JIDC | THE JOURNAL OF INFECTION IN DEVELOPING COUNTRIES

Original Article

Does organophosphorus poisoning increase the risk of staphylococcal ventilator associated pneumonia? – a retrospective study

Avijit Chauhan[1], Hariswar Pari[1], Radha Sugumaran[2], Venkateswaran Ramanathan[1]

[1] Department of Medicine, Jawaharlal Institute of Postgraduate Medical Education and Research, Puducherry, India
[2] Department of Microbiology, Jawaharlal Institute of Postgraduate Medical Education and Research, Puducherry, India

Abstract

Introduction: The aim of this study was to determine the clinical predictors of staphylococcal ventilator-associated pneumonia (VAP) and to compare the outcomes of staphylococcal VAP with non-staphylococcal VAP.

Methodology: A retrospective observational study was conducted among adult patients admitted to the medical intensive care unit (MICU) in a tertiary care hospital in India from January 2017 to December 2019. The patients were grouped based on their diagnosis into staphylococcal and non-staphylococcal VAP, and the baseline characteristics, clinical parameters, co-morbidities, and outcome parameters were compared.

Results: Out of 2129 MICU admissions, 456 patients with microbiologically confirmed VAP were included, of which 69 (15.1%) had staphylococcal VAP, and the remaining 387 (84.9%) had non-staphylococcal VAP. Organophosphorus (OP) poisoning was identified as an independent predictor of staphylococcal VAP (odds ratio: 2.57; 95% CI: 1.4 to 4.73). The median duration of mechanical ventilation before VAP diagnosis was less in the staphylococcal VAP group (4 vs. 5 days; $p = 0.004$). The staphylococcal group also showed a better in-hospital outcome.

Conclusions: OP poisoning was an independent predictor of staphylococcal VAP. Staphylococcal VAP was diagnosed earlier in patients than non-staphylococcal VAP. Screening for nasal carriage for *Staphylococcus*, especially in patients with OP poisoning at the time of MICU admission, may help guide antibiotic therapy.

Key words: organophosphorus poisoning; *Staphylococcus aureus*; ventilator associated pneumonia; MRSA; developing countries.

J Infect Dev Ctries 2024; 18(2):277-284. doi:10.3855/jidc.18125

(Received 23 February 2023 – Accepted 21 July 2023)

Introduction

Nosocomial infections are common in intensive care units (ICU). Ventilator-associated pneumonia (VAP) is one of the most common nosocomial infections, with a high level of mortality of 15 to 50% [1]. The definitive diagnosis of VAP, defined conceptually as pneumonia occurring more than 48 hours after initiation of mechanical ventilation, remains elusive [2]. The incidence of VAP which is diagnosed as patients having modified clinical pulmonary infection score (mCPIS) ≥ 6, can be as high as 22-26 per 1000 ventilator days [3,4]. VAP is predominantly caused by Gram-negative bacilli. However, when VAP is caused by Gram-positive organisms, *Staphylococcus aureus* (*S. aureus*) is the most common culprit [3]. VAP caused by *S. aureus* is less common in India than in the western countries [5,6]. However, unlike VAP caused by most Gram-negative bacilli, VAP caused by *S. aureus* has an acute fulminant course. In case of any delay in the diagnosis of staphylococcal VAP, the outcomes may be detrimental.

Clinical practice guidelines recommend empirical therapy with methicillin-resistant *Staphylococcus aureus* (MRSA) coverage only when risk factors for MRSA are present, and this usually requires additional antibiotics [7,8]. While the risk factors for MRSA infection are well established, risk factors for staphylococcal VAP (including methicillin-sensitive *Staphylococcus aureus* [MSSA]) are not available from recent studies and guidelines.

Organophosphorus (OP) poisoning is quite common in developing countries [9]. An early diagnosis of VAP in patients with OP poisoning is challenging due to an overlap in clinical manifestations. We have clinically observed increased frequency of staphylococcal VAP among patients with OP poisoning. Thus, identifying risk factors for *S. aureus* would help consider the early initiation of empirical antibiotic therapy in patients with clinically suspected staphylococcal VAP. Hence, we undertook this study to determine the clinical predictors of VAP caused by *S. aureus* (MSSA and MRSA). We also compared the

outcomes of patients with VAP due to *S. aureus* to those with VAP caused by organisms other than *S. aureus*.

Methodology

Study design

This retrospective observational study was conducted in the medical intensive care unit (MICU) of a tertiary care center in southern India between January 2017 and December 2019.

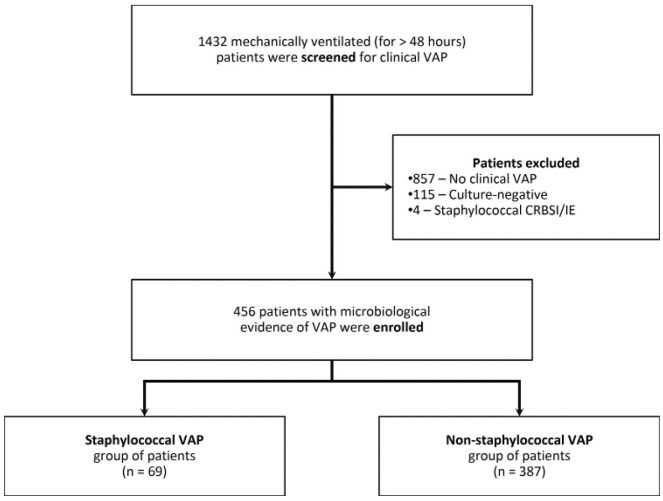
Study participants

In this case record based study, medical records of patients ≥ 18 years of age, mechanically ventilated for more than 48 hours, and clinically diagnosed with the first episode of VAP as per mCPIS ≥ 6 were included [10]. The Institute Ethics Committee at Jawaharlal Institute Post-Graduate Medical Education and Research, Puducherry approved the study and issued a waiver of consent (Certificate No.: JIP/IEC/2020/216). Case records of patients without microbiological evidence of VAP (culture-negative), patients from whom organisms that were not known to cause VAP were isolated, and those with a primary staphylococcal focus of infection other than lungs, such as staphylococcal infective endocarditis, were excluded.

Sample size estimation

Case records of patients admitted to the MICU between Jan 2017 and Dec 2019 were screened and those who met the eligibility criteria were enrolled. The minimum sample was estimated to be 100 patients with staphylococcal VAP, assuming the need to correct for confounding in multivariable logistic regression among ten predictors.

Figure 1. Patient flow diagram.



VAP: ventilator associated pneumonia; CRBSI: central line related blood stream infection; IE: infective endocarditis.

Study procedure

Baseline demographic characteristics, clinical profile, laboratory parameters, and in-hospital outcomes were recorded. For the purpose of this study, 'clinical VAP' was defined based on mCPIS of ≥ 6 calculated after 48 hours of mechanical ventilation. Patients whose transbronchial aspirate (TBA) culture was positive for potentially pathogenic microorganisms (PPM) with a semi-quantitative estimation of TBA culture of PPM ≥ 10^5 CFU/mL were considered to be 'microbiologically confirmed VAP'. Only patients with clinical VAP and microbiological evidence of infection with PPM were enrolled. The following culture isolates were not considered as PPM: *Candida* spp., *Neisseria* spp., *Enterococcus* spp., *Corynebacterium* spp., *Streptococcus viridans*, and *Staphylococcus epidermidis*. When more than one organism was isolated, if at least one of the organisms isolated was *S. aureus*, either MSSA or MRSA, then the patient was included in the staphylococcal VAP group. Only the first episode of VAP was included in risk factor analysis. The risk factors were compared between the staphylococcal and non-staphylococcal VAP groups.

Statistical analysis

The data was compiled using Microsoft Excel spreadsheet and analyzed using IBM SPSS Statistics for Windows, version 19.0 (IBM Corp., Armonk, NY, USA). The distribution of categorical data was expressed as frequency and percentages. The data on continuous variables were expressed as mean with standard deviation or median with interquartile range. The incidence of staphylococcal and non-staphylococcal VAP was expressed as percentages. Outcomes of continuous data between staphylococcal and non-staphylococcal VAP that were normally distributed were compared by independent Student t-test. Outcomes of categorical data between staphylococcal and non-staphylococcal VAP were compared using Chi-squared test, and the strength of association was measured as odds ratio using logistic regression. All statistical analyses were carried out at a 5% level of significance. Independent predictors of staphylococcal VAP were explored using multivariable logistic regression by including age, gender, established risk factors for staphylococcal infection, and baseline variables with $p < 0.2$ on univariate analysis.

Results

Of the 2129 admissions in the MICU during the study period, 1432 (67.26%) patients were mechanically ventilated for more than 48 hours and were screened for clinical evidence of VAP. Among the 571 patients who developed the first episode of clinical VAP based on the mCPIS score, 456 patients also had microbiologically confirmed VAP and were included in the study. The patients with *S. aureus* isolated from TBA were included in the staphylococcal VAP group (n = 69; 15.13%) and the others were included in the non-staphylococcal VAP group (n = 387; 84.87%) (Figure 1).

The baseline demographic characteristics of staphylococcal VAP and non-staphylococcal VAP groups were comparable. Among the critical illness characteristics, empirical antibiotic therapy for primary illness in the week before VAP onset was significantly higher (51% vs. 72%; $p < 0.001$) in the non-staphylococcal VAP group, whereas early onset VAP defined as VAP onset within 96 hours of mechanical ventilation was significantly higher in the staphylococcal VAP group (62% vs. 37%; $p < 0.001$). Among the primary illnesses, OP poisoning was more common among the staphylococcal VAP group (45% vs. 18%; $p < 0.001$). Similarly, poor sensorium, defined as Glasgow Coma Scale (GCS) of ≤ 8, during intubation, was significantly higher in the staphylococcal VAP group (Table 1).

Most staphylococcal VAP cases with early onset were caused by MSSA, compared to cases with late-onset (VAP onset after 96 hours of ventilation), where MRSA is the primary cause. Among the microbiologically confirmed VAP, around one-sixth (15.13%) were staphylococcal VAP, of which 9.86% (45) were MSSA and 5.26% (24) were MRSA. Twenty-

Table 1. Baseline clinical characteristics of the study participants and predictors of staphylococcal VAP by univariate analysis.

Characteristic	Staphylococcal VAP (n = 69)	Non-staphylococcal VAP (n = 387)	Univariate analysis	
			Unadjusted OR, (95% confidence interval)	*p* value
Age in years, mean (SD)	40.61 (16.66)	43.82 (16.06)	0.99 (0.97-1.00)	0.12
Female, n (%)	23 (33.33)	117 (30.23)	1.15 (0.67-1.99)	0.61
Critical illness characteristics, n (%)				
APACHE II score, mean (SD)	16.69 (7.28)	16.84 (7.42)	0.99 (0.96-1.03)	0.76
GCS ≤ 8 at the time of intubation	31 (44.92)	126 (32.55)	1.69 (1.01-2.84)	0.05
Empirical antibiotic therapy*	35 (50.72)	278 (71.83)	0.40 (0.24-0.67)	< 0.001
Reintubation	15 (21.74)	63 (16.23)	1.43 (0.76-2.69)	0.27
PaO_2/FiO_2, mean (SD)	237.25 (119.30)	254.64 (129.95)	0.99 (0.99-1.00)	0.32
Modified CPIS, mean (SD)	6.55 (0.69)	6.39 (0.56)	1.50 (1.00-2.26)	0.05
Days of MV before VAP, median (IQR)	4 (3-5)	5 (4-7)	0.83 (0.74-0.93)	0.002
Early-onset VAP#	43 (62.32)	144 (37.2)	2.79 (1.65-4.74)	< 0.001
Corticosteroid therapy	4 (5.80)	55 (14.21)	0.37 (0.13-1.06)	0.06
Primary illness, n (%)				
Stroke	9 (13.04)	37 (9.56)	1.42 (0.65-3.09)	0.38
Neuromuscular disease	7 (10.14)	41 (10.59)	0.95 (0.41-2.22)	0.91
CNS infection	1 (1.45)	48 (12.40)	0.10 (0.01-0.77)	0.007
Altered mental status	18 (26.10)	148 (38.4)	0.57 (0.32-1.01)	0.05
Cardiovascular disease	1 (1.45)	12 (3.10)	0.46 (0.06-3.59)	0.45
Acute kidney injury	4 (5.80)	21 (5.43)	1.07 (0.36-3.23)	0.90
Pulmonary disease	5 (7.24)	53 (13.69)	0.49 (0.19-1.28)	0.14
Gastrointestinal disease	2 (2.89)	9 (2.32)	1.25 (0.27-5.93)	0.77
Autoimmune disease	1 (1.45)	17 (4.39)	0.32 (0.042-2.45)	0.25
Sepsis	1 (1.45)	18 (4.65)	0.30 (0.04-2.30)	0.22
OP poisoning	31 (44.93)	69 (17.83)	3.76 (2.19-6.46)	< 0.001
Other primary diagnoses	8 (11.59)	30 (7.75)	1.56 (0.68-3.56)	0.29
Co-morbidities, n (%)				
Diabetes mellitus	14 (20.29)	92 (23.77)	0.82 (0.43-1.54)	0.53
Chronic kidney disease	3 (4.35)	31 (8.01)	0.52 (0.16-1.76)	0.29
Systemic hypertension	16 (23.19)	88 (22.73)	1.03 (0.56-1.88)	0.94
Smoking	13 (18.84)	63 (16.28)	1.19 (0.62-2.31)	0.60
Alcoholism	17 (24.63)	94 (24.29)	1.02 (0.56-1.85)	0.95

The values are expressed in numbers (percentage) or mean (standard deviation, SD). APACHE: acute physiology and chronic health evaluation; CNS: central nervous system; GCS: Glasgow coma scale; CPIS: clinical pulmonary infection score; MV: mechanical ventilation: VAP: ventilator associated pneumonia; OR: odds ratio; OP: organophosphorus. *Empirical antibiotic therapy for the infectious syndrome of the primary illness in the week before VAP onset. #Early-onset VAP is defined as VAP onset within 96 hours of mechanical ventilation.

Table 2. Independent predictors of staphylococcal VAP by multivariable logistic regression.

Predictor	Staphylococcal VAP (n = 69)	Non-Staphylococcal VAP (n = 387)	Adjusted OR (95% confidence interval)	*p* value
Age in years, mean (SD)	40.61 (16.66)	43.82 (16.06)	0.99 (0.97 - 1.01)	0.21
Female, n (%)	23 (33.33)	117 (30.23)	1.06 (0.58 - 1.95)	0.85
GCS < 8 at the time of intubation, n (%)	31 (44.92)	126 (32.55)	1.58 (0.91 - 2.75)	0.11
Empirical antibiotic therapy*, n (%)	35 (50.72)	278 (71.83)	0.59 (0.33 - 1.07)	0.08
Reintubation, n (%)	15 (21.74)	63 (16.23)	1.19 (0.6 - 2.37)	0.62
Early-onset VAP#, n (%)	43 (62.32)	144 (37.2)	2.62 (1.51 - 4.56)	0.001
Corticosteroid therapy, n (%)	4 (5.80)	55 (14.21)	0.54 (0.18 - 1.63)	0.28
OP poisoning, n (%)	31 (44.93)	69 (17.83)	2.57 (1.4 - 4.73)	0.002
Diabetes mellitus, n (%)	14 (20.29)	92 (23.77)	1.18 (0.56 - 2.46)	0.66
Chronic kidney disease, n (%)	3 (4.35)	31 (8.01)	0.89 (0.24 - 3.23)	0.86

GCS: Glasgow coma scale; MV: mechanical ventilation: VAP: ventilator associated pneumonia; OR: odds ratio; OP: organophosphorus. *Empirical antibiotic therapy for the infectious syndrome of the primary illness in the week before VAP onset. #Early-onset VAP is defined as VAP onset within 96 hours of mechanical ventilation.

nine cases of staphylococcal VAP were monomicrobial and the remaining 40 were polymicrobial. The common organisms among the non-staphylococcal VAP group were *Acinetobacter baumannii* (264, 68.22%), *Pseudomonas aeruginosa* (194, 50.13%), and *Klebsiella pneumoniae* (181, 46.77%).

To adjust for confounding, ten selected baseline variables were included in the analysis using multivariable logistic regression. After adjusting for confounding, OP poisoning showed a significantly increased risk of staphylococcal VAP (odds ratio, 2.57; 95% CI, 1.4 to 4.73). The proportion of early-onset VAP was significantly higher in the staphylococcal group as compared to the non-staphylococcal group (62.32% vs. 37.2%; odds ratio, 2.62; 95% CI, 1.51 to 4.56) (Table 2).

Among the different OP compounds, monocrotophos and chlorpyrifos significantly increased the risk of staphylococcal VAP. There were few patients with profenophos, carbofuran, phorate, and dimethoate poisoning and they did not show any statistically significant difference in risk for staphylococcal VAP (Table 3).

There were no significant differences between the duration of mechanical ventilation, length of MICU stay, and duration of mechanical ventilation after VAP diagnosis between the two groups. The staphylococcal VAP group showed a significantly better in-hospital outcome (Table 4).

Table 3. Types of chemical compounds among patients with organophosphorus (OP) poisoning.

Type of OP Poisoning	Staphylococcal VAP (n = 69) (%)	Non-staphylococcal VAP (n = 387) (%)	*p* value
Monocrotophos	9 (13)	21 (5)	0.02
Chlorpyrifos	7 (10)	11 (3)	0.004
Profenophos	3 (4)	5 (1)	0.08
Carbofuran	-	5 (1)	0.34
Phorate	-	4 (1)	0.4
Dimethoate	2 (3)	3 (0.7)	0.12
Unknown	10 (14.5)	19 (5)	0.003

VAP: ventilator associated pneumonia.

Table 4. Comparison of clinical outcomes between staphylococcal and non-staphylococcal VAP groups.

Outcome parameter	Staphylococcal VAP (n = 69)	Non- staphylococcal VAP (n = 387)	*p* value
Duration of ventilatory and inpatient care Median (IQR) in days			
Days of MV after VAP diagnosis	7 (4-10)	7 (4-11)	0.77
Days in ICU	12 (7-18)	13 (9-19)	0.12
Duration of mechanical ventilation	12 (8-17)	12 (9-18)	0.26
In-hospital outcome n (%)			
Discharge from hospital	55 (80)	250 (64.6)	0.007
Death	14 (20)	137 (35.4)	

Outcome parameters were measured in both the groups. Continuous variables were compared by Mann-Whitney U test and categorical variables were compared using Chi-squared test. MV: mechanical ventilation; VAP: ventilator associated pneumonia; ICU: intensive care unit.

Discussion

Our study indicates that OP poisoning is strongly and independently associated with staphylococcal VAP. The association remains strong even after adjusting for potential confounders and established risk factors for staphylococcal infections. We propose that OP-induced bronchorrhea in the background of nasal carriage of *Staphylococcus aureus* could possibly be the most likely mechanism for this association.

About one-third of the patients who were mechanically ventilated for more than 48 hours developed microbiologically confirmed VAP and were included in the study. Compared to the results of studies conducted in western countries on the prevalence of VAP, the proportion of staphylococcal VAP in our study is much less. The proportion of VAP due to MSSA was almost double that of VAP due to MRSA, indicating that the staphylococcal infection was community-acquired. A 2019 study by Feeney *et al.* found 32% of VAP cases to be caused by *S. aureus*, and more than two-thirds were MRSA [11]. However, similar studies conducted in an Indian setting have a staphylococcal prevalence similar to ours, with around 15% of VAP being caused by *Staphylococcus* and nearly half were MRSA [3]. The most common organisms causing VAP were Gram-negative organisms such as *Pseudomonas*, *Acinetobacter*, and members of Enterobacteriaceae similar to studies conducted in various ICU settings [12].

The previously established risk factors for VAP such as age, male predominance, increased duration of mechanical ventilation, poor sensorium, corticosteroids, smoking, reintubation, and chronic diseases (like diabetes mellitus and chronic kidney disease) were all considered for univariate analysis in our study [13,14]. For staphylococcal VAP, the high-risk groups include neurosurgical patients receiving mechanical ventilation, critically ill comatose patients, and patients who did not receive antibiotics before VAP [15,16]. Another well-known risk factor for staphylococcal VAP as well as community-acquired pneumonia (CAP) is prior viral pneumonia, like influenza (H1N1), and COVID-19 [17–19]. Risk factors for MRSA infection include renal failure requiring dialysis, diabetes mellitus, corticosteroid use, and altered mental status. However, in our study, these risk factors did not show an association with staphylococcal VAP, wherein MSSA and MRSA are considered together. We have not studied the other established predictors of MRSA infection, namely, nasal carriage state, prior hospitalization, and the presence of a central venous catheter. Antibiotic use for other indications prior to VAP onset significantly reduced the risk of staphylococcal VAP as these antibiotics would have primarily prevented the development of MSSA-VAP. This contrasts the evidence that prior antibiotic use is a risk factor for the development of MRSA VAP [20]. Since *S. aureus* is a virulent organism, the clinical course of staphylococcal VAP is fulminant and the patient shows rapid deterioration of clinical parameters. This is consistent with our observation that a higher proportion of patients with early-onset VAP had staphylococcal VAP and that the number of days of mechanical ventilation before onset of VAP was shorter in staphylococcal VAP. Most importantly, we identified OP poisoning as an independent predictor of staphylococcal VAP. Other established risk factors significant in the univariate analysis did not show any statistical significance after adjusting for confounding by multivariable logistic regression.

The respiratory tract is the most likely site of origin of *S. aureus* because we did not include patients with other primary staphylococcal foci of infection, such as infective endocarditis, surgical site infection, and central-related bloodstream infection. Nasal carriage of *S. aureus* is quite common in the community, and studies have shown that about 20% of individuals are persistent *S. aureus* carriers and about 30% are intermittent carriers [21]. Also, hospitalized patients are known to develop oropharyngeal colonization with nosocomial flora rapidly and can subsequently manifest lower respiratory tract infections related to these organisms. Most *S. aureus* strains from VAP are derived from the nasal cavity. Oropharyngeal secretions are probably contaminated with *S. aureus* strains from the nasal cavity, and patients tend to aspirate oropharyngeal secretions when consciousness is altered or during intubation, reintubation, and mechanical ventilation [22]. Therefore, the risk of VAP increases with factors that facilitate the movement of oropharyngeal organisms to the lower respiratory tract.

OP poisoning is characterized by cholinergic features that include bronchorrhea. In patients with nasal carriage of *S. aureus*, bronchorrhea may enhance the transmission of *S. aureus* to the lung parenchyma. The time that is taken for staphylococcal VAP onset after poisoning is also consistent with the implication of bronchorrhea in causing staphylococcal VAP. The OP compounds are also known to be directly epitheliotoxic to the tracheal airways, mimicking a situation similar to post-viral bacterial pneumonia [23]. Mucosal damage caused by OP compounds may enhance the attachment and colonization of opportunistic microbes like *S.*

aureus [24]. There is also a possibility of OP compound-mediated damage to the commensal flora of the oral and upper respiratory tract, which may result in dysbiosis favoring colonization with pathogenic microbes like *S. aureus* [25]. Atropine which is given as an antidote for the muscarinic features of OP poisoning may also play a role in the pathogenesis by causing paralysis of the mucociliary ladder. The study has also shown a significant association of increased staphylococcal VAP infection with highly potent OP compounds, namely, monocrotophos and chlorpyrifos. Potent OP compounds would produce a greater degree of bronchorrhea, as well as require a higher dose of atropine causing a greater extent of paralysis of mucociliary ladder.

The possibility of other mechanisms that may increase staphylococcal VAP needs to be considered. The routine decontamination procedures done in poisoning patients, such as the placement of a nasogastric tube for stomach wash, and the frequent neck movement due to atropine delirium, may facilitate the trickling of contaminated oropharyngeal secretions into the lower respiratory tract, leading to VAP. The possibility of OP compounds harboring *S. aureus* and these chemical compounds being selectively detrimental to Gram-negative organisms giving a selective advantage of survival to *S. aureus* were deemed highly unlikely possibilities.

While the Centers for Disease Control and Prevention (CDC) criteria for probable VAP, which has a high specificity, is primarily used for surveillance, the presumptive clinical diagnosis of VAP is often made using mCPIS. The mCPIS is based on five criteria that overlap with the clinical features seen in OP poisoning patients undergoing treatment; namely, atropine fever, leukocytosis, copious airway secretions, impaired oxygenation, and lung infiltrates in chest X-ray due to bronchorrhea. Hence, the diagnosis of VAP in patients with OP poisoning is challenging. In the background of the elusive nature of VAP diagnosis in these patients and an increased risk of staphylococcal VAP, which is often fulminant, we recommend a low threshold to initiate antibiotic therapy for OP poisoning patients who develop oxygen desaturation after 48 hours of mechanical ventilation. Since most of the staphylococcal VAP in these patients was caused by MSSA, we also recommend screening for nasal carriage of staphylococcus especially in these patients, which may help to reduce the empirical use of vancomycin.

Though the duration of inpatient care did not show any significant difference between the two groups, patients with staphylococcal VAP had lower mortality and better in-hospital outcome. This outcome is probably due to early diagnosis and good response to antibiotic therapy despite *S. aureus* being highly virulent. While outcomes of MRSA-VAP are available in the literature, we could not find studies on the outcomes of staphylococcal VAP (MRSA and MSSA). MRSA, compared to non-MRSA VAP, had shorter ICU stay and mechanical ventilation duration, and lower mortality [11,26]. However, when compared with MSSA-VAP, MRSA-VAP was associated with higher disease severity and longer duration of mechanical ventilation, although the mortality was not significantly different between the two [27].

The study included a large sample size (> 400) of patients who developed microbiologically confirmed VAP with mCPIS ≥ 6. A considerable number of patients with a clinical diagnosis of VAP but without isolation of the organism from the endotracheal aspirate were excluded. Though the single-center design limits generalizability, the findings of the study are quite relevant to many developing countries where OP poisoning is quite common. The confounding effect of atropine could not be addressed as all the patients with OP poisoning had received atropine. We could not include the staphylococcal carriage status of our patients, as nasal swabs are not routinely collected upon admission to our MICU. Further multi-centric prospective studies may confirm the findings of this study.

Conclusions

VAP due to *S. aureus* was common in our institution and occurred in just over 15% of patients who developed microbiologically confirmed VAP. While knowledge of the critical risk factors predisposing to staphylococcal VAP might help initiate early appropriate empirical therapy, our study identified OP poisoning as an independent predictor that more than doubles the risk of staphylococcal VAP in MICU patients. A nasal swab for staphylococcal carriage in OP patients at the time of MICU admission may help in making a guided choice of empirical antibiotics to include MRSA coverage in these patients when VAP is clinically suspected.

Funding

This research was supported by the Indian Council of Medical Research - Short-Term Studentship Program (Grant number 2020-03262).

References

1. Safdar N, Dezfulian C, Collard HR, Saint S (2005) Clinical and economic consequences of ventilator-associated pneumonia: a

systematic review. Crit Care Med 33: 2184-2193. doi: 10.1097/01.CCM.0000181731.53912.D9.
2. Davis KA (2006) Ventilator-associated pneumonia: a review. J Intensive Care Med 21: 211-226. doi: 10.1177/0885066606288837.
3. Joseph NM, Sistla S, Dutta TK, Badhe AS, Parija SC (2009) Ventilator-associated pneumonia in a tertiary care hospital in India: incidence and risk factors. J Infect Dev Ctries 3: 771-777. doi: 10.3855/jidc.396.
4. Rakshit P, Nagar VS, Deshpande AK (2005) Incidence, clinical outcome, and risk stratification of ventilator-associated pneumonia-a prospective cohort study. Indian Journal of Critical Care Medicine 9: 211-216. doi: 10.4103/0972-5229.19761.
5. Shorr AF, Tabak Y, Gupta V, Johannes R, Liu LZ, Kollef MH (2004) The burden of methicillin resistant *Staphylococcus aureus* in ventilator-associated pneumonia. Chest 126: 716S. doi: 10.1016/S0012-3692(16)46401-9.
6. Hashemian M, Talaie H, Akbarpour S, Mahdavinejad A, Mozafari N (2016) Central nervous system depressants poisoning and ventilator-associated pneumonia: an underrated risk factor at the toxicological intensive care unit. Iran Red Crescent Medical Journal.18: e30989. doi: 10.5812/ircmj.30989.
7. Kett DH, Cano E, Quartin AA, Mangino JE, Zervos MJ, Peyrani P, Cely CM, Ford KD, Scerpella EG, Ramirez JA, Improving Medicine through Pathway Assessment of Critical Therapy of Hospital-Acquired Pneumonia (IMPACTT-HAP) Investigators (2011) Implementation of guidelines for management of possible multidrug-resistant pneumonia in intensive care: an observational, multicentre cohort study. Lancet Infect Dis 11: 181-189. doi: 10.1016/S1473-3099(10)70314-5.
8. Kalil AC, Metersky ML, Klompas M, Muscedere J, Sweeney DA, Palmer LB, Napolitano LM, O'Grady NP, Bartlett JG, Carratalà J, El Solh AA, Ewig S, Fey PD, File TM Jr, Restrepo MI, Roberts JA, Waterer GW, Cruse P, Knight SL, Brozek JL (2016) Management of adults with hospital-acquired and ventilator-associated pneumonia: 2016 clinical practice guidelines by the Infectious Diseases Society of America and the American Thoracic Society. Clin Infect Dis 63: e61-111. doi: 10.1093/cid/ciw353.
9. Karunarathne A, Bhalla A, Sethi A, Perera U, Eddleston M (2021) Importance of pesticides for lethal poisoning in India during 1999 to 2018: a systematic review. BMC Public Health 21: 1-3. doi: 10.1186/s12889-021-11156-2.
10. Zilberberg MD, Shorr AF (2010) Ventilator-associated pneumonia: the clinical pulmonary infection score as a surrogate for diagnostics and outcome. Clinical Infect Dis 51 Suppl 1: S131-135. doi: 10.1086/653062.
11. Feeney ME, Lindsey DE, Vazquez DE, Porter K, Murphy CV (2019) A risk factor analysis for MRSA ventilator-associated pneumonia to guide empiric therapy in the surgical intensive care unit. J Infect Dis Epidemiol 5: 075. doi: 10.23937/2474-3658/1510075.
12. Hill DM, Schroeppel TJ, Magnotti LJ, Clement LP, Sharpe JP, Fischer PE, Weinberg JA, Croce MA, Fabian TC (2013) Methicillin-resistant *Staphylococcus aureus* in early ventilator-associated pneumonia: cause for concern? Surgical Infections 14: 520-524. doi: 10.1089/sur.2012.166.
13. Wu D, Wu C, Zhang S, Zhong Y (2019) Risk factors of ventilator-associated pneumonia in critically ill patients. Front Pharmacol 10: 482. doi: 10.3389/fphar.2019.00482.
14. Xu Y, Lai C, Xu G, Meng W, Zhang J, Hou H, Pi H (2019) Risk factors of ventilator-associated pneumonia in elderly patients receiving mechanical ventilation. Clin Interv Aging 14: 1027. doi: 10.2147/CIA.S197146.
15. Rello J, Torres A, Ricart M, Valles J, Gonzalez J, Artigas A, Rodriguez-Roisin R (1994) Ventilator-associated pneumonia by *Staphylococcus aureus*. Comparison of methicillin-resistant and methicillin-sensitive episodes. Am J Respir Crit Care Med 150: 1545-1549. doi: 10.1164/ajrccm.150.6.7952612.
16. Rello J, Quintana E, Ausina V, Castella J, Luquin M, Net A, Prats G (1991) Incidence, etiology, and outcome of nosocomial pneumonia in mechanically ventilated patients. Chest 100: 439-444. doi: 10.1378/chest.100.2.439.
17. Morris DE, Cleary DW, Clarke SC (2017) Secondary bacterial infections associated with influenza pandemics. Front Microbiol 8: 1041. doi: 10.3389/fmicb.2017.01041.
18. Kallen AJ, Brunkard J, Moore Z, Budge P, Arnold KE, Fosheim G, Finelli L, Beekmann SE, Polgreen PM, Gorwitz R, Hageman J (2009) *Staphylococcus aureus* community-acquired pneumonia during the 2006 to 2007 influenza season. Ann Emerg Med 53: 358-365. doi: 10.1016/j.annemergmed.2008.04.027.
19. Signorini L, Moioli G, Calza S, Van Hauwermeiren E, Lorenzotti S, Del Fabro G, Renisi G, Lanza P, Saccani B, Zambolin G, Latronico N, Castelli F, Cattaneo S, Marshall JC, Matteelli A, Piva S (2021) Epidemiological and clinical characterization of superinfections in critically ill coronavirus disease 2019 patients. Crit Care Explor 3: e0430. doi: 10.1097/CCE.0000000000000430.
20. Oztoprak N, Cevik MA, Akinci E, Korkmaz M, Erbay A, Eren SS, Balaban N, Bodur H (2006) Risk factors for ICU-acquired methicillin-resistant *Staphylococcus aureus* infections. Am J Infect Control 34: 1-5. doi: 10.1016/j.ajic.2005.07.005.
21. Wertheim HF, Melles DC, Vos MC, van Leeuwen W, van Belkum A, Verbrugh HA, Nouwen JL (2005) The role of nasal carriage in *Staphylococcus aureus* infections. Lancet Infect Dis 5: 751-762. doi: 10.1016/S1473-3099(05)70295-4.
22. Corne P, Marchandin H, Jonquet O, Campos J, Bañuls AL (2005) Molecular evidence that nasal carriage of *Staphylococcus aureus* plays a role in respiratory tract infections of critically ill patients. J Clin Microbiol 43: 3491-3493. doi: 10.1128/JCM.43.7.3491-3493.2005.
23. Hulse EJ, Davies JO, Simpson AJ, Sciuto AM, Eddleston M (2014) Respiratory complications of organophosphorus nerve agent and insecticide poisoning. Implications for respiratory and critical care. Am J Respir Crit Care Med 190: 1342-1354. doi: 10.1164/rccm.201406-1150CI.
24. Tai J, Han MS, Kwak J, Kim TH (2021) Association between microbiota and nasal mucosal diseases in terms of immunity. Int J Mol Sci 22: 4744. doi: 10.3390/ijms22094744.
25. Hanada S, Pirzadeh M, Carver KY, Deng JC (2018) Respiratory viral infection-induced microbiome alterations and secondary bacterial pneumonia. Front Immunol 9: 2640. doi: 10.3389/fimmu.2018.02640.
26. Athanassa Z, Siempos II, Falagas ME (2008) Impact of methicillin resistance on mortality in *Staphylococcus aureus* VAP: a systematic review. Eur Respir J 31: 625-632. doi: 10.1183/09031936.00081007.
27. Zahar JR, Clec'h C, Tafflet M, Garrouste-Orgeas M, Jamali S, Mourvillier B, De Lassence A, Descorps-Declere A, Adrie C, Costa de Beauregard MA, Azoulay E, Schwebel C, Timsit JF (2005) Is methicillin resistance associated with a worse prognosis in *Staphylococcus aureus* ventilator-associated

pneumonia? Clin Infect Dis 41: 1224-1231. doi: 10.1086/496923.

Corresponding author
Dr. Venkateswaran Ramanathan, MD
Department of Medicine, JIPMER, Puducherry.
16, Sixth Cross, Bharathy Nagar, Pondicherry-605008, India.
Tel: 091-9488505555
Email: drvenks@gmail.com

Conflict of interests: No conflict of interests is declared.