**Review Article**

# Ventilator-associated pneumonia: Revisited

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## ABSTRACT

Ventilator-associated pneumonia (VAP) is a type of hospital acquired pneumonia commonly encountered in patients who receive mechanical ventilation and is associated with significant mortality and morbidity. VAP is associated with prolonged ventilation, increased antibiotic use, emergence of multidrug resistant organisms, prolonged critical care unit stay resulting in increased cost of care. It has been reported to occur in 9 to27 percent of all intubated patients. As per International Nosocomial Infection Control Consortium (INICC) report data summary, the overall rate of VAP was 13.6 per 1,000 ventilator days. Preventive measures, early diagnosis and treatment of VAP result in better outcome. The aim of this review was to search the literature for incidence, various risk factors, etiology, pathogenesis, treatment, and prevention of VAP. A literature search for VAP was done through the PUBMED/MEDLINE database. VAP is a commonly encountered nosocomial infection occurring in ventilated patients and is associated with increased mortality and morbidity. Outcome of patient with VAP depends on hospital setting, patient group, infection control policy, early diagnosis and judicious antibiotic use.

**Keywords:** Ventilator-associated pneumonia, mechanical ventilation, prevention

## Introduction

Ventilator-associated pneumonia (VAP) is a type of hospital acquired pneumonia commonly encountered in patients who receive mechanical ventilation and is associated with significant mortality and morbidity. [1] VAP is defined as per Center of Disease control (CDC) as pneumonia occurring 48 h after the initiation of mechanical ventilation. It has been reported to occur in 9 to 27 percent of intubated patient. [2] As per International Nosocomial Infection Control Consortium (INICC) report data summary, the overall rate of VAP is 13.6 per 1,000 ventilator days. [3] The incidence of VAP varies from 13–51 per 1,000 ventilation days depending on hospital setting and patient group. [4] Usually patients' develop VAP within first week of mechanical ventilation. High mortality rates are associated with VAP ranging from 24–76 percent and even higher in terminally ill patients. [5] VAP increases the cost of patient management by increasing duration of ICU stay. VAP can be divided into two types depending on duration of onset. Early-onset VAP occurs during the first four days of initiation of

mechanical ventilation and is most commonly caused by antibiotic sensitive bacteria. Late-onset VAP develops five or more days after mechanical ventilation and is caused by multidrug-resistant organism. [6] Early diagnosis and judicious antibiotic therapy can reduce the emergence of multidrug resistant organisms.

**Pathophysiology**

VAP occurs in mechanically ventilated patients. In healthy individuals multiple mechanisms work together against the development of pneumonia; but the presence of an ETT as well as the typical clinical circumstances of ventilated patients which includes supine positioning, sedation and colonization of the upper airway with pathogenic microorganism interfere with patients' already compromised native defense mechanisms [7] and predispose ventilated patients to the development of VAP. A clear understanding of the pathophysiology is important to understand the targets of VAP-prevention strategies.

VAP occurs when the bacteria gain access into lower respiratory tract and defense mechanisms are ineffective due to reduced immune response in mechanically ventilated patients. Lower respiratory tract invasion is attributed to two mechanisms: most significant mechanism is microaspiration of pathogenic organisms from the upper respiratory tract/gastrointestinal tract around the ETT, and the second is biofilm production on the ETT itself. In majority of mechanically-ventilated patients, oropharynx is colonized with potentially pathogenic microorganisms. Presence of enteric gram-negative bacteria in the oropharynx of 75 per cent of critically ill patients was first established in a study published in 1969. [8] A proposed explanation is bacterial overgrowth of the upper gastrointestinal tract and retrograde movement and aspiration of secretions containing these pathogens. Similarly another study published in 2007 confirmed the presence of similar pathogenic microorganisms in the lower respiratory tract by comparing DNA samples from bacteria on the tongue and obtained from bronchoalveolar lavage (BAL) in intubated patients. [9]

The second potential source of introduction of bacteria into the lower respiratory tract can be attributed to the ETT itself. Biofilm, a network of secretions and microorganisms that develop along the ETT cuff and inside the lumen of the ETT are easily transferred to the lower respiratory tract and subsequently may cause infection. The source of infection in most patients with VAP is either the oral flora or bacteraemia. The other sources can be the stomach contents, ventilator circuits, humidifiers, and nebulizers.

**Risk Factors**

Many factors contribute to the development of VAP. Any patient who is mechanically ventilated is at risk for VAP. The rate of contracting VAP increases by 3 per cent per day during the first week of mechanical ventilation, 2 per cent per day during week 2 and 1 per cent per day after second week. [10] Other risk factors that have been associated with increase the rates of VAP can be divided into non-modifiable and modifiable categories. Non-modifiable risk factors include male sex, increased age, preexisting pulmonary disease, chronic obstructive pulmonary disease, AIDS, presence of a tracheostomy, head trauma , post surgery , burn patients, acute respiratory distress syndrome, multiorgan system failure, and coma. Potentially modifiable risk factors include

supine positioning, gastric overdistension, colonization of ventilator circuits, low pressure in the ETT cuff and repeated patient transportation. [11, 12]

**Microbiology of VAP**

The microbial flora that causes VAP usually depends on duration of mechanical ventilation. Organisms causing early onset VAP are usually sensitive to antibiotics whereas the organism associated with late onset VAP are multidrug resistant making treatment difficult. Typically, organisms associated with early-onset VAP are Streptococcus pneumoniae, methicillin-sensitive Staphylococcus aureus (MSSA), Hemophilus influenzae and antibiotic-sensitive enteric Gram-negative bacilli like Escherichia coli, Klebsiella pneumonia, Enterobacter species, Proteus species and Serratia marcescens. Organism associated with late VAP are typically MDR bacteria, such as methicillin-resistant S. aureus (MRSA), Acinetobacter, Pseudomonas aeruginosa, and extended-spectrum beta-lactamase producing bacteria. [13] Patients receiving antibiotics or chemotherapy in the last month, residents of nursing home, history of hospital admission for 2 days or more in the last 90 days, and patients undergoing hemodialysis are susceptible to drug resistant bacteria. [2, 13] Usually VAP is due to polymicrobial infection. Incidence of VAP from viral and fungal organism is very low, especially in the immunocompromised patients. There is inter-institute and intra institute variation of multidrug resistant organisms. [2]

**Diagnosis**

There is no universally accepted diagnostic criterion for VAP. Recommended clinical methods lack the sensitivity or specificity to accurately identify this disease. Autopsy finding suggested 69 percent sensitivity and 75 percent specificity in comparing VAP diagnosis based on clinical criteria. [14] The clinical examination includes systemic signs of infection and chest radiograph. The chest radiograph determines lung parenchymal involvement and the presence of any pleural effusion or cavitation. The systemic signs of infection include fever, leukocytosis, tachycardia, and some non-specific signs like release of cytokines. Similarly, a leukocytosis (count of more than 11,000 cells/cu mm) or leukocytopenia (count less than 5,000/cu mm) can help in diagnosis. Fàbregas et al. reported a diagnostic rule for VAP; namely, that patients with chest radiograph showing infiltration along with any two of the following—fever greater than 38.3$^{o}$C, leukocytes more than 12 x 10$^{9}$/ml, and purulent tracheobronchial secretions—had VAP. It had a sensitivity of 69 per cent and specificity of 75 percent. [14] In a study conducted by Wunderink et al., all the four signs were taken into consideration resulting in increased the specificity but decreases sensitivity to 50 per cent. [15]

Pugin et al introduced the new scoring system known as clinical pulmonary infection score (CPIS). This scoring system includes the following variables: temperature, leukocyte count, volume and purulence of tracheal secretions, oxygenation, chest roentgenogram, and semi-quantitative analysis of the ETA, with gram stain. [16] Score varies from 0–12. Patients with CPIS more than six were considered to be affected with pneumonia. [17] Papazain et al described that CPIS more than six had a sensitivity of 72–85 per cent and specificity of 85–91 per cent. [18] Gibbot s et al described that the triggering receptor expressed on myeloid cells (TREM-1) as an immunological method for diagnosis of VAP. It was found to be an accurate method

for diagnosis of fungal or bacterial pneumonia with sensitivity of 98 per cent and specificity of 90 percent. [19]

**Treatment**

The main stay for treatment of VAP is antimicrobial antibiotics but selecting the appropriate antibiotic remains crucial. Generally early onset VAP patient are infected with less virulent organisms so it can be treated with limited spectrum antibiotics whereas Late onset VAP usually requires broad spectrum antibiotics. [2] Depending upon local bacteriological patterns and susceptibilities updated antibiogram for each intensive care unit should be constructed to guide optimally dosed initial empiric therapy. [2] Antibiotic de-escalation is the key to reduce the development of resistance. [20] De-escalation refers to the use of aggressive broad-spectrum antimicrobials followed by narrowing or reducing the antimicrobial dose once the results of antimicrobial tests are available. The American Thoracic Society/Infectious Disease Society of America Guidelines advise starting on a broad-spectrum therapy for the VAP patients followed by de-escalation to a narrow-spectrum drug for the specific pathogen. Delays in initiation of antibiotic treatment may lead to the excess mortality risk. [2] Initial empiric therapy for early onset VAP includes floroquinolones ( levofloxacin 750 mg od) second or third generation cephalosporin(ceftriaxone 2g daily or cefotaxime 2g tds) or aminopenicillin plus betalamase inhibitor (ampicillin-sulbactum 3 g tds) and for late onset VAP includes third or fourth generation cephalosporin (cefipime or ceftazidime 2g tds), carbepenem (imipenem-cilastin 1g tds or meropenem 1g tds), antipseudomonal flouroquinolone plus coverage for MRSA (levofloxacin 750mg od plus vancomycin 15mg/kg bd or levofloxacin 750 mg od plus linezolid 600mg bd), ureidopenicillin – betalactamase inhibitor plus aminoglycoside (piperacillin-tazobactum 4.5g qid plus amikacin 20mg/kg/day). [2, 21, 22]

Reconsider diagnosis, if no response is observed, reassess the organism being treated or search for the other reasons. IDSA/ATS guidelines highlight the importance of reassessing patients at 48-72 hours when data are available to determine whether the patient should continue antibiotic therapy for VAP or whether an alternative diagnosis should be considered. The prevalence of antimicrobial resistance both intrinsic and acquired resistance among VAP pathogens is steadily increasing [23] Pseudomonas resistance to imipenem, fluroquinolones, and third-generation cephalosporins has increased to 15, 9, and 20 per cent, respectively. Staphylococcus resistance to methicillin and Klebsiellae resistance to third-generation cephalosporins has increased to 11 and 47 per cent respectively. [24] Usually 7–10 days treatment is recommended for VAP however longer duration of treatment is needed for patients with multidrug resistant organisms. [25] Three day Short course treatment is recommended for low-risk patients and treatment can also be discontinued on the basis of clinical response. Antibiotic Rotation antimicrobial reduces the development of resistant strains for a particular drug. [26] Aerosolised antibiotics can reduce the systemic toxicity and can prevent biofilm formation around endotracheal tube especially aerosolised gentamicin is effective. [27]

**Prevention of VAP**

VAP is hospital acquired infection occurring in mechanically ventilated patients. Culprits for development of VAP include colonization of microorganism in upper respiratory tract, microaspiration of pathogens from upper respiratory and gastrointestinal tract, and biofilm formation on endotracheal tube. From above discussion it is clear that VAP preventive strategy should focus on infection control in ICU, need for ventilator support, prevention of colonization of upper respiratory and gastrointestinal tract, prevention of microaspiration and biofilm formation.

**Infection Control in ICU**

The strategy for infection control in ICU should focus on education of healthcare providers, use of personal protective equipment, hand hygiene and microbial surveillance. [28] Education of all healthcare provider results in better VAP prevention if recommendations for VAP prevention are properly followed. [29, 30, 31, 32] VAP prevention bundles have been proposed to address the gap in implementation of guidelines.

Ventilatory Support: Whenever possible avoid or limit the use of mechanical ventilation. To achieve this goal many strategies are described which includes use of non-invasive positive pressure ventilation (NPPV), judicious use of sedation and sedation free periods (sedation holidays), daily weaning trials, preventing re-intubation. A meta-analysis of 12 studies confirmed NPPV to significantly lower the risk of VAP and mortality benefit in variety of illnesses. [33, 34] Therefore, it is recommended to use NPPV when possible to prevent mechanical ventilation. Daily weaning trials and sedation holidays is well recognized method to reduce the time of mechanical ventilation. [35, 36] Re-intubation increases risk of aspiration resulting in increased chances of contracting VAP. [37] Needleman J and colleagues in their study demonstrated the need of adequate ICU staff should to minimize unplanned extubations necessitating re-intubation, [38] and planned extubations should be carefully considered balancing the risk of reintubation.

Prevention of colonization: Prevention of upper airway and gastrointestinal tracts colonization for VAP prevention ranges from oral decontamination to selective digestive tract decontamination. Oral antiseptic Chlorhexidine use, its concentration and frequency of adminstration has been associated with reduction of VAP. [39, 40, 41, 42, 43, 44] Povodine iodine and Iseganan have also been studied for oral decontamination but only povodine iodine demonstrated benefit in VAP reduction. [45, 46] Selective oropharygeal decontamination and selective digestive tract decontamination with antibiotic therapy has been associated with only modest mortality benefits [47, 48, 49] but increases the risk for emergence of antibiotic resistant microorganisms. [50] Because of risk of resistant pathogens selective oropharyngeal decontamination and selective digestive tract decontamination should not be recommened as for VAP prevention. Prophylactic probiotic (lactobacillus rhamnosus GG) use is safe and effective in preventing VAP in a select, high risk patient population. [51]

Prevention of Microaspiration and Biofilm formation: Endotracheal tube contributes to VAP by micro-aspiration of secretions that contain pathogenic microorganisms, and secondly by biofilm formation. Prevention strategies include elevation of head end of bed, usage of antimicrobial

coated endotracheal tubes and endotracheal tubes with subglottic suctioning port. Head end elevation upto 45 degree reduces aspiration of gastric content [52, 53] resulting in significant VAP reduction. [54] Endotreacheal tubes with subglottic suction port to remove the secretions that pool above the endotracheal tube cuff demonstrated lower incidence of VAP. [55, 56] Antimicrobial coated endotracheal tube prevents biofilm formation and bacterial colonization. [57] NASCENT study confirmed Silver coated endotracheal tube not only reduces microbiologically confirmed VAP but also delays the onset of VAP. [58, 59] Other coating material like Chlorhexidine with or without sulphadiazine are still in experimental stage. [60]

## Conclusion

VAP is a commonly encountered nosocomial infection occurring in ventilated patients and is associated with increased mortality and morbidity. Outcome of patient with VAP depends on hospital setting, patient group, infection control policy, early diagnosis and judicious antibiotic use.

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