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Review Article

Nosocomial Infections-An Overview of Prophylactic Approaches to Control VAP

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ABSTRACT

Ventilator-Associated Pneumonia (VAP) is a prevalent and serious hospital-acquired infection occurring in critically ill patients who have been mechanically ventilated for over 48 hr. It is primarily caused by Gram-negative pathogens such as *Pseudomonas aeruginosa, Acinetobacter baumannii*, and members of the *Enterobacteriaceae* family. Reported global incidence rates range from 8.9 to 46 cases per 1,000 ventilator days, reflecting variability in ICU practices and patient populations. VAP is a major contributor to antibiotic overuse in intensive care units, fuelling the rise of Multidrug-Resistant (MDR) organisms and complicating patient management. Its pathogenesis involves the disruption of natural airway defenses by endotracheal intubation, which promotes bacterial colonization and micro aspiration of contaminated secretions. Key risk factors include mechanical ventilation, extended ICU stays, and underlying conditions such as Chronic Obstructive Pulmonary Disease (COPD) and cystic fibrosis. Preventive strategies emphasize rigorous infection control, such as maintaining appropriate endotracheal cuff pressure, routine oral hygiene, and timely ventilator circuit maintenance. While prophylactic antibiotics have been used, their application must be judicious to prevent the emergence of resistant pathogens. Emerging biomarkers-including soluble Triggering Receptor Expressed on Myeloid cells-1 (sTREM-1), Procalcitonin (PCT), and C-Reactive Protein (CRP)-are under investigation for their potential to enhance diagnostic accuracy and guide antimicrobial stewardship.

Keywords: Ventilator-Associated Pneumonia (VAP), Prophylaxis, Infection control, Formulations, Biomarkers and antimicrobial resistance.

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INTRODUCTION

Ventilator-Associated Pneumonia (VAP) is a severe and prevalent form of Hospital-Acquired Pneumonia (HAP) that develops more than 48 hr after endotracheal intubation in patients receiving mechanical ventilation (Zhao *et al*., 2020). Recognized as the most common nosocomial infection in Intensive Care Units (ICUs), VAP affects approximately 20-36% of critically ill patients, with incidence rates ranging from 2 to 16 cases per 1,000 ventilator days, depending on geographic location, ICU protocols, and diagnostic criteria (Papazian *et al*., 2020).

VAP presents a significant clinical and public health concern, particularly in patients with compromised immune systems, including those undergoing chemotherapy, long-term corticosteroid therapy, organ transplantation, or living with HIV. Elderly individuals and patients with chronic respiratory conditions such as COPD or a history of pulmonary infections are also at heightened risk. The duration of mechanical ventilation is a key determinant of VAP development, with prolonged intubation exponentially increasing susceptibility.

The pathogenesis of VAP is multifactorial. The endotracheal tube bypasses natural upper airway defenses, allowing for microaspiration of contaminated oropharyngeal or gastric secretions. Colonization of the lower respiratory tract may occur via several mechanisms, including gastric reflux, aspiration, and contamination from medical devices such as humidifiers, nebulizers, ventilator circuits, and even the nasogastric tube, which may promote oropharyngeal colonization and increase the risk of reflux and aspiration (Hammermeister *et al*., 1990; Braun *et al*., 1986; Kollef *et al*., 1995; Cook *et al*., 1998).

Reintubation is another critical risk factor, introducing new opportunities for mucosal trauma, microbial colonization, and disruption of host defenses. Each episode of reintubation not only extends the duration of mechanical ventilation but also exacerbates the risk of lower airway infection.

Microbiologically, VAP is most often caused by Gram-negative pathogens such as *Pseudomonas aeruginosa, Acinetobacter baumannii*, and *Klebsiella pneumoniae*, though the microbial profile may vary by region, hospital unit, and patient population (Torres *et al*., 1995). Identification of the causative organism is

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challenging but vital for optimizing antibiotic therapy. Routine microbiological surveillance and unit-specific antibiograms are essential tools in guiding empiric therapy and improving treatment success rates.

VAP also exerts a profound influence on antibiotic utilization, accounting for nearly 50% of all antibiotic prescriptions in ICUs (Chastre and Fagon, 2002).

This overuse contributes to the emergence of Multidrug-Resistant (MDR) organisms, resulting in longer hospital stays, increased healthcare costs, and elevated mortality rates (Strausbaugh and Joseph, 2000). Therefore, the effective prevention, early diagnosis, and appropriate treatment of VAP remain critical priorities in critical care medicine.

PREVALENCE OF VAP

The global incidence of Ventilator-Associated Pneumonia (VAP) has shown considerable variation depending on geographic region, healthcare infrastructure, and surveillance methodologies. According to data from the International Nosocomial Infection Control Consortium (INICC), the average global incidence of VAP is reported at 13.6 cases per 1,000 ventilator days (Rosenthal *et al*., 2021). In the Indian context, studies have reported a wide range in VAP incidence, with values spanning from 8.9 to 46 cases per 1,000 ventilator days, reflecting disparities in infection control practices, diagnostic criteria, and patient populations (Joseph *et al*., 2009). This variability highlights the need for standardized diagnostic protocols and strengthened surveillance systems. A global survey comparing regional VAP prevalence rates reported the following average prevalence among ventilated patients (Refer to Figure 1 for regional distribution). In terms of microbial prevalence, a large multicenter international study identified *Pseudomonas aeruginosa* as the most commonly isolated Gram-negative organism in VAP, with an overall global prevalence of 4.1% (Kollef *et al*., 2014).

In Indian ICUs, *Pseudomonas aeruginosa* and *Acinetobacter baumannii* were identified as the most frequent causative organisms associated with VAP (Joseph *et al*., 2009). Other pathogens include a diverse group of both Gram-negative and Gram-positive organisms, as well as fungal species. The relative prevalence of various VAP-associated pathogens is summarized in Figure 2. The distribution of these organisms varies between 1% and 24%, depending on the clinical setting, patient population, and region.

PATHOGENESIS OF VENTILATOR-ASSOCIATED PNEUMONIA (VAP)

Ventilator-Associated Pneumonia (VAP) primarily develops due to the use of an endotracheal tube, which bypasses the natural defenses of the upper airway. The tube interferes with essential protective reflexes-such as coughing and mucociliary clearance leading to oropharyngeal contamination and subsequent colonization by pathogenic organisms (Morris *et al*., 2009). Secretions tend to accumulate above the endotracheal cuff, and if intracuff pressure is insufficient, microaspiration of these secretions into the lower respiratory tract can occur, significantly increasing the risk of infection.

Once colonization occurs, bacteria can form a biofilm along the inner lining of the endotracheal tube. These biofilms are resistant to both host immune defenses and systemic antimicrobial agents. During each ventilator cycle, bacterial discharges may be propelled into the distal airways, further facilitating infection and inflammation (Zolfaghari and Wyncoll, 2011; Morris *et al*., 2011).

The gastrointestinal tract-particularly the stomach-can also act as a reservoir for pathogenic organisms. This colonization may arise from bacteria migrating from the oropharynx or proliferating after translocation from the intestines. A key contributing factor is gastric alkalinization, often a result of stress ulcer prophylaxis, which disrupts the normally acidic environment that suppresses bacterial growth (Chastre and Fagon, 2002).

VAP occurs when microbes breach the lung's defenses and invade the lower respiratory tract and lung parenchyma, leading to inflammation and consolidation. Several factors contribute to this process: impairment of host immunity, exposure to virulent pathogens, or a large infectious inoculum that overwhelms normal defense mechanisms (Strausbaugh and Joseph, 2000; Baker *et al*., 1996).

Under healthy conditions, the respiratory tract employs a variety of innate defense strategies such as alveolar macrophages, neutrophils, and epithelial barriers-to prevent infection (Figure 3). However, when these mechanisms are compromised, either by disease or interventions like mechanical ventilation, the lungs become susceptible to microbial invasion.

Other important immunological factor involved in VAP is the complement component C5a, which has been implicated in phagocytic dysfunction.

PATHOPHYSIOLOGY OF VAP

The development of Ventilator-Associated Pneumonia (VAP) is closely linked to the introduction of a foreign body the Endotracheal Tube (ETT) into the upper airway. This intervention disrupts natural defense mechanisms such as mucociliary clearance and cough reflexes, facilitating the descent of microorganisms into the lower respiratory tract (Zolfaghari and Wyncoll, 2011).

The ETT further promotes the accumulation of secretions above the cuff, where leakage into the lower airways may occur, particularly when intracuff pressure is suboptimal (Rubin *et al*., 2011). These secretions can be rich in oropharyngeal and gastric flora, predisposing patients to microaspiration. Additionally,

positive pressure ventilation contributes to the gravitational and mechanical spread of these secretions into the distal airways.

A critical feature of VAP pathogenesis is the formation of biofilms along the ETT lumen. These structured microbial communities offer protection against systemic antimicrobials and immune clearance, allowing bacteria to persist and migrate into the lungs. Meanwhile, gastric colonization potentially resulting from reflux or stress ulcer prophylaxis can serve as an additional reservoir for pathogens. Alkalinization of the gastric environment facilitates the proliferation of enteric and oropharyngeal microorganisms, increasing the risk of aspiration-related infection (Morris *et al.*, 2013).

Immune Dysregulation in Critically Ill Patients

Recent insights highlight that critically ill patients often exhibit dysregulated innate and adaptive immune responses, rendering them more vulnerable to infections such as VAP. Dysfunctions in neutrophil activity, complement signaling (e.g., C5a-C5aR interaction), and phagocytic capacity have been linked to increased infection risk (Strausbaugh and Joseph, 2000).

In particular, C5a-mediated impairment of phagocytosis can be prevented by blocking CD88 or phosphoinositide-3-kinase and reversed with Granulocyte-Macrophage Colony-Stimulating Factor (GM-CSF). Notably, elevated C5a levels have been observed prior to the onset of hospital-acquired infections, suggesting a potential role in predisposing patients to VAP (Hospital-acquired pneumonia in adults: diagnosis, assessment of severity, initial antimicrobial therapy, and preventive strategies. A consensus statement, American Thoracic Society, November 1995. 1996), (Anand *et al.*, 2009).

Bacterial Etiology and Timing of Onset

Bacterial VAP is predominantly caused by Gram-negative bacilli, which account for 50-80% of all cases. The most frequently identified pathogens include *Pseudomonas aeruginosa, Acinetobacter baumannii*, and members of the *Enterobacteriaceae* family, such as *Escherichia coli* and *Klebsiella pneumoniae*. Among Gram-positive organisms, *Staphylococcus aureus* including MRSA is the most common (Kreitmann *et al.*, 2023; Bassetti *et al.*, 2018).

The timing of VAP onset plays a role in predicting the likely pathogens: Early-onset VAP (≤5 days after intubation): Commonly associated with *Streptococcus pneumoniae, Haemophilus influenzae*, and *Staphylococcus aureus*. Late-onset VAP (>5 days): Typically involves *Pseudomonas aeruginosa, Acinetobacter baumannii*, and Methicillin-Resistant *Staphylococcus aureus* (MRSA) (Chastre and Fagon, 2002; Park, 2005). However, this distinction is not always reliable, especially in patients with prior antibiotic exposure, where Multidrug-Resistant (MDR) pathogens may also cause early-onset VAP (Donald *et al.*, 1984; Chi *et al.*, 2012).

Patient-Related Risk Factors and Microbial Associations

Various comorbidities and clinical factors significantly influence both the risk and microbial profile of VAP:

Chronic Obstructive Pulmonary Disease (COPD): Associated with infections by *Haemophilus influenzae, Moraxella catarrhalis*, and *Streptococcus pneumoniae*.

Cystic fibrosis: Frequently linked to *Pseudomonas aeruginosa* and *Staphylococcus aureus*.

Trauma and neurological patients: More susceptible to *Staphylococcus aureus* infections (Kalil *et al.*, 2016; Timsit *et al.*, 2017; Tantipong *et al.*, 2008). Interestingly, while immunocompromised patients (e.g., transplant recipients, cancer patients) are at high risk for hospital-acquired infections, VAP may paradoxically be less common in this group compared to immunocompetent patients, potentially due to stricter infection control practices. Nonetheless, when VAP occurs in immunocompromised individuals, it is more likely to involve MDR organisms, likely due to prior antimicrobial exposure (Park, 2005).

Other factors associated with MDR VAP include:

- Previous colonization or infection with MDR organisms.
- Presence of Acute Respiratory Distress Syndrome (ARDS).
- Receipt of renal replacement therapy.
- Septic shock at the time of VAP onset (Chi *et al.*, 2012; Kalil *et al.*, 2016; Timsit *et al.*, 2017).

Non-Bacterial Pathogens and Host Factors

While bacteria are the most common cause of VAP, fungal pathogens have also been implicated in select cases, particularly among immunosuppressed individuals (Charles *et al.*, 2014; Hidron *et al.*, 2008).

Moreover, host factors such as antimicrobial peptides (e.g., protegrins) may play a role in modulating oropharyngeal colonization. These peptides exhibit broad-spectrum antimicrobial activity and represent a potential therapeutic angle for infection control (Messika *et al.*, 2018).

RISK FACTORS FOR VENTILATOR-ASSOCIATED PNEUMONIA (VAP) IN DIFFERENT SURGICAL ICU POPULATIONS

Different patient populations within the surgical ICU exhibit varying risks for developing Ventilator-Associated Pneumonia (VAP). These variations are influenced by the type of surgical procedure, pre-existing medical conditions, and patient-specific risk factors.

Cardiothoracic Surgery

Patients undergoing procedures such as Coronary Artery Bypass Grafting (CABG), valve replacement, or lung surgery are at heightened risk for developing VAP. This increased susceptibility is attributed to:

- Prolonged operative times.
- Intraoperative manipulation of the airway and lung tissues.
- Impaired postoperative respiratory mechanics.
- Obstructive Pulmonary Disease (COPD) or congestive heart failure (Goularte *et al.*, 1987).

Trauma

Trauma patients particularly those with head injuries are also highly susceptible to VAP. Factors contributing to this risk include:

- Impaired consciousness, leading to compromised airway protective reflexes.
- Increased risk of aspiration and impaired mucociliary clearance.
- Prolonged immobilization and mechanical ventilation (Braun *et al.*, 1986).

In comparison, medical ICU patients and those undergoing other types of surgical procedures (e.g., gastrointestinal or genitourinary surgeries) present different VAP risk profiles. For instance:

- Underlying conditions like sepsis, Acute Respiratory Distress Syndrome (ARDS), or multisystem organ failure may increase susceptibility to VAP.
- GI surgeries may impair gut motility, leading to bacterial translocation.
- Urologic procedures involving catheters may result in urinary tract infections that can evolve into systemic infections (Craven *et al.*, 1984).

MECHANICAL VENTILATION AND ITS ROLE IN VAP DEVELOPMENT

Mechanical ventilation itself is a significant contributor to the development of VAP, largely due to its components and the environment it creates:

Tubing Colonization

The warm, moist environment within ventilator tubing promotes bacterial growth. Over time, bacteria can form biofilms on the inner surfaces, which are resistant to cleaning and disinfection. These pathogens can be introduced into the patient's airway during ventilation, significantly increasing the risk of VAP (Goularte *et al.*, 1987).

Condensate Formation

As humidified air travels through ventilator circuits and encounters cooler surfaces, condensation occurs. If this condensate accumulates and is not adequately drained, it can become a reservoir for bacteria. Contaminated condensate may then be aerosolized and delivered to the patient's lungs, further elevating the risk of pneumonia (Craven *et al.*, 1984; Braun *et al.*, 1986).

Additionally, VAP shows a higher incidence among patients with concurrent infectious sinusitis, suggesting a possible path of infection from the upper to lower respiratory tract (Craven *et al.*, 1984). Figure 4 indicates Mechanical Ventilation and its role in VAP development.

MANAGEMENT OF VAP

Antibiotic Prophylaxis and the Challenge of Multidrug Resistance in ICU Settings

The prophylactic administration of antibiotics in hospitalized patients-particularly those in the ICU raises significant concerns, especially regarding the emergence and spread of Multidrug-Resistant (MDR) organisms. While prophylaxis may provide short-term benefits by preventing early-onset infections, it often comes at the cost of long-term complications.

Prophylactic antibiotic use represents a double-edged sword. On one hand, it may delay the onset of nosocomial infections; on the other, it fosters an environment conducive to antimicrobial resistance. By exposing bacterial populations to sub-therapeutic levels of antibiotics, prophylaxis exerts selective pressure that promotes the survival and proliferation of resistant strains. This selective environment accelerates the emergence of superinfections, which are often resistant to standard antimicrobial therapies (Sousa *et al.*, 2021; Trouillet *et al.*, 1998; Rello *et al.*, 1993).

Furthermore, the benefits of prophylaxis are often transient and fail to address the core issues contributing to infection spread within the ICU, such as inadequate infection control practices and environmental contamination (Johanson *et al.*, 1972; Richards *et al.*, 1999).

For mild to moderate cases. In more severe or complicated cases, a minimum of 14 days of antibiotic therapy is recommended.

Antibiotic therapy should begin promptly upon clinical suspicion of VAP, even before culture results are available. The selection of empirical antibiotics must be guided by:

- Local antibiogram data.
- The timing of VAP onset (early vs. late).

Patient-specific risk factors, including previous antibiotic exposure (Metersky and Kalil, 2024; Torres *et al.*, 1995).

Initial treatment generally involves broad-spectrum antibiotics to cover a wide range of potential pathogens. However, it is essential to reassess the treatment within 48-72 hr based on the patient's clinical response and results of culture and sensitivity testing. This approach supports antimicrobial stewardship by allowing for de-escalation to a narrower spectrum or shorter duration of therapy whenever appropriate (Craven *et al.*, 1984).

A history of recent antibiotic use significantly increases the risk of developing VAP, due to the potential colonization with resistant organisms.

Interestingly, some studies have indicated that the use of sucralfate, a gastrointestinal mucosal protectant, may reduce the incidence of VAP compared to other stress ulcer prophylactic agents. This benefit is believed to stem from sucralfate's lesser effect on gastric pH, which may reduce bacterial overgrowth and subsequent aspiration (He H, *et al*, 2014).

Infection Control Strategies for Preventing Ventilator-Associated Pneumonia (VAP)

Limiting Ventilation Duration

The use of the ABCDE technique (Awakening, Breathing, Coordination, Delirium, and Early Mobility) has proven to be an effective strategy for reducing the duration of mechanical ventilation. ICU nurses and respiratory therapists play a critical role in implementing ventilator weaning protocols, which include regular sedation interruption and daily trials of normal breathing. By minimizing the time spent on mechanical ventilation, this approach reduces the risk of VAP development.

Patient Positioning

Proper positioning of the patient is a key factor in preventing VAP. Studies have shown that patients positioned flat (0º angle) are at a higher risk of developing VAP due to increased gastroesophageal reflux and aspiration into the lower respiratory airways. The ideal positioning involves elevating the patient's head at a 45º angle to the bed, which has been associated with a reduced risk of VAP (Boltey *et al.*, 2017).

Avoiding Unnecessary Inter-Hospital Transfers

Frequent transfers of ICU patients to different hospital wards can increase the risk of VAP. These transfers often expose patients to more potential sources of infection and disrupt the continuity of care. Minimizing unnecessary inter-hospital transfers helps reduce the likelihood of VAP development.

Modifications to Endotracheal Tubes

Endotracheal tube modifications can significantly reduce the risk of VAP. Standard endotracheal tubes are often prone to microaspiration of contaminated secretions, which can lead to bacterial colonization in the lower respiratory tract. Modifying these tubes-such as by lining them with antibacterial silver material-has been shown to reduce biofilm formation and bacterial colonization, thereby lowering the incidence of VAP. Several studies have demonstrated a reduction in VAP incidence and improved patient outcomes when silver-coated endotracheal tubes are used. Notably, the cost of using silver-coated tubes is relatively low, making this a cost-effective strategy for preventing VAP (Tokmaji G 2015).

Cuff Pressure Management

Maintaining optimal cuff pressure within the endotracheal tube is essential for preventing VAP. Inadequate cuff pressure can lead to microaspiration, which increases the risk of infection. Both

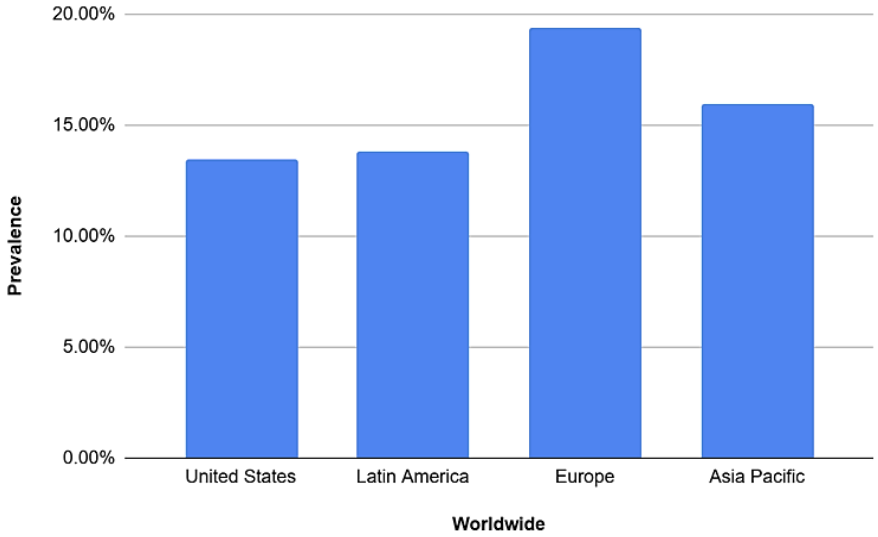

Figure 1: Worldwide prevalence of VAP.

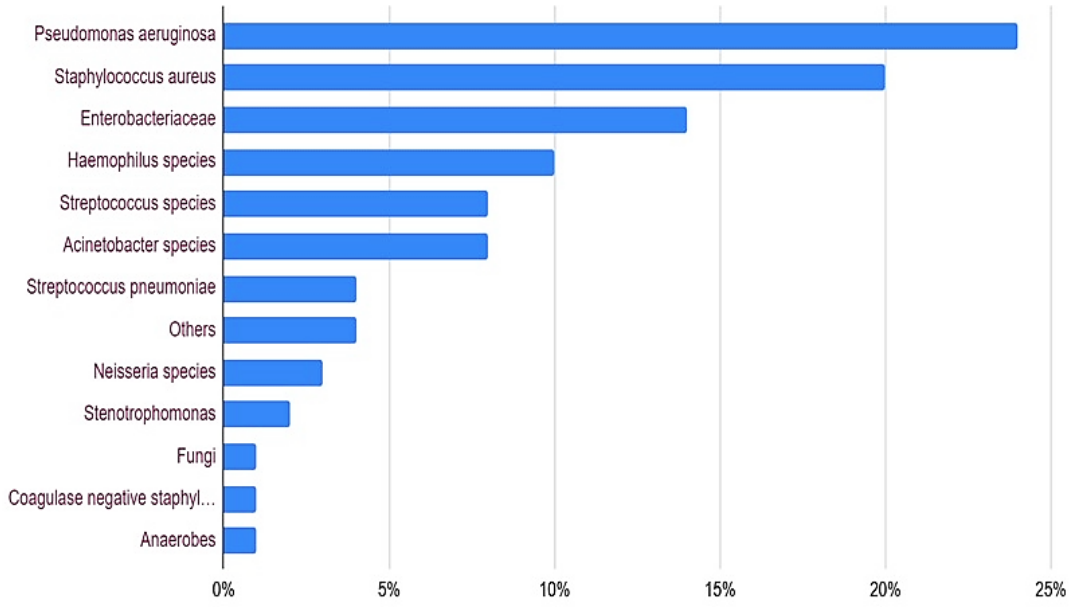

Figure 2: VAP pathogens and it's prevalence.

British and American guidelines recommend maintaining cuff pressures within a specified range to prevent VAP.

PROPHYLACTIC APPROACHES FOR VENTILATOR-ASSOCIATED PNEUMONIA (VAP)

The prevention of Ventilator-Associated Pneumonia (VAP) in critically ill patients relies on a range of prophylactic strategies that aim to minimize the risk of infection during mechanical ventilation. These approaches, grounded in current evidence, include non-invasive ventilation, oral care, tube care, and positioning techniques, among others.

Non-Invasive Positive Pressure Ventilation (NIPPV)

Non-Invasive Positive Pressure Ventilation (NIPPV) has become an important strategy in preventing VAP, particularly by either avoiding intubation or facilitating early extubation. This approach helps reduce the duration of mechanical ventilation, which is a key risk factor for VAP. A meta-analysis of 12 studies showed that the incidence of pneumonia was significantly lower in patients receiving NIPPV compared to those on mechanical ventilation (2% vs. 10%, respectively). Recent evidence from a Cochrane Review further supports using NIPPV as a weaning strategy for patients, particularly those with Chronic Obstructive Pulmonary Disease (COPD), showing a reduction in VAP incidence without an increased risk of reintubation (Waters and Muscedere, 2015).

Oral Care

Effective oral care plays a vital role in reducing the risk of VAP by preventing bacterial colonization in the oropharynx and reducing the spread of bacteria from the stomach or oropharynx to the trachea. Regular cleaning of the oropharynx can significantly reduce bacterial load and prevent aspiration. Moreover, acid-suppressive medications, although useful for managing gastric acidity, should be used cautiously as they can increase gastric pH, fostering bacterial growth in the stomach, which may contribute to VAP.

Tube Care

Proper care of the Endo Tracheal Tube (ETT) is essential in preventing biofilm formation, which can harbor pathogenic bacteria and increase the risk of VAP. Cleaning the inner lumen of the ETT helps prevent the accumulation of secretions and biofilm. One innovative approach is the use of devices such as the Mucus Shaver, which mechanically removes secretions and biofilms from the ETT. Though the impact of these devices on VAP rates is still under investigation, they show promise in reducing contamination and improving patient outcomes (Trouillet *et al.*, 1998).

Cuff Care

Maintaining appropriate cuff pressure on the Endotracheal Tube (ETT) is critical in minimizing the risk of VAP. Proper cuff pressure helps prevent the leakage of oropharyngeal and gastric secretions around the tube, which can lead to aspiration. A recommended cuff pressure range of 20 to 30 cm H_2O is considered optimal to prevent secretion leakage while minimizing mucosal damage. Additionally, devices that monitor and adjust cuff pressure have been shown to reduce microaspiration and lower VAP incidence, supporting their efficacy in improving patient outcomes (Berra *et al.*, 2004).

Tube Modifications

Several modifications to the Endotracheal Tube (ETT) have been explored to decrease the incidence of VAP.

Subglottic Secretion Drainage

ETTs equipped with subglottic secretion drainage systems are designed to remove secretions from the area above the cuff, which is a common site for bacterial accumulation. Intermittent aspiration systems are preferred over continuous aspiration to avoid mucosal injury. Studies have demonstrated that these systems can significantly reduce the incidence of VAP, decrease ICU stay, and shorten ventilation duration (Berra *et al.*, 2004).

ETT Coating

Antimicrobial-coated ETTs, such as those coated with silver, are designed to prevent the formation of biofilms and bacterial colonization. Clinical trials, including the NASCENT study, have shown that silver-coated ETTs reduce the incidence of VAP, particularly in patients requiring prolonged ventilation. These coatings offer a promising preventive strategy for patients at high risk of VAP (Kollef, 2008).

Positioning

The positioning of intubated patients is an important factor in VAP prevention. While the semi-recumbent position has been traditionally recommended, emerging evidence suggests that alternative positioning strategies may be more effective in preventing VAP.

Semi-Recumbent Position

Keeping patients in a 45° semi-recumbent position has been shown to reduce the risk of gastric reflux and aspiration, thereby lowering the risk of VAP. Studies support the effectiveness of this position compared to the supine position, although there are concerns regarding its ability to prevent aspiration of subglottic secretions in patients with prolonged intubation (Coppadoro *et al.*, 2012).

Lateral Positioning

Recent studies suggest that lateral positioning may be more effective than the semi-recumbent position in preventing VAP. This position helps with better clearance of secretions from the lower respiratory tract and does not cause the reversal of mucus flow, which is a risk factor for aspiration (Mauri *et al.*, 2010).

Kinetic Therapy

This involves rotating patients at 40° intervals, may improve pulmonary function by facilitating the movement of secretions and preventing mucus accumulation. Although a meta-analysis found that kinetic therapy could reduce VAP incidence, its impact on ICU stay, ventilation duration, and mortality remains uncertain. Potential complications, such as patient intolerance and unplanned extubation, limit its widespread recommendation (Delaney *et al.*, 2006).

ANTIBIOTIC STEWARDSHIP AND FOLLOW-UP

Following the completion of antibiotic therapy for VAP, it is essential to practice antibiotic stewardship principles to minimize the development of antibiotic resistance and other adverse effects. This includes appropriate selection of antibiotics based on culture and sensitivity results, as well as reassessment of therapy duration and de-escalation when indicated. Close monitoring for signs of recurrent infection or antibiotic-related complications is paramount during the post-treatment phase. Table 1 Antibiotic currently in use in the management of VAP.

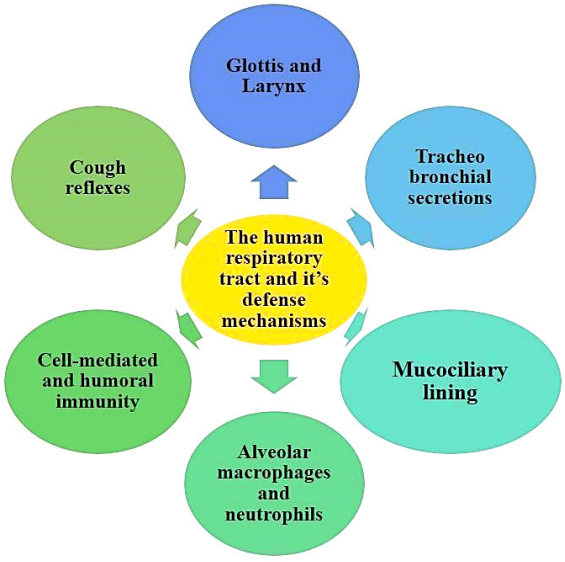

Figure 3: The human defense mechanisms and VAP.

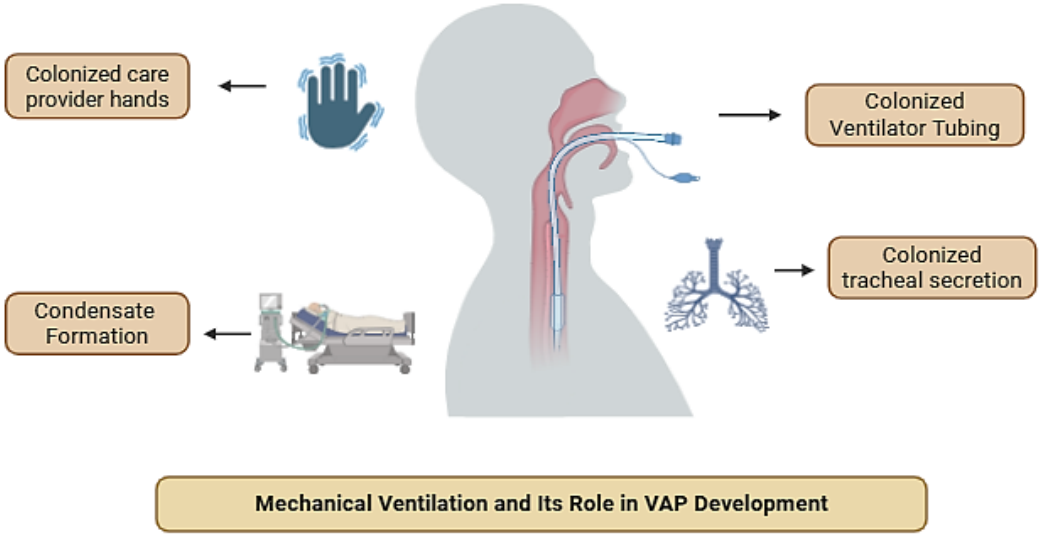

Figure 4: Mechanical Ventilation and its role in VAP development.

NUTRITIONAL SUPPORT

Nutritional support is crucial in the recovery phase of patients who have undergone treatment for Ventilator-Associated Pneumonia (VAP), as it aids in restoring immune function, promotes wound healing, and supports overall recovery. Malnutrition can be a common issue in critically ill patients, and ensuring adequate caloric and protein intake is essential for rebuilding muscle strength and endurance compromised during prolonged periods of mechanical ventilation. Nutritionists typically assess the patient's dietary needs and caloric requirements to create a personalized nutritional plan. This may involve oral, enteral, or parenteral nutrition, based on whether the patient can ingest and absorb food normally. Key nutritional goals include maintaining energy balance, providing sufficient protein to prevent muscle loss, and supplying vitamins and minerals to support the immune system and other bodily functions, ultimately facilitating a quicker and more robust recovery.

BIOMARKERS FOR VENTILATOR-ASSOCIATED PNEUMONIA (VAP)

The identification and validation of biomarkers for VAP are critical for improving diagnostic accuracy and patient outcomes. This article reviews three biomarkers soluble Triggering Receptor Expressed on Myeloid cells type 1 (sTREM-1), Procalcitonin (PCT), and C-Reactive Protein (CRP)-which have been investigated for predicting VAP (Palazzo *et al.*, 2011)

Soluble Triggering Receptor Expressed on Myeloid Cells Type 1 (sTREM-1)

TREM-1 is a glycoprotein that upregulates in response to bacterial and fungal infections, amplifying the inflammatory response. Soluble TREM-1 (sTREM-1) is released during infection and can be measured in body fluids, including Bronchoalveolar Lavage (BAL) and Exhaled Breath Condensate (EBC). Early studies suggested high specificity and sensitivity for sTREM-1 in diagnosing VAP. However, subsequent studies showed lower sensitivity and specificity, possibly due to factors such as prior antibiotic use and variations in VAP diagnostic criteria. Recent findings also suggest that sTREM-1 might be elevated in non-infectious inflammation, reducing its specificity for infection. Further research with standardized methods is needed to confirm its role as a reliable VAP biomarker (Bouchon *et al.*, 2001; Bouchon *et al.*, 2000; Anand *et al.*, 2009).

Procalcitonin (PCT)

PCT is a prohormone secreted in response to bacterial infections, with elevated levels often indicating systemic bacterial inflammation. PCT has shown variable diagnostic performance in identifying VAP, with sensitivities ranging from 41% to 100% across studies. Although specificity was high in some studies, the use of variable cutoff values, differing diagnostic criteria for VAP, and patient population heterogeneity complicate its utility. Despite these challenges, recent meta-analyses suggest that PCT-guided strategies may be effective in reducing antibiotic duration in septic patients without adverse effects. Thus, while PCT is not a strong predictor for diagnosing VAP, its use in guiding antibiotic therapy, particularly for discontinuation, has

shown promise (Ramirez *et al.*, 2008; Palazzo *et al.*, 2011; Maruna *et al.*, 2000).

C-Reactive Protein (CRP)

CRP is a non-specific marker of inflammation that is synthesized in the liver in response to infections, trauma, or other inflammatory stimuli. Elevated CRP levels can indicate the presence of bacterial infections, including VAP. However, studies on CRP as a VAP biomarker have been limited, with mixed results. Some studies found high specificity for CRP, while others reported low sensitivity, leading to many false negatives. The sensitivity and specificity of CRP may vary depending on the sampling method (serum vs. BALF) and cutoff values used. The lack of standardized protocols for CRP measurement and sample collection further limits its application in VAP diagnosis. Overall, CRP appears to have limited utility as a standalone biomarker for VAP (Oppert *et al.*, 2002; Póvoa, 2002).

The potential use of biomarkers such as sTREM-1, PCT, and CRP for diagnosing VAP remains an active area of research. Each of these biomarkers has demonstrated some promise, yet they also present significant challenges, including variability in diagnostic performance and limited specificity. Standardized protocols, larger multicenter trials, and clearer cutoff values are needed to establish these biomarkers as reliable diagnostic tools for VAP.

sTREM-1 stands out for its ability to reflect infection, but its application is hindered by the influence of non-infectious inflammation and prior antibiotic use. PCT, while not an ideal biomarker for VAP diagnosis, has shown potential in guiding antibiotic therapy and reducing treatment duration. CRP, being a general marker for inflammation, has limited specificity for VAP and would benefit from being used in combination with other diagnostic tools.

EFFICACY OF VARIOUS FORMULATIONS EVALUATED USING ANIMAL INFECTION MODELS

Animal infection models provide essential insights into the efficacy of formulations for preventing and treating Ventilator-Associated Pneumonia (VAP). These studies offer a controlled environment to test antimicrobial agents and methods under conditions mimicking human clinical scenarios. Table 2 indicates key studies evaluating the efficacy of various formulations using animal models.

Diagnostic Methods: Comparative studies identified BAL, PSB, and tracheal secretions for diagnosing VAP.

Pneumonia Development: Both spontaneous and pathogen-induced VAP models in ventilated animals highlighted the role of airway colonization.

Pathogen Identification: Pathogens like *Pseudomonas aeruginosa, Staphylococcus aureus*, and *Escherichia coli* were major contributors to VAP in the models.

Treatment Impact: Studies underscore the importance of timely antimicrobial therapy and mechanical ventilation strategies in controlling VAP development.

FORMULATIONS FOR ORAL CARE IN VENTILATOR-ASSOCIATED PNEUMONIA (VAP)

Oral care is an essential component in preventing and managing Ventilator-Associated Pneumonia (VAP), as it helps reduce bacterial colonization in the oropharynx and prevents microaspiration of pathogens into the lower respiratory tract. A variety of formulations and approaches are available to manage oral hygiene in intubated patients. These formulations range from aerosolized antimicrobial agents to gel-based solutions, each offering distinct advantages for preventing VAP. Below are the key formulations currently available for oral care in the context of VAP:

Nebulized Antimicrobial Agents

Nebulized antimicrobial agents have become a key part of VAP treatment, offering direct delivery of antibiotics to the lungs, which allows for higher local concentrations and minimizes systemic side effects.

Metered Dose Inhalers (MDI) vs. Vibrating Mesh Nebulizers

A retrospective study comparing MDIs with vibrating mesh nebulizers found no significant differences in clinical outcomes such as length of hospital stay and VAP rates, suggesting that both delivery methods are equally effective. However, MDIs may reduce bacterial contamination due to their design, while vibrating mesh nebulizers help minimize circuit disruption, offering advantages in infection control (Dubosky *et al.*, 2017; Dhand, 2017).

Efficacy of Nebulized Antimicrobial Agents

Studies have shown nebulized antibiotics, such as tobramycin, can reduce VAP incidence and recurrence, particularly for *Pseudomonas aeruginosa* infections. A study administering a 14-day course of aerosolized Tobramycin Inhalation Solution (TIS) alongside systemic antibiotics resulted in reduced recurrence of VAP and improved clinical outcomes, including lower ICU mortality rates (Migiyama *et al.*, 2017). This supports the use of nebulized therapies as part of a comprehensive VAP management regimen.

Aerosolized Spray for VAP

The use of aerosolized tobramycin has demonstrated clinical benefits in preventing and managing *Pseudomonas*

aeruginosa-induced VAP. This approach targets direct antibiotic delivery to the lungs, enhancing bacterial eradication and reducing recurrence of infection. The 14-day regimen of aerosolized tobramycin alongside systemic antibiotics was found to reduce ICU mortality and recurrence of VAP, further highlighting the utility of aerosolized therapies in improving patient outcomes (Migiyama *et al.*, 2017).

Toothpastes for Oral Hygiene

Oral hygiene plays a crucial role in reducing the microbial load in the oropharynx, which can prevent the aspiration of harmful bacteria into the lower respiratory tract.

Recommendations suggest brushing the teeth of ventilated patients twice daily, each session lasting at least 2 min. This regular oral hygiene routine helps maintain oral health and prevent the build-up of pathogens in the oral cavity, which can be aspirated into the lungs, leading to infections like VAP. Comprehensive oral care is necessary for patients who cannot manage their own hygiene, such as those with critical conditions (Collins *et al.*, 2021).

Chlorhexidine (CHX) Solutions

Chlorhexidine (CHX) is a widely used antimicrobial solution for managing oral hygiene in critically ill patients. Studies have demonstrated that 2% CHX is particularly effective in reducing oral infections and inflammation in high-risk patients.

Laboratory experiments have shown that 2% CHX has superior antimicrobial activity against Multidrug-Resistant (MDR) bacteria, making it an effective tool in preventing infections in patients who are highly susceptible to resistant strains (Tantipong *et al.*, 2008).

In clinical settings, 2% CHX solutions have been widely used for their ability to combat a range of bacteria and reduce the risk of aspiration pneumonia, a common complication in mechanically ventilated patients.

Gel Formulations for Oral Hygiene

Gel formulations have emerged as a more manageable option for patients who are critically ill or unable to perform their own oral care. Gels like 1% Chlorhexidine (CHX) have demonstrated higher efficacy in preventing infections compared to liquid solutions. A disk diffusion assay study found that 1% CHX gels exhibited the highest bacterial stasis compared to other formulations, especially in cases of aspiration pneumonia (Han *et al.*, 2022). These gels are easier to apply and stay in place longer, making them ideal for intubated patients who may have difficulty with traditional liquid solutions.

Novel Approaches to Counter Biofilm Formation

Endotracheal intubation often leads to biofilm formation on the surface of the tube, which can harbor bacteria and serve as a reservoir for infection. To combat this, novel approaches like the use of Epigallocatechin Gallate (EGCG), a polyphenol derived from green tea, are being explored.

One study showed that formulations combining EGCG stearate (EGCG-S) with selected antibiotics could inhibit biofilm formation by common respiratory pathogens such as Escherichia coli, *Pseudomonas aeruginosa, Staphylococcus aureus*, and *Staphylococcus epidermidis*. This suggests a potential role for EGCG-based formulations in improving oral hygiene and preventing biofilm-related infections, particularly in ventilator-associated pneumonia (Shinde, Lee, and Chu 2021).

Table 1: The Antibiotics which are in present use to treat VAP.

Drug	Dose	Dosage form
Oxazolidinones: Tedizolid Linezolid (Bassetti *et al.*, 2018).	200 mg, 24 hr 600 mg, 12 hr	IV and Oral
Cephalosporins: Cefiderocol Cefipime (Portsmouth *et al.*, 2017).	2 g, 8 hr 1 g/50 mL 8 hr	IV IV
Cephalosporin + beta lactamase inhibitor Ceftolozane-tazobectam (Haidar *et al.*, 2017). Ceftazidime-avibactam (Keepers *et al.*, 2014).	1.5,3 g 8 hr 2.5 g, 8 hr	IV IV
Carabapenem + novel beta lactamase inhibitor Meropenem-vaborbactam Imipenem-relebactam (Bassetti *et al.*, 2018).	2 g, 8 hr 500/250/125 mg, hr	IV IV
Aminoglycosides Plazomicin (Li *et al.*, 2015).	15 mg, 24 hr	IV
Fluoroquinolones: Ciprofloxacin Levofloxacin (Bassetti *et al.*, 2018).	400 mg, 24 hr 750 mg, 24 hr	Oral Oral
Glycopeptide: Vancomycin (Bassetti *et al.*, 2018).	15 mg/kg, 12 hr	IV
Fosfomycin & Polymixins Colistin Polymixin B (Colistin and polymyxin B: A re-emergence) (Bassetti *et al.*, 2018).	1.5 to 2.5 mg/kg/day	IV
Beta-lacatam antibiotics (Monobactams) Aztreonam (Kaye *et al.*, 2015).	2 g, 8 hr	IV

Table 2: Efficacy of VAP Formulations in Animal Models.

Key Findings	Animal Species
Investigated diagnostic methods and antimicrobial efficacy in VAP using baboons. Compared tracheal secretions, BAL, and PSB, with animals ventilated for 7-10 days. Assessed treatment effectiveness based on diagnostic results and clinical outcomes (Luna *et al.*, 2009).	Baboons
Studied spontaneous pneumonia development in mechanically ventilated piglets. Pneumonia emerged after 4 days, with common airway colonization. Ventilation lasted 3-4 days, followed by lab tests and post-mortem cultures for confirmation (Hugo Marquette *et al.*, 1995).	Landrace-White piglets
Investigated pneumonia induction in ventilated piglets through high-dose pathogen inoculation (*P. aeruginosa, E. coli, S. aureus*). Inoculation (10^6-10^8 CFU/mL) led to consistent pneumonia and airway colonization. Post-mortem exams confirmed disease development (Marquette *et al.*, 1999).	Landrace-White piglets

Others

Probiotics

Probiotics, consisting of live non-pathogenic microorganisms, may help prevent VAP in ICU patients by competing with VAP-causing bacteria in the oropharynx and stomach, and through their immunomodulatory effects. A meta-analysis found a lower incidence of VAP and reduced ICU stay and *Pseudomonas aeruginosa* colonization in patients receiving probiotics.

Early and Enteral Feeding

Enteral feeding can increase the risk of aspiration and VAP. Post-pyloric feeding tubes may reduce VAP risk, but studies show no statistically significant difference in VAP incidence or mortality compared to gastric feeding. Additionally, early enteral feeding (within 48 hr of ventilation) has been linked to a higher VAP risk, though it may reduce ICU and hospital mortality. Therefore, no definitive recommendations can be made for these practices (Coppadoro *et al.*, 2012; Artinian *et al.*, 2006).

POTENTIAL FORMULATIONS FOR PROPHYLAXIS IN VAP

The oral cavity is a significant entry point for pathogens that can lead to Ventilator-Associated Pneumonia (VAP), especially in intubated and mechanically ventilated patients. As such, the development of effective oral formulations for managing infections in the oral cavity is critical for preventing VAP. This section reviews current oral formulations used for treating oral infections, highlighting their potential application in VAP prophylaxis.

Adhesive Tablets

Adhesive tablets have shown significant promise in treating oral infections by delivering antifungal and antibacterial agents directly to the mucosal site. These tablets adhere to the oral mucosa, providing a prolonged release of active ingredients and ensuring consistent therapeutic levels over an extended period.

Given their sustained-release mechanism, adhesive tablets could be beneficial in mechanically ventilated patients by providing consistent antimicrobial coverage to prevent the colonization of respiratory pathogens in the oral cavity, thus reducing the risk of VAP. Their localized delivery and prolonged action minimize the need for frequent administration, improving patient compliance and comfort (Mizrahi and Domb, 2007).

Adhesive Patches and Films

Adhesive patches and films have been developed for sustained drug release, demonstrating effectiveness against a wide range of microorganisms, including Candida albicans and resistant bacteria like *Pseudomonas aeruginosa* and *Staphylococcus aureus*. These patches have been extensively evaluated using methods like disc-diffusion to confirm their broad-spectrum antimicrobial properties.

The sustained release of active ingredients from adhesive patches could effectively reduce the bacterial load in the oropharynx, a key site for VAP pathogens. These formulations could be particularly useful for patients on mechanical ventilation, offering long-duration antimicrobial effects to prevent the development of VAP by reducing oral and airway colonization (Obaidat *et al.*, 2011).

Gel Formulations for Oral Infections

Gel formulations, such as those containing chitosan and chlorhexidine, or metronidazole Solid Lipid Nanoparticles (SLNs), have shown sustained release profiles, allowing prolonged antimicrobial action. These gels are bioadhesive and can deliver active ingredients directly to the oral mucosa, increasing the duration of the therapeutic effect.

These gels offer significant potential in the prophylaxis of VAP, as they can maintain therapeutic drug levels for extended periods, reducing the bacterial burden in the oral cavity (Kloster *et al.*, 2018; Ho *et al.*, 2022).

Oral Spray

Recent research on xibronol-based oral sprays highlights their robust antibacterial action against several pathogens, including *Streptococcus pneumoniae, Staphylococcus aureus*, and *Corynebacterium ulcerans*. These sprays are effective in

treating respiratory tract infections, demonstrating significant antimicrobial potential.

The targeted action of oral sprays in the respiratory tract could be beneficial for preventing VAP. By directly applying antimicrobial agents to the oropharyngeal area, xibronol-based sprays may reduce the colonization of pathogenic bacteria that can lead to VAP in mechanically ventilated patients. This approach could provide an easy-to-use, non-invasive option for VAP prophylaxis (Celandroni *et al*., 2021).

Oral Solutions

Mouth paints and oral solutions containing nanomaterials like Titanium Dioxide Nanoparticles (TiO2NPs), along with natural extracts such as lemongrass and dry ginger, offer unique antimicrobial benefits. These formulations target both inflammation and bad breath, with enhanced effectiveness from the nanomaterial's unique properties.

Oral solutions, particularly those formulated with TiO2NPs, can offer targeted antimicrobial activity in the oral cavity. The inclusion of natural extracts further enhances the formulation's antimicrobial properties, which could be useful in preventing oral colonization by pathogens that contribute to VAP. The non-invasive nature of oral solutions allows for easy integration into routine oral care for ventilated patients (Rifaath *et al*., 2023).

Oral Emulsions

Oregano Essential Oil-based Nanoemulsions have shown antibacterial and antifungal properties, particularly against oral microbiota. These emulsions enhance the solubility and bioavailability of lipid-based therapeutics, improving their efficacy.

The nanoemulsion formulation of oregano oil could be explored for its ability to target oral pathogens and reduce the risk of VAP. Its enhanced antimicrobial properties and targeted delivery system could help prevent bacterial colonization in the oral cavity, a key step in VAP prevention (Manaa, Baghdadi *et al*. 2022).

Nanoparticulate systems

Liposomal and nanoparticle-based drug delivery systems offer promising strategies for preventing and treating various infectious diseases including VAP (Sreeharsha *et a*l., 2021; Vanaja *et al*., 2021, (Kenchappa *et al*. 2022). Traditional systemic antibiotics often suffer from poor retention in the oral cavity and respiratory tract, reducing local efficacy and increasing the risk of resistance. Nanoparticulate delivery systems offer a promising alternative due to their ability to enhance drug stability, prolong local drug retention, allow for controlled release and reduce systemic side effects. Liposomes, especially when incorporated into thermosensitive *in situ* gels, enable sustained antibiotic release and improved retention in the oral cavity, aiding in prophylaxis (Vanaja *et al*., 2020). Polymeric nanoparticles, solid lipid nanoparticles, and metallic nanoparticles enhance drug stability, mucosal adhesion, and biofilm penetration.

CONCLUSION

Biomarkers such as sTREM-1, PCT, and CRP offer valuable insights into the diagnosis and management of Ventilator-Associated Pneumonia (VAP). However, their clinical utility is still subject to ongoing research and refinement. The integration of these biomarkers into diagnostic algorithms, coupled with improvements in diagnostic accuracy and treatment strategies, could significantly enhance patient outcomes in VAP management. Future studies should focus on standardization, clinical validation, and exploring new biomarkers to optimize VAP diagnosis and treatment.

The formulations reviewed above adhesive tablets, patches and films, gels, oral sprays, solutions, and emulsions offer promising approaches for oral cavity management in mechanically ventilated patients. Their potential in VAP prophylaxis lies in their ability to deliver sustained antimicrobial effects, reduce oral colonization by harmful pathogens, and improve patient compliance with minimal intervention. Further research into their effectiveness in preventing VAP, particularly in critical care settings, is essential for optimizing prophylactic strategies and improving patient outcomes.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

VAP: Ventilator-associated pneumonia; **MDR:** Multidrug-resistant; **ICU:** Intensive Care Unit; **COPD:** Chronic obstructive pulmonary disease; **strem-1:** Soluble Triggering Receptor Expressed on Myeloid cells-1; **INICC:** International Nosocomial Infection Control Consortium; **c5a:** Complement component 5a; **CD88:** Cluster of Differentiation 88; **ARDS:** Acute Respiratory Distress Syndrome; **MRSA:** Methicillin-resistant *Staphylococcus aureus*; **MV:** Mechanical ventilation; **ETT:** Endotracheal tube; **CABG:** Coronary artery bypass graft; **NIPPV:** Non-invasive positive pressure ventilation; **ABCDE:** Awakening, Breathing; Coordination, Delirium and Early mobility; **Pao2:** Partial pressures of oxygen; **PEEP:** Positive End-Expiratory Pressure; **fio2:** Fraction of Inspired Oxygen; **SBT:** Spontaneous Breathing Trials; **NIV:** Non-invasive ventilation; **CPAP:** Continuous positive airway pressure; **bipap:** Bilevel positive airway pressure; **PTSD:** Post-Traumatic Stress Disorder; **PSB:** Protected Specimen Brush (diagnosing pneumonia); **BAL:** Bronchoalveolar Lavage; **CFU:** Colony Forming Unit; **PCT:** Procalcitonin; **CRP:** C-reactive protein; **MDI:** Metered-dose inhalers; **TIS:** Tobramycin inhalation solution; **CHX:** Chlorhexidine; **EGCG:** Epigallocatechin gallate; **tio2nps:**

Titanium dioxide nanoparticles; **OEO-SNEDD:** Oil-based Self-Nanoemulsifying Drug Delivery; **NEs:** Nanoemulsions.

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