

# Clinical usefulness of ventilator associated events in predicting ventilator associated pneumonia

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## Abstract

Ventilator-associated pneumonia (VAP) is the most common nosocomial infection in intensive care unit (ICU) patients. Traditionally the clinical pulmonary infection score (CPIS) has been used in the diagnosis of VAP. There is no firm agreement among critical care and infectious disease specialists regarding the diagnosis of VAP. The aim was to study the association between new conditions, ventilator-associated conditions (VAC) and infection related ventilator-associated complications (IVAC) and VAP and whether if any of these precedes the diagnosis of VAP by CPIS.

A prospective observational study was conducted from January 2014 to 31st March 2014 (IEC ref 2014/226A). Inclusion criteria of our study were patients requiring invasive mechanical ventilation for > 2 calendar days. VAC and IVAC were diagnosed based on Centers for Disease Control and Prevention criteria. VAP was diagnosed using modified CPIS score if the score was > 6.

One hundred consecutive patients were screened for the study. Thirteen patients were excluded. Out of 87 patients, 15 developed VAC of whom 13 developed IVAC, and seven patients developed VAP as per CPIS. Diagnosis of VAC preceded diagnosis of VAP in three patients. No temporal relationship was noted in four patients.

This study has shown significant association between VAC, IVAC and modified CPIS criteria for VAP. From our study, there is a suggestion of VAC preceding the diagnosis of VAP by CPIS criteria. However, this needs further validation from the future studies with a larger number of patients.

**Keywords:** ventilators, complications, associated conditions, ventilator-associated pneumonia, India

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## Introduction

Ventilator-associated pneumonia (VAP) is one of the most serious and common nosocomial infections in the intensive care unit (ICU).<sup>1,2</sup> Development of VAP is associated with increased length of ICU stay and mortality. Timely diagnosis of VAP is important and essential in order to plan further management.<sup>1-4</sup> Traditionally the diagnosis of VAP has been made with the clinical pulmonary infection score (CPIS) criteria.<sup>5</sup> The sensitivity and specificity of CPIS has been questioned. It has been proposed that early diagnosis of VAP may reduce the unfavorable outcomes of patients with VAP in the critical care setting. Also, in certain countries such as the United States, reimbursements for VAP-related expenses are routinely denied by third party insurances as a punitive action.<sup>6,7</sup>

The US Centers for Disease Control and Prevention (CDC) proposed a new surveillance system for VAP, which included ventilator-associated conditions (VAC), infection related ventilator-associated complications (IVAC), and possible and probable pneumonia. These surveillance definitions were suggested by CDC for public reporting and interfacility comparisons, and VAP was used only in internal quality improvement.<sup>5,8,9</sup>

After the development of this new surveillance system there have been many studies trying to evaluate the utility of this newer system of reporting and comparing it with existing CPIS criteria.<sup>10-15</sup>

There are certain changes as per the 2015 CDC update, in which possible and probable VAP are combined into one as against earlier CDC update. There is also specific mention about the list of pathogens excluded as a cause for VAP. Special mention of episodes on mechanical ventilation (EMV), ventilator free days and airway pressure release ventilation (APRV) days.<sup>16,17</sup> For analysis of data these changes were taken into account.

The aim of our study was to evaluate the association between diagnosis of VAC, IVAC and VAP in our subset of patients.

## Materials and Methods

After obtaining institutional ethical committee approval (ref 2014/226A), this study was

conducted in the medical ICU of a tertiary care center (Mazumdan Shaw Medical Centre, Narayana Health, Bangalore) for a period of 3 months (1st January 2014 to 31st March 2014). Inclusion criteria for the study were patients requiring invasive mechanical ventilation support for > 2 calendar days. Patients transferred from other healthcare facilities and patients unlikely to survive > 48 hours were excluded from the study.

VAC was defined as per the CDC guidelines as increase in FIO<sub>2</sub> by 20% or increase in positive end expiratory pressure (PEEP) of 3 cm H<sub>2</sub>O after 2 calendar days of stability. Diagnostic criteria for IVAC included patients with VAC who developed temperature >38°C or <36°C, or WBC count >12000/mm<sup>3</sup> or < 4000/mm<sup>3</sup> and commencement of a new antimicrobial agent(s) and their continuation for >4 calendar days. VAP was diagnosed by modified CPIS score, which includes temperature, leucocyte count, tracheal secretions, oxygenation and chest radiograph findings. The modified CPIS score does not include microbiology or culture as against CPIS score. Patients with modified CPIS score > 6 were diagnosed as having VAP. In our study microbiological data were not included in CPIS calculations. Patients were followed up until ICU discharge.

Statistical analysis was done using STATA 13 (StataCorp, College Station, TX). Continuous variables were expressed as mean  $\pm$  SD (standard deviation) or median IQR (interquartile range). Continuous variables were analyzed by 't' test and categorical variables were analyzed by ' $\chi^2$ ' test. A standard 95% confidence limit and a p value at 0.05 were used for assessing statistical significance.

## Results

One hundred consecutive patients were screened for the study. Out of these 13 patients were excluded (1 patient was transferred to another healthcare facility, 6 patients expired, and 6 patients got extubated within 48 h). Among the baseline characteristics, mean APACHE II score was 20 (SD 6.04) (Table I).

Out of 87 patients, 15 satisfied criteria for diagnosis of VAC, 13 for IVAC, and 7 for VAP by CPIS. Figure 1 shows seven cases of VAP and the day on which VAC, IVAC and VAP diagnosis was made. Diagnosis of VAC

Table I. Baseline characteristics of patients with ventilator-associated condition (VAC), infection-related ventilator-associated complication (IVAC), and ventilator-associated pneumonia (VAP)

Parameter	All Mean (SD)/ Median (IQR) (87)	VAC (15)	NO VAC (72)	P value	IVAC (13)	NO IVAC (74)	P value	VAP (7)	NO VAP (80)	P value
Age	56.01 (15.76)	53.28 (15.21)	56.61 (15.81)	0.47	52.16 (16.20)	56.70 (15.60)	0.35	50.16 (17.67)	56.51 (15.54)	0.34
Gender (Male/ Female)	58/29	8/7	50/22	0.229	7/6	51/23	0.288	5/2	53/27	0.78
APACHE II score	20 (6.04)	21.13 (5.51)	19.76 (6.16)	0.42	21.15 (5.94)	19.79 (6.08)	0.45	18.71 (3.59)	20.11 (6.21)	0.56
Days on Ventilator	5.32 (2.56)	7.57 (3.22)	4.88 (2.18)	*<0.001	8 (3.19)	4.89 (2.18)	*<0.001	8.14 (2.73)	5.07 (2.41)	*0.002
Fio2 on Day1	61.72 (19.30)	68 (20.07)	60.41 (19.02)	0.16	68.46 (21.54)	60.54 (18.79)	0.17	61.42 (20.35)	61.75 (19.34)	0.96
CPIS on day1	4.04 (1.80)	4.73 (1.48)	3.90 (1.83)	0.10	4.92 (1.38)	3.89 (1.83)	0.056	4.57 (1.71)	4 (1.81)	0.42
Lung infiltrate on CXR at admission	34 (39.08)	9 (60)	25 (34.72)	0.068	9 (69.23)	25 (33.78)	*0.016	5 (14.70)	29 (85.29)	0.067
LOS ICU	6.22 (2.90)	8.33 (2.90)	5.87 (2.77)	*0.006	8.8 (2.93)	5.87 (2.74)	*0.002	9.5 (1.87)	5.97 (2.82)	*0.003
28day Mortality	31 (35.63)	13 (86.66)	18 (25)	*<0.001	11 (84.61)	20 (27.02)	*<0.001	5 (71.4)	26 (32.5)	*0.039
Comorbidities										

\*significant p &lt; 0.05

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VAC: ventilator-associated condition; IVAC: infection-related ventilator-associated complication; VAP: ventilator-associated pneumonia; CPIS: Clinical Pulmonary Infection Score; CXR: chest X-ray; LOS: length of stay; ICU: intensive care unit; CVS: cardiovascular disease; RS: respiratory disease; CNS: neurologic disease

Parameter	All Mean (SD)/ Median (IQR) (87)	VAC (15)	NO VAC (72)	P value	IVAC (13)	NO IVAC (74)	P value	VAP (7)	NO VAP (80)	P value
Diabetes	26 (29.88)	2 (13.33)	24 (33.33)	0.124	2 (15.38)	24 (32.43)	0.216	1 (14.28)	25 (31.25)	0.347
CVS	28 (32.18)	2 (13.33)	26 (36.11)	0.086	1 (7.69)	27 (36.48)	*0.04	0	28 (35)	0.057
RS	9 (10.34))	0	9 (12.5)	0.148	0	13 (17.56)	0.184	0	9 (11.25)	0.349
CNS	2 (2.29)	0	2 (2.77)	0.514	0	2 (2.70)	0.54	0	2 (2.5)	0.672
Hepatobiliary	4 (4.59)	1 (6.66)	3 (4.16)	0.674	0	4 (5.40)	0.391	0	4 (5)	0.545
Renal	7 (8.04)	0	7 (9.72)	0.208	0	7 (9.45)	0.248	0	7 (8.75)	0.414
Autoimmune	1 (1.14)	1 (6.66)	0	*0.028	1 (7.69)	0	*0.016	0	1 (1.25)	0.766
Malignancy	6 (6.89)	2 (13.33)	4 (5.55)	0.279	2 (15.38)	4 (5.40)	0.190	0	6 (7.5)	0.453

preceded diagnosis of VAP by two days in one patient (case no.5), and by three days in another patient. In one patient (case no.4), VAC preceded VAP by five days (case no.6). Among four patients (cases no. 1,2,3,7) no temporal association was noted between VAC and VAP, as shown in Figure 1. Baseline mortality was around 31%. Patients who developed VAC, IVAC or VAP had higher mortality and more ventilator days (Table I).

Among 13 patients with IVAC, 11 patients were classified as pneumonia. One patient who satisfied the criteria for IVAC was subsequently diagnosed as tumor lysis syndrome. In two patients diagnosed as IVAC by CDC classification, diagnosed as VAP as per the CPIS, lung infiltrates were not present on chest X ray and

hence should accurately be diagnosed as ventilator associated tracheobronchitis (VAT) (Figure 2).

Fisher's exact test was performed to look for the association between VAC, IVAC and VAP. There was a statistically significant association among VAC and VAP,  $\chi^2 (1) 36.54, p < 0.001$  and among IVAC and VAP,  $\chi^2 (1) 43.33, p < 0.001$ . Among 15 VAC patients 7 developed VAP (46.66%), and among 13 IVAC patients 7 developed VAP (53.84%) (Table II, III).

### Discussion

This prospective observational study has shown significant association between VAC, IVAC and VAP. The incidence of VAC was 17.24%. Out of 15 patients with VAC, 13 (86.66%) developed IVAC and 7 patients

**Table II. Association between ventilator-associated condition (VAC) and ventilator-associated pneumonia (VAP)**

VAC: ventilator-associated condition; VAP: ventilator-associated pneumonia; 0 = absent, 1 = present

VAC	VAP 0	VAP 1	Total
0	72	0	72
1	8	7	15
	80	7	87

P=\*<0.001

\*significant p < 0.05

**Table III. Association between infection-related ventilator-associated complication (IVAC) and ventilator-associated pneumonia (VAP)**

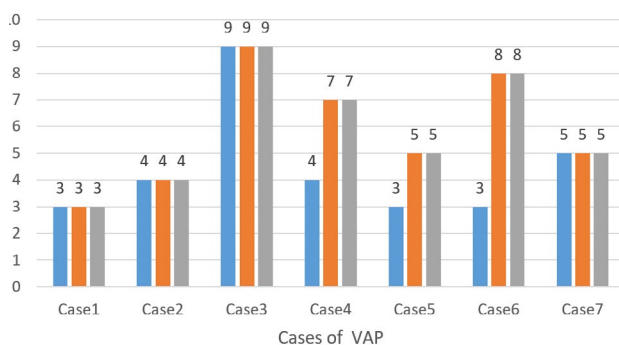
IVAC	VAP 0	VAP 1	Total
0	74	0	74
1	6	7	13
	80	7	87

P=\*<0.001

IVAC: infection-related ventilator-associated complication; VAP: ventilator-associated pneumonia; 0 = absent, 1 = present

\*significant p < 0.05

**Figure 1. Timeline of ventilator-associated condition (VAC), infection-related ventilator-associated complication (IVAC), and ventilator-associated pneumonia (VAP)**



developed VAP (46.66%). In our study there was a higher incidence of VAC and IVAC as compared with the meta-analysis data of Boyer's study.<sup>13,14</sup>

The diagnosis of VAP in the ICU can be quite challenging. Historically chest X-ray was used initially to diagnose VAP. The study by Wunderink *et al* showed that there was no good correlation between radiological signs of pneumonia with autopsy findings.<sup>18</sup> The major limitation for using X-ray is that it has nonspecific findings and abnormalities may not accurately reflect infection as a cause of X-ray abnormalities. There can also be inter-observer variability. Diagnosis by clinical signs and symptoms such as fever, leukocytosis can also nonspecific. Evaluation of different scoring systems has not reached any consensus in the critical care field.<sup>12</sup>

The routine CPIS score which comprises of different parameters such as fever, leukocytosis, radiological, tracheal aspirate, oxygenation and microbiology, is associated with variable sensitivity and specificity as reported in the different studies.<sup>6,7</sup> The modified CPIS score which excludes microbiological data is also shown to have limitations.<sup>6,7</sup>

One study comparing CPIS vs. CDC criteria for different facets of VAP showed no clear advantage either in terms of reliability or specificity. Hence CDC criteria in the diagnosis of VAP has been used for surveillance purposes only.<sup>11</sup>

A multi-center study showed high predictive accuracy for ventilator associated events (VAE) with respect to

tracheobronchitis but not VAP. It also showed that a differentiation between tracheobronchitis and VAP is essential as there is a significant difference in the mortality between the two conditions.<sup>15</sup> Results of this study were consistent with the meta-analysis data by Yunzhou Fan *et al.*, which showed VAE could not accurately and consistently detect cases of VAP.<sup>13</sup>

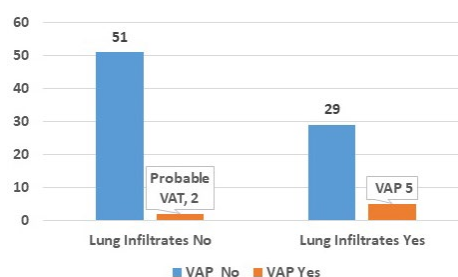
In our study, two patients with VAP who had no new lung infiltrates can be classified as VAT who survived, as compared with five patients with VAP who died. In our study more severe VAP cases were captured with compromised oxygenation for > 24hr as reflected by serial CPIS.

There were certain limitations to our study. It was a single center study. Results of the statistical analysis on our data should be taken in the context of low number of patients studied. In the exclusion criteria, we excluded patients who died or extubated within 48hrs. Ideally the cut off should have been 96 hours to correctly identify VAE episodes.<sup>13</sup>

However, the present study did find a statistically significant association between VAE and 28-day mortality. These results were in accordance with study by Boyer *et al.*<sup>14</sup> Possible reason for such results could be use of ultrasonography was already in place and that could have minimized interobserver variation in interpreting CXR findings, although use of ultrasonography was not a part of study methodology.

The CDC criteria for diagnosis of VAE could alert the possibility of developing IVAC. VAE is a useful tool for surveillance purposes but cannot be used for diagnosis of VAP. In our opinion the modified CPIS score is still useful in the diagnosis of VAP. Nonetheless it is important to recognize these

**Figure 2. Lung infiltrates and ventilator-associated pneumonia (VAP)**





two conditions as there is a correlation between them and 28-day mortality. There are reasons why CDC classification of VAE is not recommended for the diagnostic purposes of ventilator associated infection. VAE can be due to multiple causes such as atelectasis, pulmonary edema, pulmonary embolism, acute respiratory distress syndrome, pneumothorax and sepsis. In most cases it can be said that IVAC can identify the infective cause for VAE but the criteria including the presence of fever, change in WBC count and antibiotic change could be secondary to multiple other causes in ICU.<sup>19</sup> Diagnosis by the modified CPIS as well as VAC have certain limitations. The CPIS score can be elevated when a patient gets admitted with community acquired pneumonia and later develops VAP. The timing of this complication then becomes difficult. Similarly, with regard to VAC it must be said that IVAC identifies only severe cases of VAP with compromised oxygenation for two calendar days and may miss less severe VAP. IVAC does not differentiate between VAP and VAT, as the management and prognosis are perhaps different. The higher mortality associated with VAE reported in the literature is again shown in our current study.<sup>20, 21</sup>

### Conclusions

Our study has shown a statistically significant association between VAE and VAP. The results of our study need to be validated by larger multi-center studies.<sup>20-22</sup> Looking at recent studies use of VAE for surveillance itself is questionable and needs modifications.

### Declarations

Ethics approval and consent to participate- This study was approved by Institutional Ethics Committee, ref no. (2014/226A).

Consent for publication- Not applicable

Availability of data and material- Data are available from the authors upon reasonable request

Competing interest- The authors declare that they have no competing interest

Funding- Not applicable

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