Original Article

Predictors and microbiology of ventilator-associated pneumonia among patients with exacerbation of chronic obstructive pulmonary disease

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ABSTRACT

Background: Understanding the risk factors and microbiology of ventilator-associated pneumonia (VAP) among patients with chronic obstructive pulmonary disease (COPD) is important for the application of preventive and therapeutic interventions. Therefore, this study was planned to assess the clinical predictors and microbiological features of VAP among COPD patients. **Materials and Methods:** This prospective study involved patients with exacerbation of COPD who required mechanical ventilation and admitted in respiratory intensive care unit at a tertiary care teaching hospital. Various baseline demographic and clinical features were compared between patients with VAP and without VAP. Univariate and multivariable analyses were done to assess the impact of demographic and clinical features on the development of VAP. **Results:** The study included 100 intubated patients with age (mean ± standard deviation [SD]) of 62.45 ± 8.32 years, duration (median) of COPD of 6 years, and Acute Physiology, Age, and Chronic Health Evaluation score (mean ± SD) of 18.60 ± 4.30. In this cohort, 17 patients developed VAP. Multivariable analysis showed that Sequential Organ Failure Assessment (SOFA) score at admission, re-intubation, and history of previous hospitalization were independent predictors of VAP with odds ratio (95% confidence interval) of 2.70 (1.24, 5.63; $P = 0.012$), 66.96 (4.86, 922.72; $P = 0.002$), and 35.92 (2.84, 454.63; $P = 0.006$), respectively. *Acinetobacter baumannii* was the most frequent organism ($n = 8$; 47%), followed by *Klebsiella pneumoniae* ($n = 5$; 29%), *Pseudomonas aeruginosa* ($n = 1$; 6%), and *Enterobacter* spp. ($n = 1$; 6%). All organisms were multidrug resistant (MDR). **Conclusions:** SOFA score at admission, re-intubation, and history of previous hospitalization were independent predictors of VAP. Antimicrobial therapy for VAP should cover MDR Gram-negative organisms.

KEY WORDS: Chronic obstructive pulmonary disease, pathogens, predictor, ventilator-associated pneumonia

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INTRODUCTION

Ventilator-associated pneumonia (VAP) is the second most common infection acquired during stay in the intensive care unit (ICU).[1,2] The incidence of VAP may be as high as 40% among patients on mechanical ventilation.[3-5] It has been associated with significantly increased morbidity, mortality, and health-care costs. Mortality rates among patients with

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VAP differ in different settings; however, it may be as high as 78%.[6] Furthermore, VAP led to increased duration of hospital and ICU stay, antibiotic usage, and cost of care.[3-5] Diminishing occurrence of VAP remains a challenge since a long time. Knowledge of risk factors associated with development of VAP and its causative pathogens may be one of the important steps toward achieving this goal. Risk factors which have been associated with development of VAP include the presence of chronic obstructive pulmonary disease (COPD), organ failure, coma, and re-intubation.[7] Common pathogens causing VAP include *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, *Klebsiella pneumonia,* and *Staphylococcus aureus*.[4,5] However, these risk factors and microbiology of VAP may vary according to the study population and ICU settings.

COPD is an inflammatory disease of airways characterized by persistent airway symptoms and airflow limitation, usually caused by significant exposure to the noxious particles or gasses.[8] The natural course of COPD is characterized by exacerbations leading to acute respiratory failure and hospitalization. Majority of these patients with respiratory failure due to exacerbation of COPD may be managed with application of noninvasive ventilation (NIV).[9] However, a significant proportion of such patients requires endotracheal intubation and mechanical ventilation due to various causes.[9] Data suggest that in up to 6%–12% of patients in ICU receiving mechanical ventilation, the underlying reason for intubation was an exacerbation of COPD.[10] In patients of COPD, although endotracheal intubation is lifesaving, it can be complicated by the development of VAP.

As mentioned above, COPD has been demonstrated as an independent risk factor for the development of VAP.[7] Furthermore, >50% of patients of COPD who developed VAP succumb to it.[11,12] It is, therefore, important to understand the risk factors and pathogens causing VAP among intubated COPD patients for appropriate risk stratification, development of preventive strategies, and selection of appropriate antimicrobial agents. However, data regarding the predictors of VAP and its microbiology among patients with COPD requiring endotracheal intubation and mechanical ventilation are sparse.

We planned this study with the objective to describe the predictors and profile of pathogens causing VAP among COPD patients.

MATERIALS AND METHODS

Study design, patients, and setting

This prospective observational study was conducted between June 2016 and January 2018 at a tertiary care teaching hospital. All patients admitted with exacerbation of COPD and requiring mechanical ventilation for >48 h were eligible for participation in the study. Exacerbation of COPD was defined clinically as an episode of worsening of respiratory symptoms, particularly dyspnea, cough, sputum production, and sputum purulence.[13] Patients with community-acquired lobar/bronchopneumonia at admission and acute respiratory distress syndrome, immunocompromised patients, and those who were transferred from other hospitals after stay of >48 h were excluded from the study.

All patients were given inhaled bronchodilators (metered-dose inhaler or nebulization), injectable antibiotics (amoxicillin-clavulanic acid or piperacillin-tazobactam plus fluoroquinolone or macrolide), and low-dose corticosteroids as a standard of care for the management of the exacerbation of COPD.

For prevention of VAP, the following strategies are followed routinely, unless contraindicated: elevation of the head end of the bed by 30°–45°, peptic ulcer prophylaxis, daily sedation-free time, daily assessment for readiness for extubation, endotracheal cuff pressure checked at least three times per day and kept 20–30 mmHg, and chlorhexidine mouthwash twice daily. We do not use selective gut decontamination routinely.

Definitions

Diagnosis of COPD was based on the existing guidelines.[8] Clinical diagnosis of VAP was based on criteria – new or progressive infiltrates on chest radiograph (with no other obvious causes such as atelectasis, embolism, and heart failure) and at least two of the following variables – fever >38°C, leukocytosis (>12000/dl), or leukopenia (<4000/dl), purulent secretions, isolation of pathogenic organism, or increased oxygen requirement.[14] Those patients with clinical diagnosis of VAP underwent flexible bronchoscopy and bronchoalveolar lavage (BAL) for microbiological diagnosis. In case bronchoscopy was contraindicated, a patient underwent nonbronchoscopic BAL or endotracheal aspirate (ETA). Microbiological diagnosis was achieved by gram stain and culture on appropriate culture media with thresholds of $\geq 10^4$ CFU/ml and $\geq 10^5$ CFU/ml in BAL and ETA, respectively.

Data collection

All baseline demographic and clinical data were recorded. Furthermore, data regarding size of endotracheal tube at admission, use of vasopressors at admission, use of systemic corticosteroids prior to admission, smoking history, duration of symptoms of the current exacerbation of COPD, use of antibiotics in the past 90 days, number of exacerbation episodes in the past 1 year for which a patient required hospitalization, history of pulmonary tuberculosis (TB), presence of any comorbidities such as diabetes, chronic liver, or kidney disease, and need of reintubations were required during the current admission were recorded.

Statistical analysis

Data were managed on Excel spreadsheet and analyzed using statistical software Stata version 14 (StataCorp, Texas, USA). Quantitative variables were expressed as

mean ± standard deviation and median for normal and skewed data, respectively. Univariate analysis was done for identification of potential risk factor for the development of VAP. Independent *t*-test (for normal data) and Mann–Whitney U-test (for skewed data) were used to compare mean/median values between the groups. Change in mean was compared using paired *t*-test (for normal data) and Wilcoxon signed-rank test (for skewed data). Fisher's exact test and Chi-square test were used to check the statistical significance for categorical variable. Stepwise multivariate logistic regression analysis was carried out taking probability of removal as 0.1 and entry as 0.05 to find the independently associated factor of VAP, and adjusted odds ratio was calculated. All tests were two-tailed, and $P < 0.05$ was considered statistically significant.

RESULTS

During the study period, 120 of 208 patients of COPD with exacerbation admitted under pulmonary medicine services required upfront intubation and mechanical ventilation. NIV was initiated in 88 patients; among these, 29 failed NIV and subsequently required intubation. Thus, a total of 149 patients were available for study. Patient recruitment has been shown in Figure 1.

Baseline characteristics

Study cohort ($n = 100$) consisted predominantly of male, heavy smokers, with median duration of COPD of 6 years and Acute Physiology, Age, and Chronic Health Evaluation score of 18.60 ± 4.30. The baseline patients' characteristics are shown in Table 1.

Median (interquartile range [IQR]) duration of ICU stay was 7 (5, 10.5) days. Fifteen (15%) patients required re-intubation. Median (IQR) duration of time spent on mechanical ventilation was 4 (3, 8) days. Among the study cohort, 17 patients developed VAP. Median (IQR) duration of endotracheal tracheal intubation before the development of VAP was 7 (6, 10) days. The overall inhospital mortality among intubated patients with acute exacerbation of COPD was 18% ($n = 18/100$). Among patients with VAP, 11 (61%) died.

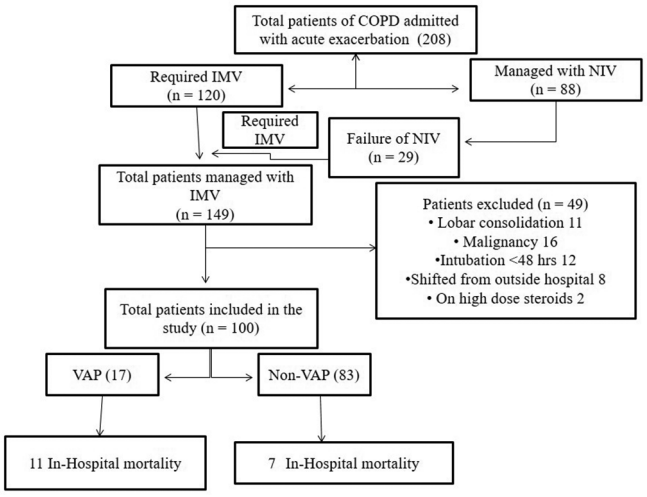

Figure 1: Flow diagram showing the recruitment of the patients

Predictors of ventilator-associated pneumonia

Various clinical characteristics were compared between patients having VAP and without VAP [Table 1]. On univariate analysis, Sequential Organ Failure Assessment (SOFA) score at admission, use of vasopressor, presence of comorbid conditions (diabetes mellitus and chronic kidney disease), history of pulmonary TB, previous COPD exacerbations requiring hospitalization, antibiotics use in the past 90 days, use of systemic corticosteroids prior to current admission, size of endotracheal tube, and re-intubation were associated with development of VAP [Table 2]. On multivariable analysis, only SOFA score at admission, re-intubation, history of previous hospitalization, and history of pulmonary TB significantly predicted the development of VAP [Table 2].

Pathogens associated with ventilator-associated pneumonia

Bronchoscopic ($n = 8$) and nonbronchoscopic ($n = 9$) BALs were used for microbiological diagnosis of VAP. Microbiological etiology of VAP could be established in 15/17 (88.23%) patients. Gram staining showed Gram-negative organisms in all 17 (100%) BAL specimens obtained by nonbronchoscopic or bronchoscopic technique.

A. baumannii was the most frequent organism ($n = 8$; 47%), followed by *K. pneumoniae* ($n = 5$; 29%), *P. aeruginosa* ($n = 1$; 6%), and *Enterobacter* spp. ($n = 1$; 6%). In 2 (12%) patients, only Gram staining was positive while cultures showed no growth. All the pathogens were multidrug resistant (MDR). The antibiotic resistance pattern is shown in Table 3.

DISCUSSION

This single-center prospective study has shown that history of pulmonary TB, previous COPD exacerbations, antibiotic use in the past 90 days, and re-intubation were independent predictors of the development of VAP among patients with exacerbation of COPD requiring mechanical ventilation. *A. baumannii* was the most common pathogen causing VAP. All pathogens causing VAP were MDR.

The development of VAP is a serious event during the ICU course of the patients and may lead to fatal outcome. There has been established guidelines proposed by various scientific organizations for the prevention of the development of VAP.[15-17] However, despite these efforts, a significant number of patients develop this complication. Finding the risk factors which may predispose these patients to the development of VAP may help in the stratification of these patients. This study has demonstrated that SOFA score at admission, re-intubation, history of previous

Table 1: Comparison of baseline characteristics between ventilator-associated pneumonia and nonventilator-associated pneumonia group

Clinical parameters	Whole cohort (*n*=100)	VAP (*n*=17)	Non-VAP (*n*=83)	*P*
Age, mean±SD years	62.45±8.32	62.82±7.74	62.37±8.47	0.840
Gender, *n* (%)				
Male	63 (63)	10 (15.87)	53 (84.13)	0.695
Female	37 (37)	7 (18.92)	30 (81.08)	
Smoking status, *n* (%)				
Nonsmoker	14 (14)	2 (11.76)	12 (14.46)	0.457
Smoker	57 (57)	8 (47.06)	49 (59.04)	
Reformed smoker	29 (29)	7 (41.18)	22 (26.51)	
Smoking index, median (range)	250 (100-1200)	350 (250-1200)	200 (100-600)	<0.001
Duration of COPD, median (range)	6 (2-25)	10 (5-20)	5 (2-25)	<0.001
Number of exacerbation in the past 1 year, median (range)	1 (0-4)	2 (0-4)	0 (0-4)	<0.001
Duration of worsening before hospitalization, mean±SD days	7 (3-15)	8.41±2.89	6.39±2.41	<0.006
Previous hospitalization for COPD, *n* (%)				
Yes	63 (63)	14 (82.35)	23 (27.71)	<0.001
No	37 (37	3 (17.64)	60 (72.29)	
Indication of ET, *n* (%)				0.771
NIV failure	29 (29)	13 (76.47)	58 (69.88)	
Severe respiratory failure	71 (71)	4 (23.53)	25 (30.12)	
Place of ET, *n* (%)				
Emergency room	78 (78)	12 (70.59)	66 (79.52)	0.520
ICU	22 (22)	5 (29.41)	17 (20.48)	
Time interval between hospitalization and intubation, median (range) h	4 (0-90)	3 (0-90)	5 (0-72)	0.767
Size of ET tube at admission (mm), *n* (%)				
7.75	52 (52)	13 (76.47)	39 (46.99)	0.027
8-8.5	48 (48)	4 (23.53)	44 (53.01)	
Comorbidities, *n* (%)				
DM	28 (28)	10 (58.82)	18 (21.69)	0.002
Hypertension	38 (38)	9 (52.94)	29 (34.94)	0.06
Chronic kidney disease	8 (8)	3 (17.06)	5 (6.02)	0.10
Chronic liver disease	1 (01)	0	1 (1.20)	1.00
Old tuberculosis	24 (24)	9 (52.94)	15 (18.07)	0.002
Obstructive sleep apnea	7 (7)	2 (11.76)	1 (1.20)	0.074
APACHE-2, mean±SD	18.60±4.30	21±2.45	16.6±3.68	<0.001
SOFA score on admission, mean±SD	5.07±1.07	7.27±3.24	4.75±1.33	<0.001
Vasopressor use at admission, *n* (%)	25 (25)	8 (47.06)	12 (15.38)	0.004
Antibiotics used in the past 90 days, *n* (%)				
Yes	38 (38)	11 (64.70)	27 (32.23)	0.027
No	35 (35)	3 (17.64)	32 (38.55)	

VAP: Ventilator-associated pneumonia, SD: Standard deviation, COPD: Chronic obstructive pulmonary disease, NIV: Noninvasive ventilation, ICU: Intensive care unit, SOFA: Sequential Organ Failure Assessment, ET: Endotracheal, DM: Diabetes mellitus

Table 2: Predictors associated with the development of ventilator-associated pneumonia

Factor	OR (95%CI); *P*
Univariate analysis	
Size of ET tube at admission (8-8.5)	3.66 (1.10-12.18); −0.034
SOFA score at admission	2.65 (1.65-4.28); <0.001
Vasopressor use at admission	4.89 (1.57-15.19); −0.006
Systemic corticosteroid use prior to admission	14.43 (4.08-51.09); <0.001
Antibiotics in the past 90 days	4.34 (1.09-17.19); −0.036
Number of exacerbations of COPD in the past 1 year	19.02 (2.40-150.34); −0.005
History of previous hospitalization	12.17 (3.19-46.32); <0.001
Presence of comorbidity (DM, chronic renal or liver disease)	7.08 (2.23-22.48); −0.03
History of pulmonary tuberculosis	5.10 (1.69-15.38); −0.001
Re-intubation during current admission	22.28 (5.93-83.6); <0.001
Multivariate analysis	
SOFA score at admission	2.70 (1.29-5.63); −0.012
Re-intubation	66.96 (4.86-922.72); −0.002
History of previous hospitalization	35.92 (2.84-454.63); −0.006
History of pulmonary tuberculosis	6.95 (0.99-48.64); −0.051

OR: Odds ratio, SOFA: Sequential Organ Failure Assessment, ET: Endotracheal, COPD: Chronic obstructive pulmonary disease, CI: Confidence interval, DM: Diabetes mellitus

hospitalization, and history of pulmonary TB are predictors of the development of VAP among COPD patients requiring mechanical ventilation. The association of re-intubation and VAP has also been observed by other authors.[18] There have

Table 3: Pathogens isolated and their antibiotic resistance pattern

Antibiotics	Resistance pattern (%)			
	Acinetobacter baumannii	*Pseudomonas aeruginosa*	*Klebsiella pneumoniae*	*Enterobacter* spp.
Amikacin	100	0	100	100
Ceftazidime	87.75	100	100	100
Cefotaxime	100	100	100	100
Cefoperazone-sulbactam	50	0	100	100
Ciprofloxacin	100	100	100	100
Imipenem-cilastatin	100	100	80	100
Meropenem	87.75	100	80	100
Piperacillin-tazobactam	100	100	100	100
Colistin	0	0	0	0

been few other studies which have reported an association between history of pulmonary TB and VAP.[19,20] In our study, history of pulmonary TB has shown a trend toward association with VAP; however, it did not reach statistical significance. The possible explanation for the association of past TB and VAP seems underlying structural lung disease as a sequela of pulmonary TB which increases the propensity for the development of VAP. It should be noted that all these studies included patients who required mechanical ventilation for heterogeneous causes of respiratory failure and primarily were not focused on COPD. Badawy *et al.* reported prior antibiotic use, re-intubation, and presence of diabetes as risk factors for VAP among COPD patients.[21] In that study, the VAP rate was higher (60%) as compared to our study (17%). This may be because of the use of different diagnostic criteria and method of respiratory sampling technique. Badawy *et al.* used ETA for microbiological diagnosis as compared to BAL in our study.

A. baumannii was the most common isolate among patients with VAP in our study. Globally, commonly isolated organisms among patients with VAP include *P. aeruginosa*, *S. aureus,* and extended-spectrum beta-lactamase-producing *Enterobacteriaceae* (*Klebsiella* spp., *E. coli*, *Proteus* spp., *Enterobacter* spp., *Serratia* spp., and *Citrobacter* spp.); *A. baumannii* accounts for only 7%–8% isolates.[4] The microbiology may vary depending on the settings; however, over the years, MDR Gram-negative pathogens including *A. baumannii* have emerged as a major threat to critically it patients in ICU.[22,23] Our observation that all isolated organisms were MDR has further highlighted this alarming situation. In fact, all the isolates of *A. baumannii* were resistant to amikacin, cefotaxime, ciprofloxacin, and piperacillin plus tazobactam leaving only a few antimicrobials for treatment. The interventions which may be effective in controlling emergence of MDR include strict environmental cleaning, effective sterilization of reusable equipment, proper hand hygiene and contact practices, and effective antibiotic stewardship.[24,25] Our results emphasized that the organism isolated from VAP cases showed a similar pattern and not dependent on the duration of the onset of VAP, so empirical therapy for VAP should not be based on the concept of early or late.

Our study is a prospective controlled study, and the strength of this study is good sample size and homogeneous cohort of acute exacerbation of COPD cases. Our study has provided much-needed data regarding this clinically important global scenario, VAP among patients with COPD. We recognize that there are few limitations to our study. First, being confined to a single center, the results may not be applicable to other ICUs in different settings. However, such studies have an advantage in term uniformity of the care received by the study participants including the VAP prevention bundles and antimicrobial usage. Low endotracheal tube cuff pressure leading to leaks and microaspiration is one of the important factors responsible for VAP.[26] Therefore, reporting and comparison of endotracheal cuff pressures between patients with and without VAP may be interesting. In our ICU, endotracheal cuff pressure is routinely monitored as a standard of care and maintained at 20–30 cm of H_2O; hence, we did not record it for this study purpose. Furthermore, the rates of VAP and pathogens responsible for VAP were comparable to prior studies; hence, the results seem valid. This study was conducted in a medical respiratory ICU, so its results may not be extrapolated to other ICUs with nonrespiratory or surgical cases. Furthermore, the sample size was based on feasibility without using any statistical method; therefore, it may not be powered enough to detect some of the outcomes.

CONCLUSIONS

Our study revealed that systemic corticosteroid use prior to admission, number of exacerbations in the past 1 year, and history of pulmonary TB were independent predictors of VAP among patients with COPD. These data may help clinicians to formulate preventive measures for the occurrence of VAP in patients getting mechanically ventilated for exacerbation COPD. Antimicrobial therapy for VAP should cover MDR Gram-negative organisms.

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Conflicts of interest
There are no conflicts of interest.

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