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Review

Carbapenem-resistant *Acinetobacter baumannii* raises global alarm for new antibiotic regimens

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SUMMARY

Carbapenem-resistant *Acinetobacter baumannii* (CRAB) is a top-priority pathogen causing a nosocomial infection that increases morbidity and mortality. Treatment options for CRAB are relatively limited by pharmacokinetic restrictions, such as substantial toxicity. Therefore, we must better understand this pathogen to develop new treatments and control strategies. The review aims to provide an overview of the current understanding of acquired, adaptive, and intrinsic Carbapenem-resistant pathways in *A. baumannii*, as well as its consequences on healthcare systems, particularly critical care units. The review also provides insights into how CRAB infections are currently managed worldwide and why novel therapeutic regimens are needed. The peculiarity of *A. baumannii* and its often reported virulence factors have been discussed further. In conclusion, the purpose of this review is to emphasize the current knowledge on CRAB, as it causes major worry in the field of nosocomial infections as well as overall public health.

INTRODUCTION

Antimicrobial resistance (AMR) is a global concern. The World Health Organization (WHO) has identified AMR as one of the top 10 global public health threats confronting humanity. As of 2019, it is estimated that approximately 1.3 million deaths have been directly linked to AMR bacterial pathogens on an international level.[1] The Centers for Disease Control and Prevention (CDC) have reported more than 2.8 million infections in the United States that were caused by AMR pathogens between 2012 and 2017 with over 35,000 fatalities recorded.[2] These records further prove that there is an urgent need to have an effective surveillance system as a part to fight against antimicrobial resistance, which will contribute to evidence-based policies at both the state and national levels.

Beta-lactams are undoubtedly the most widely used class of antibiotics worldwide, with penicillin, cephalosporins, monobactams, and carbapenems being commonly administered. Carbapenems are used as the last line of defense against gram-positive and gram-negative, multidrug-resistant bacteria.[3] Because carbapenems are increasingly being used in clinical practice, the rise of carbapenem-resistant bacteria poses a significant hazard to human health.[4] Carbapenem resistance mechanisms observed in bacteria in general are due to either carbapenemase production or mutations that affect structural integrity with the production of β-lactamases (AmpC and ESBL).[4–6]

It was during the early 1985s in Scotland that the first known *A. baumannii* were identified to be resistant to carbapenem.[7] Since then, nosocomial outbreaks of CRABs have become a worldwide concern, and in the past few decades, this gram-negative pathogen has been regarded as one of the ESKAPE organisms that causes high mortality and morbidity rates.[8] It can be extremely difficult to treat infections caused by CRAB bacteria. CRAB strains in general are resistant to nearly all antibiotics, including broad-spectrum carbapenems such as meropenem, imipenem, and doripenem. They are commonly classified as extensively drug-resistant (XDR) or pan-drug-resistant (PDR) strains. Certain regions of the globe have more than 90% carbapenem resistance, and hospital-acquired pneumonia and bloodstream infections from CRAB can result in the death of up to 60% of patients.[9] Treatment options for CRAB infections are still relatively limited. Polymyxins and tigecycline have traditionally been regarded as the medications that are most effective for CRAB infections. Nevertheless, resistance to these antibiotics is also increasing. In addition to these antibiotics, aminoglycosides and fosfomycin are occasionally used to treat CRAB infections.[10] However, it is still important to use carbapenems in the treatment of CRAB infections,

especially when they are combined with other active antibiotics (combinational therapies). Further, through this review, we believe the information provided might help the scientific community understand the need to develop new strategies and therapies to manage CRAB infections, as we are currently running out of therapeutic regimens. The review also has summarized current challenges and resistance mechanisms associated with CRAB that may help to understand the pathogen better and may aid to prevent further dissemination of this pathogen.

WHAT ARE CARBAPENEMS?

Antimicrobial drugs called carbapenems are crucial for treating nosocomial infections because they have the broadest range of activity and the greatest effectiveness against gram-positive and gram-negative bacteria.[11] They are typically given to critically ill patients as a last-resort antibiotic for these reasons. *Acinetobacter* sp. have recently emerged as a significant contributor to serious illnesses and infections. Skin, bloodstream, urinary tract, as well as other soft tissue infections, caused by *A. baumannii* are mostly linked to hospital-acquired infections globally.[12] Thus, the worldwide spread of *A. baumannii*, a bacterium resistant to the antibiotic carbapenem, is perilous for human health and contemporary healthcare systems.[13–17] A solid understanding of carbapenems, their biochemical properties, and their application, along with a solid understanding of the epidemiology, virulence factors, and resistance mechanisms in *A. baumannii* may help to control outbreaks in the coming years or prevent the development of carbapenem resistance. To address the problems brought on by CRAB as well as to stop the infection from spreading further, this review could provide a deeper understanding of the need for new antimicrobial agents or innovative therapeutic approaches.

The term "carbapenem" refers to a group of broad-spectrum β-lactam antibiotics that are semi-synthetic and structurally related to penicillin.[11] The carbon atom at position C1 is replaced by a sulfur atom with an unsaturated bond between positions C-2 and C-3 in contrast to the structure of penicillin.[18] The carbapenem's 6-trans-hydroxyethyl group at C-6 is crucial to the drug's stability and activity; penicillin and cephalosporins possess cis configuration, which makes them less stable.[19] Because of their effectiveness and safety, β-lactams are among the most frequently recommended antimicrobial agents in both clinical care and community settings; carbapenems, in particular, due to their efficacy in managing infections, are a widely utilized class of antibiotics.[20] Carbapenems are often considered a cornerstone of antibiotic therapy as they remain very critical in managing severe to complicated infections. In the case of major nosocomial infections, carbapenems are often recommended in combinational therapies that involve the use of carbapenem with other antimicrobial agents that target pathogenic bacteria. Carbapenems have remained a major boon for patients suffering from infections in the lower respiratory tract, urinary tract, central nervous system (CNS), skin and soft tissues, and muscle joints as well as disorders related to cystic fibrosis and febrile neutropenia.[19] Between 2000 and 2010, the rate of carbapenem usage grew by 45% worldwide. Carbapenems have been the most prescribed antibiotics worldwide for community-acquired infections in intensive care units (ICUs) as well as with nosocomial infections, as they act strongly against potentially important gram-positive/negative bacteria.[21] Further, owing to their concentration-independent ability to kill bacteria, they are preferred as alternate antimicrobial agents in treating invasive and life-threatening illnesses.[22] Carbapenems are generally well tolerated by patients with allergic responses and have an excellent safety profile.[20] Carbapenems are more frequently used because they are less harmful than other last-resort medications, such as polymyxins.[3] Additionally, they continue to target Penicillin-binding proteins (PBPs) and are largely resistant to hydrolysis by most β-lactamases.[11] Infections caused by *A. Baumannii* and other severe nosocomial infections are typically successfully treated with β-lactams.[3]

CARBAPENEMS AND THEIR TYPES CURRENTLY AVAILABLE

Carbapenems are the most potent class of β-lactam antibiotics, with the broadest breadth of antibacterial action and the best safety and tolerability characteristics. As a result, they are frequently given to treat serious infections brought on by MDR pathogens. Imipenem, meropenem, ertapenem, and doripenem are among those that have been approved by the Food and Drug Administration (FDA) and are accessible for clinical usage (Figure 1).[20]

Based on their antibacterial action, carbapenems were categorized using clinical studies and clinical use data. Ertapenem, a group 1 carbapenem, may be better suited for treating community-acquired infections because it is ineffective against non-fermentative gram-negative bacilli.[23] In addition to having broad-spectrum activity and being active against non-fermentative gram-negative bacilli, group 2 agents, including meropenem, imipenem, and doripenem, are also efficacious against nosocomial infections.[24] Group 3 carbapenems, like razupenem and tomopenem, prove to be effective against methicillin-resistant *Staphylococcus aureus* and non-fermentative gram-negative bacilli. Imipenem is the oldest carbapenem and has been administered to over 26 million patients for the past 20 years[25] *Pseudomonas aeruginosa* and *Acinetobacter* sp., which are typically associated with critical nosocomial infections, are successfully treated with imipenem due to its high affinity for PBPs, better stability against β-lactamases, and efficacy; regrettably, after 1986, treatments comprising imipenem have grown less effective.[20] The effectiveness of this carbapenem against gram-positive bacteria is to a small extent higher than that of other drugs. Additionally, imipenem is frequently provided along with cilastatin or betamipron because it is susceptible to the renal tubular dipeptidase enzyme dehydropeptidase I (DHP-I), which results in its breakdown. Cilastatin, a competitive antagonist, helps to shield the kidneys from the damaging effects of greater dosages of imipenem.[26] The US FDA forbids the usage of imipenem in the treatment of meningitis or infections of the CNS in patients with renal and brain disease risk factors that may result in seizures.[20]

The insertion of a 1-β-methyl group at position 1, C-1 led to the discovery of meropenem in 1995. Since cilastatin is resistant to DHP-I hydrolysis due to the 1-β-methyl group, it does not need

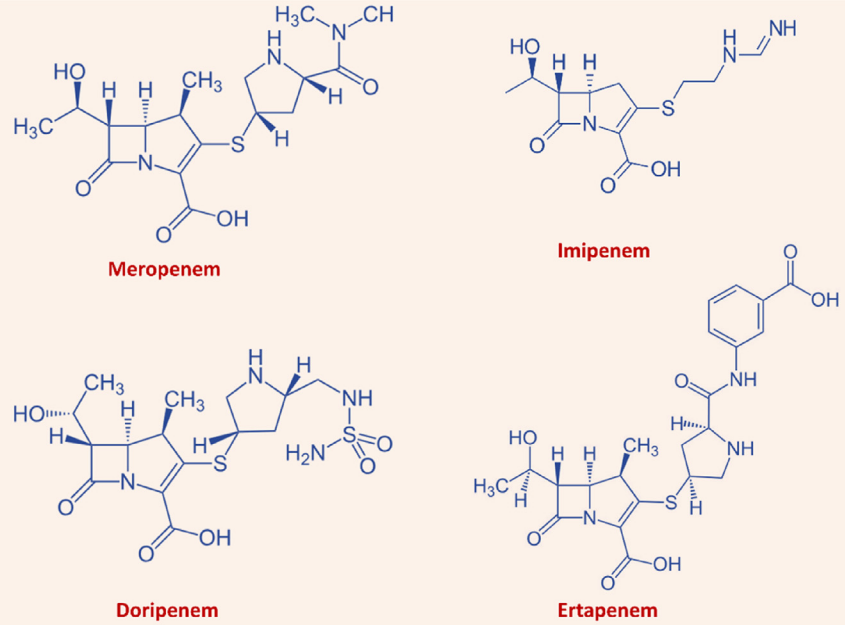

Figure 1. FDA approved carbapenems that are widely used in the management of infections

to be taken concurrently with imipenem.[24] Since the US FDA has authorized its use, meropenem may be used to treat bacterial meningitis in children over the age of 3 months and in adults. Although with a similar spectrum of activities to that of imipenem, meropenem is slightly more efficacious in managing infections caused by gram-negative bacteria.[20] It is further believed that the structural dimensions of being minute and its zwitterion state have helped them to be trafficked into the cell membrane of gram-negative bacilli without much hindrance.[27] As clinical effectiveness of meropenem has been demonstrated over time by the extensive clinical usage of this carbapenem, doctors have come to view it as one of the most dependable and widely available medications for the treatment of critically ill patients with nosocomial infections.[24]

Ertapenem is a 1-β-methyl carbapenem that has been effectively used against infections caused by gram-negative bacteria harboring AmpC type β-lactamases or/and spectrum extended-spectrum β-lactamases (ESBLs).[20,24] However, ertapenem has been found less effective against *Acinetobacter* sp., *P. aeruginosa,* and *enterococci* than imipenem and meropenem, which explains why it is not indicated in clinical settings where there is a possibility of nosocomial infection. Ertapenem also shows more resistance to DPH-I inactivation as compared to imipenem. Ertapenem is a critical component of the management of complex intra-abdominal, cutaneous, or urinary tract infections, which are acquired in the community and are likely to have a mixed flora of anaerobes and aerobes.[24] This is because it just has to be taken once a day and its elimination half-life is rather long. Doripenem is resistant to DPHI inactivation and exhibits a persistent b-lactamase activity, much like meropenem.[28] Although it also exhibits sustained activity against *Staphylococcus aureus*, methicillin-resistant *S. aureus*, *Enterococcus faecalis*, and vancomycin-resistant *enterococci* (VRE), it is less effective against these pathogens. Pyelonephritis and severe urinary tract or intraabdominal infections were among the conditions for which meropenem was approved by the US FDA in 2007.[28]

CARBAPENEMS AND THEIR ACTION MECHANISMS

Since carbapenems are β-lactams, they are incapable of easily passing through the bacterial cell walls. Instead, they use porins, also referred to as outer membrane proteins (OMPs), to invade gram-negative bacteria.[11] Carbapenem exhibits bactericidal activity by attaching to PBPs, for instance, enzymes with high molecular weight, such as PBP1a, PBP1b, PBP2, and PBP3.[29,30] PBPs, which are cytoplasmic membrane proteins, are responsible for generating and maintaining the peptidoglycan in bacterial cell walls.[31,32] Because of their structural resemblance to acylated D-alanyl-D-alanine, carbapenems can bind to the active site of PBP irreversibly. The construction of a bacterial cell wall is interrupted when a β-lactam molecule attaches to PBPs because it prevents the bacteria from completing transpeptidation and also other peptidase processes of the peptidoglycan layer. Autolysin activity causes the death of bacterial cells. A class of bacterial surface enzymes known as autolysins creates nicks in cell walls that act as sites for attaching new peptidoglycan units. The cell membrane shows protrusion at the weak areas within the cell wall due to β-lactam drugs' inhibition of cell wall synthesis and the cell wall's self-destruction.[33] As a result of osmotic shock, the membrane of the hypertonic cell becomes too thin to remain intact, causing the cell to explode. According to distinct bacterial species and also strains, carbapenems have varied affinities for specific PBPs, making them distinguishable from one another.[19] Because of their ability to bind to and connect with so many crucial PBPs of gram-negative bacteria, carbapenems are effective. Additionally, what sets carbapenems apart from other β-lactams like cephalosporins and penicillin is the stronger affinity that carbapenem possesses for PBP-1a and PBP-1b. In contrast to other β-lactams, carbapenems are distinguished from one another by their affinity for PBP-2/PBP-3 of gram-negative bacteria.[31] For instance, imipenem prefers PBP2 the most, followed by PBP-1a, PBP-1b, and PBP-3. Contrarily, PBP-2, PBP-3, as well as PBP-1a and PBP-1b, are the PBPs for which ertapenem and meropenem have the strongest affinity. Additionally, doripenem binds to PBP-1, PBP-2, and PBP-4 in the case of *S. aureus*, PBP-3 in the case of *P. aeruginosa,* and PBP-2 in the case of *E. coli*. The discrepancies in antibacterial activity may be explained by the heterogeneity in carbapenem-binding affinities for various PBPs.

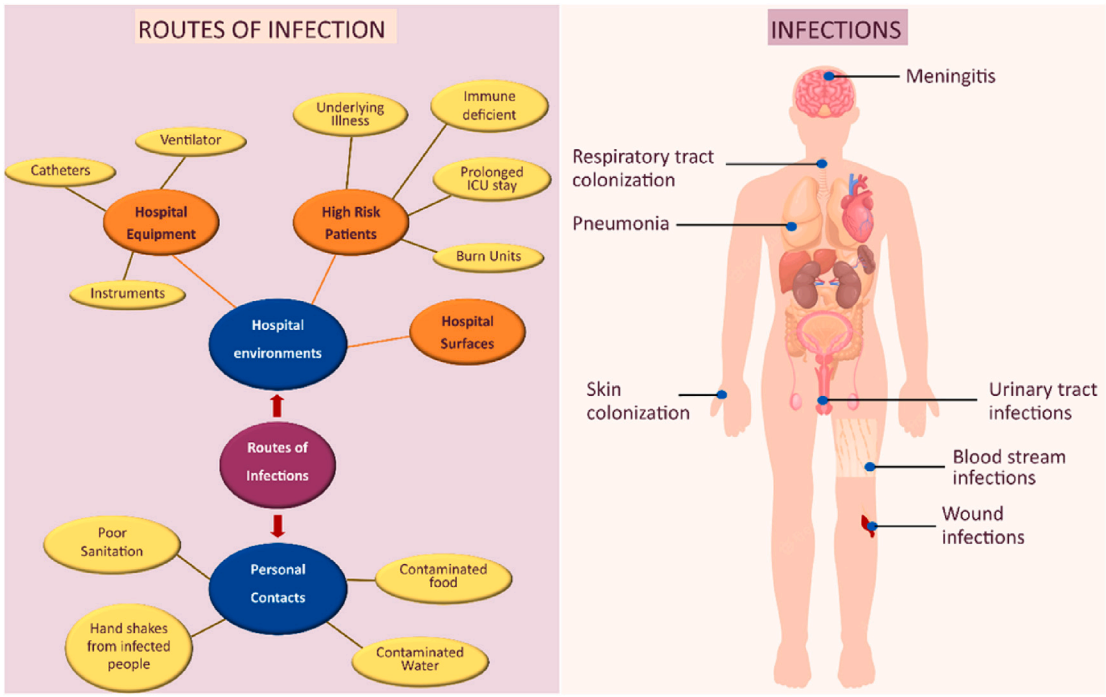

Figure 2. Infections caused by *A. baumannii*

A. BAUMANNII AN ALARMING PATHOGEN

A. baumannii—a bacterial pathogen—causes nosocomial infections, notably in ICUs. To find effective methods for controlling infection and for treating critical patients whom this pathogen has infected, it is critical to have knowledge and understanding of MDR *A. baumannii* attributable to the recent spike in infections triggered by this pathogen.

Epidemiology of *A. baumannii*

Acinetobacter infections have diverse epidemiology, including epidemics in hospitals in temperate climates, infections linked to natural disasters and war, and infections linked to tropical environments. *A. baumannii* is also found primarily in hospital environments in neonatal and adult ICUs and burn/neurosurgical, surgical, medical, and cancer units. The respiratory system (in the pharynx, trachea, or bronchi), bloodstream, and central nervous system are the areas of the body where *A. baumannii* is most frequently isolated. Additionally, it is connected to catheter-associated urinary tract infections (UTIs) and skin and tissue infections at surgical sites.[17] Anatomical barriers that allow *A. baumannii* to enter the affected area directly are the common element in those circumstances. Overall, *A. baumannii* causes a wide range of hospital-acquired infections in a patient's body, although it frequently manifests as bloodstream infections or ventilator-associated pneumonia (VAP).[17]

As *A. baumannii* can externally form biofilms on endotracheal tubes, resulting in extreme colonization in the lower respiratory tract, pneumonia poses a risk to patients who rely on mechanical ventilation. According to studies from the CDC and Prevention's Healthcare Safety Network, the following percentages indicate that *A. baumannii* nosocomial infections are occurring more frequently: 84% of VAP, 22% of bloodstream infections caused by central lines, 12% of urinary tract infections caused by catheters, and 6% of surgical wound infections.[34] *A. baumannii* strain can grow on surfaces with little nutritional availability if introduced to a hospital ward by an already colonized patient. During an epidemic, several items in the patient's environment, such as bed curtains, furnishings, sinks, and other assorted medical devices such as arterial pressure trackers, ventilator tubing, and humidifiers, might become infected. Although the bacteria may propagate through the air or colonized skin of the patients, the main mechanism of infection transmission is through the hands of medical staff members (Figure 2). Patients who are unwittingly infected can have the infection for days or even weeks before the *A. baumannii* strain is detected in clinical specimens.

A. BAUMANNII AND THEIR POTENTIAL VIRULENCE FACTORS

A. baumannii has been reported as using a variety of virulence factors and methods to cause host harm. Porins are one of the main protein classes that have emerged as a result of numerous investigations. Porins are proteins in the outer membrane that control cellular permeability. Major porin protein OmpA is found in abundance in the outer membrane of this pathogen. OmpA protein, which targets host cell mitochondria and causes mitochondrial fragmentation and apoptosis by releasing proapoptotic chemical

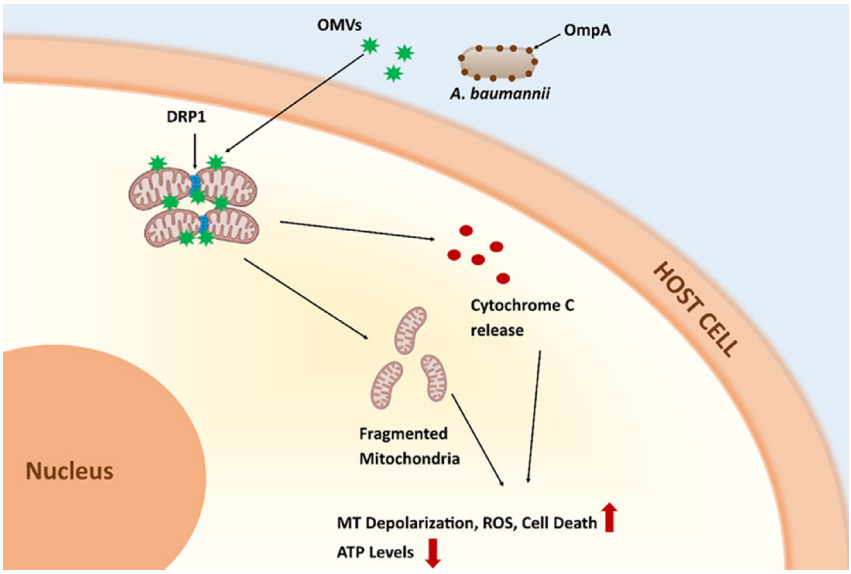

Figure 3. Virulence factor associated with *A. baumannii*

The OmpA protein causes mitochondrial fragmentation and apoptosis through the release of the proapoptotic chemical cytochrome *c*. In addition, OmpA increases ROS levels while reducing mitochondrial polarization and ATP levels in the mitochondria.

cytochrome *c*, is released by *A. baumannii* through its outer membrane vesicles (OMVs) (Figure 3).[35–37] OmpA further raises ROS concentrations while lowering mitochondrial polarization and ATP levels. By interacting with extracellular matrix proteins like fibronectin, OmpA also aids in the adhesion and subsequent invasion of epithelial cells.[38] Further, OmpA adheres to factor H in human serum, thereby preventing this pathogen from being killed through complement.[39] OmpA is required for the efflux of antibiotics from bacterial cells and leads to the multidrug-resistant (MDR) phenotype of *A. baumannii*; furthermore, its absence decreases antibiotic resistance to several antibiotics including aztreonam and chloramphenicol.[40] The 33- to 36-kDa Omp known as Omp33-36 is another significant porin protein connected to the pathogenesis of *A. baumannii*. The inability of macrophages and human lung epithelial cells to adhere or to be cytotoxic in the absence of this protein demonstrates the importance of this protein for host cell attachment.

To interfere with autophagy, Omp33-36 causes an upregulation of LC3B-II (an autophagosomal membrane protein) and p62/SQSTM1 (a selective autophagy receptor) in cells of the immune system and connective tissue. It also promotes apoptosis by activating caspases. *A. baumannii* can survive within cells and reside in autophagosomes.[41] Additionally, Omp22 is yet another significant outer membrane porin protein that has been proposed as an effective vaccine target to reduce infections caused by *A. baumannii*. Even while the exact role of Omp22 in the pathophysiology of *A. baumannii* infections is unclear, it shows promise as a vaccine target in the ongoing hunt for effective treatments. The OMVs generated by many gram-negative bacteria are spherical in shape and may be used effectively by *A. baumannii* to deliver toxins. Toxins such as OmpA, phospholipases, and cytotoxic proteases are examples of these.[42]

The bacterial capsule is a significant factor in the pathogenicity of *A. baumannii*. Capsular exopolysaccharide-deficient mutants are more sensitive to peptide antibiotics. Additionally, *A. baumannii* becomes more susceptible to a variety of antibiotics due to changes that disrupt the precursor sugars that help build the capsule and lipopolysaccharide (LPS).[43] The genes *ptk* and *epsA* were identified to be crucial for capsule assemblage in *A. baumannii*, and harboring any mutations in these genes impaired capsule formation.[44] The O-pentasaccharide present in glycoproteins is produced only in the presence of PglC. Further, loss of PglC in this pathogen inhibited capsule synthesis, which interfered with the formation of the biofilm and lowered pathogenicity in mice.[45]

Further, the pathogenicity of *A. baumannii* also relies on lipopolysaccharide (LPS) production. *A. baumannii* harbors the enzyme LpsB glycosyltransferase to produce LPS. Any modification of this gene through acquired mutations or deletions makes the bacterium incapable of producing LPS, resulting in increased sensitivity to human serum.[46] Several research has found that the survival and pathogenicity of *A. baumannii* are both impacted by LPS.[47] Another potentially pathogenic tactic employed by *A. baumannii* is protein secretion systems. The Type I, Type II, Type IV, Type V, and Type VI secretion systems are yet to be researched extensively. In *A. baumannii*, the Type II secretion system plays a potent role in secreting effector lipases (LipA and LipH) and proteases (CpaA), which is associated with the pathogenicity of this bacterium.[48] For instance, in the mouse model of pneumonia, the pathogenicity induced by CpaA was well studied.[49] Furthermore, *A. baumannii* also uses Type VI secretion systems for bacterial competition albeit its role in cytotoxicity remains yet to be identified.[50]

Clinical significance of *A. baumannii*

The clinical importance of *A. baumannii* began to emerge in the 1980s, and its capacity for nosocomial dissemination began to increase; the Infectious Diseases Society of America (IDSA) has referred to it as one of the greatest nosocomial germs.[51] Due to their immunosuppression and prolonged hospitalization, most patients in ICUs are particularly vulnerable to the spread of *A. baumannii*.[34] *A. baumannii* is responsible for a wide range of infections, including meningitis, wound infections, VAP, UTIs, and infections of the eye, skin, soft tissues, and ear (Figure 2). Major risk categories of these infections include patients who are immune suppressed, patients in burn wards, prolonged ICU stay, advanced age groups,

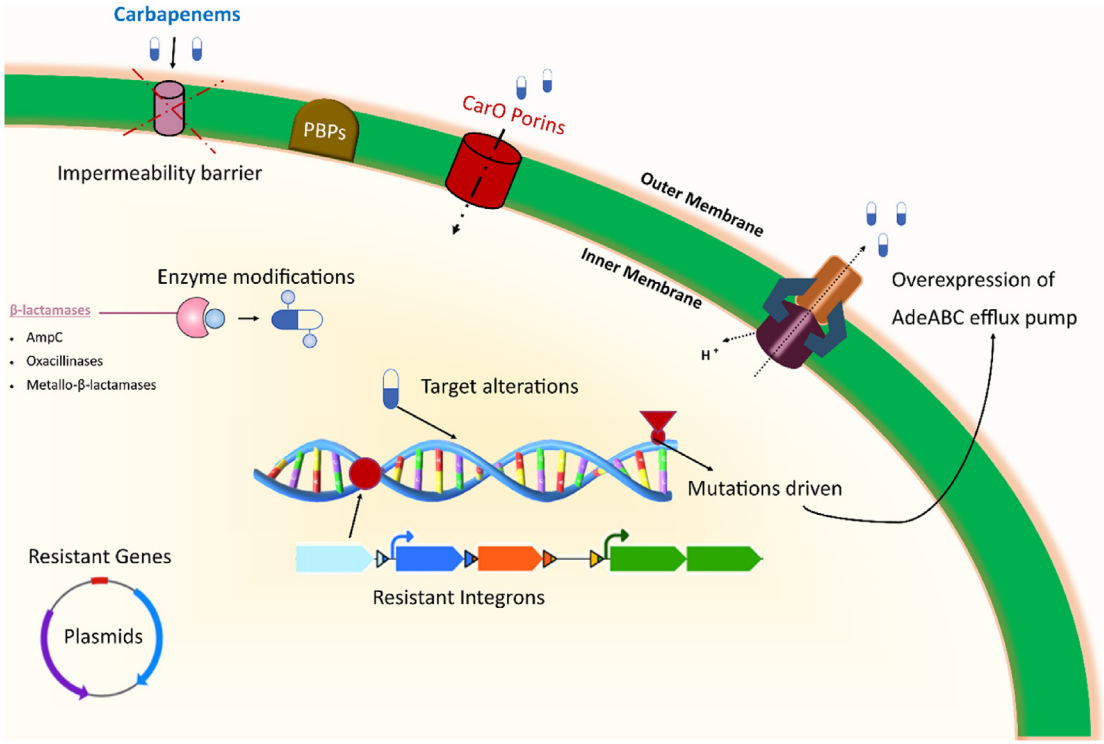

Figure 4. Common resistance mechanisms of CRAB infections

Resistance to carbapenems is achieved through penicillin-binding proteins and their modifications and reduced permeability: porin loss in the outer membrane, overfunctional efflux pumps, enzyme modifications (oxacillinases, metallo-β lactamase genes, AmpC enzymes), acquiring resistance through genetic elements (insertional sequences, integrons, resistant island, conjugative plasmids).

and surgeries that involve invasive procedures or utilize indwelling devices such as catheters, mechanical ventilators, and dialysis tubes (Figure 2). Further, the likelihood of contracting MDR *A. baumannii* strain resulted in increased disease severity, prolonged mechanical ventilation, prolonged ICU or hospital stays, vulnerability to infected patients, and prolonged ICU or hospital stays despite the use of broad-spectrum antibiotics, specifically third-generation cephalosporins, carbapenems, and fluoroquinolones.[52,53]

The prevalence of diseases attributed to *A. baumannii* constitutes around 2% of healthcare-associated illnesses in the United States and Europe, as of 2018. In Asia and the Middle East, this proportion is almost twice as high.[17] Although *A. baumannii* may cause infections at a higher rate than other gram-negative pathogens, the proportion of MDR *A. baumannii* isolates is about 45%, quadrupling that of other gram-negative pathogens like *Klebsiella pneumoniae* and *P. aeruginosa.* For Latin America and the Middle East, the rates might reach as high as 70%. Additionally, nosocomial *A. baumannii* infections can increase mortality risk from 8% to 40%.[51] CDC views MDR *Acinetobacter* sp. as a serious threat to human health due to the rising incidence of MDR *A. baumannii* infections globally. According to the WHO, CRAB is also a crucial global priority.[54] As a result, constant monitoring and prevention efforts as well as the need for innovative treatments against *A. baumannii* are of utmost importance.

COMMON CARBAPENEM RESISTANCE MECHANISMS IN *A. BAUMANNII*

Penicillin-binding proteins and their modifications

PBPs are an integral part of cell wall biosynthesis that promotes transglycosylation (the final phase of polymerization) and peptidoglycan cross-linking via transpeptidation. However, PBPs are also the major targets for β-lactam antibiotics (Figure 4). Several studies have demonstrated that modifications to PBPs contribute to β-lactam resistance in gram-negative bacteria.[55,56] *A. baumannii* is therefore likely to be drug-resistant due to alterations in PBPs. Resistance to carbapenem in *A. baumannii* strains is associated with lower drug affinity caused by PBP downregulation. Further, mutations in PBPs have been reported in *A. baumannii* to induce clinical levels of drug resistance, while reports are sparse.[56] This pathogen has eight putative PBPs identified through sequence analysis, of which four of them are high molecular weight (PBP1a, PBP1b, PBP2, PBP3), three low molecular weight (PBP5/6, PBP6b, PAP7/8), and a monofunctional enzyme, MtgA.[57] A vast majority of mutations found in these proteins were susceptible variants identified to be silent mutations that do not link to β-lactam resistance.[30] This indeed proves that the ability of *A. baumannii* to induce carbapenem resistance is quite modest through modifications in PBSs.[58]

Reduced permeability: porin loss in the outer membrane

Acinetobacter sp. also exhibit carbapenem resistance due to membrane impermeability as a result of reduced expression or mutation of porins (Figure 4). *P. aeruginosa* is a classic example that is innately resistant to a wide range of antibiotics due to the low expression of high permeability porins.[59] Porin channels and outer membrane proteins (OMPs) are generally in charge of transporting antimicrobial substances into cells. In *A. baumannii*, there are several OMPs, such as CarO (carbapenem-associated OMP), HMP-AB, and OmpW, that are linked with trafficking β-lactams across the membrane, which results in carbapenem non-susceptibility. The intrinsic carbapenem resistance of *A. baumannii* is caused by a change in the primary structure or the loss of 25/29-kDa in CarO.[60] The absence of CarO in diverse carbapenem-resistant clinical isolates of *A. baumannii* further confirmed the contribution of CarO in carbapenem antibiotic influx.[61] Similarly, a decrease in the expression of CarO has also been linked to reduced meropenem and imipenem susceptibility.[62]

Overfunctional efflux pumps

The efflux pumps display broad substrate specificity, to exclude unrelated chemical compounds with a wide range of chemistry, despite the presence of several resistance mechanisms targeting a specific antibiotic group (Figure 4). Currently, three resistance-nodulation-division (RND) type efflux pumps have been thoroughly characterized in *A. baumannii*: AdeABC, AdeFGH, and AdeIJK. Aside from these three recognized pumps, five more uncharacterized RND pumps have been described in this pathogen using in silico models using the NCBI database and are identified to be of clinical importance.[63] The RND efflux pumps are typically composed of outer membrane protein (OPM), membrane fusion protein (MFP), and an inner membrane that helps in the transport of key antibiotics.[64] AdeA, adeB, and AdeC encode MFP, and multidrug transporter and OPM of the AdeABC efflux system have the strongest correlation toward carbapenem resistance in *A. baumannii*.[65] The expression of the AdeABC efflux pump is influenced by *adeRS* (response regulator, adeR and a sensor kinase, adeS), provided the expression levels of *adeA*, *adeB*, and *adeC* vary greatly among themselves. In addition, according to a Chinese study, *A. baumannii* with no mutations in its regulatory genes was resistant to carbapenem with overexpressed AdeABC efflux pumps, indicating a multifactorial pathway involving interactions of multiple genes, as seen in *P. aeuginosa*.[66,67] Further, combined with carbapenem-hydrolyzing oxacillinases (OXAs), overexpression of the AdeABC efflux pump leads to high-level carbapenem resistance.[68]

ENZYME MODIFICATIONS IN *A. BAUMANNII* TO CAUSE CARBAPENEM RESISTANCE

A. baumannii exhibits carbapenem resistance through inactivation or enzyme degradation of carbapenems. This is usually accomplished by carbapenemase enzymes, which are usually found on plasmids and are extremely transmissible. As a result of horizontal gene acquisition, *A. baumannii* shows a high level of carbapenem resistance due to the expression of carbapenem-hydrolyzing enzyme classes D (oxacillinases) or B (metallo-β-lactamases) or Class A (Figure 5). Among them, carbapenemases belonging to OXA type such as blaOXA-23 and blaOXA-24/40 are plasmid-borne and are easily transferable, causing great menace in hospital care settings, leading to higher mortality rates.[69]

The OXA-type carbapenemases (oxacillinases)

In *A. baumannii*, carbapenem resistance conferred through OXA-type carbapenemases are very ubiquitous worldwide. Although the first OXA-type enzymes were identified on plasmids, now these enzymes are found cardinal among both plasmids and chromosomes in *A. baumannii*. Of the different types of oxacillinases, the OXA types *bla*OXA-23, *bla*OXA-24/40, *bla*OXA-51, *bla*OXA-58, *bla*OXA-143, and *bla*OXA-235 have been very frequently identified among CRAB isolates from hospitals.[70] In the United States, overfunctional *bla*OXA-23, *bla*OXA-24/40, and *bla*OXA-58 have been identified to be a major determinant of carbapenem resistance through carbapenemases in *A. baumannii*. Of these identified determinants, *bla*OXA-23 is the most common cause of carbapenemase-mediated resistance in *A. baumannii* in the United States.[71] However, *bla*OXA-23 can also be a major determinant of carbapenem resistance in India and South Korea.[72] It was also determined that two carbapenem-resistant strains that infected hospitals in the UK over the course of 2003 and 2004 had the *bla*OXA-23 gene.[73]

Among the carbapenem-resistant isolates of *A. baumannii* recovered from Spain, the *bla*OXA-24 and *bla*OXA-25 variants were identified. Similarly, the *bla*OXA-40 determinant was found to confer carbapenem resistance in *A. baumannii* strains isolated from a hospital sample in France.[74] The blaOXA-51 enzymes are identified among *A. baumannii* and are capable of hydrolyzing meropenem and imipenem even though they are expressed low and requires to be expressed from insertion sequences. Although *bla*OXA-51 are found cardinal among all strains of *A. baumannii*, they are much more ubiquitously found in Brazil, Germany, and Japan.[72] Following an outbreak of CRAB infections in a burn unit in France, the strains were identified to harbor *bla*OXA-58 genes that were major determinants of carbapenem resistance. Further epidemiological surveys have found *bla*OXA-58-resistant determinants spread worldwide with majority of reports from the US, the UK, Turkey, Greece, Argentina, Kuwait, Italy, Spain, and Austria.[61] *Bla*OXA-143 and *bla*OXA-253 were also detected from clinical samples of *A. baumannii* from Latin America.[58]

The metallo-β-lactamase genes

There are four common metallo-β-lactamase genes that are identified in *A. baumannii*, such as, IMP (imipenemase), VIM (Verona integron-encoded metallo-β-lactamase), SIM (Seoul imipenemase), and NDM (New-Delhi metallo-β-lactamase). The VIM and IMP variants identified in *A. baumannii* have been found to confer resistance to the majority of β-lactams except for the case of aztreonam due to their efficient hydrolytic nature (Figure 5).[75] To date, six IMP variants (IMP-1, IMP-2, IMP-4, IMP-5, IMP-6, and IMP-11) have been identified in *A. baumannii* to confer resistance to carbapenems, whereas VIM enzymes are not very common in

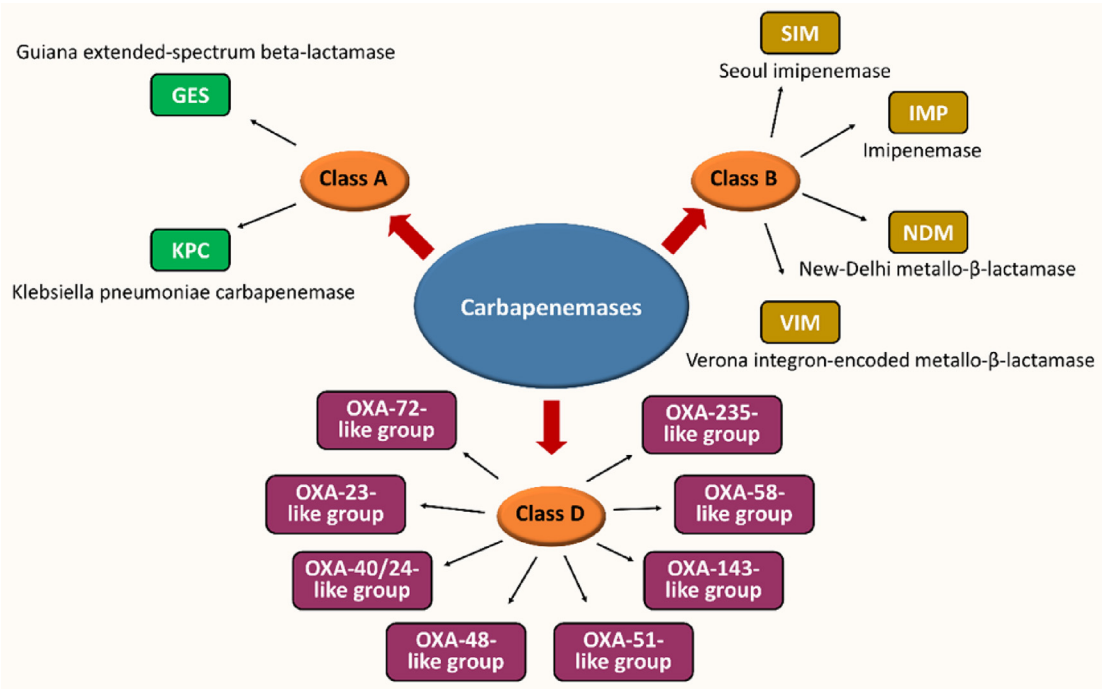

Figure 5. Acquired resistance mechanisms in *A. baumannii*

Acquired resistance through Class A, Class B, and Class C carbapenemases have been illustrated.

A. baumannii except as shown in few reports from Korea.[76] Further *A. baumannii* strains from South Korea were found to harbor SIM-1, which is believed to be widespread in the country causing carbapenem resistance.[75] NDM-1 is a novel metallo-β-lactamase gene that is capable of causing resistance to nearly all β-lactams including carbapenems. NDM-I are usually carried on transmissible plasmids that result in the spread to XDR type CRAB infections and hence are highly threatful during clinical manifestations.[77]

AmpC enzymes

The other resistant mechanisms that have been described in *Acinetobacter* sp. are through AmpC enzyme-mediated mechanisms. These AmpC in general are usually found cardinal in the chromosomes of this pathogen. Also, the IDSA recently updated their guidelines on treating AmpC-producing CRAB.[78] One of the most worrying elements is the hyperproduction of AmpC-lactamases and the overexpression of efflux pumps, which may confer further resistance to carbapenems in a synergistic manner.

ACQUIRED RESISTANCE IN *A. BAUMANNII* THROUGH GENETIC ELEMENTS

A. baumannii genomes contain genes that encode carbapenemases on either chromosomes or plasmids that are being trafficked through horizontal gene transfer mechanisms. However, mobile genetic elements, such as insertion sequences, integrons, and resistance islands, are other important carbapenem resistance strategies in *A. baumannii*.

Insertion sequences in *A. baumannii*

As a result of the high genetic plasticity observed in *A. baumannii*, resistance determinants can be acquired by horizontal gene transfer (HGT), leading to multidrug resistance.[79] It is estimated that there are about 30 different types of IS in *A. baumannii*, but the most widespread type is ISAba1. The ISAba1 insertion sequence is quite ubiquitous and is found to transfer and express increased carbapenem resistance in *A. baumannii*. These insertion elements are also found to be in close association with OXA-type carbapenemase genes such as *bla*OXA-23-like, *bla*OXA-51-like, and *bla*OXA-58-like that confer to carbapenem resistance.[80] For example, an ISAba1 gene promoter is found upstream of *bla*OXA23, *bla*OXA58, and *bla*OXA51, which may contribute to decreased carbapenem susceptibility in *A. baumannii.*[81]

Integrons in *A. baumannii*

An integron is a conserved sequence (3′CS and 5′CS) that is capable of acquiring gene cassettes that can contain antibiotic-resistance genes through site-specific recombination.[82] These gene cassettes do contain a recombination site (*attI*), a promoter (*PC*), and an *intI* gene (integrase).[83] The transportable class I (*Tn*402 derivatives) integron is the most widespread type of integron, which is followed by class II and III integrons. The Class I integrons have also been found to harbor VIM, IMP, and SIM-type enzymes in *A. baumannii.*[84,85] Numerous other resistance genes are found in correlation on class 1 integrons that encode resistance toward β-lactams, quinolones, tetracyclines, aminoglycosides, disinfectants, sulfonamide, and tetravalent ammonium compounds, with *P. aeruginosa* being a

Table 1. List of first- and second-line antibiotics

First-line antibiotics	Second-line antibiotics
Beta lactam antibiotics	**Polymyxins**
Ceftazidime	Colistin
Cefepime	Polymyxin B
Piperacillin-tazobactam	
Ampicillin-sulbactam	
Carbapenems	**Tetracyclines**
Meropenem	Minocycline
Imipenem-cilastatin	Tigecycline
	Doxycycline
Fluoroquinolones	
Ciprofloxacin	
Levofloxacin	
Aminoglycosides	
Gentamicin	
Tobramycin	
Amikacin	
Sulfonamides	
Trimethoprim-sulfamethoxazole	

classic example.[86] Hence, the clinical importance of integrons is that the overuse of a single antimicrobial medication might induce the common promoters of integrons, there by overexpressing numerous other resistance genes. *A. baumannii* strains with these integrons are considerably more resistant to antibiotics versus strains without integrons.[84]

Resistance islands that are common in *A. baumannii*

The first significant antibiotic resistance gene cluster identified and sequenced in an *A. baumannii* isolate (from France) had an 86 kb resistance island known as *AbaR1*. *AbaR1*, being a complex transposon, is more persistent on chromosomes than plasmids and carries multiple copies of 18 resistance genes, including a *bla*OXA51-like group along with other resistance genes that confer resistance toward aminocyclitols, aminoglycosides, chloramphenicol, and tetracycline.[51,87] Currently, different resistance islands have been identified and characterized in *A. baumannii*, which includes *AbaR1*, *AbaR3*, *AbaR4*, *AbaR5-Aba19*, and *AbaR25*.[88] In this pathogen, *AbaR25* were found to carry *bla*OXA-23-like genes that were associated with decreased carbapenem susceptibility.[51]

Conjugative plasmids and phage-assisted resistance in *A. baumannii*

Conjugative plasmids and phage-assisted transfer are other possible mechanisms through which the genetically resistant elements are transferred from one species to another. *In vitro* studies on conjugation revealed resistant genes such as *bla*OXA-23 and *bla*OXA-58 are easily transmissible across different *Acinetobacter* sp.[89] Further research indicates that conjugation mechanisms in *Acinetobacter* spp. prevail as the dominant mechanisms for the widespread carbapenem resistance.[79] Furthermore, recent scientific evidence has identified transposon (*Tn*125) harboring *bla*NDM genes from a CRAB isolate transferred to an *A. baumannii* strain that is sensitive to carbapenem via phage-mediated transduction and led to decreased carbapenem susceptibility.[88] To prevent the further spread of carbapenem resistance in *A. baumannii*, there is an urgent need to understand the mechanism that underpins the genetic exchange of resistance genes.

MANAGEMENT OF CARBAPENEM RESISTANCE IN *A. BAUMANNII*

Acinetobacter is usually the culprit in many hospital-acquired infections and is identified while culturing relevant clinical specimens. However, it can be truly tricky and challenging to differentiate colonization and true infection. This depends on the patient's clinical presentation.[90] Cultures from sterile sites (pleural fluid, peritoneal fluid, cerebrospinal fluid, or blood) are considered true infections and will require proper treatment. Culture from unsterile sites may represent colonization and need not warrant treatment. Clinical assessment is important in such cases and helps in deciding on the treatment of such infections.[91] Pneumonia (new pulmonary infiltrate on imaging, increased requirement of oxygen, fever or leukocytosis) in a patient along with the growth of *Acinetobacter* on respiratory cultures may represent true infection and warrants urgent treatment.[92] Asymptomatic bacteriuria may not be treated.[93] At times, treatment of *Acinetobacter* infections warrants empiric therapy based on length of stay in the hospital with prior antibiotic exposure history and local resistance rates.[94] The severity of the infections needs to be decided based on clinical judgment. A complete flow chart on how CRAB infections are managed has been depicted in Figure 5.

Management of mild *Acinetobacter* infections

Mild infection includes infection of the urinary tract, skin and soft tissues, and tracheitis without any signs of hemodynamic instability.[95] For any mild infection, monotherapy is advised as per the susceptibility of the isolate on culture. The first-line agent is preferred over a second-line agent in treating mild infections (Table 1). An aminoglycoside or trimethoprim-sulfamethoxazole (TMP-SMX) is a suitable choice to treat UTIs if the bug is susceptible to these agents.[96] If and where empiric therapy is warranted, the local pattern of resistance (of a particular hospital or ICU) takes precedence in regimen selection. If resistance to any of the first-line agents is unlikely, monotherapy is an acceptable choice of antibiotic for such infections. If resistance is highly likely, combination therapy for moderate/severe infections can be followed. As soon as the results of antimicrobial susceptibility are made available, a regimen can be formed from among the active agents.

Management of moderate to severe *Acinetobacter* infections

In the case of infections that are moderate to severe, a combination therapy is recommended, and the choice of agents is based on the susceptibility reports for that particular isolate (Figure 6). The list of first-line and second-line antibiotics is listed in Table 1.

Managing *Acinetobacter* infections with antimicrobial susceptibility results

Acinetobacter isolates that have been found as susceptible to one or more first-line antibiotics are frequently treated with a

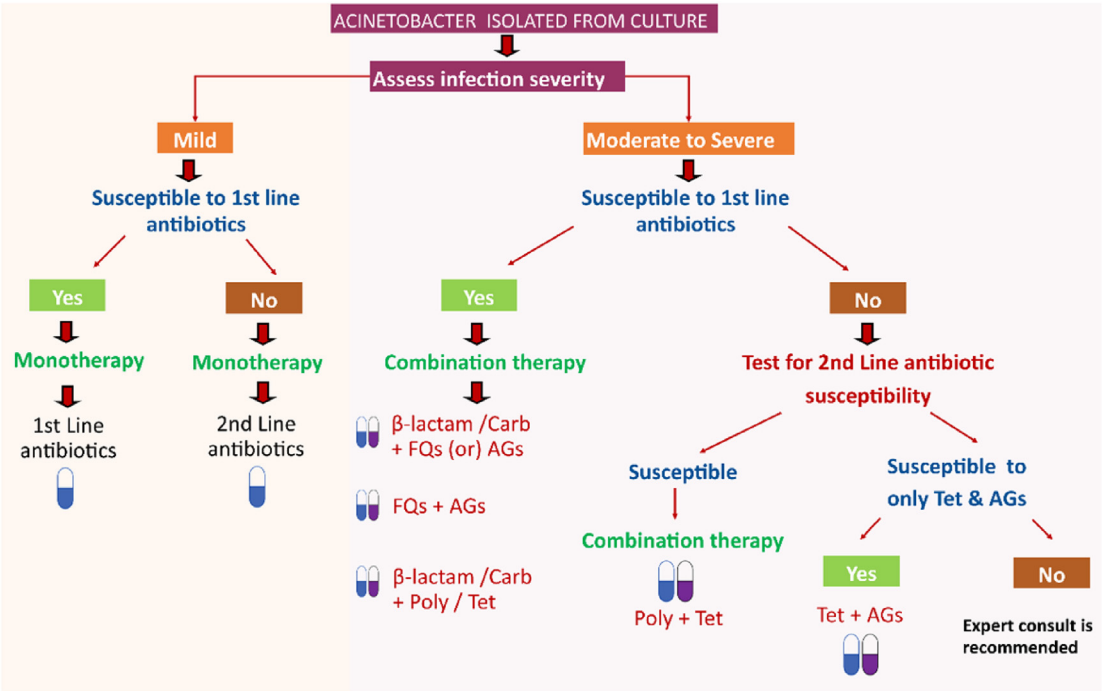

Figure 6. Management of CRAB infections

Different antibiotic strategies to manage CRAB infections have been illustrated. Antibiotic representations are as follows: Carb,"Carbapenem"; FQs, "Fluroquinolones"; AGs,"Aminoglycosides"; Tet, "Tetracyclines"; Poly, "Polymyxins".

combination of two active first-line antibiotics from different classes (Table 1). However, for isolates that are only susceptible to one first-line antibiotic, a combination of one first-line and a second-line antibiotic is administered. Combinations of other beta-lactams with carbapenems or polymyxins with aminoglycosides are generally avoided to prevent cumulative unfavorable effects of combinational therapy. Combining polymyxins with carbapenems has also been proven in studies to be inferior to colistin monotherapy and should not be recommended in patients.[97] In contrast, for *Acinetobacter* isolates that are resistant to all tested first-line antibiotics, combinational therapy warranting two second-line antibiotics is advised based on the patient's condition. In cases where isolate is susceptible to only an aminoglycoside and any one of the tetracyclines, a combination of these two classes of antibiotics is warranted. Similarly, triple therapy (one second-line agent and two first-line antibiotics to which the isolate is resistant) is indicated for isolates that are only susceptible to one class of second-line antibiotic or an aminoglycoside. In rare circumstances, if an *Acinetobacter* isolate is resistant to all antibiotics, the best way to manage the infection is uncertain. In such cases, consultation with an infectious disease specialist is advised for certain infections (Figure 5).

Managing *Acinetobacter* infections with pending antimicrobial susceptibility results

Combination therapy with either a carbapenem or ampicillin-sulbactam as an upfront choice of antibiotic is advised for this group of patients, depending on the isolate's probable susceptibility profile based on locally available data. Once antimicrobial susceptibility is available, therapy can be tailored appropriately.[98]

CRAB infections—a common burden for low- and high-income countries

Alarming increases in CRAB infections have been documented by epidemiological studies, which have resulted in a notable fatality rate varying from 27.8% to 35% worldwide.[99,100] The lack of surveillance data, lax implementation of infection prevention and control protocols, overuse and misuse of antibiotics, and inadequate healthcare infrastructure all contribute to an estimated CRAB burden in many low- and middle-income countries.[101] Insufficient epidemiological data on CRAB, particularly in patients referred to ICUs, exists in Sub-Saharan Africa. This poses a crucial knowledge gap that must be filled to develop evidence-based policies and effective interventions to reduce the hazards associated with this multidrug-resistant organism. It is also critical to acknowledge that the uncontrolled "over-the-counter" distribution of restricted antibiotics, the indiscriminate use of antimicrobials in hospitals, and the absence of infection control procedures like isolation and contact precautions have all contributed to the issue of antimicrobial resistance in developing nations. A single clone of CRAB is introduced and spreads across the hospital by violating IPC protocols, frequently resulting in CRAB epidemics in high-income nations.[102] Clonal epidemics of this kind are usually contained following an investigation into the outbreak and focused interventions. Whole-genome sequencing (WGS) is useful for high-resolution characterization of these single-center epidemics or populations in recent research.[103,104] This developing

pandemic of gram-negative resistance may be effectively controlled with the help of a rigorous hospital infection control policy and an effective antibiotic stewardship program.

TREATMENT OPTIONS FOR CRAB INFECTIONS

IDSA has recently established guidelines for the management of CRAB infections, and we have summarized their opinions as well as our thoughts on currently available treatment options.[95] A list of treatment options and the dosage information available are listed in Table 2.

Managing with first-line antibiotics

(1) Beta-lactams: there are four (ceftazidime, cefepime, piperacillin-tazobactam, and ampicillin-sulbactam) traditional first-line antibiotics that are active against *Acinetobacter* sp. Ampicillin-sulbactam is unique in the sense that the sulbactam component alone (beta-lactamase inhibitor) has bactericidal activity against *Acinetobacter.* In one meta-analysis that included 18 studies and 1,800 patients, researchers concluded that combination therapy (ampicillin-sulbactam as a part of therapy at doses of at least 18 g per day) had mortality benefit and had a lower incidence of renal toxicity in critically ill patients than colistin-based regimens.[106] Similarly, another meta-analysis that included 23 studies showed that sulbactam-containing regimens when compared with polymyxin-based or tigecycline-based regimens showed lower mortality rates.[107] According to the IDSA recommendations, high-dose ampicillin-sulbactam is the preferred backbone therapy for treating life-threatening CRAB infections either as monotherapy or as a part of combination therapy

(2) Carbapenems: recently, high-dose extended infusion of carbapenems has been used to treat serious infections caused by MDR gram-negative pathogens, particularly in combination with other antibiotics. Imipenem and meropenem have bactericidal activity against *Acinetobacter*, whereas ertapenem do not have any intrinsic activity against *Acinetobacter.* Carbapenems are usually combined with other agents to treat CRAB infections. Carbapenems are given as prolonged infusions to improve pharmacodynamics

(3) Fluoroquinolones: several oral and parenteral formulations of ciprofloxacin and levofloxacin are effective against *Acinetobacter.* Fluoroquinolones are used to treat susceptible isolates either as monotherapy or combination therapy based on the severity of infection

(4) Aminoglycosides: aminoglycosides are considered as excellent agents for urinary tract infections against *Acinetobacter* infections without bacteremia, as they achieve very high concentrations in the urine[108,109]

(5) Trimethoprim-sulfamethoxazole (TMP-SMX): TMP-SMX can be used in UTIs if susceptibility is demonstrated; however, most isolates are resistant[110]

Managing with second-line antibiotics

(1) Polymyxins: polymyxins are used to treat *Acinetobacter* infections if the isolate is resistant to first-line antibiotics. Colistin is preferred for UTIs and polymyxin B for other infections. Polymyxins do not penetrate into the lung. Resistant bugs have been demonstrated in Europe and in North and Latin America.[111] Despite poor penetration into the lung, colistin is equally efficacious as other antibiotics in treating ventilator-associated pneumonia.[112] Many of the studies here used intravenous plus nebulized colistin. Toxicity associated with polymyxins is largely renal toxicity. According to the recommended dose, colistin plasma concentration should be at least 2 mg/L to ensure adequate activity against colistin-susceptible CRAB infections in a dose-dependent manner[113]

(2) Tetracycline: tetracycline group of antibiotics are used to treat *Acinetobacter* infections. Minocycline available both orally and intravenously was shown to be successful in terms of clinical and microbiological outcomes in a retrospective cohort.[114] Minocycline can be used alone in mild infections as a monotherapy regimen and in conjunction with other antibiotics in moderate to severe infections. Doxycycline is infrequently used, as susceptibility rates are lower. Tigecycline is available in parenteral formulation and has activity against *Acinetobacter.* Tigecycline is used at a higher dose (100 mg intravenous [IV] Q12H) and has shown better outcomes when compared with conventional dosing (50 mg IV Q12H)[115–117]

Combination therapy

Combination therapy is generally recommended in moderate to severe infections. In deciding empiric therapy, in places where local resistance rates are higher, at least one antimicrobial is likely to be effective. Also, this delays the emergence of resistance with time. However, this is not so in clinical trials.[118]

Various combination therapies have been tried in treating CRAB infections. Some of these combinations are listed below.

(1) Colistin-rifampicin vs. colistin alone was tried in a randomized controlled trial in 210 patients and did not show any mortality benefit in the combination therapy[119]

(2) Colistin-rifampicin vs. colistin alone in 43 patients of ventilator-associated pneumonia did not show statistically significant mortality benefit[118]

(3) Colistin-fosfomycin vs. colistin alone in 94 patients with various types of CRAB infections did not show a mortality benefit with combination therapy[120]

(4) Colistin-meropenem vs. colistin alone in a large trial consisting of 312 patients did not show a mortality benefit with combination therapy[107]

(5) Colistin-ampicillin-sulbactam vs. colistin alone in 39 patients with CRAB infection showed early cure rates with the combination therapy[121]

Despite no clear and robust evidence of combination therapy over monotherapy, due to severely impaired immunity in critically

Table 2. Antibiotics used for the management of CRAB infections

Antibiotics	Adult dosage	Additional remarks	Toxicity	Toxicity (%)
Ampicillin-sulbactam	9 g IV every 8 h over 4 h	For moderate infections caused by ampicillin-sulbactam-susceptible CRAB isolates, 3g IV every 4 h is appropriate, especially if intolerance or toxicities limit the use of greater dosages A high dose that is appropriate for ampicillin-sulbactam-resistant CRAB	Hepatotoxicity	1
Cefepime	Cystitis: 1 g IV every 8 h For other infections: 2 g IV every 8 h, infused over 3 h	–		
Cefiderocol	2 g IV every 8 h infused over 3 h	–	Elevated liver tests Hypokalemia	2–16 11
Minocycline	200 mg IV/PO every 12 h for 2 doses	–	CNS	1–3
Polymyxin B	–	Refer to international consensus guidelines on polymyxin[105]	–	–
Colistin	–	Refer to international consensus guidelines on polymyxin[105]	Nephrotoxicity Neurotoxicity	1–18 1–7
Tigecycline	200 mg IV × one dose, then 100 mg IV every 12 h	High dose	Hepatotoxicity Pancreatitis	2–5 <−1
Trimethoprim-sulfamethoxazole	Cystitis: 160 mg (trimethoprim component) IV/PO every 12 h Other infections: 8–12 mg/kg/day (trimethoprim component) IV/PO divided every 8–12 h	Consider maximum dose of 960 mg trimethoprim component per day for other infections		
Meropenem	Cystitis (standard infusion): 1 g IV every 8 h infused over 30 min Other infections: 2 g IV every 8 h, infused over 3 h		Seizures	<−1
Imipenem-cilastatin	Cystitis (standard infusion): 500 mg IV every 6 h, infused over 30 min Other infections: 500 mg IV every 6 h, infused over 3 h		Seizures	<−1
Ciprofloxacin	400 mg IV every 8–12 h or 500–750 mg PO every 12 h			
Levofloxacin	750 mg IV/PO every 24 h			
Gentamicin	Cystitis: 5 mg/kg/dosed IV once All other infections: 7 mg/kg/dosed IV × 1 dose	Subsequent doses and dosing interval based on pharmacokinetic evaluation		
Amikacin	Cystitis: 15 mg/kg/dosed IV once All other infections: 20 mg/kg/dosed IV × 1 dose	Subsequent doses and dosing interval based on pharmacokinetic evaluation		

ill patients along with the emergence of resistance to therapy, combination therapy would still be a prudent choice in patients with moderate to severe infections.

Other therapies

(1) Cefiderocol: cefiderocol, a siderophore antibiotic, has not been shown to be superior to other therapies available for CRAB infections; however, this is the only option when the isolate is resistant to most of the available agents (XDR CRAB).[122] However, it is also reported that most CRAB isolates, even with OXA-type beta-lactamases, are susceptible to cefiderocol[123]

(2) Eravacycline: eravacycline, usually used for complicated intra-abdominal infections, can be a viable option in treating CRAB infections resistant to first- and second-line antibiotics. Although *in vitro* assays do report activity against CRAB, due to the lack of information on CLSI breakpoints, these interpretations are meaningless and are not approved for treating CRAB infections[124]

(3) Personalized bacteriophage-based therapeutic cocktails: with the rise in antibiotic-resistant bacteria, bacteriophage therapy (or phage therapy) may be an appropriate choice for the treatment of CRAB infections. It is possible to reduce the likelihood of new resistance by using lytic

bacteriophage as a monotherapy treatment option or in combination therapy with other classes of antibiotics.[125] Although different case reports are there in the literature, the clinical and practical applications are still far from applied in daily life[126,127]

(4) Sulbactam-durlobactam: this is a beta lactam-beta lactamase inhibitor combination that has shown to be non-inferior to colistin in terms of 28-day mortality in treating CRAB infections[128]

Disease-specific therapies

(1) Pneumonia: in cases of pneumonia, inhaled polymyxin can be added to systemic therapy. Inhaled drugs reach a very high concentration in the lungs and cause minimal systemic toxicity. Inhaled polymyxins can cause bronchospasm, and it is advised to pre-nebulize the patients with a bronchodilator

(2) Bacteremia: CARB bacteremia if associated with an intravascular catheter should be removed. Combination therapy is beneficial

(3) Meningitis: intrathecal administration of colistin is advised in refractory cases. If associated with a device, revisiting the operated site and removing the device along with antibiotic wash is recommended

(4) Skin and soft tissue infections: duration of therapy becomes longer in these cases, and tigecycline has better penetration into these tissues

(5) Urinary tract infections: it is key to differentiate colonization from infection, and removal of the catheter is the first step. If antibiotics are indicated, there is poor penetration of minocycline, tigecycline, and polymyxin B. Other antibiotics can be considered

STRENGTHS AND WEAKNESSES OF CURRENT STRATEGIES AGAINST CRAB—PROMISING NEW THERAPIES

Nowadays, polymyxins—which were initially identified in the 1950s and dropped in the 1980s because of their toxicity profile and the availability of carbapenems and cephalosporins—are used as first-line antimicrobials against CRAB, either alone or in conjunction with other medications. Despite their strong *in vitro* effectiveness against strains of *A. baumannii*, polymyxins have a limited therapeutic scope, a lack of clinically meaningful susceptibility breakpoints, and severe nephrotoxicity and neurotoxicity side effects.[129] Moreover, resistance arising during treatment as a result of colistin-resistant bacteria and challenges in identifying heteroresistance are significant problems that could lead to adverse clinical results. CRAB infections cannot be safely and effectively treated with polymyxin-based medications due to their high toxicity, unclear optimal dosage, and growing resistance.[130–133] It has recently been suggested that an individually tailored approach that takes into account host factors, the infection site, pharmacokinetic-pharmacodynamic principles, the local molecular epidemiology of CRAB isolates, and the cautious interpretation of antibiotic susceptibility test results is necessary for the effective treatment of CRAB infections.[134] A sulbactam-based regimen with at least one additional *in vitro* active drug is advised in the majority of clinical situations.

Bacteriophage therapy, often known as phage therapy, is a viable alternative option for the management of *A. baumannii* infection due to the rise in antibiotic-resistant bacteria.[135] Although the results of this clinical use of bacteriophages indicate that phage therapy may be used to treat critically ill patients in whom *A. baumannii* strains were found, bacteriophage medicine currently lacks regulatory approval in both the US and the EU.[125,136] According to Styles et al.,[125] certain bacteriophages, including vPhT2, can even be transformed into antimicrobials or safe hand sanitizers for use in medical facilities. This indicates further potential for phage therapy in the future; nevertheless, further research is necessary to properly understand phage therapy as a strategy to combat *A. baumannii* strains. Antimicrobial peptides (AMPs) are effective against strains of *A. baumannii*. The combination of cecropin A and melittin is effective in causing peritoneal sepsis in an animal model of *A. baumannii* infection; brevinin-2, alyteserin-2, and cationic α-helical peptides have bactericidal activity; proline-rich peptide A3-APO effectively controls the bacteria in a mouse model more effectively than imipenem; and AMP LL-37 (human AMP) or WAM-1 (marsupial AMP) prevents the formation of biofilms.[137,138] AMPs must be further developed to increase their selectivity against infectious pathogens, decrease their cytotoxicity to mammalian cells, increase stability, and reduce costs by creating peptides as short as feasible before they can be considered for therapy.[135]

Another tactic against *A. baumannii* infections is the CRISPR system, which stands for clustered regularly interspaced short palindromic repeats. By altering the genome of bacterial strains resistant to antibiotics, this technique can be utilized to eliminate the resistance determinants for use in antimicrobial therapy.[137] The short, repeated sequences in CRISPR loci, which are separated from one another by single sequences of 26–72 pairs of lengths derived from plasmids, transposons, or other mobile genetic elements, give CRISPR great specificity. Although CRISPR is a new therapeutic approach to manage *A. baumannii* outbreaks, it has drawbacks in treating infections, such as the requirement for specific protospacer adjacent motif (PAM) sequences, off-target mutations, and the delivery of the protein–RNA complex through the bacterial membrane.[135] Therefore, more research should be done to validate its application in bacterial resistance management. The development of vaccines against *A. baumannii* is a potential and affordable way to protect vulnerable groups, including the elderly and immunocompromised people.[139] However, there is not a licensed vaccine at this time. The quest for the best vaccine and/or medication option to prevent *A. baumannii* infection is currently ongoing, and more research is required for vaccine development.[139,140] The development of new medicines, quick and precise methods for identifying organisms, and other anti-virulence therapy approaches are all necessary given the increasing prevalence of MDR *A. baumannii*. Repurposed medications, naturally occurring compounds, nanoparticle-based therapy, anti-virulence tactics, immunotherapy, photodynamic and sonodynamic therapy, and other novel approaches are being tested as additional alternative therapies for *A. baumannii*-associated pneumonia.[141]

CRAB INFECTIONS—PRACTICAL IMPLICATIONS FOR HEALTHCARE PRACTITIONERS

In healthcare settings, CRAB can proliferate rapidly and be challenging to eliminate. Prompt implementation of infection control treatments is crucial to safeguard hospitalized patients and residents of nursing homes upon identification of CRAB. Public health agencies and healthcare facilities must work together to stop the spread of CRAB.[142] Healthcare facilities are urged to get information from their state health departments and public health laboratories regarding the availability of CRAB carbapenemase and antimicrobial susceptibility tests, as well as CRAB epidemiology, including underlying mechanisms of resistance and hospitals and can be challenging to get rid of. Prompt implementation of infection control treatments is crucial to safeguard hospitalized patients and residents of nursing homes upon identification of CRAB. To effectively treat severe nosocomial infections and reduce the frequency and likelihood of outbreaks caused by *A. baumannii*, the government, industry, scientific community, doctors, and other healthcare professionals must cooperate. Patients who are CRAB-infected should be housed in single-patient rooms whenever possible. Patients with the highest risk of transmission (such as those with incontinence) should be assigned single-patient rooms if there are only a limited number of them. Put on a gown and gloves in long-term care settings when in contact with patients who are colonized or infected with CRAB. For patients being transferred from high-risk environments, think about using these safeguards empirically. Examine the facility's infection prevention and control procedures and provide personnel comments, paying special attention to adherence to hand hygiene donning, doffing, and adhering to personal protective equipment cleaning and disinfecting the environment.

CONCLUSIONS

The emergence of carbapenem-resistant *A. baumannii* (CRAB) poses a significant and formidable obstacle to contemporary healthcare systems, as it has acquired resistance to a very effective category of antibiotics. The rise of CRAB infections has resulted in heightened rates of morbidity, death, and healthcare expenditures. The resolution of this dilemma requires the advancement of novel medicines capable of efficiently combating infections caused by CRAB. In recent times, there has been a noticeable lack of progress in the development of novel antibiotics. The absence of motivating factors for pharmaceutical enterprises to allocate resources toward antibiotic research, along with the intricate nature and financial burdens connected with medication development, has impeded advancements in this field. Nevertheless, the pressing nature of the CRAB crisis necessitates prompt intervention. The establishment of collaborative initiatives among governments, academics, and the pharmaceutical sector is vital to provide the necessary motivation for antibiotic discovery and facilitate the timely implementation of novel treatment alternatives. Furthermore, the exploration of innovative strategies for the creation of antibiotics is of utmost importance. It is recommended that researchers undertake investigations into alternate modes of action that specifically address the vulnerabilities of CRAB. These mechanisms may involve the disruption of CRAB's biofilm formation, quorum sensing, or virulence factors. The use of combination therapy that incorporates established antibiotics alongside novel drugs has the potential to successfully address infections caused by CRAB. Regulatory authorities play a crucial role in expediting the licensing process for novel antibiotics. The acceleration of the availability of life-saving medicines can be facilitated by the implementation of expedited routes for pharmaceuticals targeting CRAB, the adoption of simplified clinical trial designs, and the establishment of adaptable post-market surveillance systems. The prevention of the continued dissemination of CRAB necessitates the implementation of a comprehensive and multidimensional strategy. The use of infection control measures, including enhanced hygiene practices, isolation protocols, and judicious antibiotic usage, is crucial for effectively controlling the propagation of the infection. It is imperative to enhance surveillance methods to effectively monitor the incidence and transmission of CRAB strains, hence facilitating prompt responses.

The emergence of carbapenem-resistant *A. baumannii* necessitates prompt measures to facilitate the development of novel medicines capable of successfully addressing this powerful pathogenic organism. Collaborative endeavors, pioneering investigations, regulatory assistance, and measures to manage infections are all vital constituents of a complete approach to tackling this pressing healthcare problem. Through the allocation of resources toward the advancement of antibiotic development and the implementation of a comprehensive strategy, our objective is to reclaim a position of advantage in the continuing combat against CRAB and ensure the preservation of healthcare in the years to come.

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DECLARATION OF INTERESTS

The authors declare no competing interests.

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