REVIEW

Treatment and Management of *Acinetobacter* Pneumonia: Lessons Learned from Recent World Event

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Abstract: *Acinetobacter* pneumonia is a significant healthcare-associated infection that poses a considerable challenge to clinicians due to its multidrug-resistant nature. Recent world events, such as the COVID-19 pandemic, have highlighted the need for effective treatment and management strategies for Acinetobacter pneumonia. In this review, we discuss lessons learned from recent world events, particularly the COVID-19 pandemic, in the context of the treatment and management of *Acinetobacter* pneumonia. We performed an extensive literature review to uncover studies and information pertinent to the topic. The COVID-19 pandemic underscored the importance of infection control measures in healthcare settings, including proper hand hygiene, isolation protocols, and personal protective equipment use, to prevent the spread of multidrug-resistant pathogens like *Acinetobacter*. Additionally, the pandemic highlighted the crucial role of antimicrobial stewardship programs in optimizing antibiotic use and curbing the emergence of resistance. Advances in diagnostic techniques, such as rapid molecular testing, have also proven valuable in identifying *Acinetobacter* infections promptly. Furthermore, due to the limited availability of antibiotics for treating infections caused *A. baumannii*, alternative strategies are needed like the use of antimicrobial peptides, bacteriophages and their enzymes, nanoparticles, photodynamic and chelate therapy. Recent world events, particularly the COVID-19 pandemic, have provided valuable insights into the treatment and management of *Acinetobacter* pneumonia. These lessons emphasize the significance of infection control, antimicrobial stewardship, and early diagnostics in combating this challenging infection.

Keywords: *Acinetobacter baumannii*, ventilator-associated pneumonia, VAP, hospital-acquired pneumonia, HAP, carbapenem-resistant *A. baumannii*, CRAB, pneumonia, COVID-19

Introduction

Nosocomial pneumonia (NP) or healthcare-associated pneumonia (HCAP) is typically categorized into two types: hospital-acquired pneumonia (HAP), defined as pneumonia acquired within 48 hours of hospital admission or within 14 days after hospital discharge, and ventilator-associated pneumonia (VAP), defined as pneumonia that develops 48 to 72 h after endotracheal intubation or tracheostomy[1] These types of pneumonia constitute common challenges in healthcare, responsible for 25% of all healthcare-associated infections (HAIs) in both high-income and low/middle-income countries.[1,2]

Mechanical Ventilation (MV) is a non-curative supportive method with specific indications, potential hemodynamic implications, and associated complications.[3] This type of support is essential for patients with altered respiratory function, which impairs gas exchange, oxygen supply for tissue perfusion, and cellular reactions.[4] Pneumonia arises in response to the invasion of microorganisms into the lower respiratory system and lung parenchyma. Intubation compromises the integrity of the oropharynx and trachea, potentially enabling gastric and oral secretions to enter the lower airways.[5]

In Intensive Care Units (ICUs), VAP is among the most common infectious processes among invasively intubated patients receiving mechanical ventilation. It has garnered significant research attention due to its high mortality rate, adverse clinical outcomes, and the substantial costs associated with prolonged hospitalization.[6]

In patients with VAP, various symptoms manifest, including secretions, leukocytosis, new or progressing infiltrates, declining oxygenation, systemic infection (fever, altered white blood cell count), purulent tracheobronchial secretions, changes in sputum characteristics, and the detection of a pathogenic agent.[7] Studies have reported that VAP develops in approximately 10% to 40% of intubated patients on MV, with a hospital mortality rate ranging from 24% to 76%, depending on specific circumstances and pathogens.[8,9]

HAP is a significant yet often underestimated patient safety concern that can affect any hospitalized patient, not just those who are critically ill. Efforts to prevent HAP should be elevated to the same level of concern as the prevention of VAP. Its overall incidence is approximately 1.6%, although this figure may be underestimated as hospitals are not obligated to report cases of HAP as they are for VAP.[10] Interest in HAP has grown due to its high occurrence rate, prolonged hospital stays, substantial cost increases, and elevated mortality rates among adults (ranging from 13.9% to 30%).[10,11]

Acinetobacter baumannii, the predominant pathogen in healthcare-associated infections (HAIs), frequently displays significant acquired resistance and adaptability to various environments, which facilitates its widespread dissemination. The prevalence of carbapenem-resistant *A. baumannii* (CRAB) has notably surged among critically ill patients in recent years. CRAB represents a significant pathogen associated with both mono and polybacterial VAP, posing substantial challenges for healthcare providers.[12] VAP caused by CRAB predominantly affects patients with compromised physiological status.[13] Disease severity is often linked to late-onset HAP/VAP, which is a critical factor associated with increased mortality rates.[14,15] Ciginskiene et al reported a hospital mortality rate of 63.3% in patients with VAP caused by drug-resistant *A. baumannii*.[16]

A growing concern is the escalating multi-drug resistance displayed by this organism, which lacks a unanimous consensus on the optimal antibiotic treatment for VAP caused by CRAB.[17] However, colistin remains the most frequently used primary agent in targeted treatment regimens despite concerns about its ability to achieve adequate lung exposure safely, the risk of renal toxicity, and suboptimal clinical response rates.[18–20] During the COVID-19 pandemic, the excessive use of antibiotics, coupled with disruptions in infection control measures, exacerbated the nosocomial spread of CRAB.[21] Severe infections resulting in crude mortality rates as high as 50% were notable, primarily due to patients' underlying high-risk conditions, the severity of VAP, delays in targeted CRAB treatment, and the absence of scientifically validated effective antibiotics.[22–24] In this article, we will explore essential aspects of this emerging pathogen, with a specific focus on pneumonia.

Taxonomy

The discovery of the *Acinetobacter* spp. Genus traces back to 1911 when microbiologist Martinus Beijerinck isolated a microorganism by enriching the soil with a medium containing calcium acetate. This microorganism was initially described as *Micrococcus calcoaceticus*.[25] Later, in 1954, Brisou and Prévot, through transformation tests and motility assessments, renamed the genus *Acinetobacter* spp.[26] Then, in 1968, Baumann et al, after conducting biochemical evaluations of the genus's nutritional properties, suggested its inclusion in the Moraxellaceae family.[27] Despite two species of *Acinetobacter* spp. Already being identified by that time, Bouvet and Grimont (1986) found the characterization unsatisfactory. They proposed a study to define genospecies (genomic groups) using the thermal stability of hybrids in the DNA-DNA hybridization technique as a criterion.[28] This effort led to the discovery of 12 genospecies, some of which were formally named, including *A. baumannii, A. calcoaceticus, A. haemolyticus, A. johnsonii, A. junii*, and *A. lwoffii*.[28,29] To date, 108 species have been described, with 83 having validated nomenclature, including synonyms.[30]

Notably, the *A. calcoaceticus – A. baumannii* complex (ACB complex) consists primarily of nonpathogenic environmental species, such as *A. calcoaceticus* (genomic species 1), along with five pathogenic species linked to human diseases: *A. baumannii* (genomic species 2), *A. pittii* (formerly genomic species 3), and *A. nosocomialis* (once genomic species 13 TU), *A. seifertii* and *A. dijkshoorniae*.[31–33] Among these species, *A. baumannii* is the most clinically significant due to its complex reservoir of resistance genes resulting from its high genetic plasticity, which has a direct and detrimental influence on the clinical outcomes of patients with infections caused by this pathogen.[34]

Acinetobacter species are gram-negative, non-fermentative, non-spore-forming, strictly aerobic, immobile, catalase-positive, non-pigmented, oxidase-negative, and exhibit coccobacillary and pleomorphic forms. Occasionally, they may

appear Gram-variable or even Gram-positive during the initial Gram stain, with their morphological characteristics changing based on the growth phase. During rapid growth, they may occur rod-shaped, transitioning to a coccobacillary form during the stationary phase.[35] On common diagnostic media like sheep blood agar and tryptic soy agar at 37°C, *Acinetobacter* colonies are grayish-white, smooth, and mucoid. Its DNA G+C content varies from 39% to 47%.[29] These microorganisms belong to the phylum Proteobacteria, class γ-proteobacteria, order Pseudomonadales, and the family Moraxellaceae.[29,36] They are ubiquitous and can be isolated from clinical human samples, as well as various environments such as soil, water, food, and even wild animals.[37]

Identification

Identifying *Acinetobacter* at the species level remains a complex and challenging task due to the close genetic relatedness of species within the ACB complex, coupled with their similar phenotypic and biochemical properties.[38] Protocols for differentiating *Acinetobacter* species have been established using phenotypic traits recorded at different growth temperatures, hemolysis assays, glucose-induced acidification, and carbon/energy sources,[39] as well as through the utilization of commercial automated systems (such as API 20 NE, BD Phoenix, Microscan WalkAway, Vitek 2) and DNA-based tests like PCR (16S rRNA gene amplification). However, these approaches are labor-intensive, time-consuming, and often take several days.[40] Consequently, there is a growing need for molecular or genomic methods to achieve accurate identification.[38,41]

The $bla_{OXA-51-like}$ gene stands as one reliable biomarker for identifying *A. baumannii*, which is located chromosomally and exhibits weak hydrolysis of carbapenems. This gene, while primarily associated with *A. baumannii*, has also been identified in non-*baumannii* species.[28,29,42] To enhance accuracy, techniques such as 16S rRNA sequencing, DNA-DNA hybridization, and matrix-assisted laser desorption time-of-flight mass spectrometry (MALDI-TOF-MS) are steadily employed for species identification.[43–45]

Innovative rapid detection assays have been developed, including the MALDIxin test, which enables the precise and swift identification of colistin-resistant *A. baumannii* pathogens in under 15 minutes.[46] Additionally, the multiple cross-displacement amplification (MCDA) technique coupled with lateral flow biosensors (LFB) has been created for the rapid and sensitive detection of *A. baumannii*. This method targets the pgaD gene, a sequence-specific and conserved marker for *A. baumannii*.[47] The results are obtained quickly, with high specificity and sensitivity, visual interpretation, without the need for specialized equipment, and at a low cost. The results obtained have shown has shown that the detection capacity of this assay exceeds that of culture methods and conventional PCR, indicating its potential as a valuable tool for the swift identification of *A. baumannii* in hospital settings.[48]

Epidemiology

Acinetobacter sp are widely distributed in nature and can be found in various ecological niches across the globe, including animals, humans, and the environment.[49] Despite limited research in this area, it has become evident that food can also serve as a significant reservoir for *Acinetobacter* spp., including multidrug-resistant (MDR) strains. These bacteria have been isolated from various food products, including but not limited to meat, vegetables, fruit, cheese, milk, fish, and drinking water.[50–52] This highlights the critical role of food as a potential source for the spread of Acinetobacter spp between community and clinical environments. It underscores the importance of conducting investigations into the potential health risks associated with foodborne pathogens.[51] Moreover, it's worth noting that meals served in healthcare facilities may act as vehicles for pathogenic bacteria, especially among vulnerable individuals, and there have been documented outbreaks in such settings.[53]

Acinetobacter spp. has been found in various anatomical locations in humans and may constitute a part of the skin microbiota in at least 25% of healthy individuals, with even higher prevalence rates observed among patients and hospital staff.[54] In hospitalized patients, particularly during ICU outbreaks associated with mechanical ventilation or other respiratory support, colonization by *A. calcoaceticus* species has been reported at high percentages, including in the hands of healthcare professionals.[55] Recent studies demonstrated a decrease in the rate of colonization by MDR microorganisms in ICU patients following enhanced environmental cleaning and hand hygiene in a university hospital in China.[56]

HAIs caused by *Acinetobacter* spp. can affect multiple body sites, with a predominance of respiratory, urinary tract, and surgical wound infections, especially in immunosuppressed individuals or those receiving mechanical ventilation in

ICUs.[57,58] Reports have also indicated the presence of *Acinetobacter* spp. on sink and floor surfaces in healthcare facilities, emphasizing the challenges in eradicating them even with adequate disinfection measures.[59] Of significant concern is the resistance of the ACB complex to multiple antimicrobials, which is directly associated with high rates of therapeutic failure and mortality, both in Brazilian ICUs and globally.[60] In recent years, there has been an evolution in the resistance profile of *Acinetobacter* spp., particularly an increase in the minimum inhibitory concentration (MIC) to aminoglycosides, fluoroquinolones, and carbapenems, especially imipenem.[60]

Among the species within the ACB complex, *A. baumannii* is considered a global threat in healthcare settings and has been rapidly acquiring resistance.[58] In early 2019, the World Health Organization (WHO) categorized MDR *A. baumannii* (MDRAB) as one of the most critical pathogens due to its resistance to multiple classes of antibiotics, particularly carbapenems and third-generation cephalosporins.[61] The highest incidence of *A. baumannii* is reported in hospital environments, especially in adult and neonatal ICUs, burns units, neurosurgery units, surgical units, medical units, and oncological units.[58] While the bacterium is often found in healthcare facilities, the initial infection can also be introduced by patients admitted from outside the facility.[62] Colonized or infected patients serve as reservoirs for the infection, with direct contact and the hands of healthcare staff being the primary modes of transmission.[63] Airborne transmission is also possible, with the microorganism being isolated at a distance of more than four meters from patients with airway colonization.[64]

Extensive resistance to carbapenem antibiotics is indicative of extensively drug-resistant (XDR) bacteria, and CRAB has posed significant challenges.[65] In some regions, approximately 90% of clinical isolates of *A. baumannii* are resistant to carbapenems. A multinational study of ICUs revealed varying prevalence rates of *A. baumannii* infection in different regions, with particularly high rates in Asia.[66] Globally, about 45% of *A. baumannii* isolates are MDR, with even higher rates in Latin America and the Middle East.[67] Mortality rates due to *A. baumannii* infections have increased in many regions over the last decade, ranging from 30% to 75%.[68]

The first case of NP linked to CRAB was reported in Spain in 1998,[69] marking the beginning of investigations into risk factors[70,71] and the impact of empirical use of antibiotics.[71,72] In recent years, specifically in 2019 (51.4%) and 2020 (53%), a strong connection was established between VAP due to *A. baumannii* caused by MDRAB and CRAB in ICU patients.[73,74] This correlation was supported not only by clinical observations but also by molecular studies.

Furthermore, an increased incidence of VAP attributed to MDRAB and CRAB was observed among patients admitted to ICUs. Molecular studies, as well as clinical data, continue to underscore this alarming trend.[71,75,76] The increasing prevalence of VAP caused by MDRAB and CRAB emphasizes the critical need for focused attention on preventative strategies and alternative treatment approaches in the ICU setting.[77–79]

Research conducted over seven years at a tertiary center in Lebanon, focusing on MDRAB infections, revealed that the respiratory tract was the most frequent site of infection/colonization, with rates of 53.1% and 80.8%, respectively.[80] In a study conducted at a university hospital, the rates of multidrug-resistant *A. baumannii* (MDRAB), XDR, and pan drug-resistant (PDR) strains recovered from VAP cases were 13.3%, 68.3%, and 18.3%, respectively. Within these cases, two independent risk factors for mortality were identified, namely, female sex and red blood cell transfusion.[16] Furthermore, in southern Vietnam, an analysis conducted on 97 patients infected by *A. baumannii* through screening samples from the lower respiratory tract revealed their resistance to carbapenems and multi-drug resistance (MDR) at rates of 80% and 90%, respectively.[81]

A. baumannii may establish a subtle and persistent presence in patients who spend extended periods in the ICU, and this presence is closely related to the patient's immunological status and the treatment of the primary disease. NP poses a significant threat to ventilator-dependent patients since *A. baumannii* can form biofilms externally in the endotracheal tube (ET), leading to excessive colonization in the lower respiratory tract. *A. baumannii* is capable of adhering to the respiratory tract or invasive channels within the biofilm. This fact facilitates the colonizing of the host. Therefore, it is challenging to eradicate these bacteria, and as a result, the presence of *A. baumannii* can persist in some patients for an extended period.[82,83] According to a longitudinal prospective cohort study, the estimated risk of VAP was 1.5% per day during the first two weeks, decreasing to less than 0.5% per day after the 14th day of mechanical ventilation.[84]

Patients with NP, particularly those caused by MDRAB, have reported prevalence rates ranging from 40% to 95%,[85–87] with associated mortality rates ranging from 45% to 85%.[88] Various factors have been identified as predictors of mortality in these patients, which include unsuccessful empiric antibiotic therapy, septic shock, immunosuppression, septicemia,

mechanical ventilation, long-term ICU stay, malignity, Pitt bacteremia and APACHE II score at the beginning of infection.[89,90]

In a study involving 164 respiratory ICU patients with *A. baumannii* lower respiratory tract infection, which included HAP and VAP cases, CRAB accounted for 84.8% (all MDRAB), and the mortality rate was 56.7%. The study identified several predictors strongly associated with mortality, such as the number of days spent in the ICU, the presence of CRAB infection, the duration of carbapenem use within 90 days of isolating *A. baumannii*, and the occurrence of septic shock.[90] Furthermore, a systematic review and meta-analysis comprising 16 observational studies revealed that the mortality rate in patients infected with CRAB was twice as high as that in patients infected with carbapenem-susceptible *A. baumannii*.[91] Additionally, another systematic review and meta-analysis, which aggregated data from 114 studies, indicated that the global prevalence of multi-drug resistance in HAP and VAP caused by *A. baumannii* was 79.9%.[92] The highest prevalence was observed in Central America, Latin America, and the Caribbean (100% each), followed by Western Europe (91.4%), while East Asia had the lowest prevalence (64.6%). The collective mortality estimate, derived from a pooling of data from 27 studies, was found to be 42.6%.[92] In a systematic review focusing on mortality predictors in a cohort of 1706 patients infected with CRAB, the reported mortality rate was 52.7%.[93]

A single-center, retrospective study conducted in four ICUs of a prominent Lithuanian university hospital aimed to compare the clinical features and 30-day mortality of monobacterial and polybacterial MDRAB VAP episodes. It was observed that the majority of MDRAB VAP episodes were monomicrobial (67.5%), and the study concluded that monobacterial MDRAB VAP exhibited different demographic and clinical characteristics compared to polybacterial infections and was associated with worse outcomes.[94]

HAP caused by *A. baumannii* is also a growing concern, mostly in tropical regions, identified by a serious course, a high level of bacteremia, and a remarkable mortality rate. People with a history of diabetes mellitus, alcoholism, smoking, and chronic lung disease are largely affected.[95] HAP is prevalent in portions of Asia, Oceania, and Australia, including China, Taiwan, and Thailand.[37]

One of the most concerning manifestations of *A. baumannii* is the occurrence of epidemic and endemic MDR strains in hospital settings. The pattern of outbreaks may vary based on local factors and the specific strain involved, as some strains exhibit a greater propensity for epidemic dissemination than others. Epidemic strains are typically introduced into hospital environments through the admission of colonized patients.[96] Since the late 1980s, *A. baumannii*'s clinical significance has increased dramatically due to the occurrence of outbreaks in hospitals across England, France, Germany, Italy, Spain, and Holland.[29,97] Studies conducted during these outbreaks have described the coexistence of multiple clones within the same hospital, with one or two clones often predominating.[98,99] The transfer of infected or colonized patients to other hospital units has been a contributing factor to inter-institutional and even international spread. In 2005, Schulte and collaborators demonstrated the clonal transmission of strains resistant to meropenem from Greece to Germany.[100] Outbreaks of MDRAB infections have also been documented as complications of combat trauma in military patients during the Vietnam War and in the Middle East. Additionally, in 2004, an outbreak affected victims of a tsunami in Southeast Asia. However, the exact source of contamination remains undefined, with potential contributions from individual microbiota, the environment, or hospital units. In a study covering 12 hospital centers across three different European countries, a main clonal lineage of *A. baumannii* was related to VAP.[101] This suggests the emergence of an XDR or PDR epidemic of *A. baumannii*, with resistance rates approaching 100% for carbapenems and 50% for colistin.[84] Regarding HAP caused by *A. baumannii*, a Chinese study reported the presence of a rare sporadic clone (ST880) carrying the plasmid-encoded blaOXA-72 gene, conferring resistance to carbapenems.[102]

Virulence Factors and Pathogenesis

Virulence consists of the ability of the microorganism to cause disease through the production of molecules that help the microorganism in the invasion, colonization, and immunosuppression of the host.[103] Among the virulence mechanisms studied, we can highlight the formation of biofilm, porins, outer membrane proteins (OMPs), outer membrane vesicles (OMVs), penicillin-binding proteins (PBPs), polysaccharide capsules, metal acquisition system, dysfunction proteins, phospholipases, lipopolysaccharides, and others.[104]

Studies related to genomic and phenotypic *A. baumannii* investigations have recognized important virulence factors responsible for its pathogenicity, demonstrating how the intrinsic and acquired mechanisms make this bacterium a major challenge for health care.[105] Among the critical antigenic factors that enable immune evasion, we find the capsule polysaccharide and OmpA. Additionally, certain virulence factors promote the in vivo survival of pathogens by countering the host's immune response, including lipopolysaccharides, phospholipase D, the iron acquisition system, outer membrane vesicles, and PBPs.[106]

Outer Membrane Proteins (Porins)

Porins are OMPs that are crucial in modulating cell permeability in *A. baumannii*.[107] Among these porins, OmpA (initially identified as Omp38) stands out as the most abundant external porin found in the outer membrane of this bacterium. OmpA is the most broadly defined virulence factor in *A. baumannii* and exhibits in vitro model systems with many intriguing biological aspects.[107,108] It possesses the capability to bind to host epithelial cells, leading to the release of proapoptotic molecules such as Cytochrome C, thereby inducing apoptosis.[105] Through its interaction with fibronectin, this porin has a fundamental role in the adhesion and subsequent invasion of epithelial cells.[109] Additionally, OmpA contributes to antibiotic resistance by expelling antimicrobials such as chloramphenicol, aztreonam, and nalidixic acid.[105] Furthermore, it facilitates the bacteria's persistence and promotes motility and biofilm formation.[107]

Another notable *A. baumannii* porin is the protein Omp34, previously known as Omp33-36. This porin functions as a water channel, and its expression is correlated with resistance to carbapenem antibiotics.[109] Molecular research has shown that this protein is liberated inside immune and connective cells, which, by blocking autophagy, induces apoptosis, ultimately allowing for intracellular persistence with the subsequent development of cytotoxicity.[110] Knockout strains of *A. baumannii* lacking functional Omp34 exhibit a faulty growth rate and notably lowered capacity for adhesion, invasion, and cytotoxicity, underscoring the pivotal role of Omp34 in the fitness and virulence of *A. baumannii*.[109] CarO, also known as the carbapenem-sensitive porin, shares structural similarities with Omp34 and serves as an outer membrane channel protein with an 8-strand β-barrel structure. CarO lacks a continuous channel but mediates the influx of beta-lactam antibiotics, primarily imipenem, into *A. baumannii*. The CarO, like other outer membrane proteins, has the function of carbapenem resistance by facilitating antibiotic uptake.[111] In clinical isolates of *A. baumannii* the elevated expression of CarO involveses delays pulmonary neutrophil infiltration by attenuating pro-inflammatory responses in the lungs and trachea. As a result, bacterial proliferation occurs, resulting in severe pneumonia.[112]

OmpW, identified in *A. baumannii*, bears a high resemblance to OmpW found in *P. aeruginosa* and *E. coli*. While the direct role of OmpW in *A. baumannii* remains unknown, in vitro-cultured colistin-resistant mutants of *A. baumannii* (ΔOmpW) exhibited decreased porin expression and showed less biofilm formation. However, reports have highlighted OmpW's involvement in iron assimilation and its capacity to accommodate colistin molecules.[113] Other porins, such as OprB, Omp25, OprC, and OprD, also play roles in *A. baumannii* physiology and virulence.[114]

Outer Membrane Vesicles

OmvS are spherical vesicles, typically measuring between 20–200 nm in diameter, discharged by the outer membranes of many Gram-negative bacteria, including *A. baumannii*.[115] OMVs serve as delivery vehicles for various virulence factors into host cells and comprise lipopolysaccharides (LPS), periplasmic proteins, phospholipids, outer membrane components, and RNA or DNA.[116] Numerous studies have demonstrated that *A. baumannii* strains secrete OMVs, carrying virulence factors like OmpA proteases, phospholipases, superoxide dismutase, and catalase. These OMVs also promote biofilm formation on abiotic surfaces.[117] Interestingly, *A. baumannii* OMVs have been linked to the dissemination of antibiotic resistance, facilitating horizontal gene transfer of the OXA-24 carbapenemase gene.[118] Given their notable part in *A. baumannii* virulence, OMVs from this bacterium have been investigated as potential acellular vaccines to enhance protective immunity.[119]

Cell Envelope Factors (Lipopolissacarídeo and Capsule)

Another crucial virulence factor is lipopolysaccharide (LPS), which is situated in the outer layer of the plasma membrane. It serves as a fundamental component of the cell surface in Gram-negative bacteria, acting as a permeability barrier that

regulates the diffusion of substances into the cell. Additionally, LPS protects against environmental factors like water scarcity and antiseptics, as well as defense against phagocytosis.[58,120] A key role of LPS is its contribution to resistance against normal human serum, providing a survival advantage in vivo and triggering pro-inflammatory responses.[121]

A. baumannii 's LPS consists of several components, including an O antigen, a carbohydrate core, and a lipid A moiety. It acts as a chemotactic agent, attracting inflammatory cells and inducing them to release cytotoxic substances.[122]

Moreover, pili, in conjunction with the antigenic polysaccharide of LPS, serve as the initial step in colonization, playing a pivotal role in promoting adhesion to host cells.[123] The presence of a capsule on the bacterial surface represents another significant virulence determinant of A. baumannii. This capsule, comprised of densely packed, repetitive sugar units, forms a protective shield against environmental factors, immune system responses, and certain antimicrobial agents.[124]

Phospholipases

Phospholipases are crucial lipolytic enzymes involved in phospholipid metabolism and serve as important virulence factors in many Gram-negative bacteria. These enzymes exhibit lipolytic activity against phospholipids found in human cell membranes, which are the primary building blocks of biological membranes and a source of carbon and energy within the human host.[125] Bacterial phospholipases generate products that aid the microorganism in evading phagocytic processes, thereby facilitating tissue colonization, infection progression, and suppression of the immune system.[126]

In the case of A. baumannii, three types of phospholipases are described: phospholipase A (PLA), phospholipase C (PLC), and phospholipase D (PLD), each contributing to different virulence mechanisms.[127] PLCs are cytotoxic to epithelial cells, and their combined action with ethanol intensifies A. baumannii's cytotoxicity. Specifically, 1,2-diacylglycerol, released by cellular phospholipase C, plays a role in modifying the biophysical properties of the membrane, including charge, fluidity, and permeability. It can also recruit cytosolic proteins, leading to spatial reorganization of signaling complexes that affect various cellular processes.[127] PLDs, on the other hand, collectively promote serum resistance, epithelial cell invasion, and in vivo pathogenesis.[128] When acting together with PLA and PLC, PLD contributes to cell invasion by hydrolyzing the fatty acids of the glycerol backbone, with subsequent PLC-mediated cleavage of the phosphorylated head group released from the glycerol backbone. PLD specifically cleaves its main group, generating instability in host cells and affecting cell signaling.[128]

All these phospholipases exhibit substrate specificity for phosphatidylcholine,[127] a prominent component of eukaryotic membranes, constituting 50% of all phospholipids and increasing to 80% in pulmonary and tracheobronchial secretions.[129] Experimental evidence suggests that phosphatidylcholine can serve as a nutrient source during pulmonary infections caused by pathogens like *Pseudomonas aeruginosa* and *A. baumannii*.[130] The degradation of phospholipids by these enzymes compromises the stability of host cell membranes and directly interferes with cell signaling, resulting in alterations in the host's immune response.[127]

Another identified virulence factor is the CpaA enzyme, characterized as a metallo-endopeptidase with similarities to adamalysin, specifically targeting glycans. CpaA interferes with the blood clotting cascade by inactivating factor XII, leading to an increase in clotting time, as observed in human and murine serum (PTTa).[131] CpaA can cleave coagulation Factor V in human plasma, and analyses of Prothrombin Time (PT), fibrinogen, and TTPa have shown reduced coagulation in TTPa and fibrinogen but an increase in PT. Consequently, CpaA attenuates thrombus formation in intravascular sites, facilitating *A. baumannii* 's spread.[132]

Metal Acquisition System

The acquisition of essential micronutrients such as iron, zinc, and manganese are critical for *A. baumannii* and other bacterial species, both for host-pathogen interaction, reproduction, and pathogenesis.[133] Despite iron's abundant presence in both environmental and biological systems, the accessibility of biologically active ferric iron (Fe+3) remains relatively limited. This limitation arises from its reduced solubility under aerobic conditions and at neutral pH, as well as its propensity for chelation by low molecular weight compounds like heme or high-affinity iron-binding molecules such as lactoferrin and transferrin (iron-binding proteins).[134] Hosts restrict the availability of these nutrients in their bloodstream to prevent bacterial propagation in the organism.[135] In mammals, iron is usually bound to proteins such as transferrin, lactoferrin, and ferritin, thus limiting its serum availability.[136] Nevertheless, to surmount this iron scarcity, the majority of aerobic bacteria synthesize high-affinity iron-chelating agents known as siderophores. These are low molecular weight compounds with a pronounced affinity

for iron.[137] Acinetobactin is the best-characterized siderophore in *A. baumannii*, occurring more frequently in MDRAB isolates.[138] *A. baumannii* expresses several genes related to the iron acquisition system, such as bas A-J, which are responsible for the synthesis of these siderophores, barA/B which carry out the efflux and bauF accountable for the uptake of iron after its chelation.[139] Hosts defend themselves against microorganisms through the sequestration of metals through nutritional immunity, where proteins called calprotectin are recruited to sites of infection with the function of restricting the access of bacteria to zinc and magnesium through a chelation process. Restriction of these compounds leads to inhibition of microbial growth and reduces virulence.[140] *A. baumannii* has important mechanisms involved in establishing and progressing infections that are still poorly understood. Among these factors, there are protein secretion systems (SSP) named according to their type, 2 (T2SS) and 6 (T6SS).[141] Most *A. baumannii* strains have T6SS. However, studies show that even with this factor, activation or deactivation occurs through interbacterial interactions or the loss of T6SS repressor plasmids.[142] T2SS exhibits a structural resemblance to type IV pili systems and functions by facilitating the transport of proteins from the periplasmic space to the external environment.[143]

Biofilm/Quorum-Sensing

Among all virulence determinants, biofilm formation on biotic and abiotic surfaces has become an important feature of A. baumannii pathogenesis, making the MDR organism challenging in healthcare.[144] Biofilms are complex three-dimensional structures composed of bacteria, which live in an extracellular matrix made of polysaccharides, proteins, cellular debris, and genetic material and are produced by microorganisms serving as protection against desiccation, oxidation, resistance to some antibiotics, radiation, and host defense cells.[145]

Biofilm formation begins differently between biotic and abiotic environments, where in biotic environments protein-protein bonds occur on the bacterial surface with the human cellular matrix. In abiotic locations, bacterial interaction with the surface depends on its hydrophobicity.[146] The following steps are the same for both environments, which involve bacterial proliferation at the adhered site, followed by incorporation into an extracellular matrix, where maturation occurs where biofilm maturation occurs and, finally, its dispersion.[120]

A. baumannii possesses a chaperon/usher pilus system referred to as Csu pili, which is under the regulation of the BfmRS two-component system. This intricate network of molecules plays a pivotal role in influencing gene expression, enabling the formation of a protective capsule in response to antibiotic exposure and environmental stress. Furthermore, this same system regulates the formation of pili, an essential process for adhesion and biofilm formation for cell attachment.[147] The presence of another regulatory system is also observed, GacSA, which can affect biofilm formation through the expression of Csu and thus intervene in the microorganism's ability to produce biofilm.[106] Another virulence mechanism is the protein associated with biofilm production, known as BapAb, which has also been described in S. aureus. This protein has the function of modulating the hydrophobicity of the cell surface, thus resulting in better adherence to epithelial cells.[148] A significant factor contributing to *A. baumannii*'s biofilm formation is the production of the exopolysaccharide poly-β-1,6-N-acetylglucosamine (PNAG), a trait common among many Gram-negative species. PNAG is crucial for adhesion and aggregation processes.[149]

Studies have revealed that over 60% of hospital-acquired infections are attributed to bacteria capable of forming biofilms on medical devices.[150] Among these devices, the ET presents an ideal environment for bacterial and fungal adhesion, supporting biofilm development on both its inner luminal surface and outer surface.[151] The ET is recognized as an independent risk factor for pulmonary infections in intubated patients, elevating this risk by a factor of 6 to 10.[152,153]

In intubated patients, biofilm formation within the ET is an early and persistent occurrence, effectively serving as a reservoir for infectious microorganisms. Almost immediately after intubation, a mixed biofilm with the potential to harbor various microbial pathogens takes shape within the ET.[154] Microorganisms can inhabit liquid mediums as solitary cells or form immobilized communities within biofilms. These microorganisms can enter the trachea through micro-aspiration or via biofilm development, particularly on the inner surface of the distal third of the ET.[155,156]

Transmission of these biofilms to the lower airways leads to serious complications such as pneumonia or sepsis.[157] Different tracheostomy tube materials showed no change in susceptibility to biofilm formation.[158] Prolonged tracheostomy duration had no significant correlation with biofilms, and they were formed as early as seven days.[158,159] In a study that assessed the biofilm formation and antibiotic resistance of bacterial profile from ET of patients admitted to ICUs in

southwest Iran, 22% (n = 121/546) of GNB isolated were *A. baumannii* with most exhibiting MDR (77%) and 74% (n=89) were biofilm producers.[160] A prospective observational study carried out intending to know the most common organisms capable of forming a biofilm on the ET and their sensitivity to antibiotics showed that *A. baumannii* (45%) was the most common biofilm producer isolated exhibiting 35.7% MDR.[161]

The formation of biofilms on the surface of the ET is intricately tied to the pathogenesis of VAP. Fragments of biofilm become dislodged and are passively transported towards the lungs.[162] Additionally, biofilm cells can become aerosolized and aspirated into the lungs due to gas flow during mechanical ventilation. In contrast, individual cells may be dislodged by fluids and migrate deeper into the lungs.[154,162] A noteworthy study indicated that 70% of VAP patients harbored the same pathogens in both ET biofilms and lung tissues. This observation underscores the substantial and persistent role that biofilms play as a source of pathogenic bacteria.[163] In a separate study aimed at understanding biofilm production by pathogens responsible for VAP and its connection to drug resistance, it was found that out of the 71 isolates examined, the *A. calcoaceticus-baumannii* complex was the second most frequently isolated organism, accounting for 16.9% of cases.[164]

Recently, a study compared the biofilm formation capacity, antimicrobial resistance patterns, and molecular typing based on Pulsed-Field Gel Electrophoresis (PFGE) in *A. baumannii* isolated from burn (23/50) and VAP patients (27/50). Overall, 74% of the strains were MDR and 26% were XDR. Regarding biofilm formation capacity, 52%, 36%, and 12% of the isolates were strong, moderate, and weak biofilm producers, and all the isolates harbored at least one biofilm-related gene.[165]

In A. baumannii, quorum sensing (QS) plays a crucial role in bacterial survival and pathogenicity. QS is recognized as a communication mechanism between bacterial communities to maintain population density. The QS system coordinates the behavior of individual bacteria in a population by mediating the synthesis, secretion, and binding of easily diffusible small hormone-like molecules known as autoinducers (AIs) that are released in proportion to cell density.[166] These mechanisms are advantageous for the entire community, particularly at a higher cell density, eg, synthesis of virulence factors, formation of biofilms, and production of siderophores and proteases.[167]

Acinetobacter generates acyl homoserine lactones (AHLs) as signaling molecules for both inter- and intraspecies communication. The Quorum Sensing (QS) cycle in *A. baumannii* is orchestrated by the presence of the inducer AbaI and its cognate receptor AbaR. AbaI, which is encoded by the abaI gene, serves as a sensory protein responsible for producing AHL signaling molecules as autoinducers.[168] In contrast, AbaR functions as a receptor protein, and upon binding to AHLs, it initiates a cascade of reactions. This binding event triggers a positive feedback loop, leading to the increased production of AHLs, ultimately regulating biofilm formation. It's noteworthy that the deletion of the abaI synthase autoinducer gene in *A. baumannii* results in reduced biofilm formation and pathogenicity.[169] Furthermore, the abaI/abaR QS system has been observed to exert influence on overgrowth characteristics, morphology, biofilm formation, resistance, motility, and virulence.[170] Additionally, *A. baumannii* produces less-studied signaling molecules, such as diketopiperazines, 2-heptyl-3-hydroxy-4-quinolone, and retention factor 1, each of which contributes to the complex signaling network in the organism.[171]

Diagnosis

The diagnostic criteria for NP, including HAP and VAP, are intricate, making it challenging to differentiate between true infection and colonization. Various methodologies have been detailed in the literature for epidemiological surveillance and diagnostic purposes. However, more consensus has yet to emerge regarding the most appropriate set of criteria.[172] Despite the ongoing debate, clinical symptoms, although sometimes nonspecific, serve as initial criteria for diagnosis. Radiological examinations and laboratory and microbiological criteria, such as bacteriological cultures, are also essential for defining the etiological agent.[173] Clinical and radiological data, while valuable, exhibit limited specificity. The use of quantitative microbiological criteria can enhance specificity, but their accuracy has been called into question.[174,175]

It is crucial to note that VAP is considered a performance indicator in the USA and some other countries. According to a report by the National Healthcare Society Network (NHSC), the effective implementation of a multifaceted infection control program significantly reduced the incidence rate of VAP.[176] The Center for Disease Control and Prevention (CDC) reported a 70% decrease in the incidence of VAP between 2006 and 2012. However, during the same period, VAP rates reported by the Medicare Patient Safety Monitoring System remained consistently high, affecting approximately 10% of ventilated patients.[177] These findings highlight a notable disparity between the rates documented in a quality monitoring program and those mentioned in the patient assistance program.

Table 1 Methods Available for Diagnosing Ventilator-Associated Pneumonia (VAP)

		Cut-off (CFU/mL)	Characteristics
Non-Invasive	Endotracheal aspirate	10^4	Lower-cost alternative good sensitivity, lower specificity compared to other clinical specimens
Invasive	Bronchoalveolar lavage (BAL)	10^5	Complications associated with the technique including hypoxemia, cardiac arrhythmias, and bronchospasm
	Mini-bronchoalveolar lavage (mini-BAL)	10^5	Similar technique to BAL, but performed unthinkingly with a smaller volume of fluid

Abbreviation: CFU/mL, Colony forming units/mililitre.

Several methods are available for diagnosing VAP (Table 1), including invasive and non-invasive techniques to obtain clinical specimens:

Endotracheal aspirate: This is an easy, quick, and non-invasive technique, but it may yield high rates of false positives due to airway colonization.[178] In quantitative cultures, a cut-off value of 10^4 Colony Forming Units (CFU)/mL is used.[179] While the endotracheal aspirate offers a lower-cost alternative and good sensitivity, its specificity is lower compared to other clinical specimens. However, the analysis of the endotracheal aspirate using the quantitative technique with a cut-offpoint of 10^6 CFU/mL shows a good correlation with results obtained from minimally contaminated specimens.[174]

Bronchoalveolar lavage: This technique requires a bronchoscope to recover cellular and non-cellular components of the bronchioles and alveoli using a fluid vehicle, with a cut-off of 10^5 CFU/mL.[179] Complications associated with the technique may include hypoxemia, cardiac arrhythmias, and bronchospasm.[5]

Mini-bronchoalveolar lavage (mini-BAL): This is a similar technique to bronchoalveolar lavage but performed unthinkingly with a smaller volume of fluid while maintaining the same cut-off value.[179]

The latter two methods are considered minimally contaminated by upper respiratory tract secretions but are more expensive and invasive. Bacterial growth in quantitative cultures with counts exceeding the mentioned cut-offpoints indicates, with higher specificity, that the isolated clinical specimen is associated with the etiology of VAP, while lower counts suggest colonization.[179,180] It's worth emphasizing that routine bacteriology techniques used to detect the etiological agent of VAP are time-consuming and less sensitive compared to molecular techniques.[29] The optimization of molecular techniques for VAP diagnosis, especially for infections caused by A. baumannii, is imperative and could positively impact patients' clinical outcomes.

Treatment

Current guidelines for the treatment of *A. baumannii* infections are greatly impacted by the rapid spread of resistance to commonly used antibiotics, severely limiting therapeutic options and posing a significant challenge.[37] In the case of VAP patients suspected or confirmed to have the condition, immediate initiation of antibiotic therapy is crucial. Delaying treatment is associated with a significant increase in mortality rates and healthcare costs for survivors.[13]

The initial treatment of VAP in critically ill patients, particularly those in units with a high prevalence of *A. baumannii* infections or those previously colonized, relies on empirical choices. However, selecting the appropriate initial antibiotics is crucial, as an inadequate choice is linked to higher mortality rates.[181] Additionally, the retrieval of multidrug-resistant (MDR) bacteria is strictly related to a growing risk of unsuitable therapy.[182] Unfortunately, there is a lack of data on the optimal antimicrobial regimen for the treatment of VAP caused by MDR/XDR/PDR pathogens. Consequently, there needs to be a consensus on the strategy for treatment choice, which often relies on the doctor's experience.[183]

Numerous risk factors contribute to VAP caused by *A. baumannii*. These include the duration of mechanical ventilation, reintubation, antibiotic therapy, perioperative blood product transfusion, enteral nutrition, supine head position, nasogastric tubes intra-hospital transport, lack of subglottic secretion drainage, paralyzing agents use, continuous sedation, and constant changes in the ventilator circuit. Host-related risk factors encompass medical history, underlying diseases, male gender, extreme age, acute underlying diseases, previous central nervous system disorders, acute renal failure, immunocompromised

status, emergent surgery, neurosurgery, acute respiratory distress syndrome, thoracic and cardiac surgery, burns, intra-aortic support, reintervention, ulcer disease and extracorporeal membrane oxygenation (ECMO).[184–186]

The propensity of *A. baumannii* to develop antibiotic resistance complicates the selection of empiric antimicrobial regimens that can be applied consistently across different healthcare facilities.[187] Few randomized clinical trials have focused on defining optimal therapies for pneumonia caused by these difficult-to-treat resistant strains, resulting in limited therapeutic strategies against *A. baumannii*.[188]

For susceptible *A. baumannii* isolates, initial therapy typically involves carbapenems like imipenem-cilastatin, meropenem, or doripenem (except ertapenem), depending on local susceptibility patterns.[189] Imipenem, historically, has been regarded as the gold standard for treating VAP caused by *A. baumannii*.[190] Clinical cure rates with imipenem range from 57% to 83%.[191] It is important to highlight that susceptibility tests are necessary before clinical use, as isolates susceptible to imipenem may be resistant to meropenem and vice versa.[190]

In settings with high local resistance to carbapenems, empirical combined therapy is recommended to ensure broad coverage. This approach also guides the reevaluation of initial therapy based on microbiological results and clinical response variables such as fever and oxygenation support.[189] To enhance patient outcomes and reduce the risk of resistance, a common strategy involves the use of combination therapy until drug susceptibility test results become available, aiming to broaden antimicrobial coverage. However, the results from human trials are limited, and the clinical data supporting this approach still need to be more conclusive.[192] As an alternative to carbapenem-sparing monotherapy, high doses of sulbactam can be employed for the treatment of *A. baumannii* pneumonia, whether the strains are susceptible or resistant to carbapenems.[193] Sulbactam, an antibiotic acting as a β-lactamase inhibitor, directly exhibits antimicrobial activity against *A. baumannii* through its affinity for the bacterium's PBPs.[194]

While some studies have shown clinical and bacteriological efficacy, other evidence is contradictory, suggesting that sulbactam-based therapies may not be superior to non-sulbactam regimens (including colistin, cephalosporins, and tigecycline) for *A. baumannii* treatment.[27,195,196]

Other agents, such as minocycline and tigecycline, have shown clinical success in treating VAP caused by *A. baumannii*, particularly in cases of multi-drug resistance.[197] However, the efficacy and safety of these antibiotics can vary, with some studies indicating inferior outcomes compared to other agents.[198,199] Cefiderocol, a novel β-lactam with activity against CRAB, has shown promise, although its role in treating pulmonary infections caused by this pathogen remains controversial due to limited evidence.[200,201]

The global rise in carbapenem resistance among *A. baumannii* strains has significantly narrowed the antibiotic arsenal.[37] polymyxin B and colistin (polymyxin E) are increasingly used to treat bacteremia, *A. baumannii* meningitis, and VAP.[190] Although effective in suppressing *A. baumannii* growth in vitro, these antibiotics have limitations such as a narrow therapeutic window, bacteriostatic action, variable pharmacokinetics/pharmacodynamics, high rates of neurotoxicity, and an increased risk of nephrotoxicity, especially with loading doses.[202] Additionally, they exhibit poor pulmonary penetration, which limits their utility.[189,203] There is also a need for more consensus on whether colistin should be used alone or in combination therapy. However, combining colistin with other antibiotics like carbapenems due to synergism can lead to better results.[204]

Inhaled aerosolized antibiotics with colistin and tobramycin have been explored as treatment options for VAP, particularly in cases of difficult-to-treat pathogens. Inhaled antibiotics allow for higher local concentrations and can reduce the need for toxic intravenous antibiotics. However, there is limited and conflicting data on their efficacy and adverse effects, with some studies indicating potential benefits in terms of reduced mortality and hospital stay. In contrast, others suggest respiratory complications and no significant impact on mortality.[205–208]

Finally, the treatment of *A. baumannii* infections is a complex challenge due to antibiotic resistance, especially in the situation of VAP (Table 2). While some antibiotics, such as colistin and sulbactam, show promise in treating these infections, the choice of therapy is often based on local susceptibility patterns and clinical judgment. Further research and clinical trials are needed to establish definitive treatment guidelines for *A. baumannii* infections, especially those caused by multidrug-resistant strains.

The widespread prevalence of antimicrobial resistance in A. baumannii, especially against last-resort antibiotics, has sounded the alarm in recent years. Therefore, various studies have been conducted to provide new treatment strategies.[209] A potential alternative management for treating infections with MDR *A. baumannii* is bacteriophages, the most widely encountered organisms on the planet.[210] Bacteriophage therapy (using viruses to treat bacterial infections) is a promising

Table 2 Initial Teraphy to *A. baumannii* Pneumonia

Characteristic of Susceptibility/Resistance	Antibiotic
Susceptible A. *baumannii* isolates	Imipenem-cilastatin Meropenem Doripenem (except ertapenem)
High local resistance to CRAB	Empirical combined therapy
Alternative to carbapenem-sparing monotherapy	Sulbactam (high doses)
MDRAB	Minocycline Tigecycline
CRAB	Cefiderocol
Bacteremia, A. *baumannii* meningitis, and VAP	Polymyxin B and colistin (polymyxin E) Colistin combined with other antibiotics like carbapenems
VAP	IA antibiotics with colistin and tobramycin Colistin and sulbactam

Abbreviations: CRAB, Carbapenem resistant *A. baumannii*; MDRAB, multi-drug resistant *A. baumannii*; VAP, Ventilator associated pneumonia; IA, Inhaled aerosolized.

antibacterial approach, which treats and prevents infectious disease by lysis of bacterial cells.[211] Another approach is the use of antimicrobial peptides (AMPs), components of the innate immune system of eukaryotic and prokaryotic organisms that have broad-spectrum and low resistance, which has attracted the attention of researchers.[212] Silver nanoparticles have also demonstrated antimicrobial activity against various microbes, including A. baumannii, likely caused by their diverse bactericidal mechanisms.[213] These nanoparticles coupled with plant extract have also been intensively studied.[214]

Prevention

The guidelines provided by the Infectious Disease Society of America (IDSA) and the American Thoracic Society (ATS) offer a comprehensive overview of proven methods for preventing VAP and HAP. To effectively reduce the occurrence of these disorders, the primary approach involves minimizing exposure to previously identified intervention-related risk factors and host-related risk factors. Whenever feasible, intubation should be avoided, and alternative procedures, such as non-invasive ventilation with sedation and positive pressure, should be employed. Additionally, implementing weaning protocols is essential to reduce or shorten the duration of mechanical ventilation. However, it's worth noting that the timing of tracheotomy does not significantly impact the incidence of VAP.[215] A range of preventive measures should be considered for patients at risk of VAP. These encompass risk-reduction strategies in ventilation (such as avoiding intubation, minimizing sedation, and enhancing physical fitness), follow-up measures (including education, performance measurement with feedback, improving the overall safety culture in healthcare settings, and public reporting), and preventive measures (such as changing the ventilation circuit only when visibly soiled or malfunctioning, selective oropharyngeal decontamination (SOD) or selective digestive decontamination (SDD), using endotracheal tubes with subglottic drainage of secretions, regular mouthwash with chlorhexidine for hygiene, and prophylactic probiotics).[216]

The optimal combination of essential preventive measures remains uncertain, and it is unlikely that any single preventive strategy can eliminate VAP.[217] Utilizing a few key care interventions derived from evidence-based guidelines tends to yield more favorable outcomes when implemented consistently as a collective package rather than in isolation. It's worth noting that while recent studies have shown significant success in reducing VAP rates with specific precautions, meta-analyses have revealed that most preventive measures have failed to demonstrate sustained effectiveness.[218,219] In fact, there has been no significant improvement over the past decade.[177]

However, Selective Digestive Decontamination (SDD) and Selective Oropharyngeal Decontamination (SOD) have emerged as the only preventive measures that have a positive impact on mortality.[220] On the other hand, oral hygiene

with chlorhexidine has not demonstrated a significant effect on VAP rates, the duration of mechanical ventilation, or the length of stay in the Intensive Care Unit (ICU).[221]

Currently, a clinical trial titled "RGNOSIS: Ecological Effects of Decolonization Strategies in Intensive Care" is underway in six European countries. This trial encompasses various interventions, including a control group, oral hygiene with chlorhexidine, SDD, and SOD. The researchers intend to evaluate the effects of these treatments on the incidence of antibiotic-resistant bacteria and bacterial infections in the ICU. The study also seeks to determine the most effective treatment. The control group will receive standard treatment, while the treatment groups will receive 1% chlorhexidine oral gel (CHX), an antibiotic mouth paste containing three different antibiotics (SOD), and an antibiotic mouth paste and suspension for the stomach and intestines containing three other antibiotics (SDD). All treatments will be administered four times a day to eliminate harmful bacteria in the digestive tract (SDD) and the mouth (CHX, SOD, SDD).[222]

Some studies reported a need for more adherence by doctors and nurses in complying with published guidelines for VAP prevention.[223,224] An online cross-sectional quantitative survey was conducted in two Australian ICUs to explore nurses' knowledge of VAP and self-reported adherence to evidence-based guidelines for the prevention of ventilator-associated events.[225] According to a qualitative descriptive study on the opinion of health professionals about the barriers to the implementation of evidence-based practices in the prevention of events associated with mechanical ventilation, it was possible to address previously reported deficits in nurses' knowledge and adherence to practice based on mechanical ventilation evidence in intensive care. The results suggested the need for a well-established policy to sustain the practice. The barriers faced by nurses and physicians in preventing events associated with mechanical ventilation need to be addressed to optimize the quality of patient care in ICUs.[226]

It's essential to keep in mind that to encourage individuals to adopt specific behaviors and enhance adherence, we must address predisposing factors, which include knowledge, perceptions, and beliefs. By addressing these factors, we can facilitate access to new processes or technologies and consistently reinforce correct behaviors.

Non-compliance with these measures is likely more closely tied to behavioral, structural, and organizational aspects than to the nursing workload. Offering specific education about ventilator-associated events can be instrumental in raising awareness and promoting adherence to guidelines.[227,228]

Pneumonia and COVID-19

Infections caused by *A. baumannii* are pivotal in influencing hospital outcomes during the novel Coronavirus Disease 2019 (COVID-19) pandemic, exerting a significant impact on global public health. Overall, almost 25% of COVID-19 patients necessitated intensive care, leading to their hospitalization in the intensive care unit (ICU) because of acute respiratory distress syndrome (ARDS).[229] Recent data indicates that as many as 80% of COVID-19 patients admitted to the ICU required respiratory support via mechanical ventilation due to severe respiratory failure induced by the virus in more critical cases. This additional factor increases the risk of developing VAP(VAP).[230] Moreover, new challenges have arisen in managing the occurrence of VAPs, as the clinical and radiological criteria traditionally employed for diagnosing VAP do not apply to critically ill patients with pneumonia stemming from SARS-CoV-2 infection. Since these patients present a clinical picture that overlaps with that caused by VAPs, with fever, hypoxemia, intense leukocytosis, and extensive bilateral radiological infiltrate, the microbiological criterion was the only one to support the diagnosis of VAP in patients with COVID-19.[231] As per a conducted meta-analysis, it was found that during their stay in intensive care Unit (ICU), as many as 48% of ventilated COVID-19 patients developed VAP(VAP). Several other studies corroborate these findings, with an average of around 50% of ICU-admitted patients developing VAP.[232] The incidence of VAP ranged from 36% to 85%, while ICU mortality rates varied between 29% and 43%.[230,232,233]

Septic shock and severe acute respiratory syndrome (ARDS) are the primary factors associated with mortality in VAP. However, specific characteristics and risk factors of VAP in COVID-19 patients have yet to be established.[234] Notably, experiencing multiple episodes of VAP in the context of COVID-19 prolongs ICU stays and increases the risk of colonization and infection by CRAB by 7.5 and 5.5 times, respectively.[235,236] The literature describes a higher incidence and recurrence rate of VAP during COVID-19 than in the pre-COVID-19 period, with reports demonstrating a high rate of VAP in patients with COVID-19 when compared to those observed in non-COVID-19 patients.[237–239] However, we observed a decrease in the incidence of VAP in critically ill non-COVID-19 patients during the pandemic compared to before the pandemic, especially

concerning *A. baumannii*.[240] Although studies are heterogeneous and sample sizes are limited, the median time to onset of VAP in patients with COVID-19 does not appear to differ from that reported in VAP in non-COVID-19 patients.[229,241] Dysbiotic oral microbiota also has the potential to colonize the lower respiratory tract causing VAP and a recent study revealed substantial qualitative and quantitative dysbiosis with a high frequency of potentially pathogenic species, including *A. baumannii*.[242]

Further compounding the impact of the pandemic are bacterial coinfections and secondary infections triggered by SARS-CoV-2, which often lurk as hidden threats amidst the backdrop of COVID-19. These infections, exemplified by those attributed to *A. baumannii*, have intensified the severity and risks associated with SARS-CoV-2 infection.[243] They play a significant role in the morbidity and mortality of COVID-19 patients. Individuals with COVID-19 who develop coinfections or secondary infections involving *A. baumannii* tend to experience more adverse outcomes, including prolonged hospital and ICU stays, as well as higher mortality rates. It's vital to emphasize that these outcomes are primarily influenced by bacterial infections rather than viral ones.[244]

Given the challenges of diagnosing coinfections with VAP in intubated COVID-19 patients, a significant portion receive broad-spectrum antimicrobials preventatively, even in the absence of evidence of bacterial coinfection.[245] This approach, while aiming to be proactive, elevates the risk of selecting multidrug-resistant microorganisms, particularly in patients expected to require prolonged mechanical ventilation. Notably, implementing the cleaning and disinfection of mechanical ventilators for SARS-CoV-2 patients using enzymatic detergents and isopropyl alcohol has demonstrated positive effects by reducing post-disinfection microbial contamination rates.[246]

The challenges faced by healthcare professionals have been further compounded by the emergence of outbreaks involving multidrug-resistant (MDR) and XDR *A. baumannii*.[247–249] Approximately 50% of hospitalized COVID-19 patients' deaths are attributed to secondary bacterial infections, with MDR *A. baumannii* frequently identified as a causative agent, associated with a two-fold increase in COVID-19-related mortality.[250]

It is well-established that there is a connection between increased antibiotic use and the rise of antimicrobial resistance in ICUs. During the pandemic, in-hospital antimicrobial usage has surged due to concerns about bacterial and fungal coinfections alongside COVID-19. In the context of VAP with COVID-19, the term "early antibiotic therapy" is introduced, but treatments often commence before patients deteriorate and require endotracheal intubation and mechanical ventilation.[251]

It's important to note that antibiotic administration has been identified as a risk factor for the onset of VAP, particularly because a substantial proportion of patients with COVID-19 (73%) and those without (88%) receive high levels of antibiotic therapy before the development of VAP. Additionally, COVID-19 patients exhibit a higher rate of multidrug-resistant bacterial colonization upon ICU admission (31% vs 16%) but do not demonstrate a greater risk of acquiring multidrug-resistant bacteria during their ICU stay. Consequently, antibiotic treatment in COVID-19 patients should be reserved for cases with well-documented bacterial infections to minimize the risk of VAP caused by multidrug-resistant bacteria.[16]

Conclusion

When the acquisition of resistance traits became significant, *A. baumannii* emerged as a troublesome nosocomial pathogen, significantly complicating the treatment process. Its genetic flexibility has enabled this bacterium to evolve rapidly, thereby elevating it to one of the gravest threats facing hospitalized patients. Currently, multidrug-resistant and pan-drug-resistant *A. baumannii* strains have become pervasive, causing a depletion in available treatment options. The emergence of CRAB strains further compounds these challenges.

Several virulence mechanisms are associated with multidrug-resistant *A. baumannii* strains, particularly the development of biofilms on endotracheal surfaces, which are closely linked to the pathogenesis of VAP. This association, especially for patients admitted to Intensive Care Units, is alarming and represents a significant global medical issue. As such, the timely diagnosis of *A. baumannii* infections is of utmost priority to mitigate harm to patients, and the administration of appropriate and timely antimicrobial therapy is essential for VAP treatment.

Given the lack of effective therapeutic agents, the optimal treatment for *A. baumannii* pneumonia remains undefined, with polymyxins, either alone or in combination with other agents, being empirically recommended. VAP in patients with COVID-19 presents a unique challenge for clinicians, given the high incidence of septic shock and mortality associated with this infection. The prevalence of antibiotic resistance among pathogens isolated from mechanically ventilated

COVID-19 patients in the ICU underscores the importance of preventing coinfections caused by this pathogen. This situation calls for a standardized approach to antibiotic administration in COVID-19 patients to ensure treatment success.

From a microbiological perspective, the potential association of *A. baumannii* with bloodstream and polymicrobial infections should be carefully considered when prescribing antibiotic treatment, whether empirical or targeted, to minimize the risk of treatment failure and VAP recurrence.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, and interpretation, or all these areas; took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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