



Multidrug-resistant *Acinetobacter baumannii* as an emerging concern in hospitals

Susan Ibrahim¹ · Nadal Al-Saryi¹ · Israa M. S. Al-Kadmy¹ · Sarah Naji Aziz¹

Received: 22 June 2021 / Accepted: 24 August 2021 / Published online: 30 August 2021
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Abstract

Acinetobacter baumannii has become a major concern for scientific attention due to extensive antimicrobial resistance. This resistance causes an increase in mortality rate because strains resistant to antimicrobial agents are a major challenge for physicians and healthcare workers regarding the eradication of either hospital or community-based infections. These strains with emerging resistance are a serious issue for patients in the intensive care unit (ICU). Antibiotic resistance has increased because of the acquirement of mobile genetic elements such as transposons, plasmids, and integrons and causes the prevalence of multidrug resistance strains (MDR). In addition, an increase in carbapenem resistance, which is used as last line antibiotic treatment to eliminate infections with multidrug-resistant Gram-negative bacteria, is a major concern. Carbapenems resistant *A. baumannii* (CR-Ab) is a worldwide problem. Because these strains are often resistant to all other commonly used antibiotics. Therefore, pathogenic multi-drug resistance *A. baumannii* (MDR-Ab) associated infections become hard to eradicate. Plasmid-mediated resistance causes outbreaks of extensive drug-resistant *A. baumannii* (XDR-Ab). In addition, recent outbreaks relating to livestock and community settings illustrate the existence of large MDR-Ab strain reservoirs within and outside hospital settings. The purpose of this review, proper monitoring, prevention, and treatment are required to control (XDR-Ab) infections. Attachment, the formation of biofilms and the secretion of toxins, and low activation of inflammatory responses are mechanisms used by pathogenic *A. baumannii* strain. This review will discuss some aspects associated with antibiotics resistance in *A. baumannii* as well as cover briefly phage therapy as an alternative therapeutic treatment.

Keywords *Acinetobacter baumannii* · Multidrug resistance · Extensive drug resistance · Bacteriophage therapy

Introduction

Acinetobacter baumannii (*A. baumannii*) is gram-negative, aerobic coccobacilli, non-motile. *A. baumannii* belongs to “ESKAPE” six pathogens with multidrug resistance and virulence. This group is a responsible majority of nosocomial infections and can avoid biocidal effect of antimicrobial agents. *A. baumannii* can be identified by using 16 s ribosomal RNA as well as conserved region of seven housekeeping genes: *gltA*, *gyrB*, *gdhB*, *recA*, *cpn60*, *gpi*, and *rpoD* by using multilocus sequence typing (MLST) [1–3]. Infections of *A. baumannii* have been considered a major concern because it shows extensive resistance to antibiotics and high molarity

death associated with its infections [4–6]. Hospitalized and vulnerable patients are at higher risk of *A. baumannii* infections because it penetrates through skin and airway defects. Furthermore, most infections caused by this bacterium affect patients staying in the intensive care unit (ICU) [7–10]. *A. baumannii* causes many infections including skin and soft tissues, wound infections, bacteremia, endocarditis, urinary tract infections (UTIs), meningitis, and pneumonia [8–10]. The most common nosocomial infection associated with *A. baumannii* is pneumonia mainly in patients admitted to ICU and breathing through the ventilator. The mortality rate from *A. baumannii* caused ventilator-associated pneumonia (VAP) varies from 40 to 70% [11, 12]. Some risk factors related to acute myocardial infarction involve bloodstream infections, immunosuppression, artificial ventilation, preceding antibiotic treatment, and invasive virus colonization [13]. The rate of mortality Infections of the *A. baumannii* bloodstream range from 28 to 43% [14]. Together with other important agents, *A. baumannii* interferes with the development of

✉ Israa M. S. Al-Kadmy
israaalkadmy@gmail.com; sts@uomustansiriyah.edu.iq

¹ Branch of Biotechnology, Department of Biology, College of Science, Mustansiriyah University, POX 10422, Baghdad, Iraq

burn infections, where the existence of Multi-Drug Resistance (MDR) strains and low penetration of many antibiotics are the main problems for chemotherapy [15–18]. The rate of burn infections associated with *A. baumannii* is about 22% and mainly spread among military personnel, with an MDR rate of about 53% [19]. Additionally, *A. baumannii* can cause infections related to the central nervous system (CNS) that can be treated by colistin antibiotics [20]. Strains of *A. baumannii* can survive for long periods in the environment, which assist in the contribution of their dissemination and spread of pathogenic MDR strains. The increase in usages of β -Lactam antibiotics has contributed to the emergence of drug-resistant and rapid development of *A. baumannii* resistant strains. Infections caused by these resistant strains are treated with carbapenems. However, the emergence and spread of resistant *A. baumannii* (CR-Ab) to carbapenems has limited the effectiveness of this drug. Furthermore, the emergence of colistin resistant *A. baumannii* (Col-R-Ab) strains have been recorded and this resistance is occurred due to changes in the structure of the lipo-polysaccharide (LPS). Colistin resistance is showed to occur due to mutations in *lpxA/D/C* and *pmrA/B* genes resulting in regulation downwards and modification of lipid A biosynthesis [21, 23]. Moreover, another resistance mechanism for colistin involves plasmid-carrying three genes (*mcr-1*, *mcr-2* and *mcr-3*) and recent study isolated a novel plasmid carrying *mcr-4.3* gene [22, 23]. Since *mcr-1* first described from *Escherichia coli*, many *mcr*- genes have been identified among *Enterobacteriaceae* strains include: *mcr-1*, *mcr-2*, *mcr-3*, *mcr-4*, *mcr-5*, *mcr-6*, *mcr-7*, *mcr-8* and *mcr-10* but only *mcr1*, *mcr-2*, *mcr3* and *mcr-4* identified in *A. baumannii* [23]. Infections caused by extensively drug-resistant *A. baumannii* (XDR-Ab) and plasmid/chromosomal-mediated Col-R-Ab are the main challenge and need a well-planned control program and proper treatment [24]. The outbreaks are critical to the livestock and community that recently have highlighted the existence of large reservoirs of MDR-Ab strains [25, 26].

The antibiotic resistance in *A. baumannii*

Acinetobacter baumannii strains can develop multiple antibiotic resistance mechanisms, which cause a major health problem in immuno-compromised patients. These strains showed resistance to broad-spectrum β -lactams antibiotics involved carboxy-pencillins, the third generation of cephalosporins, and most recent carbapenems resistance. Furthermore, these strains can produce various aminoglycoside-modifying enzymes and most of these enzymes are related to fluoroquinolones resistance [10, 27]. Moreover, colistin-resistant isolates have been emerged, which restrict the choices of chemotherapy treatment for these isolates.

[21, 22]. Pan- β -lactam-resistant *baumannii* spreads widely and this gives pieces of evidence to the high ability of these bacteria to acquire different mechanisms of resistance as below:

Oxacillinases (class D β -lactamases)

Oxacillinases are specific B-lactamases, which are classified to many groups depending on structural and biochemical properties [7, 28]. The OXA-type group is primarily indicated in *Acinetobacter* spp. and *Pseudomonas aeruginosa*. These enzymes can hydrolyze methicillin, amoxicillin, and some antibiotics belong to cephalosporins. Furthermore, the hydrolysis activity of OXA-type group is more effective against oxacillin than benzyl penicillin. Generally, OXA-type enzymes are not considered ESBLs because they cannot hydrolyze the board spectrum cephalosporin, although there are some exceptions, such as OXA-20 in *P. aeruginosa* and OXA-37 in *A. baumannii* [29].

Around 350 OXA enzymes (see <https://www.lahey.org/studies/webt.asp>) have been identified depending on the surface protein recently. The class D of oxacillinases are both chromosomally and plasmid-mediated encoded enzymes [30]. The first discovery of *bla*_{OXA-5} was in *P. aeruginosa*, while *bla*_{OXA-23-like}, *bla*_{OXA-51-like}, and *bla*_{OXA-134} enzymes are isolated from *Acinetobacter radioresistance*, *A. baumannii*, and *A. lwoffii* respectively [5, 31].

*bla*_{OXA-23-like} oxacillinases

These enzymes were first carbapenem-resistant OXA-type β -lactamases identified among *A. baumannii* strains, in Scotland and renamed later as *bla*_{OXA-23-like} enzymes based on their sequence. The First description of the gene encoding these enzymes was in 1985 within a plasmid isolated from *A. baumannii* strain, which showed MIC level = 16 mg/L for Imipenem [32]. *bla*_{OXA-27} enzyme was isolated in Singapore, which shared 99% homology to a *bla*_{OXA-23}. Moreover, another type of these enzyme was identified in China known as *bla*_{OXA-49}, which is isolated from carbapenem resistant *Acinetobacter* spp., [33].

Later, the *bla*_{OXA-23} was detected from *A. baumannii* throughout the world such as Brazil, China, London, and Singapore and these enzymes are encoded by chromosomal genes or located on plasmids [34, 35]. In vivo, *bla*_{OXA-23-like} enzyme confers the antibiotics resistance mechanism to ticarcilin, meropenem, amoxicillin, and imipenem. In a study, a new strain acquired a plasmid containing the *bla*_{OXA-23-like} gene showed a MIC ranged from moderate to high levels, which equals to 16 to 32 mg/L against carbapenems and led to overexpression of Ade-ABC efflux pump, which refers to involvement other genetic factors associated related to carbapenam resistance of the *bla*_{OXA-23-like} gene [36].

Several *bla*_{OXA-23-like} enzymes were discovered including *bla*_{OXA-27}, *bla*_{OXA-102}, *bla*_{OXA-103}, *bla*_{OXA-105} and *bla*_{OXA-133}. In addition, searching BLAST tool in NCBI web shows several other related enzymes including *bla*_{OXA-146} (FJ194494), *bla*_{OXA-168} (HM488990), *bla*_{OXA-169} (HM488991), *bla*_{OXA-170} (HM488992), *bla*_{OXA-171} (HM488992) and *bla*_{OXA-225} (JN638887) genes. In addition, the *bla*_{OXA-33} was identified in *A. radioresistance* [37].

The *bla*_{OXA-134} enzyme has a 63 percent amino acid identity with the *bla*_{OXA-23} enzyme and it inherently presents in *A. lwoffii*. A gene like *bla*_{OXA-23} has also been detected with the chromosomal DNA in *Proteus mirabilis*. The *bla*_{OXA-73} was discovered in *Klebsiella pneumoniae* [38]. Isolation CR-Ab with *bla*_{OXA-23-like} gene has been found in South American and Southeast Asia [39, 40]. In a study conducted in Columbia, *bla*_{OXA-23-like} was found in 65/66 isolates of CR-Ab strains and showed the presence of a common clone in two hospitals in the city [39]. In China, it was noticed an increase in carbapenem resistance rate within training hospitals from 5 and 50% in the ICU over a 6-year period. 97.7% of these ratios belonged to CR-Ab contains the *bla*_{OXA-23-like}. Furthermore, a research in China identified major carriers for spread of the *bla*_{OXA-23-like} among *A. baumannii* include; Tn2008 transposon, which *bla*_{OXA-23-like} flanked by upstream insertion sequence *ISAbal* [41].

*bla*_{OXA-40-like} β-lactamases

The *bla*_{OXA-40-like} β-lactamases were the second group of OXA-type β-lactamases to be identified in *A. baumannii* isolates from the outbreak in Spain. These enzymes can hydrolyze penicillins but show weak hydrolytic properties against cephalosporins and carbapenems, such as imipenem and ceftazidime. These enzymes are resistant to inhibitors such as tazobactam, sulbactam clavulanic acid and NaCl. *bla*_{OXA-40-like} enzyme (initially called *bla*_{OXA-24-like}) was isolated from *A. baumannii* strains, which showed high MIC levels of carbapenem in a study conducted in Spain and amino acids similarity between *bla*_{OXA-40-like} and two others enzymes *bla*_{OXA-51/69} and *bla*_{OXA-23-like} enzymes was 63% and 60% respectively. Moreover, the group includes *bla*_{OXA-24}, *bla*_{OXA-25}, *bla*_{OXA-26}, *bla*_{OXA-72}, *bla*_{OXA-139} and *bla*_{OXA-160} genes. The *bla*_{OXA-25} and *bla*_{OXA-26} genes were isolated from Spain and Belgium. Another study from Thailand, it originally identified *bla*_{OXA-72} gene from CR-Ab strains [37, 42–45].

Although the poor hydrolyze of the enzyme against carbapenem, The MIC > 128 mg/L for imipenem was shown in isolates expressed *bla*_{OXA-40-like} [46]. After introducing *bla*_{OXA-40-like} gene to a sensitive *A. baumannii* strains, a low to moderate resistance was reported to imipenem. This resistance mostly belongs to the over-expression of the

efflux pump from the *AdeABC*, suggesting involvement of other high-standard phenotype mechanisms [47, 48].

*bla*_{OXA-51-like} β-lactamases

*bla*_{OXA-51} β-lactamase is reported from carbapenem resistance *A. baumannii* strains worldwide and was initially identified in *A. baumannii* isolates from Argentina isolated in 1996. Since then, many of these enzymes have been identified. *bla*_{OXA-51-like} β-lactamases share amino acid similarity about 56% with *bla*_{OXA-23-like} enzymes, 61–62% homolog with *bla*_{OXA-40-like} enzymes, while they share less than 50% with *bla*_{OXA-58-like} enzymes [49, 50].

The activity of these enzymes can be blocked effectively with clavulanic acid, tazobactam or NaCl [51]. Currently, ninety-five enzymes are identified belong to the *bla*_{OXA-51-like} enzymes. The *bla*_{OXA-51} genes are typically non-transferable and encoded by chromosomal DNA (34). Nevertheless, the 2009 research showed that *bla*_{OXA-51-like} gene could be transferred to other organisms by plasmid. The transformation of a *bla*_{OXA-51-like} and *bla*_{OXA-87}, pseudo-gene to DH5α *E. coli* showed the probability of transmission between plasmids and chromosomal DNA. The *bla*_{OXA-51-like} enzymes were first identified in other *Acinetobacter* species (*A. nosocomialis*) from Taiwan, which are an intrinsic carbapenemase genes in *A. baumannii*. Thus, this suggests the spread of these resistance genes among *baumannii-calcoaceticus* complex [52] and it was found that the *bla*_{OXA-51} and *bla*_{OXA-69} GC content of these genes were comparable to GC content of the *A. baumannii*, which suggested they are native to *Acinetobacter* spp. [53].

A kinetic study showed a low enzymatic activity of both *bla*_{OXA-51} and *bla*_{OXA-69} against coloxacillin and oxacillin, which is shown among carbapenem-hydrolyzing oxacillinases. This will challenge any attempts to study the hydrolysis activity of them. It has been proposed that *bla*_{OXA-51-like} expression level is weak but when insertion sequence (IS) elements such as *ISAbal* are located upstream of *bla*_{OXA} genes, high level of resistance occurs. The insertion sequence elements provide a stronger promoter for these genes [54].

A large group of enzymes around the *bla*_{OXA-66-like} enzymes are recorded in *A. baumannii* isolates, which involved the common European clone 2. However, enzymes belong to clone 1 in Europe are detected around the *bla*_{OXA-69} enzyme and the *bla*_{OXA-71} enzyme is related to clone 3 [55]. The most common enzymes in South America and Asia are typically those *bla*_{OXA-66-like} clusters, while in Eastern Europe there is a common presence of cluster enzymes of *bla*_{OXA-69}. The European clone 3-associated *bla*_{OXA-71} was widely detected in isolates from the Iberian Peninsula [55].

***bla*_{OXA-58-like} β -lactamase**

The gene related to *bla*_{OXA-58-like} enzymes was initially identified in carbapenem-resistant *A. baumannii* strain in Toulouse, France. The hydrolysis mechanism of these enzymes was against penicillin, imipenem, and oxacillin, while cannot hydrolysis expanded-spectrum cephalosporins. The gene of *bla*_{OXA-58-like} was found on a non-transferable, 30 k plasmid. When this plasmid transformed to stranded strain of *A. baumannii* showed reduced carbapenem sensitivity [56]. The gene *bla*_{OXA-58-like} has only been found in *Acinetobacter* spp. *bla*_{OXA-58-like} enzyme showed identical characteristics to other types of *bla*_{OXA} enzymes. However, hydrolysis of imipenem occurs twice as that of the *bla*_{OXA-40-like} enzyme. The activity of the enzyme against penicillin or imipenem is poor, meropenem very weak, and cerebrospinal and ceftiofams have little activity but ceftazidime or celastrol is not active [54]. Furthermore, insertion strong promoters upstream of these genes cause an increase in synergistic expression leading to high level-carbapenem resistance [54].

The *bla*_{OXA-58-like} enzymes are a weakly related to other oxacillinases and showed less than 50% amino acid similarity. For some *Acinetobacter* species, *bla*_{OXA-58-like} pseudoenzymes are found to be carried by plasmids; however, the chromosomal location is also described [57]. *bla*_{OXA-58-like} isolates have been recorded from Europe, South America, North America, Anatolia, Asia and Australia [58, 59]. Besides its dependence on IS-Elements, the degree of expression of *bla*_{OXA-58-like} genes can be related to the copy number of the gene as shown in an Italian clone [60] and the prevalence of carbapenem resistance was reported in *A. genospecies*, *A. pittii* and *A. nosocomialis* isolates [61, 62]. In *Acinetobacter* species, other types of the *bla*_{OXA-58} are *bla*_{OXA-96}, *bla*_{OXA-97} and *bla*_{OXA-164} genes [37, 63].

Biocides resistance

Resistance to antimicrobial and biocides, including antiseptic and disinfectant substances may cause the spread of multidrug resistant strains, which lead to untreatable outbreak incidences in hospitals. The relation between the increase in antimicrobial resistance and disinfectants reducing activity has been reported in some bacteria such as *Proteus*, *P. aeruginosa*, methicillin-resistant *Staphylococcus aureus* (MRSA), *Providencia* species, vancomycin-resistant *Enterococci* and *Serratia marcescens*. The same correlation was suggested for *A. baumannii* as in vitro study showed that antiseptics and disinfectants (70% ethyl alcohol, chlorhexidine, povidone-iodine, didecyltrimethylammonium chloride) are used effectively and efficiently among 81 strains against their prevalence. However, using diluted Povidone-iodine (1/3) increased the resistance of bacteria by 18.5% (64). Although antiseptic resistance has not been shown to

play an important role in the spread of MDR-Ab outbreaks, un-followed recommended protocols can result in lower concentrations or short-term disinfectant exposure may lead to cross-contamination in hospital settings [64].

Virulence and pathogenicity of *A. baumannii*

Despite extensive research supporting the *A. baumannii* as an emerging pathogen, little is still known about eminent factors affecting the epidemic, the virulence and pathogenicity of this bacterium. Nevertheless, there are remarkable pathways for attachment of *A. baumannii* strains to epithelial cells, superficial anti-phagocytic components and production enzymes, and toxins [65].

A-genetic comparative research between non-pathogenic *A. baylyi* and *A. baumannii* has identified the potential genes for the virulence in *A. baumannii*. These genes play an important role in quorum sensing, regulation of iron and pilli synthesis. A study has shown that type VI of secretion systems [T6SS] stimulates the immune response in eukaryotic cells, which suggested that it might contribute in the interactions between bacteria and host cells in *Acinetobacter* spp. [65].

Colonization of *A. baumannii* on human skin and inert surfaces is responsible for infection, disease propagation and persistence of bacteria in the environment. *A. baumannii* attachment to human bronchial epithelial cells has been demonstrated to be more effective than IC1 strains, but there has been no substantial association between infection-related strains and cell proportion [66].

A. baumannii can invade eukaryotic cells and cause apoptosis following attachment and colonization. An important virulence factor in *A. baumannii* is outer membrane protein (OmpA), which enhances cell death via mitochondrial and nuclear targeting [67]. In addition, pure OMP38 induces apoptosis of human monocytes and epithelial cells. Apoptosis of epithelial cells may reduce the mucosal surface and may provide a pathway for deep tissue infection by bacteria or in their products [68].

Furthermore, the major virulence factors for Gram-Negative bacteria are capsular polysaccharide (K), glycoproteins and lipopolysaccharide contained O antigen (LpS). Surface polysaccharides have an essential role in bacterial motility and serve as antibacterial barriers. In *A. baumannii*, the antigen K1 was indicated as required for growth in human ascites fluid, resistance to human serum killing and the mouse model of soft tissue infection [65, 69].

A study of the genome of *A. baumannii* showed that it lacks ligase-encoding gene *waal* and this gene is needed to add O-antigen to the glucose group of LPS, composition of the external leaflet of outer membrane Gram-Negative bacteria [67]. A *waal*-like gene found in the genomes of *A. baumannii* was suggested to be appreciated in protein

glycosylation but not O-antigen linkage [65]. However, there is a second *waaaL* gene in the *A. baumannii* was found in some strains, which thought to be required in O-antigen linkage as it does not contain a domain for protein glycosylation [69, 70]. In contrast to previous study, recent comparative genomics of *A. baumannii* in Brazil has suggested no *waal* was identified in the strains using BlastP and Pfam for gene identification, and Artemis compare gene arrangement [71].

In 2010, Russo et al. identified two predicted genes involved in capsule polymerization and assembly using random transposon (Tn) mutants derived from the *A. baumannii* strain AB307-0294. These two genes consist of *ptks* (tyrosine kinase encoding) required to polymerize the capsule and *epsA* (encoding polysaccharide external membrane protein (EpsA)). *Acinetobacter baumannii* AB307-0294 K1 capsule was associated with human ascetic fluid development, serum and complementary system, as well as mouse infection. Although the absence of *ptk* or *epsA* contributes to in vivo strains killing, both enzymes are possible candidates for the drug targets [69, 77, 78]. The variations between *A. baumannii* strains in the mitogenic activity of LPS are primarily due to O antigens and lipid A differences. LPS of *A. baumannii* leads to death in mice, pyrogenic effects in rabbits and triggers complement neutralization. Another factor increases the severity of the diseases during sepsis of *A. baumannii* is Endotoxin secretion. A study showed that *Acinetobacter baumannii* and *Acinetobacter* genomespecies nine endotoxins can induce inflammatory signals within human monocytes and Toll-like receptors (TLR2 and TLR4) dependent responses. Despite the ability of *Acinetobacter* spp to attached to human cells, the stimulation of inflammatory response of these bacteria is weak, which assists in the spread of bacteria and overcome the immune system defence, as defined previously for *Haemophilus influenzae* [72–75].

***Acinetobacter baumannii* quorum sensing**

Quorum sensing (QS) is a stimulant mechanism of the auto-inducer-receptor. actually, forms cell-to-cell bacterial contact through the production of a stimulating agent. Different forms of QS systems can be employed with Gram-Negative bacteria:

- (I) Acyl homoserine lactones (AHLs), called AI-1 (AutoInducer-1), are generated mainly in bacteria. Every molecule consists of a lactone ring and an aliphatic chain with different lengths and characterization such as *Pseudomonas* spp., *Acinetobacter* spp., *Burkholderia* spp.
- (II) Furanosyl-Borate Diester, Autoinducer-2 (AI-2), presents in both Gram-Negative and Gram-Positive

bacteria for example *Vibrio* spp. and *Pectobacterium* spp.

- (III) Epinephrine and norepinephrine, known as Auto-inducer-3 (AI-3) are commonly characterized in human opportunistic pathogens such as *Enterobacter* spp., *Escherichia* spp., *Klebsiella* spp. and *Salmonella* spp. In addition, other molecules have also been found such as (IV) fatty acids DSF in *Xanthomonas* spp., (V) Palmitic acid methyl ester (PAME) in *Ralstonia solanacearum*, (VI) α -Hydroxyketone in *Legionella* spp. and *Vibrio* spp. or (VII) 2-heptyl-3-hydroxy-4-quinolone (PQS) *Pseudomonas aeruginosa* [76–85].

Most of *A. baumannii* strains generate more than one molecule of AHL. The communications between cells aim to coincide with the expression of target genes and organize the biological functions of the population. This mechanism has an important role related to virulence factors expression, plasmid transformation, motility, antimicrobial compounds secretion, bacterial attachment, formation of biofilm and sporulation. None of the AHL signals may be unique to a particular *Acinetobacter* species. Furthermore, QS signals were not homogeneously distributed, making it difficult to differentiate between virulent and non-virulent strains. The *abaI* and *abaR* genes were not acquired horizontally from *Halothiobacillus neapolitanus* into strains of *A. baumannii* [82–87]. Combating QS is called quorum quenching (QQ), which can occur in different methods, like, LuxR homolog proteins inhibition, inhibition of the enzyme activity, destruction of QS signals, the destruction of AHL efflux protein and QS antagonists [78, 80, 81, 85, 88].

***A. baumannii* and host interactions**

Interactions between pathogens and host may be controlled by different factors, such as virulence, bacterial burden, and host factors beside it plays a significant role in development of infections causing serious effects on the host. It has found that cluster of 28 genes are unique to *A. baumannii* in comparison to *Acinetobacter* 17978 strain, non-pathogenic *A. baylyi* species. 16 genes of these clusters play a major role in the virulence [89]. 6 genes are present in *csu* polycistronic operon *csuA/B*, *csuA*, *csuB*, *csuC*, *csuD*, and *csuE* and Some of them are homologs to encoding chaperone-related genes, which participate in the accumulation of germ cell in Gram-Negative bacteria [87, 88]. It is probably; formation of biofilm plays an important role in the interactions of *A. baumannii* with its host besides biofilm contribution to infections associated with medical-devices [65, 90].

The biofilm formation in *A. baumannii* has been demonstrated that it is phenotypically related to the production exopolysaccharide and pilus structures as host defence-protected

bacteria. Within structures similar to the Pilli, the bone marrow of human bronchial cells and erythrocytes is also shown. Through these surface structures, *A. baumannii* strains attach to the host cells [78, 84, 91, 92]. The role of innate immunity against *A. baumannii* infections has been addressed via Toll-like receptor (TLR) signaling. In mouse model with pneumonia, mice without TLR4 showed elevated in bacteria number resulting in bacteremia, cytokine / chemokine disorders and slow lung inflammation in comparison group in the study. The LPS play a major role in triggering immune response and this result was further showed by decreased effects of *A. baumannii* in mice with a CD14 deficiency, which is an effective LPS receptor for TLR4 attachment [93].

These results confirmed by studies on mouse and human cells models demonstrating that TLR2 played important role in the signaling pathway and *A. baumannii* LPS (endotoxin) induction through stimulation of inflammatory cytokines, TNF- α (tumor necrosis factor alpha), interleucine 8 close to stimulating effects induced by *Escherichia coli* LPS [74]. These studies suggested that a strong inflammatory response during infection with the *A. baumannii* could be related to endotoxin. Antibodies, which bind to iron suppressor OMPs and the O antigen in the LPS also produce a humoral immune response to *A. baumannii* infection. Monoclonal antibodies derived from the mouse against *A. baumannii* OMPs in CDM-Fe medium showed opsonization, antimicrobial activity and iron uptake inhibition [94].

Biofilm formation

Biofilm formation on the surfaces of medical devices is considered a major source of infections in hospitals around the world. Agents like bacterial hydrophobicity are mediated the non-specific attachment [95, 96]. The interaction with the host cells, mostly through specific receptors is the initial stage in the colonization or infection cycle. Bacteria are now developing micro-colonies contributing to the creation of a cumulative structure network known as biofilm. Biofilms are formed on living and no living surfaces and their matrix is composed of carbohydrates, nucleic acids, proteins and other macromolecules. Biofilm protects bacteria from the damage of the environment as host responses, antibiotics, cleansers, and disinfectants. Therefore, biofilms contribute to prolonged and more severe bacterial effects. In addition, different factors such as bacterial structures, nutrients, surface components, QS, and bacterial hidden molecules affect biofilms [97]. A variety of regulatory networks are less known including a two-component regulatory system (TCS) and environmental reactive transcription regulatory systems, which regulate the biofilm genes expression. The formation of biofilm in *A. baumannii* depends on biosynthesis and assembly of pili, which involved in surfaces attachment and

coded via the *csuA/BABCDE* chaperon-usher system [95]. The result showed that inactivation of the *csuC* and *csuE* ORFs that locate within the *csuA/BABCDE* operon leading to non-piliated cells and abolishes cell attachment. This suggested that the *CsuA/BABCDE* system is involved in early stage of biofilm formation [95]. Another TCS regulates the expression of *csuA/BABCDE* operon involved a sensor kinase encoded by the *bfmS* gene and a response regulator encoded by the *bfmR* [97]. The *bfmR* suppression causes the lack of the *csu* operon expression level, which affects the expression of Pilli and the formation of biofilm. Furthermore, attachment between the host cell receptors and Pilli triggers the induction of inflammatory mediators such as chemokines and cytokines. A *CsuA/BABCDE* independent short pilus is produced, which assists in bacterial attachment to biotic surfaces such as human respiratory cells [87]. Moreover, another TCS known as *LuxI /LuxR QS* is involved in this process. Biofilm-producing *A. baumannii* strains showed higher survival rate than strains do not form biofilm [98]. *A. baumannii* strains showed a survival rate of about 10 to 13 days on undisturbed dry surfaces in the ICU settings in comparison to other Gram-Negative bacteria. Furthermore, these strains are able to survive on the hospital bed rails and in wet environments [99]. Polysaccharide layer has been observed outside the surface of biofilm-producing strains but not among those non-biofilm producers using electron microscopy. In addition, LPS layer is used by bacteria to protect from alterations in environmental humidity and assists in antibiotics resistance [100]. It was observed where a mutation occurs in the *abal* gene that encodes the auto-inducer synthase gene, which leads to reduce the ability to form biofilm [101].

Iron regulation

The iron deficiency increases during *A. baumannii* invasion process but these bacteria can acquire ferric ions under iron-limited conditions via siderophore [102]. Therefore, multiple siderophores expression is common between pathogenic bacteria and associated with their virulence. Siderophores synthesised by *A. baumannii* are relatively low-molecular-weight agents and able to convert polymeric ferric oxy-hydroxides to soluble iron chelates under iron stress condition. [6, 19]. Ten distinct siderophores are elaborated by *A. baumannii* and encoded by three different loci. The major siderophore for *A. baumannii* is acinetobactin, which is shown as the only siderophore associated with the virulence [103]. This is a recent study 2020 (105).

Bacteriophage as therapeutic for MDR *A. baumannii*

An increase in resistance to available antibiotics causes an urgent alarm to investigate alternative therapeutic options.

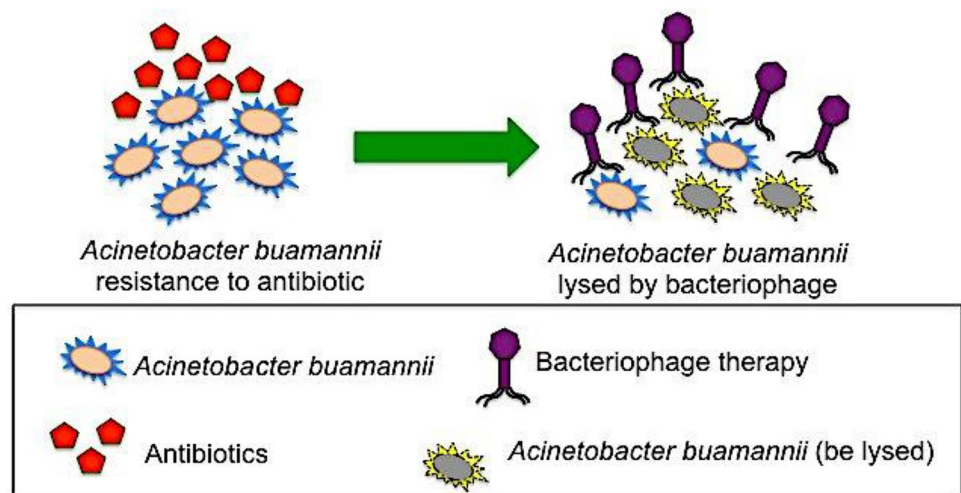
The significant clinical interest has focused on bacteriophage therapy. Bacteriophages are natural antibiotics that are able to work against Gram-Positive and Gram-Negative bacteria [104, 105]. Phages can be isolated rapidly, because of their ubiquitous nature and they are abundant in every ecological niche, which reduces their development costs compared to antibiotics. Bacteriophages are viruses restricted to bacteria and found in different environments and they can be isolated from water, soil, sewage, hospitals, hot springs, and faecal material, and also humans, soil, and animals' gastrointestinal tracts [106]. It seems that the phage therapy with no detectable side effects and high specificity to pathogen they infect on species or strain level, which reduce the effect on microflora inside human gut compared to antibiotics [107]. Another advantage of phages can spread fast in all the body and organs such as the brain, prostate gland, and bones, which usually the antibiotics do not reach. In addition, the presence of phage hosts assists in successful treatment of infections caused by these hosts. Furthermore, no cross-resistance can be developed against phage like antibiotics, which bacteria can develop resistance mechanism easily. Thus, bacteriophage therapy can provide an effective treatment against MDR, XDR, and PDR bacteria [108–110]. Using phage therapy has been studied to treat bacterial infections for about 100 years. These phages attack and kill their bacterial hosts by lysis without attacking the human cells. In addition, bacteriophages are specific to bacteria and bind to a specific receptor on bacterial cell wall followed by injection of their genetic material to lysis the cells [111]. Despite the advantages of phage therapy mentioned above and many clinical trials to use it, some drawbacks are mentioned in the literature, we enumerate a few of them: specificity of phage can be considered as a disadvantage as before any treatment need to specify the etiological microorganism causing infection. Another problem is the ability of these phages to transfer DNA between bacteria, which can transfer pathogenicity

determinants and virulence factors from one bacterium to another. This can lead to develop a more resistant microorganism or even a new one. In addition, bacteriophages are viruses and can be seen as opportunistic pathogens by the patient immune system, which leads to eliminating them especially in case of prolonged or repeated applications. Another concern is the ability of the bacterial host to develop resistance from mutation and selection or by temperate phage acquisition reviewed by [109].

Many recent attempts have been started to address bacteriophage therapy against MDR *A. baumannii* Fig. 1. A recent report has shown that an older patient with MDR *A. baumannii* was treated with bacteriophages. These patients suffered assault, subdural hematoma, and traumatic brain injury and led to complicated consequences. *A. baumannii* isolated from this patient was resistant to all antibiotics and the antibiotics combination treatment was without improvement. The patient was in the ICU during administration of the phage and this statue was frequently monitored for neurologic or hemodynamic changes. The first dose was without any complications expected after two hours he suffered hypotensive but did not require vasopressors. Even infections were started to heal, the patient was unresponsive [112]. Therefore, they did not have the complete set of data to monitor phage efficacy beyond the patient's clinical status and they cannot conclude the lack or failure of phage therapy in this patient, which requires other trails in this field.

Another study has isolated a novel *A. baumannii* phage Bφ-R2096 from sewage water to lysis carbapenem-resistant *A. baumannii* isolated from a patient in the university hospital in South Korea. They used animal model *Galleria mellonella* larvae and a mouse model of acute pneumonia to study the efficiency of *A. baumannii* phage Bφ-R2096. They showed that the phage was effective *in vitro* and showed a significant improvement in survival rates of *Galleria*

Fig. 1 Illustrate phage therapy against *Acinetobacter baumannii*



mellonella larvae without any toxicity. However, survival rates were higher in the mouse infection model [113].

Very recent study in vitro, Altamirano et al. showed that phage therapy was effective in carbapenem-resistant *A. baumannii*. The isolated mutants caused the strains to be resistant to the phage and they found these mutants in K locus, which is involved in capsular polysaccharide. This polysaccharide was hypothesized that phages used them as receptors. Thus, loss or any modification of these receptors causes a lack of phage adsorption and subsequent phage-resistance in *A. baumannii*. Furthermore, they found that these mutants showed a decrease in biofilm formation antibiotic resistance. This study suggested that these bacteriophages cannot be used for their lytic activity only but the combination between understanding of phage receptors and bacterial resistance mechanism provides the best knowledge of the potential synergy effect of both phage and antimicrobial agents [91, 114]. Therefore, future attention should be focused on bacteriophage therapy especially for *A. baumannii* with MDR resistance, which causes many epidemics in hospitals. In Iraq, these bacteria showed resistance to all antibiotics in use and cause an endemic inside Baghdad hospitals (unpublished data). Thus, any better available treatment options against MDR bacteria will save the lives of many patients attending hospitals worldwide.

Conclusion

Acinetobacter baumannii has brought attention as a public health problem and its infections prevalence and outbreaks due to extensive antibiotic resistance. Few known antibiotics are effective to treat infections caused by these bacteria. The high mortality rate caused by multi drug resistance bacteria is a serious problem challenge physician and healthcare workers to eliminate these infections either originated from the hospitals or the community settings. Most of infections caused by these emerging strains are among patients in ICU who have developed resistance to antimicrobials over the past three decades including resistance to carbapenems, which are used as the last-line antibiotics for the treatment of infections caused by Gram-Negative bacteria. Genetic elements such as transposons, plasmids or integrons, and carrying resistant cassettes have a major role in acquisition of antimicrobial resistance and dissemination of MDR strains. An increase in the prevalence of carbapenem-resistant *A. baumannii* worldwide has become a critical problem and the development of pathogenic MDR-Ab will make infections caused by these bacteria hard to be treated and Col-R Ab has been recorded. Attachment, biofilm formation, secretion of toxins beside weak induction of inflammatory responses are mechanisms associated with *A. baumannii* pathogenic strains. Therefore, to overcome the problem associated with

these infections, investigation of the pathogenesis and mechanisms of antibiotic resistance of *A. baumannii* is important. Furthermore, new strategies of treatments like phage therapy are required to overcome infections caused by these resistant bacteria.

Acknowledgements The authors would like to thank Mustansiriyah University (<https://uomustansiriyah.edu.iq/>)/Baghdad, Iraq for its support to complete this work.

Author contributions All authors contributed equally in writing—original draft preparation. All authors have read and agreed to the published version of the manuscript.

Funding This research received no external funding.

Declarations

Conflicts of interest The authors declare no conflict of interest.

Ethical approval No need approval.

Research involving human participants No human sample was used.

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