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**Original Article**

# Spectrum of Early Onset and Late Onset Ventilator Associated Pneumonia (VAP) in a Tertiary Care Hospital of Bangladesh: A Prospective Cohort Study

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**Abstract**

***Objective :*** *To compare the outcome of critically ill patients developing early onset Ventilator-associated pneumonia (VAP) occurring within 96 h of ICU admission and late onset VAP occurring after 96 h of ICU admission in critically ill patients admitted in the ICU of BIRDEM General Hospital of Bangladesh.*

***Study Design:*** *Prospective cohort study.*

***Material and Methods:*** *Study data obtained over a period of 24 months (July 2012 - June 2014) in the ICU of a tertiary care hospital was prospectively analyzed. Subjects were classified by ventilator status: early onset VAP (< 96 hrs of mechanical ventilation) or late-onset VAP (≥96 hrs of mechanical ventilation). Baseline demographics and bacterial etiology were analyzed according to the spectrum of status of VAP.*

***Results:*** *The incidence of VAP was 35.73 per 1,000 ventilator days. In our study 52% of the cases were early-onset VAP, while 48% were late-onset VAP. Acinetobacter was the commonest organism isolated from late-onset VAP (p = 0.029) while Pseudomonas was the commonest isolates obtained from early-onset VAP (p = 0.046). Klebsiella, MRSA and E. coli were almost identically distributed between groups (p > 0.05). There is significant difference of sensitivity pattern of Acinetobacter baumannii and pseudomonas aeruginosa in both early and late-onset VAP (p=0.01). The overall mortality rate in our study was 44%. The mortality was significantly higher in the late-onset VAP (62.5%) than that in the early-onset VAP (26.9%) (p=0.011).*

***Conclusion:*** *From this study we conclude that late-onset VAP had poor prognosis in terms of mortality as compared to the early-onset type. The higher mortality in the late-onset VAP could be attributed to older age, higher co-morbidities like diabetes mellitus, COPD and CKD. The findings are similar to findings of other international studies.*

***Key words:*** *Ventilator associated pneumonia, Mechanical Ventilation, Endotracheal tube.*

## Introduction

Ventilator-associated pneumonia (VAP) is defined as pneumonia that occurs 48–72 hours or thereafter following endotracheal intubation, characterized by the presence of a new or progressive infiltrate, signs of systemic infection (fever, altered white blood cell count), changes in sputum characteristics, and detection of a causative agent.[1,2] VAP contributes to approximately half of all cases of hospital-acquired pneumonia.[1,2] It is the second most common nosocomial infection in the intensive care unit (ICU) and the most common in mechanically ventilated patients.[3,4] The VAP incidence ranged from 10 to 41.7 per 1000 ventilator-days in different developing countries.[1,4] Risk for VAP is greatest during the first 5 days of mechanical ventilation (3 %) with the mean duration between intubation and development of VAP being 3.3 days.[1,2,5] This risk declines to 2 %/day between days 5 to 10 of ventilation, and 1 %/day thereafter.[1, 6] Earlier studies placed the attributable mortality for VAP at between 33–50 %, but this rate is variable and relies heavily on the underlying medical illness.[1, 2] Early-onset VAP is defined as pneumonia that occurs within 4 days of endotracheal intubation and MV and this is usually attributed to antibiotic sensitive pathogens whereas late-onset VAP is more likely caused by multidrug resistant (MDR) bacteria and emerges after 4 days of intubation.[1,2,3] The diagnosis of VAP in the ICU remains a challenge. Difficulties encountered by physicians are mainly explained by the absence of a gold standard for this diagnosis. Usually, the MV diagnostic approach is based on two successive steps: (a) the diagnosis of pneumonia must be

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established and (b) the etiologic pathogen(s) of this pulmonary parenchymal infection must be identified. Clinical suspicion of pneumonia with a new or progressive chest radiographic infiltrates after 48 hrs in patients on mechanical ventilation and one of the following characteristics[7,8]. Temperature > 38.3°C or < 36°C, leucocytosis > 12000/cmm or leucopenia < 4000/cmm, purulent respiratory secretions with gram stain demonstration of bacteria and polymorphs, quantitative positive culture of endotracheal aspirate ≥ $10^5$ colony forming units (CFU)/ml[9] or, positive culture of Bronchoalveolar lavage ≥ $10^4$ CFU/ml[10] or positive culture of protected specimen brush ≥ $10^3$ CFU/ml.[11,12] However, those who had other cause for the radiological infiltrates like pulmonary embolism, pulmonary hemorrhage, atelectasis, CCF and ARDS were excluded.

Over many years, experts have discussed the best means to diagnose VAP. Some have preferred a clinical strategy based on radiologic, clinical, and biologic signs previously described; this approach is now considered overly sensitive. Other experts preferred a bacteriologic strategy based on a positive quantitative culture of lower respiratory tract secretions to define both pneumonia and the causative pathogen(s); this approach is now considered insufficiently sensitive, especially in patients in whom an antimicrobial treatment was recently started or changed[1]. The recent Infectious Diseases Society of America (IDSA) /American Thoracic (ATS) Society guidelines propose a "mixed" diagnostic strategy. Accordingly the diagnosis of VAP is suspected in the presence of a new or progressive pulmonary infiltrate associated with at least two of the following three infectious signs: fever greater than 38°C, leukocytosis or leucopenia, and/or purulent secretions. For patients with ARDS, radiographic changes are difficult to analyze; consequently, hemodynamic instability and/or deterioration of blood gases could be considered sufficient to suspect VAP[1].

**Methodology**

**Study design:** This study was a Prospective cohort study.

**Study population**

This study was carried out in department of Critical Care Medicine, BIRDEM General Hospital, Bangladesh, from July 2012 to June 2014. A total 609 patients was admitted in ICU during above-mentioned study period. Out of them 301 were on mechanical ventilator for more than two days and 61 of them fulfilled the criteria of VAP. Of them 50 subjects met the inclusion criteria (described below) and hence were enrolled in the study. The patients who developed VAP and met the inclusion criteria within 96 hours of endotracheal intubation and mechanical ventilation were categorized as early onset VAP. The patients who developed VAP and met the above criteria after 96 hours of endotracheal intubation and mechanical ventilation were categorized as late onset VAP.

**Inclusion criteria**

1. Age >18years
2. Subjects who developed new or progressive radiological infiltrates 48 hrs after mechanical ventilation & at least 2 of the followings:
   (a) Temperature>38.3 °C or <36 °C.
   (b) Leucocytosis (>12000/cmm) or Leucopenia (<4000/cmm)
   (c) Purulent respiratory secretions.
   (d) Quantitative blind endotracheal aspirate cultures with growth ≥$10^5$ cfu/ ml.

**Exclusion criteria**

1. Age <18years
2. Patients who had pneumonia on admission or within 48hrs of endotracheal intubation
3. Other causes of radiological infiltrates like malignancy, Pulmonary TB, pulmonary embolism, atelectasis, chemical pneumonitis, asymmetric cardiac pulmonary edema, cryptogenic organizing pneumonia, pulmonary contusion, pulmonary hemorrhage, drug reaction, and asymmetric ARDS.
4. Patients in ICU transferred to inpatient and then re-admitted in ICU requiring mechanical ventilation.
5. Patients admitted to ICU with diagnosis of pneumonia or had any infiltrations in the chest X-ray at the time of ICU admission.
6. Patients who were discharged out of ICU before extubation were also excluded from study.

**Clinical Procedures and follow up investigations**

VAP was diagnosed as per CDC criteria.[2] The diagnosis of pneumonia required a consensus between the attending intensivists, radiologists and clinical microbiologist. Pneumonia was considered ventilator associated when its onset occurred at no sooner than 48 hours following intubation and was judged not to have been incubating at the time of intubation.

Chest X-ray was done at the time admission and repeated every day. When there is infiltrate in chest X-ray, then the patients were evaluated for the presence of inclusion criteria of VAP and when the patients met the inclusion criteria of VAP were included in this study. Lower respiratory tract cultures were obtained by blind tracheal aspiration and were performed for three consecutive days after radiological infiltrate was noted in all patients intubated and ventilated for more than 48 hrs, and upon suspicion of VAP. Gram stain was performed in all cases. Bacterial counts were estimated semi-quantitatively. Bacterial identification and susceptibility testing were done by standard methods, recommended by the National Committee for Clinical Laboratory Standards.

Investigations were done as routine basis on the first day of diagnosis of VAP and included the followings: Blood for total count, differential count, ESR and hemoglobin percentage (Hb%), X-ray chest portable, Blood sugar, liver function tests (Bilirubin, SGPT, SGOT, Alkaline phosphatase, GGT, albumin), renal function tests (Blood urea, serum creatinine), coagulation profile and arterial blood gas analysis.

Endotracheal aspirate (ETA) was collected under aseptic precautions using sterile suction catheters and traps. Once

specimens were obtained, the sample was sent for Gram stain, culture and sensitivity. The Gram stain was expected to provide crucial initial clues to the type of organism(s) and whether or not the material is purulent (defined as ≥ 25 neutrophils and ≤ 10 squamous epithelial cells per low power field[1]. Culture results can be reported as semi-quantitative and/or quantitative values. Semi-quantitative values obtained by endotracheal sampling are considered positive when the agar growth is moderate (+++) or heavy (++++), while quantitative positivity is defined as ≥ $10^5$ colony forming units per ml (cfu/ml). Exact speciation of pathogen bacteria and their sensitivity to antibiotics took a few days. The presence of epithelial cells of > 10% implied contamination of the specimen whilst <10% neutrophils suggested that the diagnosis of pneumonia was less likely. With quantitative analysis of ETA, threshold for diagnosis of pneumonia in this study was taken as $10^5$ cfu/ml.

**Data collection**

We prospectively collected data on all patients who received endotracheal intubation and mechanical ventilation for more than 48 hours. From each study subject the following data were collected from ICU admission sheet: name, age, gender, hospital number, primary diagnosis, date of admission in hospital and ICU. Baseline characteristics which included age, gender, admitting diagnosis, prior antibiotic exposure, APACHE II score on admission duration of mechanical ventilation, ICU stay, and onset of VAP were noted. Detailed history of the patients' illness, examination findings and relevant investigations findings were recorded on a semi-structured questionnaire.

The relevant data were recorded from medical records, bedside flow sheets, radiographic reports, and reports of microbiological studies of the patients.

Outcome measures: Study patients who met inclusion criteria were recruited consecutively. They were monitored every day following the development of VAP using clinical and microbiological criteria until either discharged from ICU after resolution of pneumonia or until death while in the hospital. Patients who were transferred from ICU after extubation or resolution of pneumonia were declared as survived. Patients who died in ICU before resolution of VAP were considered as non-survival.

**Statistical Analysis**

Data were processed and analyzed using SPSS (Statistical Packages for Social Sciences) software version 17. While categorical variables were expressed as frequency and corresponding percentage, continuous variables were described as mean and standard deviation from the mean. Categorical data were compared between groups using Chi-square or Fisher's Exact Test and continuous data were compared between groups using Unpaired t-Test. Level of significance was set at 0.05 and p <0.05 was considered significant.

The VAP rate was expressed as episodes per 1000 ventilator days as per the National Healthcare Safety Network (NHSN) definitions.[25] It is calculated as equivalent to [(Total number of VAP patients ÷ Total Ventilator days of all patients) × 1000]

**Results**

301 patients were on mechanical ventilation for more than two days during the study period. Of them 61 developed VAP giving a 20.2% incidence of VAP. Of the 61 VAP patients, 50 met the inclusion criteria for the study. 26 (52%) subjects were diagnosed as early-onset and 24 (48%)) were found to be late-onset VAP.

The general characteristics of the cohort are shown in Table I.

The late onset VAP subjects had higher incidence of co morbid conditions like diabetes mellitus, COPD, and chronic kidney disease when compared to the early-onset VAP subjects (Table II).

Table III shows that in late-onset VAP Acinetobacter baumannii was the commonest causative organism (p = 0.029) while in early-onset VAP, Pseudomonas aeruginosa was the commonest causative organism (p = 0.046). Klebsiella pneumonia was identically distributed between them.

The antibiotic sensitivity pattern of the various etiological agents of early-onset VAP and late-onset VAP are summarized in Table-IV. There is significant difference of sensitivity pattern of Acinetobacter baumannii and Pseudomonas aeruginosa in both early and late-onset VAP. The Acinetobacter spp. causing early-onset VAP and late-onset VAP were all sensitive to colistin.

Table V shows significant difference of outcome between both types of VAP. Outcome of early-onset VAP is better than late-onset (P =0.011).

**Table-I : Comparison of baseline characteristics between types of VAP**

| Baseline characteristics | Types of VAP | | p-value |
|---|---|---|---|
| | Early-onset (n =26) | Late-onset (n =24) | |
| **Age (Years)** | | | |
| <40 | 5(19.2) | 2(8.3) | |
| 40 – 60 | 15(57.7) | 10(41.7) | |
| >60 | 6(23.1) | 12(50.0) | |
| Mean ± SD | 55.5 ± 8.4 | 65.4 ± 9.6 | <0.001 |
| **Sex** | | | |
| Male | 14(53.8) | 16(66.7) | 0.355 |
| Female | 12(46.2) | 8(33.3) | |
| Onset of VAP (days) | 3.4 ± 0.6 | 7.5 ± 1.4 | <0.001 |
| Smoking | 4(16.7) | 7(26.9) | 0.298 |
| Prior antibiotic exposure | 22(91.7) | 24(92.3) | 0.664 |
| APACHE II score on admission | 20.1± 4.1 | 21.7 ± 5.4 | 0.373 |
| Duration of M/V(days) before developing VAP | 7.61± 4.77 | 13.00± 5.78 | < 0.001 |
| ICU stay (days) | 10.5 ± 2.3 | 17.2 ± 4.8 | < 0.001 |
| Incidence of VAP (both early & late-onset)[#] | 35.73 | | |

[#]Incidence of VAP is calculated as per 1,000 ventilator days

**Table-II : Comparison of co-morbidities between types of VAP**

| Co morbidities | Types of VAP | | p-value |
|---|---|---|---|
| | Early-onset (n = 26) | Late-onset (n = 24) | |
| Diabetes mellitus | 12 | 18 | 0.038 |
| COPD | 5 | 10 | 0.037 |
| Bronchial asthma | 3 | 7 | 0.114 |
| CKD | 11 | 16 | 0.047 |

**Table-III : Comparison of growth of organisms in first sample of endotracheal aspirate**

| Growth of organisms | Types of VAP | | p-value |
|---|---|---|---|
| | Early-onset (n = 26) | Late-onset (n = 24) | |
| Acinetobacter baumannii | 10 | 16 | 0.029 |
| Pseudomonas aeruginosa | 11 | 5 | 0.046 |
| Klebsiella pneumoniae | 4 | 4 | 0.601 |
| MRSA | 1 | 3 | 0.275 |
| Escherichia coli | 1 | 3 | 0.275 |

**Table-IV: Antibiotic sensitivity (positivity) pattern in the first sample of tracheal aspirate in early & late VAP:**

| Organisms | Colistin | | Carbapenam | | Pipera/Tazo | | Netlimicin | | Amikacin | | Vancomycin | | Ceftazidime | | Ceftriaxone | | Ciprofloxacin | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Early-onset VAP | Late-onset VAP | Early-onset VAP | Late-onset VAP | Early-onset VAP | Late-onset VAP | Early-onset VAP | Late-onset VAP | Early-onset VAP | Late-onset VAP | Early-onset VAP | Late-onset VAP | Early-onset VAP | Late-onset VAP | Early-onset VAP | Late-onset VAP | Early-onset VAP | Late-onset VAP | p-value |
| *Acinetobacter baumannii*(n=26) | 16 | 10 | 14 | 11 | 11 | 10 | 11 | 5 | 12 | 8 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0.01 |
| *Pseudomonas aeruginosa*(n=15) | 11 | 4 | 8 | 4 | 10 | 5 | 8 | 5 | 7 | 4 | 0 | 0 | 4 | 2 | 0 | 0 | 2 | 1 | 0.01 |
| *Klebsiella pneumoniae*(n=8) | 4 | 4 | 4 | 2 | 4 | 3 | 2 | 1 | 2 | 2 | 0 | 0 | 1 | 2 | 0 | 0 | 2 | 3 | 0.13 |
| *MRSA*(n=4) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 3 | 0 | 0 | 0 | 0 | 0 | 0 | 0.52 |
| *Escherichia coli*(n=4) | 1 | 3 | 1 | 3 | 1 | 2 | 0 | 1 | 1 | 2 | 0 | 0 | 1 | 2 | 0 | 0 | 1 | 1 | 0.47 |

**Table-V : Outcome of VAP**

| Outcome | Types of VAP | | p-value |
|---|---|---|---|
| | Early-onset (n = 26) | Late-onset (n = 24) | |
| Non-survival | 7(26.9) | 15(62.5) | 0.011 |
| Survival | 19(73.1) | 9(37.5) | |

## Discussion

Ventilator-associated pneumonia (VAP) is an important nosocomial infection among ICU patients receiving mechanical ventilation (MV). In this prospective cohort study, we compared patients with early VAP with those with late VAP. Generally, the incidence of VAP varies according to the applied diagnostic criteria and to the type of ICU. The incidence of VAP (35.73 per 1,000 ventilator days) in our study was approximately similar to another Indian study.[18] The incidence of VAP ranged from 10 to 41.7 per 1000 ventilator-days in different developing countries.[13]. But in other Asian countries the incidence rate is relatively lower, ranging from 9 to 12 per 1,000 ventilator days.[19-21]

Our study shows that patients in the age group of 40-60 years were more prone to develop VAP and this was found in accordance with earlier studies.[25] The incidence of VAP was more in males (60%) compared to females (40%) which was similar to studies conducted by Sharma et al.[24]

Non-fermenters such as Pseudomonas spp. and Acinetobacter spp. were significantly associated with late-onset VAP as it was observed by other workers.[14] But in our study even in patients with early-onset VAP, Acinetobacter spp. was the most common pathogen which is similar to a Indian study done by Joseph et al[22]. Our study showed that Pseudomonas aeruginosa was the commonest organism in early VAP (42.3%), and in late VAP Acinetobacter baumannii was the commonest organism (66.7%), isolated in tracheal aspirate culture. Dandagi (2006) showed Klebsiella pneumoniae to be the most common organism isolated in tracheal aspirate culture of the VAP patients[15] Kumar et al.[26] showed pseudomonas to be the most common organisms for both early and late VAP isolated in tracheal aspirate culture. The information on types of pathogens causing VAP in different ICU settings will guide the administration of appropriate empirical antibiotics for treatment of the infection. We observed that colistin is highly active against Acinetobacter spp. while piperacillin-tazobactam has good activity against Pseudomonas spp. But as we have studied only a small number of isolates, these findings need to be further confirmed by larger clinical trials, as they may have a major impact on the treatment of these VAP pathogens.

In our study late onset VAP had poor prognosis in terms of mortality (62.5%) as compared to the early VAP (26.9%), which is statistically significant (P=0.011) [Table 5]. A study done by Gadani et al.[16] showed mortality in late VAP (66%) and mortality of early VAP (20%). The higher mortality in the late VAP in our study could be attributed to older age, higher co-morbidities like diabetes mellitus, COPD and CKD.

Microbiological investigation of VAP is of great importance for developing appropriate antimicrobial therapy and for standardizing emperical therapies to be used in future guidelines. This is because the local susceptibility profile of bacteria commonly associated with the disease would already be known. In this context, the culture of tracheal aspirate has similar efficacy for diagnosis compared with invasive techniques like bronchoalveolar lavage and a protected specimen brush. It is also a simpler and less expensive technique[17].

Our study had several limitations. As our study hospital is primarily a diabetic hospital, critically ill patients complicated by preexisting diabetes usually referred to the ICU of this

hospital, thereby unduly increasing the prevalence of diabetes in ICU patients. Only small numbers of patients with VAP in a single center were studied. We recognize that the findings of this study may not necessarily reflect the scenarios of VAP in other centers in Bangladesh. Hence, we suggest further multi-centered studies with larger patient population to confirm our findings.

## Conclusion

From the findings it can be concluded that late VAP had poor prognosis in terms of mortality (62.5%) as compared to the early type (26.9%). The higher mortality in our study in the late VAP could be attributed to older age, higher co-morbidities like diabetes mellitus, COPD and CKD. In our study there is significant difference of sensitivity of Acinetobacter spp. and pseudomonas spp. between early and late-onset of VAP. Acinetobacter spp. positivity are higher in the late onset VAP and pseudomonas spp. are more so in early-onset VAP.

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