguero et al., 2015), indicating the potential utility of plazomicin combined with carbapenems.

The inducible DNA damage response in *A. baumannii* plays an important role in acquiring antibiotic resistance under clinically relevant DNA-damaging conditions (Aranda et al., 2011, 2014; Norton et al., 2013). The aminocoumarin novobiocin is a well-established antimicrobial agent that inhibits the DNA damage response in Gram-positive bacteria by interfering with ATPase activity of DNA gyrase (Schroder et al., 2013). One study showed that novobiocin also inhibits acquisition of antimicrobial resistance in MDR *A. baumannii* through DNA damage-induced mutagenesis (Jara et al., 2015).

Non-antibiotic Therapies: Phage and Others

The worldwide spread of MDR pathogens has renewed interest in the therapy using bacteriophage, which is a virus that infects and lyses bacteria. Various lytic *A. baumannii* bacteriophages, such as *vB_Ab-M-G7* (Kusradze et al., 2016) and Bϕ-C62 (Jeon et al., 2016), have been used to treat infections caused by MDR *A. baumannii*. Bacteriophage-encoded endolysin has also received attention. Endolysin is a lytic enzyme that degrades the cell wall of bacterial hosts and shows promise as a novel class of antibacterials with a unique mode of action (Defraine et al., 2016). For example, endolysin from *A. baumannii* bacteriophage ØABP-01 degrades the crude cell wall of *A. baumannii* strains and elevates antibacterial activity when combined with colistin (Thummeepak et al., 2016). However, most Gram-negative pathogens are generally not susceptible to endolysins, due to their protective outer membrane (Lee et al., 2013a). To overcome this problem, endolysins have recently been engineered with specific outer membrane-destabilizing peptides to obtain the ability to penetrate outer membrane and these engineered endolysins are called "artilysins" (Rodriguez-Rubio et al., 2016). Several engineered artilysins have been developed to combat MDR *A. baumannii* and show highly effective antimicrobial activity against *A. baumannii* (Briers et al., 2014; Yang et al., 2015; Defraine et al., 2016; Thandar et al., 2016). These results suggest that artilysins can be a treatment option for MDR *A. baumannii*. The diversity of the phage population was determined by analysis of viromes, endolysins, and CRISPR spacers (Davison et al., 2016). These results can be used to assist in finding an effective endolysin for combating MDR *A. baumannii*. Various peptides, such as American alligator plasma peptide (Barksdale et al., 2016) and antimicrobial peptide dendrimer G3KL (Pires et al., 2015), have *in vitro* antimicrobial activity against MDR *A. baumannii*. However, the use of antimicrobial enzymes or peptides also has some important problems, such as their short half-life in serum and high production costs compared with those of smaller molecules.

An *in silico* analysis predicted that OXA-58, OXA-23, and OXA-83 are translocated to the periplasm via the Sec system (Liao et al., 2015; Chiu et al., 2016). A SecA inhibitor (rose bengal) inhibits periplasmic translocation of these carbapenem-hydrolyzing class D β-lactamases, indicating that these β-lactamases are selectively released via a Sec-dependent system (Liao et al., 2015; Chiu et al., 2016). Imipenem or meropenem combined with rose bengal shows synergistic effects for carbapenem-resistant *A. baumannii* clinical isolates (Chiu et al., 2016). Similarly, β-aminoketone (MD3), an inhibitor of bacterial type I signal peptidases that cleaves the amino-terminal signal peptides of translocated proteins, shows a synergistic effect when combined with colistin against colistin-resistant *A. baumannii* strains (Martinez-Guitian et al., 2016).

Bulgecin A is a natural product of *P. mesoacidophila* and a lytic transglycosylase inhibitor that works synergistically with β-lactams (Skalweit and Li, 2016). Bulgecin A restores the efficacy of meropenem in suppressing growth of carbapenem-resistant *A. baumannii* strains, suggesting that Bulgecin A may be an adjunctive compound to extend the life of carbapenems against *A. baumannii* infections (Skalweit and Li, 2016). Similarly, farnesol, a natural product of *Candida albicans* for quorum-sensing, disrupts *A. baumannii* cell membrane integrity, alters cell morphology, and increases sensitivity of MDR *A. baumannii* strains to colistin (Kostoulias et al., 2015). Many herbal active compounds have potent antibacterial activities against many bacteria including carbapenem-resistant *A. baumannii* (Lin et al., 2015). For example, oleanolic acid is a triterpenoid compound that widely exists in food, medicinal herbs, and many plants and can potently inhibit various pathogenic bacteria. One study showed that oleanolic acid increases aminoglycoside uptake by changing membrane permeability and energy metabolism in *A. baumannii* (Shin and Park, 2015).

Cyanide 3-chlorophenylhydrazone (CCCP) is an efflux pump inhibitor that decreases the MIC of colistin in colistin-susceptible and colistin-resistant *A. baumannii* strains (Park and Ko, 2015; Ni et al., 2016). Other efflux pump inhibitors, such as ABEPI1 and ABEPI2, inhibit efflux-mediated minocycline tolerance of

A. baumannii. Adding these compounds during growth in human serum leads to the accumulation of minocycline within *A. baumannii* and inhibits efflux potential of the bacterium (Blanchard et al., 2014).

Gallium is a semi-metallic element in group 13 of the periodic table that binds to biological complexes containing Fe^{3+} and disrupts essential redox-driven biological processes (Bernstein, 1998). Gallium has been used as a simple inorganic or organic salt or complexed with organic compounds. Several studies have shown that gallium nitrate or gallium protoporphyrin IX could be a viable therapeutic option for treating MDR *A. baumannii* (Antunes et al., 2012; Arivett et al., 2015). Some D-amino acids, such as D-His and D-Cys, inhibit bacterial growth, biofilm formation, and adherence to eukaryotic cells in *A. baumannii* (Rumbo et al., 2016).

Probiotics are "live microorganisms that confer a health benefit on the host when administered in adequate amounts" (Reid et al., 2005) and assist in protecting against MDR *A. baumannii* infections. For example, the ability of the probiotic *Bifidobacterium breve* to protect against MDR *A. baumannii* infections has been investigated (Asahara et al., 2016). This probiotic markedly potentiates protection against fatal intestinal infections caused by MDR *A. baumannii* (Asahara et al., 2016). With probiotics, immunomodulators, such as lysophosphatidylcholine (Parra Millan et al., 2016) and macrolide antibiotics such as clarithromycin (Konstantinidis et al., 2016), can reduce *A. baumannii* infection severity by stimulating the immune response, when combined with antibiotics such as colistin, tigecycline, or imipenem.

CONCLUSION

The number of studies about *A. baumannii* is increasing dramatically because of its increasing clinical importance. Use of animal models has produced important data regarding virulence factors that contribute to *A. baumannii* pathogenesis. Notably, some studies on metal acquisition and protein secretion systems are interesting. Besides iron acquisition systems such as acinetobactin, the discovery of zinc and manganese acquisition systems in *A. baumannii* broadens our understanding of *A. baumannii* pathogenesis. More extensive studies on various protein secretion systems present in *A. baumannii* are required. About 300 genes required for *in vivo* survival of *A. baumannii* were identified using transposon screening in *G. mellonella* larvae (Gebhardt et al., 2015). Because many of these genes were not known to be associated with *A. baumannii* pathogenesis, more detailed studies are required to determine whether these genes are related to the pathogenesis of *A. baumannii*. In addition, transposon screening in other model animals will provide novel insight into *A. baumannii* pathogenesis. Knowledge of virulence factors responsible for *A. baumannii* pathogenicity will be the cornerstone for developing novel antibiotics. For example, LPS is an important virulence factor and LpxC inhibitor, which inhibits LPS synthesis, completely protects mice from lethal infection (Lin et al., 2012). These results indicate that blocking LPS synthesis is a powerful strategy for discovering novel antibiotics. However, despite recent extensive studies about *A. baumannii* pathogenesis, the toxicity and pathogenicity of *A. baumannii* remain unclear.

Recent interest about *A. baumannii* is mostly due to its seemingly endless capacity to acquire antibiotic resistance. *A. baumannii* has almost all bacterial resistance mechanisms. All class β-lactamases have been detected in *A. baumannii* and the frequency of carbapenem-resistant *A. baumannii* isolates is very high. Furthermore, almost all *A. baumannii* contain aminoglycoside-modifying enzymes and many efflux pumps responsible for resistance to various clinically important antibiotics have been identified in *A. baumannii*. Due to these abilities, available antibiotics to treat *A. baumannii* infections are significantly limited. Colistin is used as the antibiotic treatment of last resort, due to its relatively low resistance rate. However, emergence of colistin-resistant *A. baumannii* strains has increased worldwide with increasing use of colistin. Notably, some more recent studies have proposed that another polymyxin antibiotic, polymyxin B, is a potential therapeutic alternative to colistin (Lenhard et al., 2016a,b; Rao et al., 2016a; Repizo et al., 2015). Polymyxin B has not been a good antibiotic owing to dose-dependent nephrotoxicity, but recent reports show that a novel combination therapy with carbapenems or tigecycline using minimal concentrations of polymyxin B can be a good strategy to treat carbapenem-resistant *A. baumannii* infections. These results indicate the requirement for extensive studies that analyze the pharmacodynamics of polymyxin B in combination therapy.

Various trials to identify a novel alternative to carbapenem or colistin have been performed. Among them, engineered endolysins (artilysins) are particularly interesting, despite evident defects. A lytic enzyme degrading peptidoglycan of bacteria is a promising novel class of antimicrobial agents due to its unique mode of action. Similar to β-lactam antibiotics that are one of the most successful antibiotics, inhibition of peptidoglycan synthesis is a promising target of antimicrobial agents. Because lytic enzymes directly degrade peptidoglycans, but not proteins, the possibility of the emergence of a resistance mechanism is relatively low. In addition, enzymes with relatively high molecular weight are not inhibited by efflux pumps. If the short stability of artilysin in serum and high cost in its production compared with small molecules can be resolved, the improved artilysin can be a good treatment option for carbapenem- or colistin-resistant *A. baumannii* infections. In conclusion, novel, rationally designed strategies and screening-based approaches are required to discover new classes of antibiotics. If we continue to take all efforts at maintaining the effectiveness of antibiotics and developing novel antibiotics, effective control of *A. baumannii* infections can be successful.

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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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