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Review Article

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VENTILATOR ASSOCIATED PNEUMONIA (VAP) IN COVID-19 PATIENTS: AN OVERVIEW

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ABSTRACT

Pandemic corona virus disease 2019 (COVID-19) caused by severe acute respiratory syndrome corona virus 2 (SARS-CoV-2) is affecting respiratory system seriously. This may lead to acute respiratory failure and hospitalization in the ICU with use of invasive mechanical ventilation which may expose them to a risk of ventilator associated pneumonia (VAP), which may further worsen the disease condition. The primary objective of this review is to assess and report the occurrence of ventilator associated pneumonia in covid patients. It is a common nosocomial infection seen in ICU patients, especially in those who get ventilated. This review aims to highlight the incidence, diagnosis, risk factors, causative organisms, pathophysiology and the pattern of VAP occurrence in COVID-19 patients.

KEYWORDS: VAP, COVID-19, SARS-CoV-2, mechanical ventilation, pneumonia.

INTRODUCTION

The highly contagious illness corona virus disease 2019 (COVID-19) caused by severe acute respiratory syndrome corona virus 2 (SARS-CoV-2) is emerging as the most consequential global health crisis since the era of influenza pandemic of 1918.[1] SARS-CoV-2 virus is currently affecting many countries in the world. The virus affects respiratory system, generating corona virus disease 2019 (COVID-19).[2] About 5% of patients with respiratory impairment develop a severe form with acute respiratory failure requiring specialized management in ICU.[3] Mechanical organ support has always been a mainstay of intensive care and especially the use of mechanical ventilation. Among the more than 70 million people infected worldwide with SARS-CoV-2, many have required mechanical ventilation. Approximately one in ten patients with SARS-CoV-2 becomes symptomatic. Although hospital and intensive care unit (ICU) admission rates are highly dependent on resource availability, most studies from Europe and North America report that 10 –20% of the patients admitted to hospital undergo some form of mechanical ventilatory support due to acute hypoxemic respiratory failure, either in the ward or in the ICU. Overall, between one-fourth and one-third of hospitalized patients will ultimately be admitted to the ICU.[4]

Respiratory failure with need of mechanical ventilation was reported in 2.3% to 33% of the affected patients.[2] Since a few weeks after the beginning of this outbreak several thousands of patients have been receiving invasive mechanical ventilation due to severe infection.[3] A large percentage of patients hospitalized for SARS-CoV-2 infection are admitted to the intensive care unit (ICU). Instead of using high flow nasal oxygen and non-invasive mechanical ventilation frequently (55% and 16% respectively), intubation and invasive mechanical ventilation are required in approximately 10% of patients hospitalized for SARS-CoV-2 related infection.[5] The mortality of patients with critical corona virus disease 2019 (COVID-19) is strikingly high, ranging between 15 and 74%, particularly when invasive mechanical ventilation (IMV) has been required.[4]

Mechanical ventilation can be defined as a technique through which gas is moved towards and from the lungs through an external device connected directly to the patient.[6] It is a form of life support provided with the help of a device called mechanical ventilator that assist the work of breathing when a person is unable to breathe enough on their own. It is a common supportive treatment in COVID-19 patients with acute respiratory distress syndrome, although this is a predisposing factor for ventilator-associated pneumonia (VAP).[7]

Ventilator-associated pneumonia is defined as a parenchymal lung infection occurring more than 48 hours after initiation of mechanical ventilation. It is a common complication in intensive care units, occurring in 9 to 24% of patients intubated for longer than 48 hours.[8] Critically ill patients are at high risk of nosocomial pneumonia, especially when ventilated. The

reasons for this includes breach of natural defenses by invasive devices, sedation and impairment of coughing and mucociliary clearance, and the immunoparetic effects of critical illness.[9] In addition, it is associated with increased mortality and cost. Patients with SARS-CoV-2 pneumonia could be at increased risk for ventilator associated LRTI, because of acute respiratory distress syndrome (ARDS), and the long duration of mechanical ventilation depending on the severity. ARDS is a well-known risk factor for VAP, and its incidence in mechanically ventilated patients with SARS-CoV-2 pneumonia was reported to be as high as 42-89%.[5] Early reports indicated that critically ill patients infected with SARS-CoV-2 had a high prevalence of nosocomial pneumonia, especially ventilator-associated pneumonia (VAP).[9]

Fever, leukocytosis, severe hypoxemia, bilateral infiltrates, and multi-systemic inflammatory syndrome with possible multi-organ failure (MODS-CoV-2) are the clinical presentation of COVID-19 pneumonia. The requirement of prolonged mechanical ventilation in patients with COVID-19 may put them at risk of developing super-infections of bacterial origin, including ventilator-associated pneumonia (VAP), that may contribute to influencing the prognosis unfavorably. However, a clear picture of the true incidence, spectrum of causative agents, and prognostic factors of VAP in COVID-19 patients may help in improving its management.[10]

HOW IS IT DIAGNOSED?

COVID-19 was diagnosed in presence of at least one positive real-time polymerase chain reaction (RT-PCR) test for SARS-CoV-2 on respiratory specimen (nasopharyngeal swab). VAP was defined as new or changing chest X-ray infiltrate/s occurring more than 48 h after initiation of invasive mechanical ventilation, plus both of the following: (i) newly onset fever (body temperature ≥ 38℃)/ hypothermia (body temperature ≤ 35℃) and/or leukocytosis (total peripheral white blood cell count ≥ 10,000 cells/μL)/leukopenia (total WBC count ≤ 4500 cells/μL)/ > 15% immature neutrophils; (ii) new onset of suctioned respiratory secretions and/or need for acute ventilator support system changes to enhance oxygenation. Ventilator days were defined as days with an invasive device in the airways, including tracheostomy.[10]

According to ECDC criteria, VAP is diagnosed using a combination of radiological, clinical and microbiological criteria in a patient who has been receiving mechanical ventilation for at least 48 hours.[9]

Table 1: Diagnostic criteria for VAP.[9]

VAP definition by ECDC	
Radiological	New or worsening infiltrates on Chest X-ray or CT thorax
Clinical	at least one of the following: Fever > 38°C with no other cause Leukopenia (< 4 000 WBC/mm3) or leucocytosis (≥12 000 WBC/mm3). and at least one of the following new onset of purulent sputum, or change in character of sputum (colour, odour, quantity, consistency). suggestive auscultation (rales or bronchial breath sounds), rhonchi, wheezing. worsening gas exchange (e.g. O2 desaturation or increased oxygen requirements or increased ventilation demand).
Microbiological	Bacteriologic diagnostic performed by: Positive quantitative culture from minimally contaminated LRT specimen (**PN 1**). Broncho-alveolar lavage (BAL) with a threshold of $\geq 10^4$ colony forming units (CFU)/ml. Detection by TaqMan array with Ct ≤32. OR Positive quantitative culture from possibly contaminated LRT specimen (**PN 2**) Quantitative culture of LRT specimen (e.g. endotracheal aspirate) with a threshold of 10^5 CFU/ml.

RISK FACTORS OF VAP

Although its prevalence has declined in recent years, VAP remains one of the most common causes of nosocomial infections and death of critically ill patients during hospitalization in the ICUs. It further increases the need of ventilator and stay in the hospital longer, which cause a huge financial burden to patients. Therefore, it is very crucial to clarify the risk factors of VAP in order to reduce its incidence, get better prevention and control of VAP and improve the outcome in patients with mechanical ventilation. There are various risk factors for VAP. Patient's characteristics (e.g., advanced age, male), increased mechanical ventilation time and prolonged mechanical ventilation, disorders of consciousness, burns, comorbidities, prior antibiotic therapy, invasive operations and gene polymorphisms are the internationally recognized risk factors of VAP that reported in recent years. Each factor has an influence on each other.[11]

MICROBIOLOGY AND PATHOPHYSIOLOGY

Pathophysiology of VAP involves 2 factors mainly biofilm formation with in the endotracheal tube (ETT) and microaspiration of secretions. Organisms may get

expelled out through sputum upon coughing to a much extent. But, presence of ETT in mechanically ventilated patients will prevent this effective coughing by interfering with normal reflex of upper airways. Normal oropharyngeal flora is usually involved in early-onset VAP (within first 4 days of hospitalization) in previously healthy patients not receiving antibiotics, whereas in late-onset VAP (occurring after at least 5 days of hospitalization), MDR pathogens are the most likely causative agent.(12) After initial antibiotic administration following hospitalization due to illness, aerobic gram negative bacteria such as *Pseudomonas aeruginosa, Escherichia coli, Klebsiella pneumoniae and Acinetobacter* species etc., may rapidly colonize in the oropharynx of patient. Since ETT does not assure a perfect sealing due to the presence of folds along the cuff surface in contact with trachea, these contaminated oropharyngeal secretions pool above the ETT cuff and slowly gain access to the lower airway through these folds.(13) As a result, bacterial biofilm gradually forms on the inner surface of the tube and then pushed into distal airways by ventilator cycling and critical illness associated immunosuppression and thereby causes pneumonia. In order to prevent VAP, first focus on measures to reduce biofilm formation and microaspiration.(14) *Staphylococcus aureus* is the major gram-positive microorganism responsible for VAP. Fungi especially, *Candida* species rarely causes VAP. Respiratory viruses including *influenza, respiratory syncytial virus*, and others such as *Herpes simplex virus* (HSV) and *Cytomegalovirus* (CMV) can cause pneumonia in immune compromised and non-immuno compromised mechanically ventilated patients.[12]

CHARACTERISTICS OF VAP IN COVID-19 PATIENTS

A median age of 62 years and 72% of male and the median BMI of 29.0 kg/m^2 was estimated for VAP in COVID-19 patients in a study. Type 2 diabetes mellitus being the most frequent comorbidity and few of them were immunocompromised making an ideal risk for developing VAP. National Healthcare Safety Network (NHSN) 2017 criteria managed by Centers for Disease Control and Prevention (CDC) were used to define VAP. Using this criteria, VAP were diagnosed in 69% of patients admitted to ICU with COVID-19. The median time taken for VAP onset from ICU hospitalization and intubation was 16 days and 13 days respectively. 90% of VAPs were of late onset type, i.e., VAP was acquired 5 or more days after intubation. Gram negative rods especially, *Klebsiella* species was the most reported bacteria, followed by *Pseudomonas aeruginosa* with the large majority of isolated germs being MDR (71%). Gattinoni et al, previously reported two different phenotypes of pathophysiological respiratory tract involvement in COVID-19 patients. They were SARS-CoV-2 pneumonia type L, which provokes hypoxia, but minimally affects lung compliance, and SARS CoV-2 pneumonia type H, which induces hypoxia and decreases lung compliance. According to further hypothesis, vasoconstriction due to hypoxia and pulmonary micro-embolization might be responsible for pneumonia with 'normal' compliance (>40 ml/cm H_2O), whereas acute lung injury occurring in later stage of disease and bacterial super infection might be responsible for pneumonia with 'reduced' compliance. Lower average lung compliance was detected in patients with COVID-19 affected by VAP (31.5 ml/cm H_2O). Moreover, this decreased minimal lung compliance was significantly correlated with VAP occurrence.[2]

Another study performed in 188 patients showing the occurrence of VAP at an average age of 63.9 years (+/- 11.4), with predominance of males (78.2%). Majority (76.4%) of them were overweight (BMI > 25) and 37% were obese (BMI > 30). Hypertension (47.9%) and diabetes (26.6%) were major comorbidities. Few of them were immunocompromised and receiving immunosuppressive therapy, and long term corticosteroid therapy that makes them more vulnerable to infection. The median time between the hospital admission and onset of symptoms was 6.4 (+/- 8.0) days. Organisms commonly isolated were *Staphylococcus aureus, Enterobacteria, Streptococcus pneumoniae* and *Haemophilus influenzae*. The total mean duration of intubation for all patients was 22.2 (+/- 16.7) days.[3]

A higher incidence of microbiologically confirmed VAP was observed in COVID-19 patients [39 (48%)] compared to 19 (13%) patients without COVID-19] in a study. The median age for developing VAP in such patients was 62 (50-70) years. Hypertension and diabetes were the common comorbidities reported with a proportion of 27 (33%) and 18 (22%) respectively. The immunocompromised conditions in patients (15%), wide use of antibiotics in 24 h following admission (94%) and median duration of 14 days of ventilation (ranging from 10-23 days) also increases the risk. 40-86% reported VAP was amongst ventilated patients with COVID-19.[9]

In a study conducted in 2020 showing the requirement of invasive mechanical ventilation in 586 patients with severe COVID-19 infections, 171 (29%) patients were diagnosed with VAP. The incidence rate of VAP was of 18 events per 1000 ventilator days in ICU, with 30-day fatality being as high as 46%. The most frequent causative agent identified was *Pseudomonas aeruginosa*, followed by *Staphylococcus aureus* and then *Klebsiella pneumoniae*. The reasons for such a truly increased risk of VAP in COVID-19 patients were explained which might include:

1. A potential increased predisposition to bacterial super infection, on the top of lung damage caused by COVID-19;
2. The virus related immunosuppressive effect with deep lymphopenia;
3. The potential concomitant anti-inflammatory or immunosuppressive effect of steroids and biologic agents (e.g., anti-IL-6 receptor monoclonal antibodies).(10)

Another study comprising 1576 patients reported that *Pseudomonas aeruginosa*, *Enterobacter* species, and *Klebsiella* species were the microorganisms that most frequently identified in COVID-19 patients. The percentage of patients with late-onset VAP was 82.4% (169 of 200 patients in SARS-CoV-2). Median (interquartile range) time from starting invasive mechanical ventilation to VAP occurrence was 9 (6, 13) days in SARS-CoV-2. This VAP is associated with increased 28-day mortality rate and longer duration of mechanical ventilation and ICU length of stay in SARS-CoV-2 patients. Multidrug resistant (MDR) bacteria and inappropriate initial antibiotic treatment were well-known risk factors for mortality in these patients. The relationship between VAP and mortality was only significant in COVID-19 patients.[15]

A sensitivity analysis study observed significantly higher risk of VAP in patients with COVID-19 than patients without COVID-19. This comparatively higher occurrence in COVID-19 patients may be due to several factors, both disease and non-disease related. COVID-19 patients admitted to ICU generally have severe hypoxemia, with both parenchymal and micro vascular lung damage. Thus, they are reasonably at a high risk of developing VAP than any other patients admitted to ICU. Also, the severity of lung damage in patients with COVID-19 pneumonia may increases the risk. Furthermore, these patients are at a frequent need of prolonged mechanical ventilation, prone positioning and immunomodulant therapies, which may also have increased their risk of developing VAP. Patients evaluated had a median age ranging from 49 to 69.5 years, with a predominance of female gender up to 55% (ranging from 18% to 55%). The median duration of mechanical ventilation prior to VAP occurrence ranges from 7 to 13 days. Previous reports showed that VAP occurs in up to 23–40% of patients admitted to ICU. All the included studies reported the VAP occurrence (45.4%) in patients admitted to ICU with COVID-19.[16]

CONCLUSION

The study shows high incidence of bacterial VAPs in mechanically ventilated COVID-19 patients due to the prolonged ICU hospitalization. The association between risk factors and VAP occurrence is clearly understood. Initial unwanted use of antibiotics at the time of admission being a common risk factor. A reduction in this prior inappropriate use of antibiotics and immunosuppressive medications could reduce the event to a greater extent. Implementation of strict antimicrobial stewardship program could ensure judicious use of antibiotics and thereby reduce the VAP due to resistant microbials. Address the risk of infection by replacing invasive mechanical ventilation with increased use of non-invasive oxygen therapy.

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