Chapter:Understanding Ventilator-Associated Pneumonia (VAP)

Sneha Katara#,
Department of Microbiology, BIBT
Jaipur, India
snehakatara27@gmail.com

Aditi Nag#*
Department of Biotechnology, BIBT
Jaipur, India
aditinag.bibt@gmail.com

Equal Authorship, * Corresponding Author

Abstract

A ventilator is a life-critical machine that is used to help a patient breathe by giving oxygen through a tube placed in a patient's mouth or nose, or through a hole in the front of the neck. It is one of the most important equipment used in hospitals. Ventilator-associated pneumonia (VAP) is a lung infection that develops in a person who is on a ventilator, which could be life-threatening. But if detected early can be cured and lives can be saved. An infection may occur if associated microbes enter through the tube and get into the patient's lungs. The situation becomes grave quickly as most of these VAP associated microbes are drug resistant. Incidence of VAP ranges from 10% to 25% of all patients in ICU, VAP-related mortality ranges from 24% to 76%, and is 6-21 times higher in intubated patients. One study shows that, the VAP death cases where mortality in the VAP patients was 61.84%, the *Acinetobacter baumannii* (37.63%) and *Klebsiella pneumoniae* (36.55%) were the most common organism isolated followed by *Pseudomonas aeruginosa* and *Staphylococcus aureus*.

Keywords: *Acinetobacter*, Diagnosis, Molecular diagnostics, Ventilator Associated Pneumonia, VAP

Introduction

Ventilator-associated pneumonia (VAP) is a significant lung infection that develops 48-72 hours after endotracheal intubation. It is characterized by the presence of new or worsening lung infiltrates, systemic signs of infection such as fever and altered white blood cell counts, changes in sputum characteristics, and the identification of causative pathogens [1]. The main cause of VAP is the microbial contaminations occurring in body out of which the most prevalent types are the *Acinetobacter baumannii*(38.7%), *Pseudomonas aeruginosa* (17.5%), and *Klebsiella pneumoniae* (16.6%) and 780 (94.32%) gram-negative organisms and 47 (5.68%) gram-positive organisms [9]. In this chapter, we delve into the pathogenesis, microbiology, and transmission of VAP, shedding light on the intricate factors contributing to its development.

I. The Pathogenesis of VAP:

The development of VAP is influenced by a complex interplay of factors, including the presence of an endotracheal tube, bacterial invasion, and host immunity. The primary risk factor is the endotracheal tube, which compromises the body's natural defenses against microaspiration near the tube's cuff. Microaspiration can occur during intubation, leading to the formation of bacterial biofilms within the tube. These biofilms, typically

composed of Gram-negative bacteria and fungi, provide a direct route for infectious agents to reach the lower respiratory tract. Additionally, the pooling and trickling of secretions around the cuff, impaired mucociliary clearance, and gravity-dependent mucus flow further facilitate bacterial access to the lower airways [2].

II. Microbiology of VAP:

The microbial profile of VAP varies depending on the duration of mechanical ventilation. Early-onset VAP, occurring within five days of intubation, is commonly caused by antibiotic-sensitive bacteria such as *Streptococcus pneumoniae, Haemophilus influenzae, and Staphylococcus aureus* (including methicillin-sensitive strains). In contrast, late-onset VAP, manifesting five days or more after intubation, is frequently attributed to multidrug-resistant pathogens like *Pseudomonas aeruginosa, Acinetobacter baumannii,* methicillin-*resistant Staphylococcus aureus* (MRSA), and extended-spectrum beta-lactamase-producing bacteria. The choice of antibiotics for treatment is influenced by the timing and nature of the infection [2].

III. Transmission of VAP:

The pathogens responsible for VAP, their frequencies, and mechanisms of multi-drug resistance are as follows:

- *Pseudomonas* (24.4%): Upregulation of efflux pumps, downregulation of outer membrane porin channels, and acquisition of plasmid-mediated metallo-beta-lactamases [2].
- *Staphylococcus aureus* (20.4%, with >50% being MRSA): Synthesis of penicillin-binding proteins (PBPs) with reduced affinity for beta-lactam antibiotics, encoded by the mecA gene [2].
- *Enterobacteriaceae* (14.1%, including various species): Production of AmpC-type enzymes through plasmid-mediated extended-spectrum beta-lactamase (ESBL) synthesis [2].
- *Streptococcus species* (12.1%).
- *Hemophilus species* (9.8%).
- *Acinetobacter species* (7.9%): Production of carbapenemases or metallo-enzymes.
- *Neisseria species* (2.6%).
- *Stenotrophomonas maltophilia* (1.7%).
- Coagulase-negative *Staphylococcus* (1.4%).

Out of all these *Acinetobacter baumannii,* is a notorious opportunistic pathogen which is responsible for various nosocomial infections, as is a major culprit in theVAP. It possesses innate and acquired mechanisms that confer resistance to a wide array of antibiotics, which makes the treatment quite challenging [9].

A. Molecular Biology of *Acinetobacter baumannii*:

Acinetobacter is a genus of bacteria (germs) frequently found in the environment, including soil and water. Although there are other varieties, *Acinetobacter baumannii*, which is responsible for the majority of *Acinetobacter* infections in people, is the most frequent source of infections.

This pathogen can infect wounds in various tissues like blood as well organs like urinary system, and lungs (pneumonia). In particular in respiratory secretions (sputum) or open wounds, it can potentially "colonise" or

dwell in a patient without generating illnesses or symptoms. In an intensive care unit (ICU), *Acinetobacter* infections were first documented in a medical environment in the 1960s [15].

In 1911, the genus *Acinetobacter* was first identified. *Micrococcus calcoaceticus, Achromobacter, Alcaligenes, Bacterium anitratum, Moraxella glucidolytica, Neisseria winogradsky, Alcaligenes, haemolysans, Mima polymorpha, and Moraxella lwoffii*were among the names given to the soil-isolated bacteria. Brisou and Prevot suggested the present name for the genus Acinetobacter in 1954, and it was approved in 1968 (from the Greek akinetos, meaning nonmotile). *Acinetobacter calcoaceticus* was finally included as the sole species in Bergey's Manual of Systematic Bacteriology, which was published in 1974. Bouvet and Grimont later noted anomalies in the use of phenotypic testing to identify the genus and species of *Acinetobacter* in 1986 [15].

B. ATCC gene island of *A. baumannii:*

It has been shown that both gram-negative and gram-positive bacteria contain efflux genes. The AdeABC system, a member of the RND family of efflux pumps, has recently been linked to decreased sensitivity and/or resistance to tetracyclines and many other antibiotics in *A. baumannii*[16].

Prior to 1948, the American isolate ATCC 19606 of *Acinetobacter baumannii* was discovered. In numerous research on the pathophysiology of *A. baumannii*and antibiotic resistance, it has served as a reference and model organism.

It has been widely utilised in studies as a reference and model strain for researching the establishment and evolution of resistance, pathogenicity, and the discovery of new antibacterial targets because it is one of the most antibiotic sensitive strains available to researchers [16].

C. Diagnosis of Ventilator-Associated Pneumonia (VAP)

The accurate and timely diagnosis of Ventilator-Associated Pneumonia (VAP) is essential for effective management and treatment. In this chapter, we have explored various diagnostic methods and tools used to identify VAP, shedding light on their advantages, limitations, and recent advancements.

Chest X-Rays:

Chest X-rays of mechanically ventilated patients in the ICU are frequently taken, and the presence of infiltrates and/or consolidation is frequently utilized as part of the diagnostic criteria. Yet, there are a number of clinical disorders that resemble VAP on radiographs. Aspiration and chemical pneumonitis, atelectasis, congestive heart failure, acute respiratory distress syndrome (ARDS), pleural effusion, and intra-alveolar hemorrhage are a few of the disorders that are frequently seen in patients who are mechanically ventilated. Thus, it is not advised to rely solely on chest radiography for the diagnosis of VAP. The histological diagnosis of pneumonia and radiographic markers (such as alveolar infiltrates and air bronchograms) may not always agree. Furthermore uninspiring, the sensitivity and specificity of infiltration presence on chest X-rays [2].

Chest X-rays, lung ultrasounds, blood cultures, endotracheal aspirates, CRP (or PCT), and Gram stains should all be used to diagnose VAP [10]

Difference between CXR and Lung Ultrasound: The diagnosis of pneumonia on a chest X-ray (CXR) or computed tomography (CT) requires the presence of a number of clinical signs and symptoms, including tachypnea, fever, and audible crackles in the airways. The use of CXR has some restrictions, including

substantial interobserver variability in its interpretation and radiation exposure, particularly for pregnant women. Also, there is a higher danger involved with transporting critically ill patients inside the hospital to the radiology department for a CT scan, which could result in higher patient morbidity. In terms of diagnosing VAP, LUS has been said to be superior to bedside chest X-rays and nearly on par with chest CT [3].

Clinical Diagnosis:

Leukocytosis, purulent tracheobronchial secretions, and a new or expanding infiltrate on a chest radiograph are common symptoms of ventilator-associated pneumonia. However, and unlike with community-acquired pneumonia, established clinical criteria for pneumonia are only partially useful for diagnosing the existence of VAP [11].

Radiologic Diagnosis:

Like with clinical criteria for diagnosing VAP, the portable chest radiograph still has issues with both sensitivity and specificity but is still a requirement in the identification of ventilated patients with probable pneumonia. Chest X-ray accuracy is further hampered by low-quality films. VAP is improbable with a normal chest x-ray, however in one study of surgical patients, 26% of opacities were found by computed tomography scan but not by portable chest x-ray [13].

Microbiologic Diagnosis:

Cultures of pleural fluid and blood. Treatment is necessary if an organism known to cause pneumonia is cultured in the context of a clinically diagnosed pneumonia even though VAP extends to the blood or pleural space in only 10% of cases. Because of this, the majority of specialists advise that two rounds of blood cultures and a thoracentesis be performed if a lateral decubitus chest radiograph reveals non loculated pleural effusions that are less than 10 mm in diameter (30). The use of ultrasonography guidance may be necessary if the effusion is loculated. However, it is crucial to remember that when blood cultures are positive, the organisms may have come from an extrapulmonary site in addition to the fact that the sensitivity of blood cultures for the diagnosis of VAP is less than 25% [13].

Attempts for the detection of VAP:

Ventilator associated pneumonia (VAP), which involves 10–25% of all ventilated patients, and bloodstream infections (BSIs), which impact 10% of patients, are frequent complications for ICU patients. Early identification, severity categorization, prognosis evaluation, and treatment recommendation are just a few of the difficulties associated with managing these serious illnesses. The next-generation PCR technique known as digital PCR (dPCR) has a number of technological advantages over real-time PCR that can help researchers overcome these obstacles. For example, dPCR has higher sensitivity since it is less sensitive to the presence of PCR inhibitors. Moreover, dPCR delivers absolute quantification without the requirement for a standard curve and has good consistency. In this research, we reviewed the available data on the use of dPCR for infection control in critical care medicine [12].

The INHALE Randomized Controlled Trial is a multi-center, parallel investigation into the molecular diagnostic BioFilmArray's capacity to direct antibiotic treatment of HAP/VAP in intensive care units (ICU); it identifies

infections and important antibiotic resistance in around 90 minutes. The comparator is conventional care, which involves giving the patient empirical antibiotics up until the findings of the patient's microbiological culture are known, usually after 48 to 72 hours. Patients in the adult and paediatric intensive care units (ICUs) who are going to start receiving antibiotics for a suspected lower respiratory infection (including HAP/VAP) or who are changing antibiotics due to a worsening clinical condition are eligible [13].

To aid in the clinical diagnosis of ventilator-associated pneumonia (VAP), the Clinical Pulmonary Infection Score (CPIS) based on chest X-ray has been created; nevertheless, this scoring system has a poor diagnostic performance. For the purpose of early VAP diagnosis, created the Lung Ultrasound and Pentraxin-3 Pulmonary Infection Score (LUPPIS) is created and assessed its effectiveness. A class of proteins known as pentraxins is implicated in the acute phase of the inflammatory response. The short pentraxin C-reactive protein (CRP) and interleukin-6 are generated in the liver in response to inflammatory stimuli. Similar to short pentraxins, Pentraxin-3 (PTX-3), the prototype of long pentraxins, primarily functions as an immune system receptor [14].

Diagnostic kit Parameters

Since diagnostic tests help doctors determine whether a patient has a specific condition or not, diagnostic tests are an essential part of clinical practice. Any clinical test must meet a number of criteria in order to be utilised most effectively, and these criteria must be communicated to physicians in order to guide their clinical judgement. The sensitivity, specificity, predictive values, and likelihood ratios of the test fall under this category [17].

One of the essential steps for a good PCR is primer design. Primers should be constructed so that they have perfect sequence identity to the desired target fragment to be amplified for PCR applications. Primers are typically 18–35 bases in length. Primer length (12-500 nt), melting temperature for short primers calculated by nearest neighbour thermodynamic parameters, theoretical primer PCR efficiency (quality%) value, primer GC content, 3′ end terminal enforcement, preferred 3′ terminal nucleotide sequence composition in degenerated formulae, and added sequence tags at 5′ termini are the variables that can be controlled manually or automatically. The general nucleotide structure of the primer, as well as linguistic complexity (nucleotide arrangement and composition), specificity, and melting temperature of the primer, are the other primary factors considered for primer selection. Self-complementarity, secondary (non-specific) binding, and the melting points at the 3′ and 5′ termini are all factors in the complete primer.[18].

The temperature at which half of the DNA strands are in the double-helical state and the other half are in the "random-coil" state is known as the Tm. The default configuration uses nearest neighbour thermodynamic parameters to determine the Tm for short oligonucleotides with normal or degenerate (mixed or "wobble") nucleotide pairings . The main element affecting the Tm value is the CG content of an oligonucleotide. The melting temperature for mixed bases is determined by averaging the enthalpy and entropy values of the nearest neighbours at each mixed site. The extinction coefficient is also anticipated by averaging the values of the nearest neighbours at mixed sites. In the horizontal column, the first nucleotide of 5′N1N2 is displayed, and in the vertical column, the second nucleotide [18].

The range of temperatures where PCR amplification efficiency is greatest without producing non-specific products is known as the optimal annealing temperature (Ta). The primer quality, the Tm of the primers, and the length of the PCR fragment are the three most critical values for determining the Ta. In contrast to primers with low Tms(50 °C), high Tm primers (> 60 °C) can be utilised in PCRs with a wide Ta range. The

value for the primer with the lowest Tm serves as the straight calculation for the ideal annealing temperature for PCR (Tm min). Nevertheless, PCR can function in environments up to 10 °C above the Tm of the primer, particularly when reactions contain high primer concentrations (0.6-1.0 M) to promote primer target duplex synthesis [18].

IV Economic Burden of ventilator-associated pneumonia

VAP is a critical healthcare issue with significant economic implications. This hospital-acquired infection occurs in patients who require mechanical ventilation to assist with their breathing. VAP not only imposes a heavy economic burden on healthcare systems but also leads to prolonged hospital stays, increased mortality rates, and decreased overall patient quality of life. Understanding the economic impact of VAP is crucial for healthcare providers, policymakers, and researchers to develop effective strategies for prevention and management. One of the primary economic consequences of VAP is the extended length of hospital stays. Patients who develop VAP typically require longer stays in the intensive care unit (ICU) and general hospital wards. These extended hospitalizations lead to higher healthcare costs, including room and board, nursing care, and medications. A study published in the American Journal of Infection Control estimated that the additional cost of treating VAP ranged from $12,000 to $40,000 per patient, depending on the severity of the infection and complications that may arise [19].

Moreover, VAP is associated with increased mortality rates, which can result in substantial economic losses. Patients who develop VAP are more likely to die during their hospitalization or suffer long-term disabilities, leading to decreased productivity and increased healthcare costs for ongoing treatment and rehabilitation. A study conducted by [20] found that the attributable mortality rate for VAP ranged from 24% to 76%, depending on the patient population and the causative pathogens. Another economic aspect of VAP is the cost of antibiotic treatment. VAP often requires aggressive antibiotic therapy, which can be expensive and may lead to the development of antibiotic-resistant pathogens. The cost of antibiotics, along with the potential for antibiotic resistance, poses a significant economic burden on healthcare systems and society as a whole. Additionally, patients with VAP may require additional diagnostic tests, such as chest X-rays and blood cultures, further increasing healthcare costs.

Preventive measures aimed at reducing VAP rates also come with their own economic considerations. Hospitals must invest in training healthcare professionals in infection control practices, purchasing and maintaining advanced ventilator equipment, and implementing surveillance systems to monitor VAP rates. While these investments may incur initial costs, they can ultimately lead to substantial savings by reducing VAP incidence and associated healthcare expenses. The economic burden of VAP extends beyond the healthcare system itself. Patients who survive VAP often experience a reduced quality of life due to long-term complications, such as lung damage and impaired physical functioning. These individuals may require ongoing medical care, rehabilitation, and support services, further increasing the overall economic impact of VAP on society. Efforts to mitigate the economic burden of VAP have focused on prevention strategies. Implementing evidence-based practices, such as daily sedation interruption, elevation of the head of the bed, and oral care protocols, can reduce the risk of VAP. Additionally, innovations in ventilator technology, such as the

development of closed suction systems and subglottic secretion drainage, have shown promise in reducing VAP rates [20].

Thus, ventilator-associated pneumonia imposes a substantial economic burden on healthcare systems, patients, and society as a whole. Extended hospital stays, increased mortality rates, antibiotic treatment costs, and the long-term impact on patients' quality of life all contribute to the economic challenges associated with VAP. Preventive measures, such as infection control practices and advanced ventilator technology, are essential for reducing this economic burden and improving patient outcomes.

V. Conclusion:

In conclusion, ongoing research is rapidly expanding our knowledge of the fundamental mechanisms underlying Ventilator-Associated Pneumonia (VAP). This growing understanding holds the promise of uncovering potential therapeutic targets aimed at enhancing the body's defense mechanisms, mitigating lung injury, and preventing infections. Given the rising challenge of antimicrobial resistance and the limited discovery of new antibiotics, it is imperative that we continue to invest in studies focused on unraveling the intricate mechanisms of VAP. These efforts are essential in our quest to develop innovative approaches for both prevention and treatment in the battle against this serious healthcare-associated infection [8].

VI. References:

1. Kalanuria AA, Ziai W, Mirski M. Ventilator-associated pneumonia in the ICU. Crit Care. 2014 Mar 18;18(2):208. doi: 10.1186/cc13775. Erratum in: Crit Care. 2016;20:29. Zai, Wendy [corrected to Ziai, Wendy]. PMID: 25029020; PMCID: PMC4056625.
2. Zhou H, Gebhardt MJ, Czyz DM, Yao Y, Shuman HA. The *gigA/gigB* Genes Regulate the Growth, Stress Response, and Virulence of *Acinetobacter baumannii* ATCC 17978 Strain. Front Microbiol. 2021 Aug 4;12:723949. doi: 10.3389/fmicb.2021.723949. PMID: 34421881; PMCID: PMC8371402.
3. Gaber, Sayed*; Tayeh, Osama; Wahab, Khaled A.; Mohamed, Nader; Essawy, Tarek. Early Detection of Ventilator-Associated Pneumonia: Bedside Tools. The Egyptian Journal of Critical Care Medicine 7(2 and 3):p 74-79, December 2020. | DOI: 10.1097/EJ9.0000000000000015
4. Merino I, de la Fuente A, Domínguez-Gil M, Eiros JM, Tedim AP, Bermejo-Martín JF. Digital PCR applications for the diagnosis and management of infection in critical care medicine. Crit Care. 2022 Mar 21;26(1):63. doi: 10.1186/s13054-022-03948-8. PMID: 35313934; PMCID: PMC8935253.
5. High J, Enne VI, Barber JA, Brealey D, Turner DA, Horne R, Peters M, Dhesi Z, Wagner AP, Pandolfo AM, Stirling S, Russell C, O'Grady J, Swart AM, Gant V, Livermore DM; INHALE Study Group. INHALE: the impact of using FilmArray Pneumonia Panel molecular diagnostics for hospital-acquired and ventilator-associated pneumonia on antimicrobial stewardship and patient outcomes in UK Critical Care-study protocol for a multicentrerandomised controlled trial. Trials. 2021 Oct 7;22(1):680. doi: 10.1186/s13063-021-05618-6. PMID: 34620213; PMCID: PMC8496625.
6. Bruno P. The importance of diagnostic test parameters in the interpretation of clinical test findings: The Prone Hip Extension Test as an example. J Can Chiropr Assoc. 2011 Jun;55(2):69-75. PMID: 21629460; PMCID: PMC3095582.
7. Ruslan Kalendar, David Lee, Alan H. Schulman, Java web tools for PCR, in silico PCR, and oligonucleotide assembly and analysis,Genomics,Volume 98, Issue 2,2011,Pages 137-144,ISSN 0888-7543

8. Aykac, K., Ozsurekci, Y., & Tanir Basaranoglu, S. (2017). Future Directions and Molecular Basis of Ventilator-Associated Pneumonia. Canadian Respiratory Journal, 2017, 1–8. doi:10.1155/2017/2614602
9. Sangale A, Vivek B, Kelkar R, Biswas S. Microbiology of Ventilator-associated Pneumonia in a Tertiary Care Cancer Hospital. Indian J Crit Care Med. 2021 Apr;25(4):421-428. doi: 10.5005/jp-journals-10071-23790. PMID: 34045810; PMCID: PMC8138642.
10. Ferreira-Coimbra J, Ardanuy C, Diaz E, Leone M, De Pascale G, Póvoa P, Prat-Aymerich C, Serrano-Garcia R, Solé-Violan J, Zaragoza R, Rello J. Ventilator-associated pneumonia diagnosis: a prioritization exercise based on multi-criteria decision analysis. Eur J Clin Microbiol Infect Dis. 2020 Feb;39(2):281-286. doi: 10.1007/s10096-019-03720-x. Epub 2019 Oct 25. PMID: 31654147; PMCID: PMC7223949.
11. Merino I, de la Fuente A, Domínguez-Gil M, Eiros JM, Tedim AP, Bermejo-Martín JF. Digital PCR applications for the diagnosis and management of infection in critical care medicine. Crit Care. 2022 Mar 21;26(1):63. doi: 10.1186/s13054-022-03948-8. PMID: 35313934; PMCID: PMC8935253.
12. High J, Enne VI, Barber JA, Brealey D, Turner DA, Horne R, Peters M, Dhesi Z, Wagner AP, Pandolfo AM, Stirling S, Russell C, O'Grady J, Swart AM, Gant V, Livermore DM; INHALE Study Group. INHALE: the impact of using FilmArray Pneumonia Panel molecular diagnostics for hospital-acquired and ventilator-associated pneumonia on antimicrobial stewardship and patient outcomes in UK Critical Care-study protocol for a multicentrerandomised controlled trial. Trials. 2021 Oct 7;22(1):680. doi: 10.1186/s13063-021-05618-6. PMID: 34620213; PMCID: PMC8496625.
13. High J, Enne VI, Barber JA, Brealey D, Turner DA, Horne R, Peters M, Dhesi Z, Wagner AP, Pandolfo AM, Stirling S, Russell C, O'Grady J, Swart AM, Gant V, Livermore DM; INHALE Study Group. INHALE: the impact of using FilmArray Pneumonia Panel molecular diagnostics for hospital-acquired and ventilator-associated pneumonia on antimicrobial stewardship and patient outcomes in UK Critical Care-study protocol for a multicentrerandomised controlled trial. Trials. 2021 Oct 7;22(1):680. doi: 10.1186/s13063-021-05618-6. PMID: 34620213; PMCID: PMC8496625.
14. Haliloglu M, Bilgili B, Bilginer H, Kasapoglu US, Sayan I, Aslan MS, Durmusoglu LM, Cinel I. A new scoring system for early diagnosis of ventilator-associated pneumonia: LUPPIS. Arch Med Sci. 2020 Aug 10;16(5):1040-1048. doi: 10.5114/aoms.2020.97965. PMID: 32863992; PMCID: PMC7444718.
15. https://www.cdc.gov/hai/organisms/acinetobacter.html#:~:text=While%20there%20are%20many%20types,other%20parts%20of%20the%20body.
16. Beheshti M, Talebi M, Ardebili A, Bahador A, Lari AR. Detection of AdeABC efflux pump genes in tetracycline-resistant Acinetobacter baumannii isolates from burn and ventilator-associated pneumonia patients. J Pharm Bioallied Sci. 2014 Oct;6(4):229-32. doi: 10.4103/0975-7406.142949. PMID: 25400404; PMCID: PMC4231381.
17. Deeks, J. J., Altman, D. G., & Egger, M. (2008). Systematic reviews of evaluations of diagnostic and screening tests. In Systematic Reviews in Health Care (pp. 248-282). BMJ Publishing Group.
18. Warren, D. K., Shukla, S. J., Olsen, M. A., Kollef, M. H., & Hollenbeak, C. S. (2003). Outcome and attributable cost of ventilator-associated pneumonia among intensive care unit patients in a suburban medical center. Critical Care Medicine, 31(5), 1312-1317.
19. Rello, J., Ollendorf, D. A., Oster, G., Vera-Llonch, M., Bellm, L., & Redman, R. (2007). Epidemiology and outcomes of ventilator-associated pneumonia in a large US database. Chest, 132(3), 430-438.
20. Muscedere, J., Rewa, O., McKechnie, K., Jiang, X., Laporta, D., Heyland, D. K. (2011). Subglottic secretion drainage for the prevention of ventilator-associated pneumonia: a systematic review and meta-analysis. Critical Care Medicine, 39(8), 1985-1991.