Journal of Chemical Health Risks

www.jchr.org

JCHR (2024) 14(2), 1230-1243 | ISSN:2251-6727

A Review of Carbapenem-Resistant *Acinetobacter Baumannii* as A Biofilm Producer Pathogen

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(Received: 07 January 2024 Revised: 12 February 2024 Accepted: 06 March 2024)

KEYWORDS
Carbapenem-resistant Acinetobacter baumannii, nosocomial, colonization, genes, biofilm

ABSTRACT:

Acinetobacter baumannii (A. baumannii) has become a major hospital-acquired infectious agent and is rapidly developing resistance to antimicrobials that are routinely prescribed. Carbapenem-resistant A. baumannii (CRAB) was one of the strains that had been resist to carbapenem. The CRAB has ability in biofilm formation that can lead to severe nosocomial infection. It gained popularity recently for being associated with devastating soft tissue infections in humans mostly in healthcare workers and patients admitted in ICUs. The amount of data currently available provides support to the theory that rising infection rates are caused by the widespread contamination of progressively resistant A. baumannii in hospitals.

Acinetobacter baumannii (A. baumannii)

A. baumannii is a Gram-negative, rod-shaped bacterium that is found in various environmental settings. It is an opportunistic pathogen and a major causative agent of serious nosocomial infections worldwide [1]. *A. baumannii* is capable of surviving in hostile environments, displaying multiple drug resistance and an extraordinary ability to persist within healthcare-associated environments. *A. baumannii* is considered an "intelligent survivor" due to its ability to respond to environmental fluctuations and rapidly transmit plasmid-associated-resistance determinants which contribute to its high prevalence in both community as well as hospital settings [2].

A. baumannii was previously, a benign organism that was mainly found in our surroundings, especially in soil and water-wet areas such as hospital sinks. Nowadays this microorganism developed as a crucial nosocomial pathogen causing multiple problems in the healthcare system, particularly in the intensive care unit (ICU) [3]. The microorganism is especially adept at colonizing the sites of colonization (tubing used in medical procedures, ventilatory equipment, and catheters) leading to an increased risk of nosocomial infections [4,5]. *A. baumannii* can form biofilm.

Increased prevalence of drug-resistant *A. baumannii*, including CRAB, has become a major clinical threat due to the intrinsic of the bacteria and acquired resistance mechanisms. The ability of *A. baumannii* to resist several drugs is due to various resistance factors, such as the existence of extended-spectrum b-lactamases and biochemical enzymes which expressed by the bacteria, along with efflux pumps which help the removal of harmful substances from the bacterial cell [6]. Furthermore, CRAB can exist as biofilms increases its resistance to antimicrobials, and serves as a protective mechanism against potential elimination [7].

Recent studies have focused on strategies for combating drug-resistant strains of *A. baumannii*. Such strategies include the use of alternative antibiotics, plant extracts,

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JCHR (2024) 14(2), 1230-1243 | ISSN:2251-6727

and bacteriophages. Antibiotic monotherapy is often ineffective because of the highly complex microbiota of nosocomial infections and is increasingly losing its efficacy. Therefore, the problem of the resistance of *A. baumannii* towards antibiotics often necessitates the search for effective alternative therapies [8].

Taxonomic Classification *A. baumannii*

Taxonomically, the genus *Acinetobacter* belongs to the family known as Moraxellaceae. The details taxonomy hierarchy of *A. baumannii* is shown in Table 1 [9].

Table 1 Taxonomy and classification of *A. baumannii*

Rank	Name
Kingdom	Bacteria
Phylum	Proteobacteria
Class	Gammaproteobacterial
Order	Pseudomonadales
Family	Moraxellaceae
Genus	*Acinetobacter*
Species	*Acinetobacter baumannii*

Morphology of *A. baumannnii*

A. baumannii is a Gram-negative coccobacillus bacterium found in the soil and water, and it prefers moist environments. *A. baumannii* is a hospital-acquired pathogen. This microorganism was able to grow well at 37°C on routine solid media, such as sheep blood agar. *A. baumannii* is a non-motile, non-spore-forming organism that shows poor cultural and biochemical characteristics. Unlike many bacteria, *A. baumannii* can survive in diverse and hostile climates, exhibiting extreme resilience against temperatures, pH, detergents, and antiseptics [10]. When grown on cultural plates, *A. baumannii* colonies are smooth and circular, measuring 1-2 mm in diameter [9]. The colonies are shown in Figure 1.

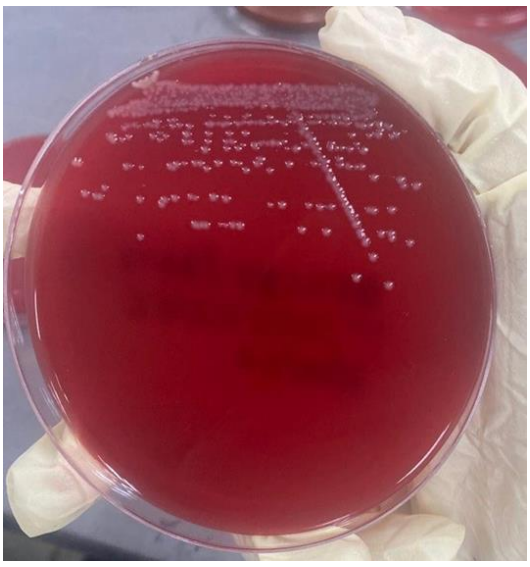

Figure 1 *A. baumannii* colonies grow on sheep blood agar.

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A. baumannii also contains a wall-less LPS (Lipopolysaccharide) layer that is surrounded by another outer capsule layer composed of lipopolysaccharide and teichoic acid [11]. Cellular components such as enzymes and toxins are also contained in the outer capsule layer. This type of capsule layer allows the bacterium to adhere to the surfaces of endotracheal tubes, providing an additional protective layer against environmental stresses [11].

Cell surface structures such as fimbriae, flagella, and pili are also important components of *A. baumannii* and help enable the bacterium to move around and adhere to surfaces [12]. Fimbriae are small protein-based structures that allow the bacterium to adhere firmly to surfaces. Flagella are filamentous organelles that allow the bacteria to move around. Pili are short appendages that are involved in specific interactions between bacteria, with the most common type being the sex pili which are responsible for interbacterial conjugation [12,13].

Ultrastructure analysis of *A. baumannii*

Scanning Electron Microscopy (SEM) analysis is the most common way used to visualize *A. baumannii* at the cellular level (Figure 2). SEM images indicate collapsible egg-shaped rods with a capsule layer of carbohydrate material around their exterior [14]. An effective method for analyzing the surface features of biological materials is SEM. An SEM analysis showed that extracellular appendages joined *A. baumannii* cells to each other. The effects of antibiotic therapy on biofilm formation were investigated, and the surface structures of biofilms formed on the MBEC test were examined using SEM.

The Gram-negative coccobacillus can be visualized by SEM analysis, the former revealing egg-shaped rods with a capsule layer of carbohydrate material and the latter showing that the cells are organized in a propeller-like arrangement.

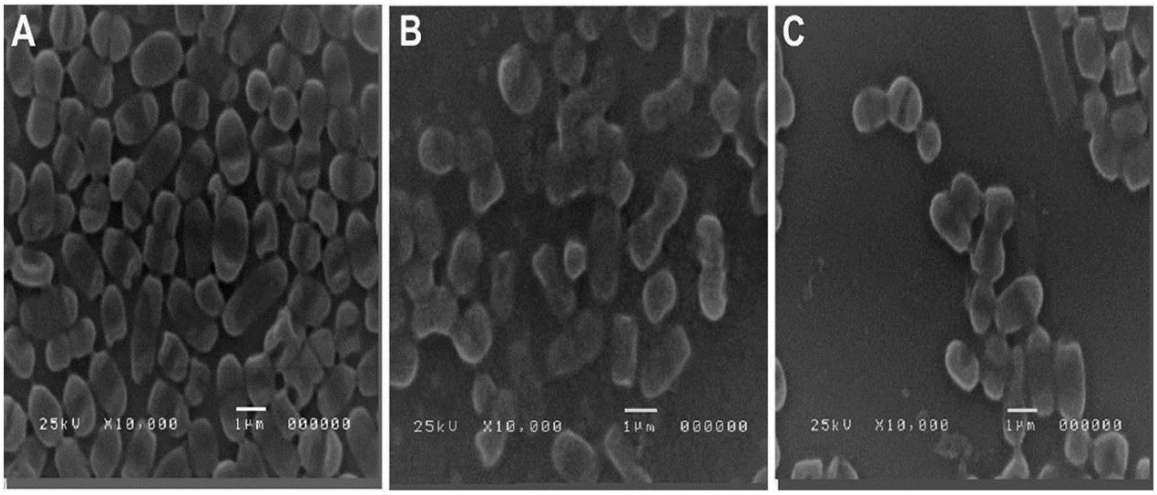

Figure 2 Scanning electron microscopy images; (A) untreated strong biofilm producer *A. baumannii* isolates, after (B) a 24-hour treatment with sub-MIC cinnamic acid, and (C) a 24-hour treatment with sub-MIC gallic acid. Magnification 10,000× [14].

History of *A. baumannii* and the emerging strain of CRAB

The *Acinetobacter* bacteria was initially isolated in 1911 by Dutch M. W. Beijerinck from soil using minimum media that was enhanced with calcium acetate [5]. *Acinetobacter* is a genus of bacteria that was first discovered in the early 20th century, but it was acknowledged in the last decade as a common pathogen. The most prevalent species of *Acinetobacter* involved in clinical infections is *A. baumannii*, which makes up 73% of all *Acinetobacter* clinical isolates and is one member of the *Acinetobacter calcoaceticus-A. baumannii* complex. *A. baumannii*, formerly known as *Acinetobacter calcoaceticus*, is a waterborne and soil-based pathogenic organism [15].

From 1992 to 1996, annual susceptibility reports showed that all isolates of *A. baumannii*, whether endemic or epidemic, were susceptible to colistin, sulbactam, and carbapenem, but resistant to two or more antibiotic families, always including gentamicin and b-lactams. Nonetheless, three main patterns of antibiotic sensitivity in the *A. baumannii* population could be identified based on the varying susceptibilities to tobramycin, amikacin, ciprofloxacin, and tetracycline [16].

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JCHR (2024) 14(2), 1230-1243 | ISSN:2251-6727

A. baumannii was vulnerable to standard antibiotics in the 1970s, but it has since evolved into an MDR bacterium that can acquire resistance genes. The first hospital-wide outbreak of *A. baumannii* infections in New York City in 1991 raised initial concerns on multi-resistant, CRAB infections [16]. In 1991, CRAB, one of the earliest strains of *A. baumannii* resistant to antibiotics, was also discovered in the United States [15]. In the 1,000-bed hospital in Barcelona, Spain, a persistent outbreak of multi-resistant *A. baumannii* infections was observed starting in 1992. This led to a significant overuse of imipenem, to which the organisms were universally susceptible. CRAB strains first appeared in January 1997 and spread quickly throughout the ICU [16].

Subsequently, reports of worldwide outbreaks and CRAB infections emerged from a number of countries, including Brazil, Cuba, France, England, Hong Kong, Singapore, Argentina, and Spain [15,16]. The possibility that the world might be approaching the post-antimicrobial era is raised by the current global concern over the increasing number of resistant organism populations in medical environments [16].

Epidemiology of CRAB

The increasing emergence of CRAB strains has become another worrisome truth in recent years and a major problem in a hospital environment that can cause elevated morbidity and mortality rates due to treatment difficulties [10,14,16,17]. Between 2005 and 2009, *A. baumannii* from a global collection developed imipenem resistance rates that exceeded 50% [17].

About two out of every three isolates in Brooklyn, New York, were found to be resistant to the antibiotic carbapenem, according to citywide surveillance. After being established in a university hospital in Chicago in 2005, one of the CRAB strain-types has become predominant. Furthermore, it was revealed by molecular epidemiological studies of successive *A. baumannii* outbreaks in ICU that carbapenem resistance first appeared in Italy between 1999 and 2002 [16,17].

In China, it has been observed that imipenem-resistant *Acinetobacter* spp. is spreading clonally, and *OXA-23* carbapenem genes are widely dispersed as well. The percentage of healthcare-associated infections in Taiwan caused by CRAB increased significantly from 14% in 2003 to 46% in 2008, compared to infections by all *A. baumannii* [17].

According to the Malaysia National Surveillance of Antibiotic Resistance (NSAR), Malaysia's overall rate of carbapenem resistance grew from 49% in 2008 to 61% in 2016, after that it remained largely stable at 60% annually [18]. The rate of CRAB in the general ICU at the University of Malaya Teaching Centre (UMMC) has remained high, at approximately 0.5 per 100 admissions annually, according to confidential hospital surveillance statistics. This percentage exceeds the national KPI for MDR *A. baumannii* incidence in Malaysia, which is 0.3 per 100 admissions. 74% of the isolates in research carried out in a tertiary-care hospital in Johor, Malaysia, demonstrated dominant genotypes [18].

Figure 3 displays the rates of carbapenem resistance in *Acinetobacter* spp. isolates from Malaysia (1987–2016). Meropenem is MEM, and imipenem is IMP. A purple font is used to indicate the NSAR data, along with the acronym "NSAR". The information below is derived from the other studies: Hospital Selayang (H. SLYG) in 2010, UMMC from 2008 to 2009, HUSM from 2003 to 2006 and 2005 to 2009, UKMMC from 2010 to 2011, and UMMC from 1987 to 1987 and 1996 to 1998. A variety of data was acquired in 2010 and 2011 from various hospitals in the state of Perak, mostly in the area of the town of Ipoh; in 2011 from HSNZ; and in 2011 and 2012 from Hospital Sultanah Aminah (HSA) [19,20].

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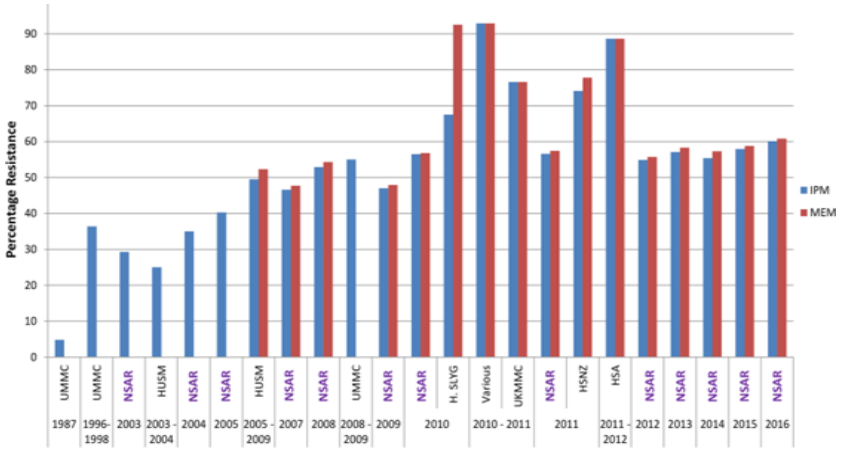

Figure 3 Carbapenem resistance rates for Malaysian *Acinetobacter* spp. isolates (1987–2016).

CRAB Colonization and Subsequent Infection

A. baumannii has been identified as a common cause of colonization in endotracheal tubes of intubated patients [20-22]. Colonization of this microorganism in the ETT of patients is an important risk factor for nosocomial pneumonia. Furthermore, *A. baumannii* has been linked to the formation of biofilms on various surfaces that provide the bacteria with protection from antibiotics, allowing them to survive in hostile environments [23,24].

A. baumannii also has a high ability to transfer genes to other bacteria in its family and transform them into more resistant strains. One main consequence of this ability is the formation of CRAB. It has been estimated that CRAB is responsible for most *A. baumannii* infections [7]. The fatality and morbidity rate of nosocomial infections have increased due to the development of a carbapenem-resistant variant of this bacterium. This variant showed high resistance to antibiotics such as carbapenem, fluoroquinolone, and polymyxin [23].

In recent years, antibiotic-resistant *A. baumannii* has become an increasingly serious matter of concern. To combat CRAB infections, it is crucial to develop alternative strategies, such as the use of natural products, that can regulate the growth of *A. baumannii*. Thus, it is important to develop novel compounds for the prevention and treatment of CRAB colonization of ETT.

Pathogenicity of CRAB

The pathogenic elements of CRAB are the secretory micro aspiration and the biofilm formation [21]. CRAB is one of the multidrug-resistant bacteria that have the ability to grow biofilms on biological surfaces that not alive, medical equipment, and host tissues in a clinical setting [23]. This capability will make it harder to treat infection since it will prevent antibiotics from diffusing to the site of action and enable the organism to resist antibiotics [7].

Then, variety of enzymes are produced during CRAB infection including enzymatic degradation by carbapenem enzymes, specifically *oxacillinases (OXA*) and metallo-β- lactamases, which is the most established mechanism of carbapenem resistance in *A. baumannii*. Most of these enzymes' genes are found in plasmids.

OXA in *A. baumannii* include *OXA-23*-like, and the intrinsic *OXA-51*-like enzymes [19]. *OXA* are significantly the most common type of *A. baumannii* carbapenem genes. *OXA-51* and *OXA-23* genes coexisted in 83% of clinical isolates. Since the *OXA-23* gene is plasmid-encoded, the fact that *OXA-23* is frequently detected in hospitals may be related to the horizontal spread of plasmid-bearing plasmids [19,25].

Metallo-β-lactamases are carbapenem-active enzymes that pose a risk to medical professionals because of the high level of resistance shown by the bacteria that produce them, as well as their capacity to hydrolyze carbapenem efficiently [26,27]. Metallo-β-lactamases variants, including imipenemase (IMP), and New Delhi metallo-β-lactamase (NDM), have been found globally in *A. baumannii* [25].

Resistance Genes Associated with CRAB

Multiple studies have identified a range of virulence factors, including resistance mechanisms, which are frequently associated with *A. baumannii.* This includes several types of resistance genes, which can be divided into several categories: multidrug-resistant (MDR) genes, such as extended-spectrum β-lactamase (ESBL), carbapenemase, quinolone resistance, aminoglycoside resistance, and macrolide resistance genes [14].

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JCHR (2024) 14(2), 1230-1243 | ISSN:2251-6727

The resistance genes are considered to be the main factors responsible for *A. baumannii* success as a nosocomial pathogen, primarily due to their ability to confer resistance to several classes of antibiotics used in the clinic. Carbapenem resistance genes have been identified as conferring resistance to β-lactam drugs [10]. These genes, which are mostly found on plasmids or transposons, can rapidly transfer to other strains that are related to them in the appropriate environmental circumstances, allowing resistance to develop quickly [10].

The emergence of carbapenem genes including *blaOXA-23* and *blaNDM-1* in *A. baumannii* has been previously identified in North Africa, more specifically in Morocco. However, there is just little data available regarding the spread of these enzymes in Moroccan hospitals [28]. Carbapenem genes are also a major concern with *A. baumannii*, as these can confer resistance to last-line antibiotics such as carbapenem [10]. They harbor chromosomal genes, rather than plasmids or transposons, and can spread to other strains through horizontal gene transfer. *BlaOXA-23* is the most often identified carbapenem gene in *A. baumannii* [10]. Thus, multiple resistance genes, including carbapenem have been associated with *A. baumannii*.

Biofilm Formation Genes with CRAB

With the ability to produce biofilms and resistance to multiple drugs, *A. baumannii* including CRAB is becoming more well-recognized as a harmful pathogen. The ability of *A. baumannii* to build biofilms substantially aids the organism's high transmissibility in healthcare settings. Pathogens acquire protection from biofilms against external stimulation [29-31]. As a result, many illnesses respond inconsistently to antibiotics. The outer membrane protein A (*ompA*), the pilus-like bundle structure mediated by the *csuE* gene, and the biofilm-associated protein produced by the *bap* gene, are among the genetic factors related to biofilm [14,24].

However, there is still disagreement regarding the relationship between biofilms and MDR *A. baumannii* isolates antimicrobial resistance. According to certain studies, *A. baumannii* exhibits significant levels of antibiotic resistance while developing weak biofilms [32], whereas other studies found a link between MDR *A. baumannii* isolates capacity to form biofilms and antimicrobial resistance.

Clinical Manifestation of CRAB

A. baumannii infection, especially CRAB is associated with a high mortality rate and is responsible for a range of severe diseases, including pneumonia (VAP), bloodstream and wound infections, sepsis, endocarditis, and urinary tract infections. This is concerning for healthcare workers because infections from *A. baumannii* can spread quickly throughout the hospital, leading to cases of nosocomial infections. Healthcare workers are at risk of contracting nosocomial infections from *A. baumannii* due to contact with infected patients, contaminated hospital environments, and inadequate infection control practices [21,22]. In addition, cross-transmission of CRAB has been reported due to contact with medical instruments and overuse of medical devices such as endoscopes and endotracheal tubes. As such, these medical devices are considered high-risk items for the spread of CRAB in hospitals [9].

(a) Ventilator-associated Pneumonia (VAP)

CRAB is a common colonizer of the ETT. ETT is an important airway management device for critically ill patients, and colonization of ETT by CRAB is associated with an increased risk for nosocomial pneumonia [33]. The CDC and the Healthcare Infection Control Practices Advisory Committee recommend an ETT with a dorsal lumen to make it easier to drain respiratory and orotracheal secretions. Uncuffed ETTs, on the other hand, are usually utilized in newborns presenting a higher risk of VAP since they are linked to a lower requirement for ETT modifications and post-extubating stridor but an increase in the duration on ventilatory support [34]. The VAP development based on biofilm formation on the ETT surface is shown in Figure 4.

VAP is a harmful, perhaps fatal illness that can cause organ damage, sepsis, and inflammation driven by endotoxins [21]. Patients either young or old may experience delirium or brain inflammation. Some management principles have been developed to stop VAP from happening. *A. baumannii* is capable of forming biofilms on the surface of ETT shown in Figure 5 which mediates its colonization and is associated with increased resistance to antibiotics. Therefore, it is imperative to develop novel compounds for the prevention and treatment of CRAB colonization of ETT.

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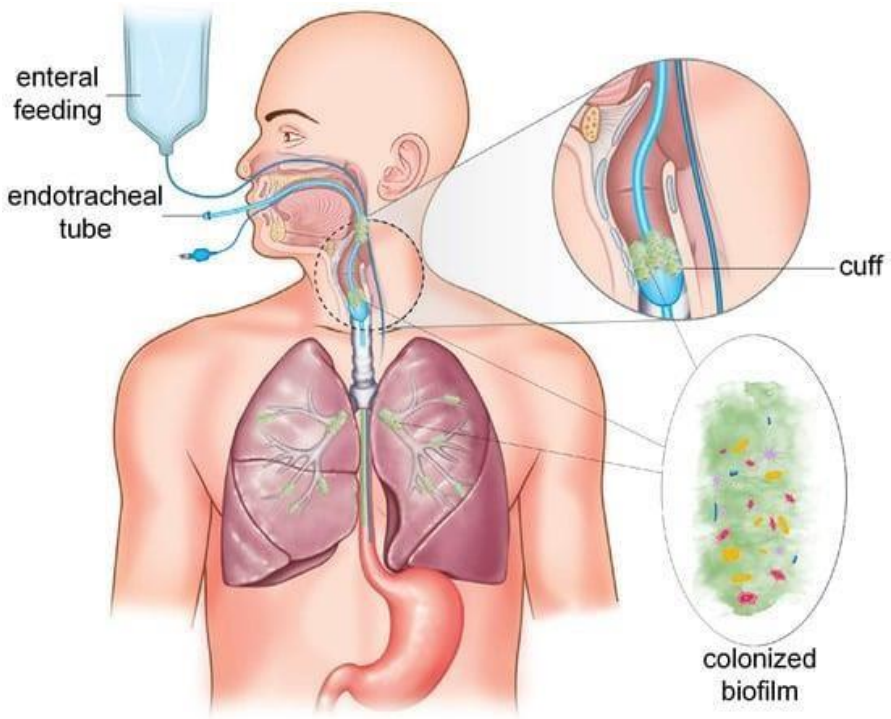

Figure 4 VAP development based on biofilm formation on the endotracheal tube surface [34].

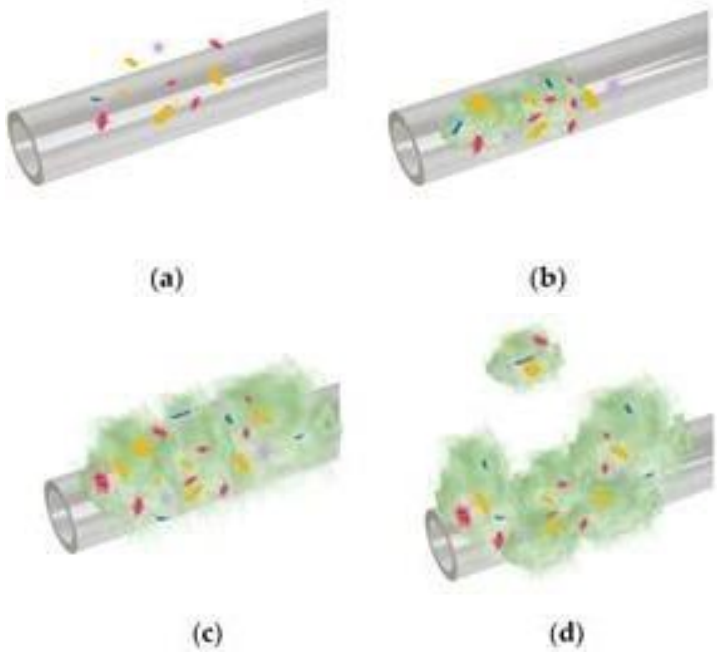

Figure 5 Complex biofilm formation on ETT surface goes through the following stages: (a) attachment phase, during bacteria transition state from planktonic to sessile; (b) establishment phase, during the biofilm extracellular matrix is secreted; (c) development and maturation of the biofilm; and (d) dispersion and disassembly of the biofilm [34].

b) Other Diseases Caused by CRAB

Other common diseases caused by CRAB are bloodstream infection, wound infection, community-acquired infections, and urinary tract infection.

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Although earlier infection acquisition may happen in outbreak situations, patients with these diseases typically had extended stays in the intensive care unit. Moreover, there are just a few case reports of endocarditis caused by *Acinetobacter*. Sometimes associated with contact lens wear or after eye surgery, *Acinetobacter* spp. can cause keratitis or endophthalmitis.

CRAB was recognized as one of the most common infectious agents in significant research on nosocomial bloodstream infections in the United States (1995–2002). This analysis found that 1.3% of all monomicrobial nosocomial bloodstream infections were caused by this agent. In those circumstances, *A. baumannii* was responsible for 1.6% of bloodstream infections obtained in the ICU as opposed to 0.9% of infections acquired outside of the ICU unit. Bloodstream infections resulted in overall death rates that varied from 34.0% to 43.4% in the ICU and 16.3% outside of ICU. The mean time between *A. baumannii* bloodstream infections and hospital admissions was 26 days, suggesting that these bloodstream infections were the most recent to occur during hospitalizations [9].

A. baumannii can cause wound infections which infect soft tissues and skin outside of the military community. In one review, 2.1% of skin and soft tissue infections obtained in the ICU were attributed to the organism. It is a well-known infection in burn units, and treating patients with it may be challenging. Its role in the poor prognosis of burn patients is debatable, but *A. baumannii* is frequently isolated from wounds of combat casualties in Afghanistan or Iraq [9].

In countries with hot, humid climates, community-acquired illnesses manifest as unique and severe clinical conditions [35]. Individuals who have underlying medical disorders such as diabetes mellitus and chronic obstructive pulmonary disease, as well as heavy smokers and excessive alcohol consumption, are more likely to contract these illnesses. Mortality rates for community-acquired *A. baumannii* infections are as high as 64% [35]. However, it is not yet known what causes the difference in disease presentation between community and hospital infections, rather host or bacterial factors.

1.6% of urinary tract infections acquired in intensive care units were caused by *A. baumannii.* The organism is usually linked to colonization or infection related to catheters. It is unusual for this organism to cause healthy outpatients to develop a simple urinary tract infection [5,9].

Treatment of CRAB Infection

Patients infected with CRAB were treated based on the type and location of the infection, severity of symptoms and antibiotics towards CRAB [36]. The treatment of CRAB infection is complex and often challenging due to the increasingly high antibiotic resistance rates of *Acinetobacter* spp. and its ability to persist on ETT. The use of antibiotics to treat *Acinetobacter* is often limited due to increasing resistance to common antimicrobials, or the development of side effects related to their use.

In addition to antibiotic treatment, researchers have explored the use of adjuvant therapies such as plant extracts and photodynamic inactivation to help reduce the carriage of *Acinetobacter* on ETT. Plant extracts provide an alternative way to reduce the colonization of CRAB on ETT due to their antibacterial and antibiofilm properties. In a study on the antibacterial activity of *S. persica* extracts conducted by Al-Ayed *et al*, it was found that methanol extract of *S. persica* exhibited a stronger antibacterial activity against Gram-negative (3.3–13.6 mm) than Gram-positive (1.8–8.3 mm) bacteria. Methanol extract also appears to be a potent antimicrobial agent in this study [8].

Moreover, a study by Balto *et al* (2017) [37] compared the effect of ethanolic and hexane extracts of *S. persica*. Ethanol and hexane extracts of *S. persica* were found to exhibit maximum antimicrobial activity against *S. mutans, S. sanguis* and *S. salivarius* at high concentrations. All isolate growth was eradicated by an ethanol extract at a concentration of 8 mg/ml (MBC value). *S. sanguis* and *S. salivarius* required just 4 mg/ml (MBC value) of hexane extract to eradicate them, although *S. mutans* was the most resistant (MBC = 8 mg/ml) [37].

Antibiotics

Treatment options for infections caused by *A. baumannii* strains especially CRAB that resistant to antibiotics typically consist of a sufficient number of safe and efficient antimicrobial drugs. Therefore, the majority of research has concentrated on finding effective treatments for carbapenem-resistant *A. baumannii* infections (Table 2.2). There is a tentative consensus that a polymyxin (colistin [polymyxin E] or polymyxin B) should be included in any treatment as the fundamental component for treatment of infections caused by colistin-susceptible isolates and likely colistin- resistant isolates as well, despite the fact that numerous treatment approaches have been proposed through in vitro, in vivo, and clinical studies [32].

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There is some reluctance to use polymyxins, despite the recent inclination toward usage. In the 1980s, polymyxins were discarded due to their toxicity profile for the majority of other illnesses. For this reason, tigecycline and sulbactam, both alone and in combination, are preferred by many clinics and medical centers as alternative therapies for isolates resistant to carbapenem [38-41].

Notably, colistin is given intravenously as the less active prodrug colistimethate (colistin methane sulfonate), which gradually transforms into the active medication colistin in the serum [41]. However, the majority of scientific publications refer to colistimethate as colin. Conversely, the active medication colistin is utilized for in vitro susceptibility and synergy testing.

Table 2.2 Agents used in the treatment of CRAB infections [32].

Drug	**Dosing for *A. baumannii* infections (normal renal function)**	**Advantages**	**Drawbacks**	**Ongoing questions**
Colistin (as colistimethate)	5 mg kg/day loading dose followed by 5 mg kg/day divided in 2 or 3doses	Mainstay of therapy; used in combination with other agents	Nephrotoxicity; low serum concentrations especially early in therapy; resistance via lipid A modification	Efficacy when optimally dosed; optimal companion agent for combination therapy
Fosfomycin*	4 g every 12 hours used in a randomized trial; potential for higher doses; used in combination	Bactericidal; relatively well tolerated	No approved intravenous formulation in the U.S.; modest activity alone; difficulties with MIC determinations	Larger trials to prove added benefit in the context of combination therapy
Rifampin*	600 mg every 12 or 24 hours; used in combination	Widely available; no renal Toxicity	Monotherapy can quickly lead to resistance; liver toxicity and drug- drug interaction	Randomized trial data conflicting regarding overall benefit of adding rifampin
Sulbactam (ampicillin-sulbactam)	3 to 9 g/day (9 to 27g/day of ampicillin-sulbactam); alone or in combination	Widely available in combination with ampicillin; relatively inexpensive	Increasing resistance; not available alone in many countries including the U.S.	Clinical correlation between MIC and outcome; optimal dosing regimen

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Tigecycline	100 mg loading dose followed by 50 mg every 12 hours; alone or in combination	Widely available; active against most strains *in vitro*	Low serum concentrations; bacteriostatic activity; may be inferior to comparators in critically ill patients	Clinical correlation between MIC and outcome; optimal dosing regimen; benefit of combination regimens
Vancomycin*	10 to 15 mg/kg every 12 hours; in combination with colistin	Widely available; strong *in vitro* synergy with colistin; often included in empiric sepsis therapy	Potential for increased nephrotoxicity; no prospective validation of clinical efficacy	Optimal dosing regimen and duration; efficacy in colistin- resistant cases

*These agents are always considered as part of combinations and are not to be used alone.

Chlorhexidine (CHX)

CHX is an age-old antiseptic that has been used in medicine for many years, with uses in both skin and mucosa disinfection, topical and systemic antiseptic therapy, and now, endotracheal tube colonization treatment of CRAB. CHX is a broad-spectrum cationic bisbiguanide used as an active ingredient in the form of aqueous solutions and gels, commercially produced from minerals, plants, and invertebrates. It operates by destroying lipid membranes of microorganisms by disrupting their permeability. It has been reported to be effective against multiple bacterial species, including Gram-positive [42-44] and Gram-negative bacteria [1,45-47], mycobacteria, fungi and viruses, especially in combination with other antimicrobials becoming a cornerstone of some antibiotic regimens.

For its application in endotracheal tube colonization, CHX is adopted as part of a broader long-term treatment for CRAB. The colonization can be achieved through a number of delivery techniques such as instillation of the antiseptic by aerosol or excessive tube colonization. Clinical studies have found that CHX is more effective for reducing endotracheal tube colonization by *A. baumannii* than other antiseptic treatments. A 2017 study conducted by Balto *et al*. on the effect of CHX on infection found 0.2% CHX antibacterial activity against *S. mutans*, *S. sanguis* and *S. salivarius* colonization with MIC and MBC value 0.2 mg/ml for both. CHX acts as a positive control in this study [37].

The use of CHX as an antiseptic has also been well documented in prevention of CRAB colonization in other critically ill patient populations. From [48] study, CHX mouthwash can be offered to patients with dental plaque-induced gingivitis. CHX appears to be more effective in controlling dental plaque and gingivitis [48]. CHX has been found to be effective for VAP in ICU and used as a part of a larger treatment regimen. Most studies have thus far focused on the use of CHX in combination with other antibiotics. CHX was effective at reducing VAP. CHX performed better in the subgroup analysis with patients who had heart surgery than with patients who were in other clinical-surgical circumstances. The reduction in VAP caused by the CHX 0.12%-0.2% achieved is substantial [20].

Despite its effectiveness in treating CRAB colonization, there have been some reports of adverse side effects, such as oral trauma, when CHX is used for prolonged periods of time in endotracheal tube colonization. Dermatitis has also been reported in some studies, leading to more studies focusing on the effects of CHX in combination with other antiseptics or antibiotics. Additionally, there have been few studies that focused on cost-effectiveness analysis when it comes to the treatment of CRAB colonization with CHX.

CHX proven as an antiseptic with both antimicrobial and anti-biofilm properties that has been used in the treatment of CRAB colonization with promising results. Studies have shown that CHX, when used as a part of a larger treatment regimen, is an effective way to reduce or eliminate the colonization of *A. baumannii* in the endotracheal tube. Still, more studies are needed to fully understand the efficacy, potential side effects, and cost-effectiveness of this treatment.

Control and Prevention of CRAB

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JCHR (2024) 14(2), 1230-1243 | ISSN:2251-6727

CRAB is a known pathogen that carried diverse carbapenem-resistant genes. Thus, precaution and prevention measures are very crucial to avoid more problems arise. It is also compulsorily to eradicate the CRAB carriage in the effort to minimize the CRAB infection. To begin with, the strengthening of healthcare infection control program should be implemented. Infections linked to health care were among the most frequent adverse events in the provision of healthcare. Antibiotic-resistant organisms are the fundamental cause of a significant fraction. Quick action is required to prevent the spread of bacteria resistant to antibiotics. Combating antibiotic resistance requires effective infection prevention and control, or IPC. The International Health Regulations (IHR) emphasize this point by designating successful IPC as a critical tactic for addressing public health risks of global concern [49]. In order to reduce the risk of nosocomial pathogens spreading from inanimate surfaces to vulnerable patients, it is important to regularly clean surfaces in a designated patient-care area. Additionally, it is significantly required to develop programs for healthcare workers that provide on-the-job training, an established basis in bacterial resistance, and proper antibiotic usage. Moreover, providing immediate diagnosis and point-of-care tests that can be applied in a doctor's office or by a patient at their bedside may be considered as concern.

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