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ANTIBIOTIC RESISTANCE OF *ACINETOBACTER BAUMANNII*: AN URGENT NEED FOR NEW THERAPY AND INFECTION CONTROL

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Acinetobacter baumannii (A. baumannii) infections became an emerging health concern in hospitals across the globe and are often related to nosocomial infections with poorer clinical outcomes in patients with prolonged hospital stay. Management of infections involves prompt identification of the infecting strain, isolating the source of infection, and proper choice of antibiotic regimen. However, resistance to first-line antimicrobial drugs, combined with a scarcity of equally effective alternatives, complicates the treatment of multidrug-resistant (MDR) A. baumannii. Presently, MDR A. baumannii may be a serious health concern in hospitals and long-term care facilities accounting for up to 20% of infections in intensive care units, and 7% of infections in patients who are physically connected to medical equipments. Immediate and sustained prevention efforts are needed to control the speed of incidence. Antibiotic use is largely under-regulated in Egypt leading to the emergence of resistant isolates. This review describes genetic markers and other factors that influence the incidence of MDR A. baumannii. Current and emerging treatments as well as infection control strategies are discussed.

INTRODUCTION

Acinetobacter baumannii (*A. baumannii*) is a Gram-negative coccobacillus, non-motile, catalase-positive, oxidase-negative, non-fastidious, and strictly aerobic bacterium that has become a growing problem in hospitals as a predominant multidrug-resistant (MDR) bacterium in the intensive care and burn units. *A. baumannii* is considered an important source of nosocomial infections and is currently considered one of the pacesetters in the antibiotic resistance crisis[1].

The evolution of MDR *A. baumannii* is well documented and is generally characterized by increasing resistance to the first- and second-generation cephalosporins in the 1970s followed by the reports of imipenem resistance in the 1980s and 1990s. Since then, several outbreaks have been reported in Asia, the Middle East, Europe, and North and South America[2-4]. MDR *A. baumannii* infections are generally defined by resistance to three or more representatives from the quinolone, cephalosporin, β-lactam, aminoglycoside, and carbapenem families of antibiotics[5].

According to the Centers for Disease Control and Prevention, the majority of clinically relevant strains of *A. baumannii* are MDR which accounts for up to 20% of infections in intensive care units, and for 7% of infections in patients who are physically connected to medical equipment[6]. Also in critically ill patients in intensive care units infected with MDR *A. baumannii*, there is a substantial rise in patient mortality rates[7]. In the USA, about 12,000 *A. baumannii* infections occur yearly with 500 deaths associated with

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these infections[8]. In Egypt *A. baumannii* infections grows rapidly in worrisome way, Many studies detected that *A. baumannii* infections may be associated with considerable mortality, however some of them support the possibility that the clinical course of debilitating patients may be influenced by many factors that subsequently the infection with *A. baumannii* may not independently lead to worst results[9]. The mortality from *Acinetobacte*r infection was from 30% to 50% of *Acinetobacter* infected patients[10]. Sentinel site surveillance in tertiary care hospitals in Egypt showed high HAI rates[11]. During the last decade, while infection prevention and control (IPC) activities were progressing in Egypt, it was deemed important to implement a standardized national HAI surveillance program to define the magnitude and scope of HAIs in the country and to allow for interhospital comparisons of HAI rates. Therefore, a plan to implement a nationwide HAI surveillance program in intensive care units(ICUs) was developed with support from several partners: the U.S. Centers for Disease Control and Prevention's (CDC's) Global Disease Detection (GDD) Program in Egypt, the U.S. Naval Medical Research Unit (NAMRU-3), and the U.S. Agency for International Development in Egypt. The objectives of the national HAI surveillance were to estimate the incidence of HAIs, obtain national benchmarks, describe the microbiologic profile of pathogens causing HAIs, and inform prevention activities of HAIs. This report describes the process of developing a national HAI surveillance program in Egypt[12]. The aim of this review is to describe mechanisms of antibiotic resistance in *A. baumannii*, and focus on the emergency of spread of multi drug resistant *A. baumannii* and the need to current and emerging treatments as well as infection control strategies.

Mechanisms of antibiotic resistance

The capacity of *A. baumannii* to rapidly alter its genome and the ability to survive on inanimate surfaces and medical equipment with high resistance to disinfectants have established MDR *A. baumannii* as a frequent cause of hospital outbreaks[13]. The antibiotic resistance phenotype in *A. baumannii* is believed to be mediated by a combination of factors including upregulation of the organism's innate resistance mechanisms, lateral gene transfer, gene amplification, and gain/loss of function as a result of mutations[14]. Rapid acquisition of drug-resistant phenotype in *A. baumannii* is often associated with the presence of genomic regions referred to as 'resistance islands', which can be found on the bacterial chromosomes and/or plasmids in regions that are interspersed with mobile genetic elements[15]. AbaR1 is an 86 kb resistant island that is a product of repetitive insertion of various mobile genetic elements and is often associated with the dissemination by homologous recombination through lateral gene transfer with the genera *Pseudomonas*, *Salmonella*, and *Escherichia*[16]. In antibiotic-susceptible *A. baumannii*, *AbaR1* is shown to correspond to a 20 kb ATPase-like open reading frame that acts as a specific hotspot of genomic instability, enabling the organism to change its genome in response to the environmental pressures[16]. Genomic islands such as *AbaR1* confer resistance to various antibiotics by carrying a cluster of genes encoding the proteins related to antibiotic inactivation. *A. baumannii* strains may become resistant to aminoglycosides by the acquisition of resistance islands that code for Aminoglycoside - Modifying Enzymes (AMEs)[14]. The genes encoding AMEs can be found on plasmids and/or transposons and include *aacC1*, *aphA6*, *aadA1*, and others that are grouped according to the type of enzyme activity[14]. A report by Namvar *et al.* examined the prevalence of AME genes in MDR *A. baumannii* isolates[17]. More than 98% of *A. baumannii i*solates had *aacC1* and *aphA6* genes, whereas 80.8% of strains had all three *aacC1*, *aphA6*, and *aadA1* genes. The presence of *aphA1*, *aacC1*, or *aphA6* was also found to confer resistance to kanamycin, gentamicin, or kanamycin and amikacin combined therapy[18].

The OXA-type (oxacillin-hydrolysing) enzymes are among the earliest detected plasmid-mediated β-lactamases. Which usually confers resistance to penicillins and possesses high-level hydrolytic activity against oxacillin[19]. A study by Davadeh *et al.* used 76 carbapenem-resistant *A. baumannii* isolates from a hospital in Turkey. Using polymerase chain reaction amplification methods, 22 strains were identified with OXA-51-like,

OXA-23-like, OXA-40-like, and OXA-58-like genes[20]. The higher carbapenem hydrolysis rate occurs due to the acquisition of the insertion sequence (IS) elements (e.g. *ISAba1*), which are from a naturally occurring plasmid upstream of the OXA-type carbapenemase encoding genes[21]. Others have reported that OXA-40 has replaced other oxacillinases such as OXA-23 as the main factor affording resistance to imipenem[22]. *A. baumannii* in clinical isolates often confers resistance to cephalosporins. The resistance profile is controlled by non-inducible *AmpC* cephalo-sporinase that is controlled by an upstream *ISAba1*[23]. Mechanisms of carba-penem resistance are illustrated in figure 1[24].

Boinett *et al.* have recently reported on MDR *A. baumannii* which is resistant to antibiotics that target lipid A[25]. The genes responsible for the modification include *IpxA*, *IpxC*, and *IpxD* that encode the lipid A component of lipopolysaccharides (LPS). The mutations in these genes cause a loss of LPS, and since the drug action requires the binding of LPS, the drugs are rendered ineffective. A study by Moffatt *et al.* examined 13 derivatives of MDR *A. baumannii* strains. From the parent strain of *A. baumannii* (ATCC 19606), derivatives were generated with the mutations in Lipid A genes. There was a strong correlation between mutation in *IpxA* gene and the emergence of MDR *A. baumannii*[26].

Moreover, *AdeABC* efflux system genes also a contributing factor in the emergence of resistance against certain antibiotics[27]. The efflux system is controlled by clustered genes *adeA*, *adeB*, and *adeC*, which were found to encode proteins for membrane fusion, drug transporter, and outer membrane components[28]. Expression of this system is regulated by two genes: a two-step regulator, *adeR*, and a sensor, *adeS*. Peleg *et al.* reported that a point mutation in *adeR* and *adeS* may lead to reduced tigecycline susceptibility in *A. baumannii* due to the *AdeABC* pump overexpression[13]. A study by Nemec *et al.* examined 116 *A. baumannii* strains for the presence of the structural genes *adeA*, *adeb*, and *adeC* and of the regulatory genes *adeS* and *adeR*; at least one of the five genes of *AdeABC* complex was found in 91% of strains[29]. Efflux pumps also reduce the intracellular accumulation of other drugs such as fluoroquinolones and aminoglycosides.

However, other primary mechanisms, such as gyrase gene mutation for fluoroquinolones and AMEs acquisition for aminoglycosides, are often required to confer resistance phenotype to the corresponding antibiotics, suggesting a secondary rather than a primary role for *AdeABC* efflux system in the emergence of aminoglycoside- and fluoroquinolone-resistant *A. baumannii* strains[14]. Different mechanisms of antibiotic resistance of *A. baumanni* are revealed in figure 2[24].

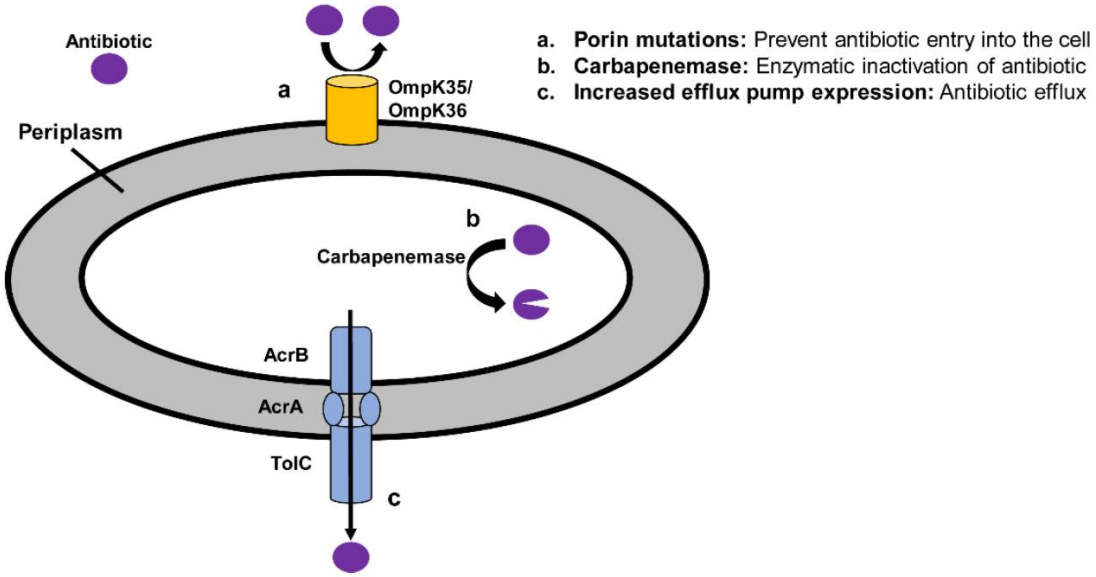

Fig. 1: Mechanisms of carbapenem resistance in *A. baumannii*.

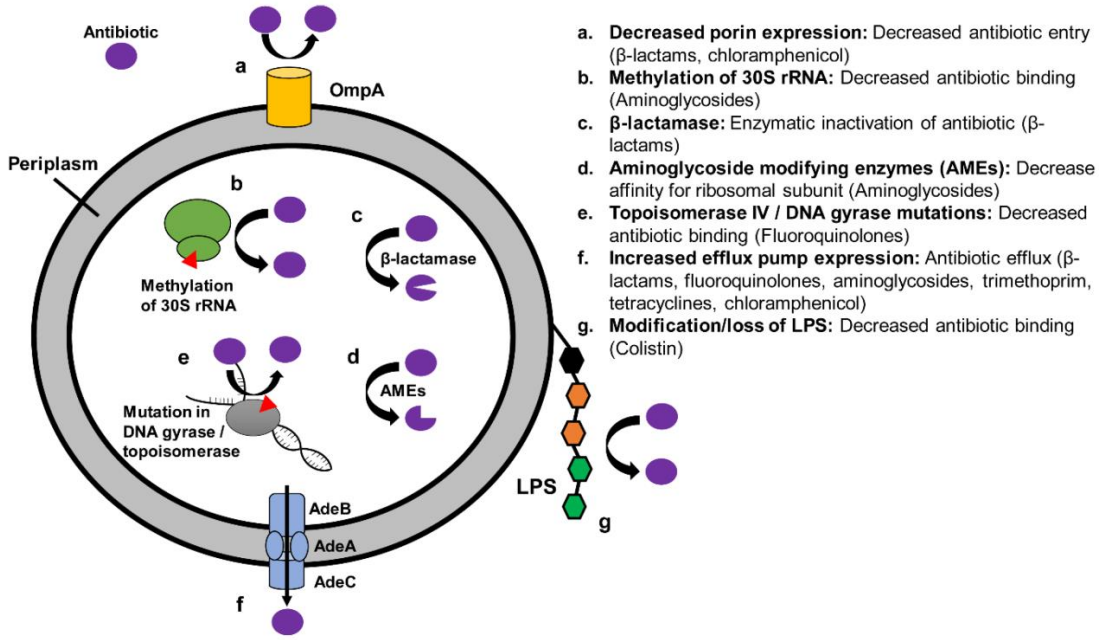

Fig. 2: Mechanisms of antibiotic resistance in *A. baumannii*.

Treatment options for *A. baumannii* infections

A. baumannii has the capacity to rapidly develop resistance through intrinsic and acquired mechanisms, thus the available treatments for *A. baumannii* infections are limited. Carbapenems used against Acinetobacter infections, but resistance rates have substantially risen in recent years.

Polymyxins show reliable antimicrobial activity against *A. baumannii* isolates. Polymyxin antibiotics are now considered to be the drug of choice for treating infections caused by carbapenem-resistant strains[30].

However, polymyxin application is also a key driver for the emergence of adaptive polymyxin resistance with the potential of generating highly polymyxin-resistant bacterial populations[31].

Tigecycline and its derivative have also shown high antimicrobial activity against *A. baumannii*. This class of antibiotics, however, is associated with higher in-hospital mortality and longer hospital stay[32].

Sulbactam has also been successfully used in the treatment of serious *A. baumannii* infections[33]. Sulbactam is relatively inexpensive and more efficient against *A. baumannii* when used as monotherapy than the ampicillin–sulbactam combination. Sulbactam alone is not available in many countries including the USA[34]. Therefore, a higher dosage of ampicillin–sulbactam combination regimen is needed for effective dosage against *A. baumannii* infections[33].

Aminoglycosides are also an important group of antibiotics in treatment of aerobic Gram-negative bacteria including *A. baumannii*, but recent reports indicate the emergence of resistance to aminoglycosides in *Acinetobacter* isolates worldwide[17].

Because of the decline in susceptibility to a wide range of antibiotic agents, the antibiotic options are often limited to synergistic application of these agents.

Based on *in-vitro* studies and observational data, the antibiotic options often used as monotherapy or in combination therapies to treat MDR *A. baumannii* infections are discussed below.

Polymyxins (cell membrane inhibitors)

Polymyxin antibiotics inhibit bacterial membranes after binding to lipopoly-saccharides, interacting with lipid A of the outer membrane, and acting as a detergent by disrupting the membrane phospholipids[35]. Polymyxins are often used as the antibiotic therapy of choice against MDR *A. baumannii*[35].

Colistin, also known as polymyxin E, is administered intravenously as an inactive prodrug, which then converts into active colistin in blood. The process of converting prodrug to active colistin can take up to several hours to reach the desired concentration in the plasma. Therefore, this delayed initiation may be associated with the increased mortality of clinically ill patients, and the low colistin concentration may be linked to the emergence of a colistin-resistant population[36&37]. Also the application of colistin may raise the probability of nephrotoxicity and neurotoxicity complications[38].

Polymyxin B is administered as an active antibiotic that rapidly achieves the desired plasma concentration and is highly effective against *A. baumannii*. Several studies[39] have reported that polymixin B is the most effective antibiotic for Acinetobacter strains. Zorgani *et al.*, Attia and ElBaradei, Josheghani *et al.*, currently, the use of polymyxin B combined with other antibiotic agents, such as carbapenems, rifampicin, and sulbactam, is recommended antibiotic therapy treatment for pneumonia and bacteraemia infections caused by MDR *A. baumannii*[40-42].

Leite *et al.*, reported that colistin resistance in *A. baumannii* isolates in Brazil reached 35%[43]. Inhaled colistin has also been recommended for treating pneumonia caused by *A. baumannii*[44]; however, not all studies support the benefits of inhaled colistin in patients with pneumonia since colistin yields a low concentration and a higher risk of bronchoconstriction[45].

Tigecycline (ribosomal inhibition)

Tigecycline is a derivative of minocycline that inhibits protein synthesis by binding to the 30S ribosomal subunit and so blocking the interaction of aminoacyl-tRNA with the A site of the ribosome. Tigecycline is an alternative antibiotic choice for treating MDR *A. baumannii*. In the study by Kim *et al*. in patients with pneumonia caused by MDR *A. baumannii*, the clinical success rates of treatments were similar between those who received tigecycline-based and those who received colistin-based treatments[46]. Aljindan *et al*.[47], reported that tigecycline resistance of *Acinetobacter* isolates reached 17.72%.

Aminoglycosides (protein synthesis inhibition)

Aminoglycosides are a broad-spectrum bactericidal agent that inhibits protein synthesis by binding to the 30S subunit of bacterial ribosomes, resulting in the release of premature proteins by misreading the mRNA[48]. Unlike tigecycline, the result of aminoglycosides is a non-functional protein, and the efficacy of aminoglycosides in treating infections increases with increasing concentrations of the drug[17]. Aminoglycosides may be used in combination therapy with β-lactams[49].

A. baumannii resistance to amino-glycosides is due to the mutations in the genes coded for aminoglycoside-modifying enzymes (AMEs). The mutated enzymes inactivate the drug and prevent ribosomal binding by catalyzing the modification at hydroxyl or amino groups of antibacterial agents. The degree of aminoglycoside resistance is influenced by multiple factors including the acquisition of enzyme-modifying genetic elements (lateral gene transfer), a decrease in the uptake of drugs in the cytoplasm (e.g. efflux pumps), and structural change in the 30S ribosome (chromosomal mutations)[49].

Emerging therapies

Iron chelation therapy

Previous studies with iron chelators have demonstrated a bacteriostatic effect on bacterial growth[50]. To survive and replicate, bacteria need iron for DNA replication and energy production; so iron chelation therapies have been exploited to target iron metabolism and achieve antibacterial activity by interrupting iron recruitment[51].

To obtain a steady supply of iron from its host, *A. baumannii* uses an iron-dependent repressor known as ferric uptake regulator (FUR) and siderophore-mediated iron acquisition systems[52]. The expression of FUR relies on the iron levels in the environment, where more FUR expression occurs when iron levels are low[53]. In the siderophore-mediated iron acquisition system, high-affinity iron-chelating compounds are secreted by bacteria and transport iron across cell membranes. Because the binding of siderophores to iron is strong, it can compete with transferrin and lactoferrin and remove iron molecules from carriers[51]. The siderophore–iron complex then

binds to the corresponding receptors on the bacterial surface and is internalized where the iron is released and used for the internal processes[53].

Although iron chelators can sequester iron and provide a non-antibiotic alternative treatment approach, a study by Thomson *et al*. demonstrated that the application of deferoxamine (a widely used iron chelator) is ineffective against *A. baumannii*; this is believed to be due to the presence of bacterial receptors for deferoxamine[54]. Even though deferoxamine can bind to iron, the deferoxamine–iron complex will bind to the deferoxamine receptors and iron is extracted and used by the bacteria[54]. However, the new generation of iron chelators in combination with other conventional therapeutic approaches may offer therapeutic value in difficult-to-treat MDR cases[51]. Further studies are required to assess the therapeutic value of the newer generation of iron chelators on growth and survival of nosocomial pathogens such as MDR *A. baumannii*.

Bacteriophage therapy

Bacteriophages – viral particles that target bacteria – have previously been used as a treatment for bacterial infections[55]. Garcia-Quintanilla *et al*. enumerated several bacteriophages that are effective for specific strains of *A. baumannii*, including phage AB-1, which is a lytic circular double stranded DNA phage, and phage AB-2 that is lytic to 27 strains of clinical MDR isolates with an adsorption rate of 99% within 9 min.[56].

Other reports have described newer phages that are being discovered with a broader host range, chiefly, AP22 that can infect 89 of 130 *A. baumannii* strains and is considered a potent phage to infect and lyse MDR *A. baumannii*[56]. Novel phages (e.g. KARL-1) are frequently reposted for use against MDR *A. baumannii* with increased efficacy when the phage treatment is synergistic with the application of traditional antibiotics[55].

However, apart from its advantages, phage therapy has its downsides. For instance, not all phages are thought fit to be used for therapeutic purposes as some phages have weak therapeutic potential, thus defeating the primary purpose of phage therapy.

Other phages can convert phage-susceptible bacteria to non-susceptible ones due to superinfection immunity in which genome integration into the host's chromosome takes place, thus blocking the obligate lytic phage to successfully infect and lyse the target bacterium. Phages can also trigger severe immune reaction which may carry major health concerns. However, recent US Food and Drug Administration approval for viral gene therapy treatments, ranging from treatments for blindness to lymphomas, suggests the tremendous potential and future application of viruses as a tool to treat various diseases including difficult cases of MDR infections[56].

Antimicrobial active herbal compounds against *Acinetobacter baumannii*

The high level of acquired and intrinsic carbapenem resistance mechanisms acquired by these bacteria makes their eradication difficult. The pharmaceutical industry has no solution to this problem. Hence, it is an urgent requirement to find a suitable alternative to carbapenem, a commonly prescribed drug for *Acinetobacter* infection.

L. salicaria shows significant activity against different bacteria but, especially *A. baumannii* and *P. aeruginosa*. Hence its topical form may be used to treat infections of skin and soft tissue (antiseptic), infections of burn wounds, diabetic foot and decubitus wound caused by these MDR bacterial strains. It is already known that this plant has been used as traditional medicine for many indications, but to use it clinically, several *in-vitro* and *in-vivo* test have to be performed[57].

Saulnier *et al*. used essential oils of herbs like Syzygium aromaticum, Cinnamomum zeylanicum, and Thymus in nano medicine against multidrug-resistant *A. baumannii*. Cinnamaldehyde prevents the activity of amino acid decarboxylase in the bacteria[58], but it is unable to disorganize outer membrane of cell or deplete intracellular ATP concentration. Hydroxyl group of carvacrol and eugenol (phenolic compounds) can disrupt the bacterial cell wall. This phenomenon has the potential to decrease intracellular ATP pool and membrane potential[59]. It also results in the leakage of various substances such as ATP, amino acids, ions, and nucleic acids ultimately leading to bacterial death. MIC of active components is

the same as MIC of those compounds when nano-encapsulated. Lipidic nanocapsules (LNC) can be made more effective by improving their presence in systemic circulation through the modifications on LNC surface. It can be a good alternative of antibiotics[60].

Curcumin alone had very little antibacterial activity against *A. baumannii* strains with high MIC (256μg/ml). The antibacterial activity of curcumin is due to several reasons for instance, disruption of folic acid metabolism (shikimate dehydrogenase) pathway and bacterial cell division[61]. Combinatorial use of curcumin and epigallocatechin gallate (EGCG) is very much effective in increasing the inhibition level by many folds, making the MIC 4 μg/ml. Synergistic effects to prevent *A. baumannii* growth between curcumin and EGCG without any antagonistic effects[62]. In the same way epicatechin, a tea polyphenol having no antibacterial properties can potentiate theaflavin, increasing its activity against *A. baumannii* and *S. maltophiliaisolates*. The probable mechanism may be that epicatechin inhibits theaflavin oxidation thus enhancing its antibacterial effect, but the exact mechanism of synergy is not yet understood and needs further study[63].

Khadri, *et al*. reported the presence of methyl allyl trisulfide (34.61%) and diallyl disulfide (31.65%) with other compounds at relatively lower levels after GC/MS analysis in Allium sativium. It showed significant activity against *P. aeruginosa in-vitro* and can be used for treating infections caused by this pathogen[64]. Aloe vera gel extract were reported to be more active for Gram-positive than Gram-negative bacteria. Ethanol extract was most active followed by methanol extract activity and least inhibition was exhibited by acetone extract[65]. Magnolia dealbata extracts showed good inhibition zone of >10 mm against *P. aeruginosa*, *Clavibacter michiganensis*, *A. baumannii*, *A. iwoffii*. Generally, the active constituents of M. dealbata like honokiol and magnolol possess selective antimicrobial activities against drug resistant Gram-negative bacterial species and fungal pathogens[66].

Miyasaki *et al*. suggested in their studies, norwogonin (5,6,7-trihydroxyflavone) extracted from Scutellaria baicalensis, has an MIC90 of 128 μg/ml against some strains of *A. baumannii*. Chebulagic acid, chebulinic acid (65%) inhibition at (62.5 μg/ml), ellagic acid (67% inhibition at 250 μg/ml), corilagin, and terchebulin extracted from Terminalia chebula had lower activity against *A. baumannii in-vitro*. Other constituents of Scutellaria baicalensis, baicalin and baicalein are also found to be active against other bacteria. Corilagin, chebulagic acid, and terchebulin of Terminalia chebula exhibit a two-step killing kinetic. The medical literature reported that many phenolic compounds of plant extracts enhance the potential of synthetic antibiotics against *A. baumannii in-vitro*[67]. For instance, activity of rifampicin, coumermycin, fusidic acid, novobiocin, and chlorobiocin was enhanced by tannic acid and ellagic acid against *A. baumannii in-vitro*[68]. Even synergy was observed between topical mafenide and green tea polyphenol against multi-drug resistance *Acinetobacter baumannii in-vitro*[69].

Some Chinese medicines extracted from different plants have been reported to exhibit significant antibacterial activities. The active constituent of Rhizoma coptidis is berberine, an alkaloid possessing various antimicrobial activities. Berberine is also isolated from Berberis fremontii and Hydrastis canadensis[70]. It has anti-Herpes simplex virus effects and at moderate concentrations (30-45 μg/ml) sufficient antibacterial effect was observed along with inhibition of biofilm formation. Plant derived antibacterial molecule are generally weak but work better in synergy with antibiotics[70]. Synergism was also seen for berberine and β-lactam antibiotics against multi drug resistant *S. aureus*. (+)-Lyoniresinol-3 alpha-O-beta-D-glucopyranoside of Cortex Lycii presented strong antimicrobial effect against multi drug resistant *S. aureus* isolated from patients and some pathogenic fungi, but it did not cause any haemolysis on human RBCs. This also possesses potent antifungal activities against *Candida albicans*. There is very limited literature concerned with the antibacterial effects of Cortex Moutan. The ethanolic extract of Cortex Moutan suppresses the growth of *S. aureus*. Only paeonol is identified as active ingredients till date, which is responsible for its anti-microbial effects on *C. albicans*, *C. tropicalis*, and *C. glabrata* etc.[71].

A very common medicinal plant A. indica is the source of various active compounds identified by GC/MS analysis possessing versatile effects like anti-bacterial, anti-inflammatory, antioxidant activities. Hence further studies can be performed to see its activity against Gram-negative bacteria and especially *A. baumannii*[72].

Prophylactic vaccination

Vaccination has been one of the most effective approaches in preventing bacterial infections. An essential element in development of an effective vaccine is the choice of the suitable target antigen that is expressed on the bacterial surface. In the mouse model, the first vaccine against *A. baumannii* had a mixture of various bacterial antigens and resulted in a lower tissue bacterial load in vaccinated mice compared to unvaccinated mice[73].

Since the original trials, other vaccines have been developed with a wide range of targets including the biofilm-associated protein (Bap), outer membrane complexes (OMCs), and the outer membrane vesicles (OMVs). The new generation of vaccines substantially decreases the bacterial loads in vaccinated mice[73].

Bap protein is an acidic high-molecular-weight protein found on the surface of organisms and is considered a key factor in biofilm formation, which is a contributing factor to the emergence of nosocomial infections[74]. Although the presence of Bap is associated with increased virulence, it is still debatable whether the Bap-based vaccine will be effective since some MDR *A. baumannii* strains do not produce biofilm.

In addition, OMC-targeted vaccines are known to induce immune response that may lead to the proliferation of non-specific natural killer lymphocytes[75]. Alternatively, OMV can increase the antibody titres against *A. baumannii* and minimize the tissue bacterial loads[76]. Although the results in the mouse model are promising, considering the evidence to date, an ideal vaccine should be a combination of OMV and OMC, as both can combat active bacterial infections. However, OMC-based vaccines exhibit higher endotoxin activity due to the lipopolysaccharide production, and there may be substantial human health and safety concerns[77].

Although successful in the mouse models, *A. baumannii* vaccine for human use is still is in its infancy and requires further studies to evaluate its efficacy and safety parameters. This goal may be accomplished with the development of techniques to detoxify the OMC/OMV vaccines to reduce the endotoxin activity as was previously shown for other organisms[76].

Preventive measures

A. baumannii is associated with both community- and hospital-acquired infections[78]. In community-acquired cases infections are associated with a high mortality rate, and are often characterized by severe and sudden onset of pneumonia coupled with secondary septicemia[79]. Hospital-acquired infections are frequently associated with monoclonal outbreaks, usually related to an environmental source, or as complex, polyclonal outbreaks, in which epidemic and sporadic clones coexist[80].

Regardless of the nature of MDR bacterial infections, it is widely accepted that practicing proper hand hygiene is an effective and simple infection control technique. Thom *et al*. evaluated the presence of *A. baumannii* on the hands and gloves of healthcare workers[81]. They reported on 254 interactions between healthcare workers and 52 patients, in which 30% of interactions were positive for *A. baumannii* on gloves or hands. More importantly, Haverstick *et al*. reported that to effectively reduce the rate of nosocomial infections it is necessary for patients to receive hand hygiene supplies and training[82].

Biswas and Tiwari have reported that 1% sodium hypochlorite, 2.5% hydrogen peroxide, and 10 mM chlorine dioxide are effective environmental disinfectants against *A. baumannii*[82]. Leung and Chan have outlined various methods of cleaning hospital air following an outbreak, which include filtration, differential pressure, directional airflow control, and ultraviolet germicidal irradiation[83]. However, they caution against the use of UV radiation because its effectiveness is based on how long the air is exposed to radiation, which is inversely proportional to the air flow rate.

Another control measure for disinfecting hospitals involves hydrogen peroxide vapor.

Cobrado *et al*. recently reported successful disinfection of a burn unit contaminated with *A. baumannii* by using an automated aerosolized hydrogen peroxide/silver cation dry-mist system[84]. Improved methods of cleaning by hydrogen peroxide vapour appear to be effective against MDR *A. baumannii* outbreaks in hospitals when used as an adjunct to standard manual cleaning and disinfection protocols[85].

Antimicrobial stewardship programmes that restrict excessive antibiotic usage and introduce alternative antibiotic regimens have also been shown to be an effective means of controlling MDR *A. baumannii* outbreaks[86]. As a long-term strategy, concomitant implement-ation of strict antimicrobial stewardship in combination with a comprehensive set of intervention measures has been shown to successfully control endemic infections of MDR *A. baumannii* in a hospital setting within 12 months[87].

Conclusion

A. baumannii is an important source of nosocomial infections in hospitals and long-term care facilities. Acquiring multidrug resistance through genetic acquisition / modification leads to increasing number of MDR *A. baumannii*. Antibiotic therapy against *A. baumannii* infections is limited, thus alternative treatment options as iron chelation therapy, bacteriophage therapy and antimicrobial active herbal compounds can be useful in some cases. Infection control measures can be costly and challenging.

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مقاومة الاسينيتوباكتر بوموناي للمضادات الحيوية: الحاجة الملحة لعلاج جديد ومكافحة العدوى

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أصبحت عدوى الاسينيتوباكتر بوموناي مصدر قلق صحي ناشئ في المستشفيات في جميع أنحاء العالم وغالبًا ما تكون مرتبطة بعدوى المستشفيات ذات النتائج السريرية الضعيفة في المرضى الذين يعانون من الإقامة الطويلة في المستشفى. تتضمن إدارة مكافحة العدوى تحديدًا سريعًا للسلالة المعدية ، وعزل مصدر العدوى ، والاختيار المناسب لنظام المضادات الحيوية. ومع ذلك ، فإن مقاومة أدوية الخط الأول من مضادات الميكروبات ، جنبًا إلى جنب مع ندرة البدائل الفعالة بنفس القدر ، تعقد علاج الاسينيتوباكتر بوموناي المقاومة للأدوية المتعددة. في الوقت الحاضر ، قد يكون الاسينيتوباكتر بوموناي المقاومة للأدوية المتعددة مصدر قلق صحي خطير في المستشفيات ومرافق الرعاية طويلة الأجل التي تمثل ما يصل إلى ٢٠٪ من العدوى في وحدات العناية المركزة ، و٧٪ من العدوى في المرضى المرتبطين جسديًا بالمعدات الطبية. هناك حاجة لجهود وقائية فورية ومستمرة للسيطرة على سرعة الإصابة. استخدام المضادات الحيوية غير منظم إلى حد كبير في مصر مما أدى إلى ظهور عزلات مقاومة. تصف هذه المراجعة الواسمات الجينية والعوامل الأخرى التي تؤثر على حدوث الاسينيتوباكتر بوموناي المقاومة للأدوية المتعددة. وتناقش العلاجات الحالية والناشئة وكذلك استراتيجيات مكافحة العدوى.