Chapter:Understanding Ventilator-Associated Pneumonia (VAP)

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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 Ventilator-associated pneumonia is found between 10% - 25% of all patients in ICU, and mortality ranges from 24% to 76%, and is at least 6 to 21 times higher in intubated patients. One study shows that, *Acinetobacter baumannii* and *Klebsiella pneumoniae* were the most common organism isolated followed by *Pseudomonas aeruginosa* and *Staphylococcus aureus* in the VAP death cases where mortality was about 61.84%.

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

Introduction

Ventilator-associated pneumonia (VAP) is a significant lung infection that develops upon endotracheal intubation of about 2-3 days. It is characterized by the presence of new or worsening lung infiltrates, whole body signs of infection such as fever and change in white blood cell counts, changes in sputum features, or alternatively to identify causal pathogens [1]. Although 780 (94.32%) gram-negative organisms and 47 (5.68%) gram-positive organisms have been 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 [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, around the cuff if there are any secretions which show pooling and trickling, impaired mucociliary clearance, and gravity-dependent flow of mucus further facilitate bacterial access to the lower airways [2].

II. Microbiology of VAP:

The microbial profile of VAP varies depending on how long the mechanical ventilation is. If VAP, is occurring within five days of intubation it is called early-onset, and is commonly caused by antibiotic-sensitive bacteria such as *Streptococcus pneumoniae, Haemophilus influenzae, and* Methicillin sensitive/resistant *Staphylococcus aureus* strains. In contrast, VAP that is manifesting five days or more after intubation, is categorized as late-onset and is frequently attributed to multidrug-resistant pathogens like *S. aureus* (MRSA), *Pseudomonas aeruginosa, Acinetobacter baumannii* and the 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 resistance to multiple drugs are as follows:

- *Pseudomonas* (24.4%): Efflux pump upregulation, downregulation of porin channels, and acquisition of horizontally transferred metallo-beta-lactamases [2].
- *Staphylococcus aureus* (about 20.4% frequent, with more than 50 percent being MRSA): Reduced affinity for beta-lactam antibiotics,by synthesis of penicillin-binding proteins (PBPs) which are encoded by the mecA gene [2].
- *Enterobacteriaceae* (14.1%, including various species): Production of AmpC-type enzymes through plasmid-mediated ESBL(extended-spectrum beta-lactamase) synthesis [2].
- *Streptococcus species, Hemophilus species, Acinetobacter species,* Production of carbapenemases or metallo-enzymes, *Neisseria species* found in 12.1%, 9.8%, 7.9%, 2.6%, 1.7% and 1.4% respectively of all bacteria .

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 frequently found in the environmental samples such as soil or water. Although there are other species of this genus, *the species baumannii*, is responsible for the majority of *Acinetobacter* infections in people, and thus is thought to be the most frequent source of infections.

This pathogen can infect wounds in various tissues like blood as well organs like urinary tract, and lungs (pneumonia).It can potentially "colonize" or dwell in a patient without generating illnesses or symptoms in case of respiratory secretions (sputum) or open wounds. 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. Although many names were given to this 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 in Bergey's Manual of Systematic Bacteriology as the sole species, and was published in 1974 edition. Bouvet and Grimont further refined the use of phenotypic testing in species identification 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].

The American isolate ATCC 19606 of *Acinetobacter baumannii* was discovered before 1948 and has been since used in research on the pathophysiology of *A. baumannii*and antibiotic resistance as well as a reference for its gene island and a model organism.

Furthermore the isolate has been a sort of model strain for researching the establishment and transmittance of resistance, pathogenicity, or for discovering antibacterial targets because it is one of the most antibiotic sensitive strains available and maintained [16].

C. Diagnosing the 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. As seen frequently in the patients who are ventilated by mechanical assistance, there are symptoms like pleural effusion, and intra-alveolar hemorrhage additionally disorders like aspiration and chemical pneumonitis, acute respiratory distress syndrome (ARDS), atelectasis and congestive heart failure. 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 the sensitivity and specificity of chest X-rays is not enough to detect infiltration presence[2]. Thus, not only the Chest X-rays, lung ultrasounds, blood cultures, endotracheal aspirates, CRP (or PCT), and Gram stains should also 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 preferred to bedside chest X-rays and comparable with chest CT [3].

Clinical Diagnosis:

Purulent tracheobronchial secretions, leukocytosis, and a new or increasing infiltrate on a chest radiograph are counted as common symptoms of VAP. However, unlike with pneumonia which is community-acquired, 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 a study showed that more than 25% of opacities were found by computed tomography scan but not by portable chest x-ray in surgical patients studied. [13].

Microbiologic Diagnosis:

This is typically done by cultures of pleural fluid and blood. Even though VAP extends to the blood or pleural space in only 10% of cases, treatment is necessary if an organism associated with pneumonia is cultured in the context of a clinically diagnosed pneumonia. 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 for the diagnosis of VAP the sensitivity of blood cultures is less than 25% [13].

Attempts for the detection of VAP:

VAP can involve up to 25% of all ventilated patients, and infections in the bloodstream, which impact at least 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. [12].

A multi-center, parallel investigation by randomized controlled trial The INHALE is looking into the molecular diagnostic BioFilmArray's capacity to direct antibiotic treatment of VAP in intensive care units (ICU); it identifies infections and important antibiotic resistance in only 1.5 hours. 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 2-3 days. Patients in the adult and pediatric intensive care units (ICUs) who are going to start receiving antibiotics for a suspected lower respiratory infection (including VAP) or who are changing antibiotics due to a worsening clinical condition are eligible [13].

Although CPIS, the Clinical Pulmonary Infection Score based on chest X-ray, has been created to aid in the clinical diagnosis of VAP, nevertheless, this scoring system has a poor diagnostic performance. For the purpose of early VAP diagnosis, the Lung Ultrasound and Pentraxin-3 Pulmonary Infection Score (LUPPIS) is created and assessed for its effectiveness. A class of proteins known as pentraxins ((PTX-3) 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,eg. PTX-3, the prototype of long pentraxins, primarily functions as an immune system receptor [14].

Diagnostic kit Parameters

Clinical practice is critically dependent on the diagnostic tests Since these tests are so crucial in helping doctors to determine if a patient has a specific condition or not therefore the stringency of the standards to which the test is held is quite high. Any clinical test must meet several criteria in order to be utilized most effectively in guiding physicians in their clinical judgment. 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. Other important criteria include probe length (200-300 nt), melting temperature theoretical primer quality% value, primer GC content, 3′ end terminal enforcement or added sequence tags at 5′ termini. These variables can be easily controlled manually or automatically. Other factors which might improve the diagnosis efficacy are general nucleotide structure of the primer, as well as nucleotide arrangement and composition, specificity, avoiding self-complementarity and secondary (non-specific) binding etc. [18].

The temperature at which half of the DNA strands are in the double-helical state and the other half are in the "melted" state is known as the Tm. The default configuration uses nearest neighbour thermodynamic parameters to determine the Tm for short oligonucleotides with normal or"wobble" (degenerate) 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 temperatures where DNA amplification efficiency is greatest in PCR 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, this reaction can function in environments up to 10 °C above the Tm of the primer, especially when reactions contain high primer concentrations (between 0.6 to 1.0 M) to promote primer target DNA 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 than originally required durations of stay 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 such a heavy 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, VAP puts a substantial economic burden on healthcare, 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:

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