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Management and Preventive Strategies for VAP

Abdel-razek Hefni El sheikh[1], Ehab Abdelmoniem Al banaa[1], Yasser Ahmed Ismail Ibrahim[1], Haytham Kamal Ahmed Mahrous[2]

[1] Pediatrics Department, Faculty of Medicine, Zagazig University, Egypt

[2] Clinical Pathology, Faculty of Medicine, Zagazig University, Egypt

Corresponding author: Yasser Ahmed Ismail Ibrahim

Email: ya318827@gmail.com

Abstract:

Background: Ventilator-associated pneumonia (VAP) is a significant nosocomial infection occurring in mechanically ventilated patients, typically developing 48 hours or more after endotracheal intubation. It contributes substantially to patient morbidity, prolonged intensive care unit (ICU) stays, increased healthcare costs, and higher mortality rates. The pathogenesis of VAP involves aspiration of oropharyngeal secretions, biofilm formation on endotracheal tubes, impaired host defenses, and colonization by multidrug-resistant (MDR) organisms. Effective management of VAP involves early diagnosis, appropriate antibiotic therapy, and supportive care. Timely identification of causative pathogens through culture of lower respiratory tract secretions, followed by targeted antimicrobial therapy, is crucial. Empiric antibiotic regimens should be selected based on local antibiograms and risk factors for MDR organisms, and de-escalated once culture results are available. Adjunctive therapies may include pulmonary hygiene, optimization of sedation, and early mobilization. Preventive strategies are paramount in reducing VAP incidence. These include both non-pharmacologic and pharmacologic approaches. The "VAP prevention bundle" — widely recommended by healthcare agencies — comprises several key elements: Elevation of the head of the bed (30–45 degrees), daily sedation interruption and assessment of readiness to extubate, peptic ulcer disease and deep vein thrombosis prophylaxis, regular oral care with chlorhexidine and subglottic secretion drainage. Strict adherence to infection control protocols, including hand hygiene and use of personal protective equipment, also plays a vital role. Additionally, minimizing the duration of mechanical ventilation through weaning protocols, using non-invasive ventilation when possible, and avoiding unnecessary intubation are essential preventive measures. The integration of evidence-based guidelines and multidisciplinary care approaches has proven effective in decreasing VAP rates. Continuous staff education, surveillance, and quality improvement programs further enhance prevention and improve patient outcomes.

Keywords: Ventilator-associated pneumonia (VAP), Mechanical ventilation, Nosocomial infections, ICU-acquired infections, VAP prevention bundle.

Introduction:

Ventilator-associated pneumonia (VAP) is one of the most common healthcare-associated infections in intensive care units (ICUs), affecting up to 10–25% of patients who undergo mechanical ventilation for more than 48 hours **(1).** VAP is associated with increased morbidity, mortality, length of hospital stay, and healthcare costs **(2).** It results primarily from the microaspiration of contaminated oropharyngeal or gastric secretions, often facilitated by biofilm formation on endotracheal tubes and compromised host defenses **(3).**

Timely and effective management includes early diagnosis, appropriate empirical antibiotic therapy, and de-escalation based on culture results. However, prevention remains the cornerstone of reducing VAP incidence. Evidence-based strategies—such as head-of-bed elevation, daily sedation vacations, oral care with chlorhexidine, and

subglottic secretion drainage—have demonstrated significant efficacy in reducing VAP rates when implemented as part of a bundled care approach **(4).**

In light of increasing antimicrobial resistance and the critical burden VAP poses, ongoing surveillance, staff training, and strict adherence to infection prevention protocols are essential to improve patient outcomes in the ICU.

Management of VAP:

Intravenous (IV) antimicrobial therapy is the cornerstone of VAP treatment. Physicians face a dilemma, however, between avoiding ineffective treatment, inappropriate initial antimicrobial treatment being associated with increased mortality; and on the other hand, reducing the consumption of broad-spectrum antibiotics, the latter being associated with increased bacterial resistance. Therefore, treatment of VAP should be a two-step process: the first step is empiric treatment, the second choice is pathogen- specific treatment **(5)**.

Empirical treatment

The choice and timing of antimicrobial agents used should take into account four parameters: severity of the current illness, type and number of underlying diseases and their severity, risk factors for MDR pathogens, and the local pattern of antimicrobial susceptibility. Risk factors for MDR pathogens include high (> 25%) local prevalence of pathogen resistance, antibiotic therapy in the previous 90 days, hospital stay > 5 days, septic shock at VAP onset, ARDS prior to VAP onset, acute renal replacement therapy prior to VAP onset and previous colonization with MDR pathogens **(6)**.

In non-immunocompromised patients with early-onset VAP and no risk factors for MDR pathogens, monotherapy with narrow-spectrum antibiotic (non-pseudomonal third generation cephalosporin) can be used. In other situations, initial empiric treatment should include a broad-spectrum β-lactam targeting Pseudomonas aeruginosa and/or ESBL-producing Enterobacteriaceae (ceftazidime, cefepime, piperacillin–tazobactam or a carbapenem) plus a non-β-lactam antipseudomonal agent, such as aminoglycosides (amikacin or tobramycin) or fluoroquinolones (ciprofloxacin or levofloxacin) **(7)**.

The choice of the β-lactam agent should take into account previously used antibiotics, local pattern of susceptibilities and patient colonization with MDR pathogen. For example, a carbapenem should be preferred in patients colonized with ESBL-producing Enterobacteriaceae. Indeed, although carbapenem are overprescribed in ESBL carriers, 7–10% of VAP episodes in these patients are due to an ESBL-producing Enterobacteriaceae, and it seems difficult not to take into account this pathogen in the empirical antimicrobial treatment. Moreover, it has been shown that 63% of infection-related ventilator-associated complications were neither VAP nor attributable to a documented ICU infection, indicating that efforts should be concentrated on the diagnostic strategy, to use carbapenems only in patients with true infection, and to withhold carbapenems when the likelihood of infection is low **(8)**.

The use of new beta-lactam agents (ceftazidime–avibactam, ceftolozane–tazobactam, meropenem–vaborbactam, imipenem–relebactam) in the empirical treatment of VAP should probably be reserved in patients colonized with MDR/XDR pathogens, such as carbapenem-resistant Enterobacteriaceae or XDR Pseudomonas aeruginosa susceptible only to these drugs **(9)**.

The 2017 IDSA/ATS (The infectious disease society of America /the American thoracic society) guidelines recommend empiric coverage of methicillin-resistant Staphylococcus aureus (MRSA) in patients who received antibiotics in the preceding 90 days or those hospitalized in units with high (> 20%) or unknown MRSA prevalence among VAP patients. European guidelines state that MRSA coverage should be considered if the unit has > 25% of Staphylococcus aureus respiratory isolates as MRSA **(10)**.

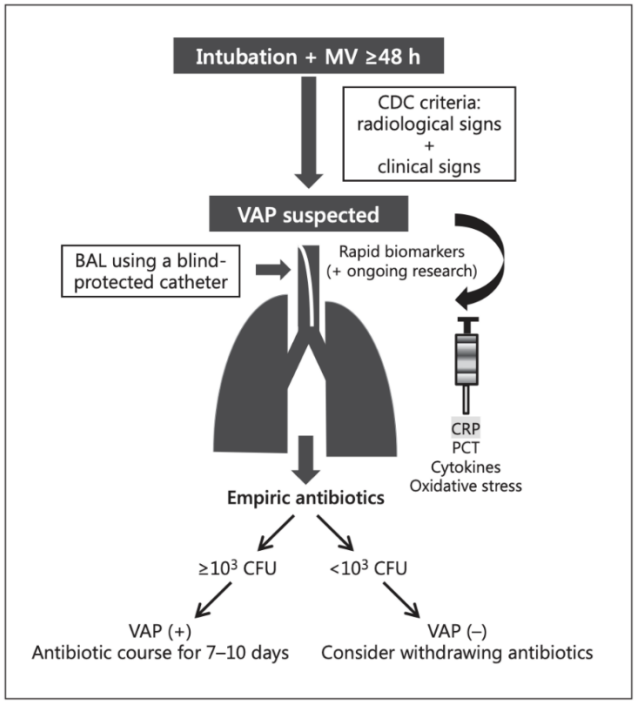

Figure (1): Algorithm for initiation and stoppage of antibiotics in VAP (10).

Pathogen-specific treatment

First, antibiotics should be stopped if no pathogen is retrieved. Indeed, many episodes of suspected VAP are not VAP. Second, in patients with bacteriologically proven VAP, antibiotics should be narrowed once culture results and susceptibility tests are available, including the following measures **(11)**:

- withdrawing of anti-MRSA antibiotics if no MRSA is recovered;
- restriction of carbapenems to carbapenem-only susceptible pathogens (ESBL-producing Enterobacteriaceae infection, carbapenem-only susceptible Pseudomonas aeruginosa or Acinetobacter spp.);
- use of narrow-spectrum agents in patients infected with susceptible strains.

In patients with ESBL-producing Enterobacteriaceae VAP susceptible to piperacillin–tazobactam, the use of this drug could be discussed as an alternative to carbapenem. Moreover, the place of new beta-lactam agents (ceftolozane–tazobactam, ceftazidime–avibactam) as carbapenem-sparing agents remains to be determined, since their impact on emergence of antimicrobial resistance as compared to carbapenem is not known. Their use should be reserved as last resort agents in MDR/XDR difficult to treat pathogens (carbapenem-resistant Enterobacteriaceae, XDR Pseudomonas aeruginosa…) **(12)**.

Antimicrobial therapy can be safely switched to monotherapy once pathogens responsible for infection are identified and susceptibility results have been obtained, even for non-fermenting Gram-negative bacilli such as Pseudomonas aeruginosa. Indeed, the usefulness of combination therapy is mostly to increase the likelihood of appropriateness of treatment rather than improving the prognosis of patients. Therefore, double antipseudomonal coverage in patients with Pseudomonas aeruginosa VAP with uncomplicated course should be avoided once susceptibility tests are available **(13)**.

Duration of treatment

Both European and US guidelines recommend that the duration of antimicrobial treatment for VAP should not exceed 7 days in most patients, including those infected with non-fermenting Gram-negative bacilli (Pseudomonas aeruginosa, Acinetobacter spp….). Longer course may be appropriate for immunocompromised patients and are likely necessary for patients with empyema, lung abscess, or necrotising pneumonia. Shortening duration of antimicrobial below 7 days is currently not recommended **(14)**.

Nebulisation

Nebulisation of antibiotics has grown in recent years, but the ideal candidates to receive this treatment are not well defined. To date, nebulized antibiotics cannot be recommended as an alternative to the intravenous route, partly because data are lacking on this indication, partly because 10–20% of patients with VAP have concurrent bacteraemia, and partly because multiple and repeated daily use of nebulisation may prolong duration of mechanical ventilation. The use of nebulised antibiotics as an adjunctive treatment (i.e., in addition to effective intravenous therapy) is also not recommended; two recent randomized-controlled trials failed to demonstrate superiority of nebulised antibiotics (amikacin alone or combined with fosfomycin) over placebo in patients with VAP due to "traditional pathogens" **(15)**.

The use of nebulised antibiotics should therefore be restricted to patients with VAP to XDR-Gram-negative pathogens susceptible only to colistin or aminoglycosides. Whether or not nebulised antibiotics may decrease emergence of bacterial resistance, as suggested by two studies performed in patients with ventilator-associated tracheobronchitis, remains to be determined **(16)**.

Preventive strategies for VAP:

Prevention of VAP is accomplished by avoiding prolonged IMV. Removing the ETT when possible is critical in preventing VAP and should be a focus of everyday clinical decision-making. The CDC and Healthcare Infection Control Practices Advisory Committee (HICPAC) recommends using orotracheal tubes and changing respiratory circuits only for malfunction or contamination. There is no recommendation for routine exchange of ETTs or circuits without any clinical indication. **Figure 2** summarizes the Common quality improvement measures and bundles used in neonatal intensive care units to prevent VAP by 4 studies **(17)**.

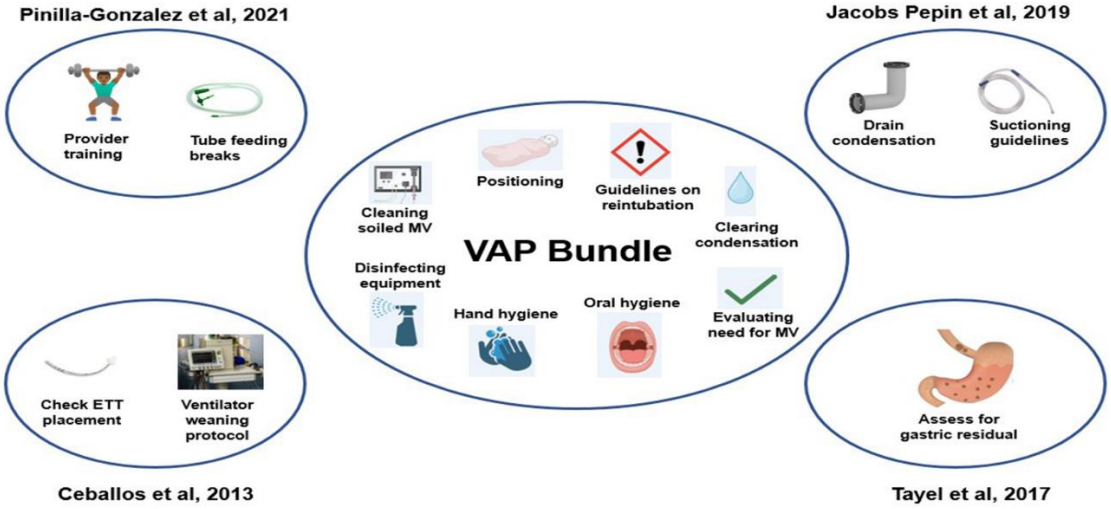

Figure (2): Preventive bundle measures for VAP (17).

General strategies:

Oral care with chlorhexidine and stress ulcer prophylaxis may be harmful, new data confirm the fear that selective oral and digestive decontamination may not be effective in ICUs with high baseline rates of antibiotic resistance, and subglottic secretion drainage may not shorten duration of mechanical ventilation or ICU length-of-stay as was once thought. The practices most consistently associated with earlier extubation and/or lower mortality rates are those focused on limiting exposure to invasive mechanical ventilation by avoiding intubation and speeding extubation **(4)**.

There is no association between oral care with chlorhexidine and lower VAP rates on meta-analysis of double-blind randomized trials. More concerningly, some meta-analyses and observational studies have reported that oral care with chlorhexidine may increase mortality rates, perhaps because some patients may aspirate some of the antiseptic triggering acute lung injury **(18)**.

The potential benefits of proposed prevention strategies include decreasing the duration of mechanical ventilation, ICU length-of-stay, ventilator-associated events, antibiotic utilization, and mortality. Comparing prevention measures' impacts on VAP rates versus more objective outcomes can sometimes lead to surprising discrepancies. For example, meta-analyses of randomized trials of oral care with chlorhexidine suggest this intervention may lower VAP rates but increase mortality **(19)**.

Several recent trials evaluated the potential benefits of modifying endotracheal tube cuff shapes and/or materials to minimize seepage of microbe-laden fluids across the cuff and into the lungs. Unfortunately, neither tapered cuffs nor ultrathin polyurethane proved to be any better than conventional cylindrical cuffs or polyvinyl chloride at preventing VAP or improving objective outcomes **(5, 18).**

Likewise, manually monitoring cuff pressures every 8 h to minimize inadvertent drops in endotracheal tube cuff pressure was no better at preventing VAP, decreasing length-of-stay, or lowering mortality in a recent single center study compared to checking cuff pressures only at intubation, following frank tube migration, or detection of a cuff pressure leak **(20)**.

Subglottic secretion drainage has repeatedly been associated with lower VAP rates in both individual randomized trials and meta-analyses but does not appear to shorten the time to extubation, ICU length-of-stay, prevent ventilator-associated events, or lower mortality rates **(21)**. Two studies have reported an association between subglottic secretion drainage and less antibiotic utilization **(22)**.

Elevating the head of the bed to prevent reflux of gastric secretions into the lungs is the most commonly practiced intervention to prevent VAP but is supported by surprisingly few randomized trials. A Cochrane review of 8 randomized trials enrolling 759 patients did report collectively fewer clinically suspected VAPs in patients randomized to head-of-bed elevation, but no effect on microbiologically confirmed VAP and no effect on objective outcomes. Some investigators have hypothesized that putting patients in the lateral Trendelenburg may be a better way to prevent VAP by recruiting gravity to carry oral secretions away from the lungs **(23)**.

Selective oral and digestive decontamination is one of the very few preventative strategies in critical care that has repeatedly been associated with lower mortality rates. This strategy is widely practiced in the Netherlands, but practitioners elsewhere have been loath to adopt antibiotic decontamination for fear that it might promote antibiotic resistance, particularly in ICUs with high baseline rates of antibiotic-resistant bacteria and antibiotic utilization. Ironically, oral and digestive decontamination may actually decrease overall antibiotic utilization presumably by decreasing the incidence of infections requiring treatment. Probiotics may protect patients from VAP by modulating the microbiome and inhibiting colonization with invasive pathogens **(24)**.

Stress ulcer prophylaxis has been associated with higher VAP rates in some observational studies and in a recent meta-analysis of randomized trials. A large randomized trial of pantoprazole vs placebo, however, reported no difference between arms in pneumonia rates. At the same time, stress ulcer prophylaxis had a relatively modest effect on gastrointestinal bleeding rates (2.5% vs 4.2%) and no impact on transfusion requirements or mortality rates **(25).**

The prevention practices that have most consistently been associated with improving objective outcomes for ventilated patients have been those focused on avoiding intubation and minimizing exposure to invasive ventilation by using high flow oxygen or noninvasive ventilation as alternatives to intubation, lightening sedation, using spontaneous breathing trials to prompt early extubation, and early mobilization. These interventions appear to be synergistic insofar as minimizing sedation facilitates mobilization and early extubation. Observational studies of quality improvement collaboratives have reported that bundling these practices together is associated with earlier extubation and lower mortality rates **(26)**.

Invasive Device Management and Care

Minimizing the duration of mechanical ventilation and the time spent with an endotracheal tube (ETT) in place is critical in reducing the risk of VAP. When possible, non-invasive alternatives should be prioritized, and when intubation is required, the ETT should be changed periodically (every 7–10 days) or as clinically indicated to prevent bacterial colonization of the tube **(27)**.

Maintaining appropriate cuff pressures of the endotracheal tube is vital for preventing aspiration and micro-aspiration of secretions, which can be a key contributor to VAP. Overinflated cuffs can damage the tracheal mucosa, while underinflation can allow for the leakage of secretions. Regular monitoring of cuff pressures should be performed as part of the ventilator care bundle (**28)**.

Utilizing closed suctioning systems (which allow for suctioning without disconnecting the ventilator) reduces the risk of VAP by maintaining a closed system that minimizes the introduction of pathogens during the suctioning process. Closed suctioning systems also prevent the aspiration of contaminated secretions during suctioning **(29)**.

ETT and Suction

To date, no specific recommendations related to types of ETT, or airway suction have been addressed for new- born infants. However, for adults and paediatric patients, the CDC and Healthcare Infection Control Practices Advisory Committee suggest the use of ETT with dorsal lumens to allow drainage of respiratory secretions, orotracheal instead of nasotracheal intubation, and a change of ventilators' respiratory circuits only if they are visibly contaminated or do not work **(29)**.

Interestingly, uncuffed ETT, commonly used in neonatal patients, could be a risk factor for increasing the incidence of VAP. Hence, in adults the use of polyurethane or taper-shaped cuffed ETT correlated with lower rates of VAP. Interestingly, the use of cuffed ETT in the paediatric population was associated with a reduced need for ETT changes and postextubation stridor but increased days of MV **(30)**.

The use of ETT with nano-modified coatings apparently reduces the incidence of infections in the respiratory airways. Recently, Machado et al. in a study performed in adults, reported that ETT with nano-modified coatings reduced the incidence of VAP by preventing biofilm formation and ETT colonization and providing free radical destruction of pathogens. Of note, published experiences in the neonatal period are lacking **(31)**.

In relation to airway suctioning, another study compared the use of closed versus open endotracheal suction systems in ventilated neonates. No differences in the incidence of VAP or mortality between groups were found. Most nurses, however, found closed suction systems easier and faster to use and better tolerated by patients **(32)**.

Hand hygiene

Routine hand hygiene is one of the most important strategies to reduce nosocomial infections. In a 2-year-long surveillance intervention with NICU patients, increased hand hygiene compliance (from 43 to 80%) significantly reduced the incidence of respiratory infections from 3.35 to 1.06 infections per 1,000 patient days. In another study, systematic use of alcohol- based gels for hand hygiene by caregivers reduced the rate of VAP in VLBW infants by 38% **(33)**.

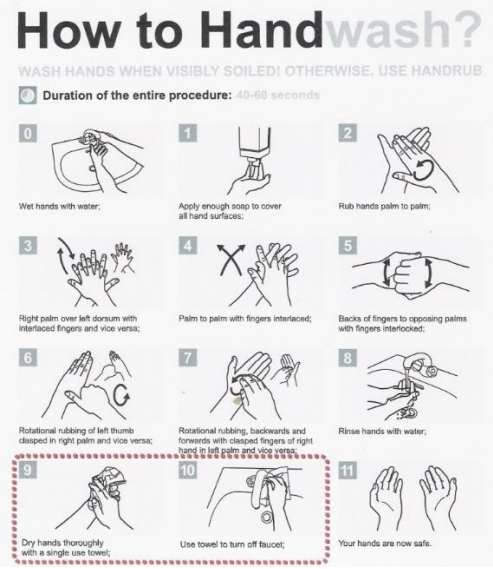

Figure (3): Steps for hand washing (33).

Head positioning

Elevating the head of the bed to prevent reflux of gastric secretions into the lungs is the most commonly practiced intervention to prevent VAP but is supported by surprisingly few randomized trials. A Cochrane review of 8 randomized trials enrolling 759 patients did report collectively fewer clinically suspected VAPs in patients randomized to head-of-bed elevation, but no effect on microbiologically confirmed VAP and no effect on objective outcomes. Some investigators have hypothesized that putting patients in the lateral Trendelenburg may be a better way to prevent VAP by recruiting gravity to carry oral secretions away from the lungs **(34)**.

Rapid Extubation

Since the duration of MV appears to be a major risk factor for the development of VAP in neonates, promptly weaning patients off the ventilator appears to be a desirable strategy to prevent VAP. One prospective study targeting reduction of the nosocomial infection rate in the NICU, implemented more aggressive strategies for the early weaning of patients off the ventilator for 3 months. When 1-year preintervention and 1-year postintervention were compared, the VAP rates de- creased from 3.3/1,000 ventilator days to 1.0/1,000 ventilator days **(35)**.

Use of Histamine 2 Receptor Antagonists or Antacids

The use of histamine 2 receptor antagonists or antacids is believed to increase the risk of VAP as acid gastric content may make colonization with pathogenic organisms difficult. However, no differences in the incidence of VAP were found when comparing patients using or not using histamine 2 receptor antagonists or antacids. There is no published experience in the neonatal period **(36)**.

Selective Decontamination

Selective decontamination consists of the establishment of a regimen of topical or intravenous antimicrobials in an attempt to reduce the burden of pathogenic bacteria in aspirated secretions. Randomized studies in paediatric patients have shown conflicting results. In a prospective cohort nonrandomized study, NICU patients received oral polymixin E, tobramycin, and nystatin correctly (during the first 5 days) or incorrectly (after 5 days) or they did not receive any decolonization. Results revealed that correct selective decolonization had a protective effect toward nosocomial infections of an intestinal origin. However, a separate analysis of the impact on respiratory infections alone was not performed. Accordingly, no recommendation regarding selective de- contamination in neonates is warranted **(37)**.

Probiotics

The loss of gut commensals such as Bifidobacterium and Lactobacilli spp. is associated with prolonged antibiotic treatments, delayed enteral feeding, or nursing in incubators and translates into proliferation of pathogenic microflora and abnormal gut colonization. Seemingly, enhancement of the enteric microbiota composition with supplementation of probiotics seems to be a good strategy to prevent sepsis and could also be applied to prevent neonatal VAP. Nevertheless, a meta-analysis of 7 randomized controlled trials conducted in adult populations concluded that probiotics showed no beneficial effect in patients who are mechanically ventilated, did not significantly decrease the incidence of VAP, and should not be recommended for routine clinical application. To date, no information regarding the use of probiotics to prevent VAP is available **(38)**.

Nutritional support

Adequate nutrition is essential for immune function and the integrity of the mucosal barriers, which are critical in defending against pulmonary infections. Early and adequate enteral feeding, when tolerated, supports gastrointestinal motility and prevents gastric overdistention, which can reduce the risk of aspiration. Furthermore, the use of probiotics or prebiotics as part of neonatal nutrition may help promote the development of a healthy microbiome, thereby potentially reducing the risk of VAP. Early initiation of total parenteral nutrition in neonates unable to tolerate enteral feeds can also prevent catabolism and support immune function during critical illness **(39)**.

Early mobilization and physical therapy

Although premature neonates often require prolonged periods of ventilation, there is increasing evidence to suggest that early mobilization and physical therapy can play a role in preventing complications such as VAP. Initiating gentle, passive range-of-motion exercises and repositioning as early as feasible improves lung expansion, enhances respiratory function, and may reduce the risk of pneumonia by preventing stasis of secretions. Additionally, early physical therapy may improve muscle tone and prevent disuse atrophy, which is critical for neonates with extended ICU stays **(40)**.

Bundle prevention for VAP:

Preventive bundles for neonatal VAP typically consist of several interrelated interventions that target the primary risk factors associated with VAP. The key components of these bundles generally include **(41)**:

1. **Elevation of the Head of the Bed:** Elevating the head of the bed (30–45 degrees) is a fundamental strategy aimed at reducing the risk of aspiration of gastric contents, which is a key factor in the development of VAP. This intervention has been shown to decrease the likelihood of oropharyngeal secretions entering the lower respiratory tract, thus reducing the risk of bacterial colonization and subsequent infection.

2. **Oral Care with Chlorhexidine:** Routine oral care, particularly the use of chlorhexidine-based solutions, has demonstrated efficacy in reducing the oral colonization of micro-organisms including Streptococcusspecies, Pseudomonas aeruginosa, and other multidrug-resistant organisms. Oral hygiene helps in minimizing the microbial load in the oral cavity, thereby reducing the risk of pathogens being aspirated into the lungs.
3. **Sedation Minimization and Weaning:** Limiting the use of sedatives and analgesics, while promoting early weaning from mechanical ventilation, is an essential strategy in the prevention of VAP. The use of sedatives is associated with longer ventilation times and increased risk of aspiration. Early extubation and use of non-invasive ventilation alternatives, such as nasal continuous positive airway pressure (CPAP), reduce the duration of mechanical ventilation and the associated risk of VAP.
4. **Subglottic Suctioning:** In mechanically ventilated neonates, the use of endotracheal tubes with subglottic suctioning ports has been associated with a reduction in VAP incidence. Subglottic suctioning helps in removing secretions that accumulate above the cuff of the endotracheal tube, preventing the aspiration of these secretions into the lungs and reducing the risk of infection.
5. **Antibiotic Stewardship and Surveillance:** Surveillance for microbial colonization of the respiratory tract is essential for early identification of potentially pathogenic organisms. The judicious use of antibiotics, guided by culture and sensitivity data, prevents the development of antibiotic resistance and minimizes unnecessary exposure to broad-spectrum antibiotics, which can disrupt the neonate's microbiome.
6. **Hand Hygiene and Infection Control Practices:** Strict adherence to infection control protocols, including hand hygiene, barrier precautions, and disinfection of ventilator circuits, is vital in reducing the transmission of pathogens within the NICU. Health care worker compliance with these practices is a cornerstone of VAP prevention.

Challenges and limitations of preventive bundle for VAP:

Variability in clinical practices and protocol adherence

One of the primary challenges in implementing a comprehensive preventive bundle is variability in clinical practices across different healthcare providers, institutions, and NICUs. Although bundle elements are evidence-based, differences in interpretation, execution, and adherence can lead to inconsistent application of interventions. For example, while the elevation of the head of the bed is a standard practice, achieving and maintaining the recommended 30–45-degree angle may be difficult due to the individual needs of critically ill neonates, such as those with severe respiratory distress or cardiovascular instability. Furthermore, some interventions (e.g., use of subglottic suctioning, aerosolized antibiotics) may not be routinely available or feasible in all settings due to resource limitations **(42)**.

Resource constraints and financial considerations

Implementing a comprehensive preventive bundle requires substantial resources in terms of both personnel and equipment. Neonatal care units may face financial constraints that hinder the ability to procure necessary materials such as subglottic suctioning catheters, aerosolized antibiotics, or specialized ventilator equipment. The need for periodic replacement of ventilator circuits, humidifiers, and other equipment, as well as the use of advanced technology for continuous monitoring, can significantly increase costs. Additionally, the use of aerosolized antibiotics or probiotics may not be universally supported by financial resources or available evidence on cost-effectiveness. In lower-resource settings or in institutions with limited access to such medications or technologies, the ability to implement all components of the extended bundle may be restricted, potentially limiting its impact **(43)**.

Clinical complexity and the immaturity of neonatal physiology

The neonatal population is inherently heterogeneous, with significant variation in terms of gestational age, birth weight, comorbidities, and response to treatment. Premature neonates, in particular, face unique challenges due to their underdeveloped immune systems, immature pulmonary function, and increased susceptibility to infections. The interventions within the bundle may need to be tailored to accommodate this variability, which can complicate clinical decision-making. For instance, while early extubation and the use of non-invasive ventilation (NIV) are beneficial, premature neonates or those with severe respiratory distress may not be suitable candidates for NIV. In these cases, prolonged mechanical ventilation may be unavoidable, and alternative preventive strategies must be optimized **(42)**.

Similarly, some preventive interventions, such as early mobilization or physical therapy, are difficult to implement in extremely premature or critically ill infants who may not tolerate physical activity. These complex clinical scenarios present significant challenges in applying the bundle universally across the neonatal population **(43)**.

Potential for increased risk of harm

While the preventive bundle aims to reduce the incidence of VAP, some interventions may carry risks or unintended consequences when not implemented correctly. For example **(44)**:

- **Overuse of Antibiotics:** The routine use of aerosolized antibiotics, while targeting potential bacterial pathogens in the lungs, may contribute to the emergence of resistant organisms. Additionally, inappropriate or unnecessary use of antibiotics can disrupt the neonatal microbiome, which is critical for normal immune function and gut health.
- **Sedation and Analgesia Management:** Efforts to minimize sedation and promote early weaning from mechanical ventilation may inadvertently result in neonatal discomfort or pain, which could lead to adverse physiological outcomes such as increased stress responses, impaired growth, and delayed neurodevelopment. Ensuring that sedation protocols strike a balance between comfort and safety is challenging.
- **Physical Therapy Risks:** Early mobilization and physical therapy, while beneficial in some cases, can be harmful if not properly tailored to the infant's clinical status. Unmonitored movements or excessive manipulation may lead to injury or hemodynamic instability, especially in extremely low birth weight infants or those with unstable clinical conditions.

Lack of Standardization and Research Gaps

While evidence supporting the effectiveness of preventive bundles is accumulating, there remains a lack of universal consensus on the exact components of the bundle and their optimal delivery in neonatal populations. There is also limited high-quality research that specifically addresses the most effective combination of interventions for preventing VAP in neonates, especially in varying clinical settings and across different NICU types. The heterogeneity of existing studies, along with differences in research methodologies (e.g., observational studies versus randomized controlled trials), creates challenges in determining which specific components of the bundle are most effective. Furthermore, not all strategies in the extended bundle (e.g., probiotic use, aerosolized antibiotics) are universally supported by robust evidence, and more research is needed to validate their role in VAP prevention **(45)**.

Training and Education of Healthcare Providers

Continuous education and training of healthcare staff are crucial to ensure optimal application of the preventive bundle. However, achieving and maintaining high levels of competency across all team members (including neonatologists, nurses, respiratory therapists, and infection control specialists) is a significant challenge.

Ongoing training can be resource-intensive, requiring dedicated time, funding, and administrative support. Moreover, staff turnover in NICUs and the transient nature of many healthcare providers—due to rotations, shifts, and recruitment—may result in inconsistent implementation of preventive practices. Failure to standardize training and ensure that all staff are consistently updated on best practices may lead to gaps in care and diminished effectiveness of the bundle **(46)**.

Interdisciplinary Collaboration and Communication

Successful implementation of a neonatal VAP preventive bundle requires strong interdisciplinary collaboration among healthcare professionals. However, in many NICUs, communication across different disciplines can be challenging due to differences in knowledge, responsibilities, and decision-making structures. In some cases, coordination between respiratory therapists, infection control teams, and nursing staff can be fragmented, especially during high-stress periods or when patient acuity is particularly high. Interdisciplinary communication is particularly important in ensuring timely initiation of interventions (such as early extubation or subglottic suctioning) and monitoring for complications (such as ventilator-associated lung injury). Without a clear and unified approach, the preventive bundle may fail to achieve its desired outcomes **(47).**

Reference:

1. Kollef, M. H., Bassetti, M., Francois, B., et al. (2021). The intensive care medicine research agenda on multidrug-resistant bacteria, antibiotics, and stewardship. Intensive Care Med, 47(6), 686–697.
2. Kalil, A. C., Metersky, M. L., Klompas, M., et al. (2016). Management of adults with hospital-acquired and ventilator-associated pneumonia: 2016 clinical practice guidelines by the Infectious Diseases Society of America and the American Thoracic Society. Clin Infect Dis, 63(5), e61–e111.
3. Chastre, J., & Fagon, J. Y. (2002). Ventilator-associated pneumonia. Am J Respir Crit Care Med, 165(7), 867–903.
4. Klompas, M., Branson, R., Eichenwald, E. C., et al. (2014). Strategies to prevent ventilator-associated pneumonia in acute care hospitals: 2014 update. Infect Control Hosp Epidemiol, 35(S2), S133–S154.
5. Papazian, L., Klompas, M., & Luyt, C. E. (2020). Ventilator-associated pneumonia in adults: a narrative review. *Intensive care medicine*, *46*(5), 888-906.
6. Zilberberg, M. D., Shorr, A. F., Micek, S. T., Vazquez-Guillamet, C., & Kollef, M. H. (2014). Multi-drug resistance, inappropriate initial antibiotic therapy and mortality in Gram-negative severe sepsis and septic shock: a retrospective cohort study. *Critical care*, *18*(6), 1-13.
7. Moreau, A. S., Martin-Loeches, I., Povoa, P., Salluh, J., Rodriguez, A., Thille, A. W., et al., (2018). Impact of immunosuppression on incidence, aetiology and outcome of ventilator-associated lower respiratory tract infections. *European Respiratory Journal*, *51*(3).
8. Cillóniz, C., Dominedò, C., Nicolini, A., Torres, A. (2019). Impact of multidrug-resistant bacteria on pneumonia outcomes. Medicina (Kaunas), 55(9), 494. https://doi.org/10.3390/medicina55090494
9. Bassetti, M., Righi, E., Vena, A., Graziano, E., Russo, A., & Peghin, M. (2018). Risk stratification and treatment of ICU-acquired pneumonia caused by multidrug-resistant/extensively drug-resistant/pandrug-resistant bacteria. *Current opinion in critical care*, *24*(5), 385-393.
10. Willis, C., Allen, B., Tucker, C., Rottman, K., & Epps, K. (2017). Impact of a pharmacist-driven methicillin-resistant Staphylococcus aureus surveillance protocol. *American Journal of Health-System Pharmacy*, *74*(21), 1765-1773.
11. Timsit, J. F., Ruppé, E., Barbier, F., Tabah, A., & Bassetti, M. (2020). Bloodstream infections in critically ill patients: an expert statement. *Intensive Care Medicine*, *46*, 266-284.
12. Zha, L., Li, X., Ren, Z., Zhang, D., Zou, Y., Pan, L., et al., (2022). Pragmatic Comparison of

Piperacillin/Tazobactam versus Carbapenems in Treating Patients with Nosocomial Pneumonia Caused by Extended-Spectrum β-Lactamase-Producing Klebsiella Pneumoniae. *Antibiotics*, *11*(10), 1384.

13. Sarda, C., Fazal, F., & Rello, J. (2019). Management of ventilator-associated pneumonia (VAP) caused by resistant gram-negative bacteria: which is the best strategy to treat?. *Expert Review of Respiratory Medicine*, *13*(8), 787-798.
14. McLeod, C. C., Tan, K. K., Kebriaei, R., & Abdul-Mutakabbir, J. C. (2023). Clinical Appraisal of Cefiderocol in the Treatment of Non-fermenting Gram-Negative Bacilli. *Current Infectious Disease Reports*, 1-16.
15. Niederman, M. S., Alder, J., Bassetti, M., Boateng, F., Cao, B., Corkery, K., et al., (2020). Inhaled amikacin adjunctive to intravenous standard-of-care antibiotics in mechanically ventilated patients with Gram-negative pneumonia (INHALE): a double-blind, randomised, placebo-controlled, phase 3, superiority trial. *The Lancet Infectious Diseases*, *20*(3), 330-340.
16. Karaiskos, I., Gkoufa, A., Polyzou, E., Schinas, G., Athanassa, Z., & Akinosoglou, K. (2023). High-dose nebulized colistin methanesulfonate and the role in hospital-acquired pneumonia caused by Gram-negative bacteria with difficult-to-treat resistance: a review. *Microorganisms*, *11*(6), 1459.
17. Mastrogianni, M., Katsoulas, T., Galanis, P., Korompeli, A., & Myrianthefs, P. (2023). The impact of care bundles on ventilator-associated pneumonia (VAP) prevention in adult ICUs: a systematic review. *Antibiotics*, *12*(2), 227.
18. Klompas, M. (2019). Prevention of intensive care unit-acquired pneumonia. In *Seminars in respiratory and critical care medicine* (Vol. 40, No. 04, pp. 548-557). Thieme Medical Publishers.
19. Izadi, M., Bagheri, M., Far, A. B., Sureda, A., & Soodmand, M. (2021). Effect of ozonated water and chlorhexidine mouthwash on oral health in critically ill patients on mechanical ventilation: A double-blind randomised clinical trial. *Intensive and Critical Care Nursing*, *66*, 2.
20. Dexter, A. M., & Scott, J. B. (2019). Airway management and ventilator-associated events. *Respiratory Care*, *64*(8), 986-993.
21. Lacherade, J. C., Azais, M. A., Pouplet, C., & Colin, G. (2018). Subglottic secretion drainage for ventilator-associated pneumonia prevention: an underused efficient measure. *Annals of Translational Medicine*, *6*(21).
22. Lorente, L., Lecuona, M., Jiménez, A., Mora, M. L., & Sierra, A. (2007). Influence of an endotracheal tube with polyurethane cuff and subglottic secretion drainage on pneumonia. *American journal of respiratory and critical care medicine*, *176*(11), 1079-1083.
23. Güner, C. K., & Kutlutürkan, S. (2022). Role of head-of-bed elevation in preventing ventilator-associated pneumonia bed elevation and pneumonia. *Nursing in Critical Care*, *27*(5), 635-645.
24. Gibson, G. A., & Owen, E. J. (2023). Non-Antibiotic Approaches to Infection that Preserve the Microbiome in Critically Ill Patients. *Surgical Infections*, *24*(3), 284-291.
25. Moayyedi, P., Eikelboom, J. W., Bosch, J., Connolly, S. J., Dyal, L., & COMPASS Investigators. (2019). Safety of proton pump inhibitors based on a large, multi-year, randomized trial of patients receiving rivaroxaban or aspirin. *Gastroenterology*, *157*(3), 682-691.
26. Alhazzani, W., Alshamsi, F., Belley-Cote, E., Heels-Ansdell, D., Brignardello-Petersen, R., Alquraini, M., et al., (2018). Efficacy and safety of stress ulcer prophylaxis in critically ill patients: a network meta-analysis of randomized trials. *Intensive care medicine*, *44*, 1-11.
27. Esianor, B. I., Campbell, B. R., Casey, J. D., Du, L., Wright, A., Steitz, B., et al., (2022). Endotracheal tube size in critically ill patients. *JAMA Otolaryngology–Head & Neck Surgery*, *148*(9), 849-853.
28. Mostafa Eleter, N., M Weheida, S., & Nagar, I. E. (2024). Effect of Body Position Changes on Endotracheal Tube Cuff Pressure Measurements for Mechanically Ventilated Patients. *Egyptian Journal of Health Care*, *15*(2), 1251-1260.
29. Majid, R. (2024). VAP Prevention in the ICU. *Infection Prevention in the Intensive Care Setting*, 41-75.

30. Dariya, V., Moresco, L., Bruschettini, M., & Brion, L. P. (2022). Cuffed versus uncuffed endotracheal tubes for neonates. *Cochrane Database of Systematic Reviews*, (1).
31. Machado, M. C., Cheng, D., Tarquinio, K. M., & Webster, T. J. (2010). Nanotechnology: pediatric applications. *Pediatric research*, *67*(5), 500-504.
32. Gahan, A. K., Jain, S., Khurana, S., & Chawla, D. (2023). Closed versus open endotracheal tube suction in mechanically ventilated neonates: a randomized controlled trial. *European Journal of Pediatrics*, *182*(2), 785-793.
33. Lotfinejad, N., Peters, A., Tartari, E., Fankhauser-Rodriguez, C., Pires, D., & Pittet, D. (2021). Hand hygiene in health care: 20 years of ongoing advances and perspectives. The Lancet infectious diseases, 21(8), e209-e221.
34. Bishop, K. L., & Malone, D. J. (2024). Pulmonary Diseases and Disorders. In *Acute Care Physical Therapy* (pp. 245-310). Routledge.
35. Sangsari, R., Saeedi, M., Maddah, M., Mirnia, K., & Goldsmith, J. P. (2022). Weaning and extubation from neonatal mechanical ventilation: an evidenced-based review. *BMC pulmonary medicine*, *22*(1), 421.
36. Bondarev, D. J., Ryan, R. M., & Mukherjee, D. (2024). The spectrum of pneumonia among intubated neonates in the neonatal intensive care unit. *Journal of Perinatology*, 1-9.
37. Marzaman, A. N. F., Roska, T. P., Sartini, S., Utami, R. N., Sulistiawati, S., Enggi, C. K., et al., (2023). Recent advances in pharmaceutical approaches of antimicrobial agents for selective delivery in various administration routes. *Antibiotics*, *12*(5), 822.
38. Sun, Y. C., Wang, C. Y., Wang, H. L., Yuan, Y., Lu, J. H., & Zhong, L. (2022). Probiotic in the prevention of ventilator-associated pneumonia in critically ill patients: evidence from meta-analysis and trial sequential analysis of randomized clinical trials. *BMC Pulmonary Medicine*, *22*(1), 168.
39. Zhao, J., Li, L. Q., Chen, C. Y., Zhang, G. S., Cui, W., & Tian, B. P. (2021). Do probiotics help prevent ventilator-associated pneumonia in critically ill patients? A systematic review with meta-analysis. *ERJ open research*, *7*(1).
40. Singam, A. (2024). Mobilizing Progress: A Comprehensive Review of the Efficacy of Early Mobilization Therapy in the Intensive Care Unit. *Cureus*, *16*(4).
41. Pinilla-González, A., Solaz-García, Á., Parra-Llorca, A., Lara-Cantón, I., Gimeno, A., Izquierdo, I., et al., (2021). Preventive bundle approach decreases the incidence of ventilator-associated pneumonia in newborn infants. *Journal of Perinatology*, *41*(6), 1467-1473.
42. Eid, M., ŢÂNŢU, M. M., Sultan, M., & Kandeel, N. (2022). Suction System Flushing with Chlorhexidine and Prevention of Ventilator Associated Pneumonia: Current Evidence. Mansoura Nursing Journal, 9(2), 69-86.
43. Noto, A., Cortegiani, A., Genoese, G., Appendini, L., Gregoretti, C., Carlucci, A., & Crimi, C. (2025). Performance of helmet CPAP using different configurations: Turbine-driven ventilators *vs* Venturi devices. *Pulmonology*, *31*(1), 2416789.
44. Marini, A. L., Khan, R., & Mundekkadan, S. (2016). Multifaceted bundle interventions shown effective in reducing VAP rates in our multidisciplinary ICUs. *BMJ Open Quality*, *5*(1), u205566-w2278.
45. Wyckoff, M. H., Wyllie, J., Aziz, K., de Almeida, M. F., Fabres, J., Fawke, J., et al., (2020). Neonatal life support: 2020 international consensus on cardiopulmonary resuscitation and emergency cardiovascular care science with treatment recommendations. *Circulation*, *142*(16_suppl_1), S185-S221.
46. Rello, J., Afonso, E., Lisboa, T., Ricart, M., Balsera, B., Rovira, A., et al., (2013). A care bundle approach for prevention of ventilator-associated pneumonia. *Clinical Microbiology and Infection*, *19*(4), 363-369.
47. Pepin, B. J., Lesslie, D., Berg, W., Spaulding, A. B., & Pokora, T. (2019). ZAP-VAP: a quality improvement initiative to decrease ventilator-associated pneumonia in the neonatal intensive care unit, 2012-2016. Advances in Neonatal Care, 19(4), 253-261.