Outcome of ventilator-associated pneumonia: Impact of antibiotic therapy and other factors

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RESEARCH

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Abstract

Background

Ventilator-associated pneumonia (VAP) is the most frequent infection in patients intubated for longer than 48 hours. There is a great interest in determining the factors influencing the outcome of VAP, as it may help in reducing the associated morbidity and mortality. This study aimed to determine the impact of appropriate antibiotic therapy based on endotracheal aspirate cultures on the outcome of VAP. We have also studied the other factors that may influence the outcome of VAP.

Method

A cohort study was conducted in the intensive care units of a tertiary care hospital in South India over a period of 15 months.

The outcome of VAP was assessed by prolongation of the duration of mechanical ventilation and/ or death of the patient.

Results

The duration of mechanical ventilation was significantly prolonged in patients with VAP (16.61 ± 8.2 d vs. 8.21 ± 5.9 d, $P < 0.0001$). VAP patients receiving partially or totally inappropriate therapy (defined as lack of coverage of one or all the significant VAP pathogens) were at significantly high risk for death (Relative risk, 2.00; 95% confidence interval, 1.14 to 3.52; P 0.0008). A delay of > 2 days in administering the first dose of appropriate antibiotic therapy significantly prolonged the duration of ventilation ($P < 0.0001$). Infection by multi-drug resistant pathogens, polymicrobial infection and time of onset of VAP did not have significant impact on the outcome of VAP.

Conclusion

Early administration of appropriate antibiotic therapy, based on the antibiogram of the VAP pathogens identified by quantitative culture of endotracheal aspirate, could lead to an improved outcome of patients with ventilator-associated pneumonia.

Key Words

Ventilator-associated pneumonia; appropriate therapy; quantitative culture; outcome

Background

Ventilator-associated pneumonia (VAP) is the most frequent intensive-care-unit (ICU)-acquired infection, occurring in patients intubated for longer than 48 hours. It is defined as pneumonia occurring more than 48 hours after the initiation of endotracheal intubation and mechanical ventilation (MV).[1] The incidence of VAP ranges from 6 to 52% and can reach 76% in some specific settings.[2] The mortality rates for VAP range from 20% to 76% in various studies.[3,4] In a retrospective matched cohort study using data from a large US inpatient database patients with VAP had a significantly prolonged duration of MV (14.3 days vs. 4.7 days), ICU stay (11.7 days vs. 5.6 days), and hospital stay (25.5 days vs. 14.0 days).[5]

Because of the large disease burden and the resultant attributable morbidity and mortality, there is a great interest in determining the factors influencing the outcome of VAP, which may help in reducing the morbidity and mortality associated with this complication.[6]

Although empirical administration of broad-spectrum antibiotics decreases the risk of early-onset VAP due to antibiotic susceptible bacteria, it predisposes to subsequent colonisation and infection with multidrug-resistant (MDR) pathogens resulting in late-onset VAP.[3,4,7]

Therefore, this study was aimed at determining the impact of appropriate antibiotic therapy (based on endotracheal aspirate cultures) on the outcome of VAP. We have also studied the other factors that may potentially influence the outcome of VAP.

Method

Setting and subjects

A cohort study was conducted in the departments of Microbiology, Medicine and Anesthesiology & Critical Care of a tertiary care hospital. During a period of 15 months (October 2006 to December 2007), all the adult patients on mechanical ventilation (MV) for > 48 hours in Medicine Intensive Care Unit (MICU) and Critical Care Unit (CCU) were included in this study. Patients with pneumonia prior to MV or within 48h of MV were excluded. Endotracheal aspirate cultures were done on the first and second day of MV to detect pneumonia prior to MV.

Study design and data collection

All the patients included in this study were monitored at frequent intervals (every third day) for the development of VAP using clinical and microbiological criteria until discharge or death. The relevant data such as age, gender, primary diagnosis, details of antibiotic therapy was recorded from medical records, bedside flow sheets, radiographic reports, and reports of microbiological studies of the patients.

Definitions

VAP was diagnosed in those patients who fulfilled both the clinical and microbiological criteria. The criteria were: Clinical criteria - Modified clinical pulmonary infection score (CPIS) > 6 (Table 1);[8] Microbiological criteria - Positive Gram stain (>10 Polymorphonuclear cells/ low power field and ≥ 1 bacteria/ oil immersion field with or without presence of intracellular bacteria) and quantitative endotracheal aspirate culture showing ≥ 10^5 cfu/ ml.[2,9,10] VAP occurring within the first four days of MV was classified as early onset and VAP developing five or more days after initiation of MV was classified as late onset.

The quantitative culture results were informed to the treating physicians and they were not blinded, as the culture results might aid them in choosing appropriate antibiotics for the patients. However, the choice of antibiotics for the treatment of VAP patients was left to their discretion. The physicians treated the patients on an individual basis using a combination of the American Thoracic Society (ATS) strategy, surveillance cultures, presence of risk factors for MDR pathogens, and their knowledge of the local microbial flora in the ICU and their antibiograms.

Appropriate therapy was defined as coverage of all the significant VAP pathogens (≥ 10^5 cfu/ ml) isolated from endotracheal aspirate, by the antimicrobial therapy administered at the onset of VAP, determined by the sensitivity pattern of the isolate. Partially inappropriate therapy was defined as lack of coverage of one of the significant VAP pathogens (≥ 10^5 cfu/ ml) isolated from endotracheal aspirate, by the antimicrobial therapy administered at the onset of VAP, based on the sensitivity pattern of the isolate. Inappropriate therapy was defined as lack of antibiotic coverage of all the significant VAP pathogens (≥ 10^5 cfu/ ml) isolated from endotracheal aspirate, based on the sensitivity pattern of the isolate.

Impact of various factors on the outcome of VAP was assessed by prolongation of the duration of MV and/ or death of the patient.

Ethics

This study was approved by the institute research and ethical committees and informed consent was obtained from the patient's next of kin.

Statistics

Results were expressed as mean± SD. The chi-square test or Fisher's exact test was used to compare patients without VAP to patients with VAP. Univariate analysis was used to compare the variables for the outcome groups of interest (patients with VAP vs. patients without VAP, etc), using statistics software (SPSS 16.0, SPSS Inc, Chicago, Illinois). Comparisons were unpaired and all tests of significance were 2-tailed. Continuous variables were compared using Student's *t*-test for normally distributed variables. All *P* values < 0.05 were considered statistically significant.

Results

Over the 15-month study period (October 2006 to December 2007), a total of 200 patients admitted to the ICUs were prospectively evaluated. Of these patients, 36 (18%) developed VAP during their ICU stay. Twenty-one patients (58.3%) had late-onset VAP, while 15 (41.7%) had early-onset VAP. The characteristics of the patients with and without VAP are summarised in Table 2.

Pseudomonas aeruginosa (21.3%) and *Acinetobacter baumannii* (21.3%) were the most common Gram negative bacteria associated with VAP and *Staphylococcus aureus* (14.9%) was the most common Gram positive bacteria among patients with VAP. In 10 (27.8%) VAP cases, more than one pathogen was isolated. *Acinetobacter baumannii* was the most common VAP pathogen associated with mortality, accounting for 37.5% of deaths. *Pseudomonas aeruginosa, Providencia* spp., MRSA, *Candida* spp. (Non-albicans), *Staphylococcus aureus* were the other pathogens associated with mortality. Of the 36 patients with VAP, 10 (27.8%) had polymicrobial infection. Twenty-nine patients were infected with MDR pathogen, while seven were infected with other micro-organisms.

Table 1: Modified Clinical Pulmonary Infection Score (CPIS)*

CPIS points	0	1	2
Temperature (^{o}C)	≥ 36.5 and ≤ 38.4	≥ 38.5 and ≤ 38.9	≥ 39 or ≤ 36
Leucocyte count (per mm^3)	4,000 - 11,000	< 4,000 or > 11,000	< 4,000 or > 11,000
Tracheal secretions	Rare	Abundant	Abundant + Purulent
PaO_2/ FiO_2 mm Hg	> 240 or ARDS	-	≤ 240 and no ARDS
Chest radiograph	No infiltrate	Diffuse infiltrate	Localised infiltrate
Culture of tracheal aspirate	Light growth or no growth	Moderate or heavy growth of pathogenic bacteria	Moderate or heavy growth of pathogenic bacteria and presence of the same bacteria in Gram stain

* Modified from Pugin *et al*[8]

Table 2: Characteristics of the VAP patients

Parameter	Non-VAP (n = 164)	VAP (n = 36)	P value (2-tailed)
Age (mean ± SD)	36.8 ± 16.3	41.4 ± 14.7	0.17
Gender			
Male	95 (57.9%)	24 (66.7%)	0.43
Female	69 (42.1%)	12 (33.3%)	
Duration of MV	8.21 ± 5.9 d	16.61 ± 8.2 d	< 0.00
Mortality	20.5%	18.2%	

Impact of VAP on outcome

The duration of MV was significantly longer among patients who suffered from VAP (16.61 ± 8.2 d vs. 8.21 ± 5.9 d, *P* < 0.0001). On an average there was about two times increase in the duration of the ICU stay among patients with VAP compared to those without VAP (16.97 ± 8.6 d vs. 8.50 ± 6.1 d, *P* < 0.0001). There was no statistically significant difference in mortality between VAP and non-VAP groups (RR, 0.89; 95% CI, 0.40 to 1.95; *P* 0.9486).

Factors influencing outcome of VAP

Inappropriate therapy was identified as the only significant factor influencing the outcome of the patients with VAP by univariate analysis (Table 3).

Impact of treatment on outcome Out of the 36 VAP patients, 24 (66.7%) received appropriate therapy based on the antibiotic susceptibility pattern of the causative organism, while seven (19.4%) received partially inappropriate therapy and five (13.9%) received totally inappropriate therapy. VAP patients receiving partially or totally inappropriate therapy were significantly at high risk for death (RR, 2.00; 95% CI, 1.14 to 3.52; *P* 0.0008) (Table 3). There was a significant prolongation of MV of the VAP patients with a time to first dose of appropriate antibiotic more than two days compared to those with a time to first dose of appropriate antibiotic ≤ 2 days (19.29 ± 7.2 d vs. 9.43 ± 3.0 d, *P* < 0.0001). However, there was no difference in the mortality of the VAP patients on the basis of the time to first dose of appropriate antibiotic, as all the patients who received appropriate antibiotic therapy recovered successfully irrespective of the time of administration.

Impact of polymicrobial VAP There was no significant difference in the duration of MV between polymicrobial VAP and monomicrobial VAP (18.00 ± 8.69 d vs. 16.17 ± 8.34 d, *P* 0.572). There was no significant increase in mortality in polymicrobial VAP compared to monomicrobial VAP (RR, 1.15; 95% CI, 0.25 to 5.30; *P* 1.000) (Table 3).

Impact of time of onset of VAP There was no statistically significant difference in the duration of MV between early onset and late onset VAP (16.07 ± 9.2 d vs. 17.21 ± 7.9 d, *P* 0.705). There was no statistically significant difference in the mortality of early onset and late onset VAP (Two-tailed *P* value is 1.000) (Table 3).

Table 3: Impact of different factors on outcome of VAP

S. No.	Factor	Outcome		Relative risk (95% confidence limits)	P value
		Death (n = 6) (%)	Recovery (n = 27) (%)		
1.	Partially or totally inappropriate therapy *	6 (100)	6 (22.2)	Infinity	0.00
2.	Polymicrobial †	2 (33.3)	8 (29.6)	1.15 (0.25 to 5.30)	1.00
3.	Late onset VAP ‡	3 (50.0)	16 (59.3)	0.74 (0.17 to 3.12)	1.00
4.	MDR pathogens	4 (66.7)	23 (85.2)	0.44 (0.10 to 1.89)	0.29

VAP – Ventilator-associated pneumonia; MDR – Multi-drug resistant
* - Three VAP patients who received appropriate therapy left against medical advice.
† - Three VAP patients with monomicrobial VAP left against medical advice and their outcome was not known.
‡ - One early-onset and two late-onset VAP patients left against medical advice (AMA)

Impact of MDR pathogens
There was a significant increase in the duration of MV among the VAP patients infected with MDR pathogens compared to those infected with other micro-organisms (18.04 ± 8.4 d vs. 10.83 ± 5.0 d, *P* 0.0378). There was no statistically significant difference in the mortality of VAP caused by MDR pathogens and others (RR, 0.44; 95% CI, 0.10 to 1.89; *P* 0.2954) (Table 3).

Impact of the treating physician
As the choice of antibiotics for the treatment of VAP patients was left to the discretion of the attending physician, the results of the mortality rate and duration of mechanical ventilation of the patients could have been confounded by the variable of attending physician. However, we have not studied the impact of the treating physician on the outcome of VAP.

Discussion

VAP continues to be an important challenge to the critical care physician and is a common nosocomial infection occurring in mechanically ventilated patients. In our study 27.8% (10 out of 36) of the VAP cases were polymicrobial, which is consistent with other reports.[1,12]

The majority of the VAP patients (66.7%) in our study received appropriate therapy based on the antibiotic susceptibility pattern of the causative organism, while 19.4% and 13.9% received partially inappropriate or totally inappropriate therapy respectively. Most of the patients, who were on inappropriate therapy, had multi-drug resistant pathogens which were susceptible only to colistin. As many of these critically ill patients did not show good renal function, colistin could not be administered to these individuals. In some patients, *Candida albicans* was isolated along with other bacterial isolates. In these patients, the *Candida albicans* was considered to be a coloniser and only antibacterial treatment was initiated, which resulted in partially inappropriate treatment. Similarly, in a few cases, when multiple bacterial isolates were obtained from quantitative EA culture, some of them were considered as colonisers by the treating physicians, which had resulted in partially inappropriate therapy.

VAP patients receiving partially or totally inappropriate therapy were found to be significantly at high risk for death. But one patient with VAP due to a non-MBL producing *Pseudomonas aeruginosa*, resistant to meropenem by Kirby Bauer disc diffusion method, had recovered despite receiving inappropriate therapy. Later when the MIC was determined for that isolate, it had a MIC of 1 µg/ ml, which was within the susceptible range. Therefore, that isolate was actually susceptible to meropenem despite being labelled as resistant by Kirby Bauer disc diffusion method and so the patient had responded to the treatment.

Another five VAP patients had recovered despite receiving partially inappropriate therapy. Those patients had polymicrobial infection and had received appropriate therapy for only one of the multiple micro-organisms isolated by quantitative culture. One reason for response to a partially inappropriate therapy could be that only one isolate which was treated with appropriate antibiotic was a true pathogen, while the other isolates could have been colonisers and falsely identified as pathogens by quantitative culture. Quantitative culture has been shown to have only 85% specificity which supports the above hypothesis.[2] Moreover the *in vitro* susceptibility testing may not accurately predict the susceptibility of the micro-organism *in vivo*, which could be the other reason for the recovery of the patients despite partially inappropriate therapy.

In our study, we observed that a delay of more than two days in administering the first dose of appropriate antibiotic therapy significantly prolonged the duration of MV in patients with VAP. Similarly, in a study by Luna et al, the mortality rate of the patients with a delay in the initiation of the appropriate therapy was 63.5%, compared to a mortality rate of 29.2% in the group which received appropriate therapy without any delay.[6] Therefore, early administration of appropriate therapy is important to prevent undue prolongation of MV and reduce the mortality rate in patients with VAP.

The duration of MV was significantly longer among patients who suffered VAP. The prolonged duration of MV and ICU stay underscore the significant financial burden imposed by the development of VAP. There was no statistically significant difference in mortality between VAP and non-VAP groups in this study. Multivariate analyses conducted to evaluate the independent role played by VAP in inducing death failed to identify VAP as a variable independently associated with mortality in two studies.[4]

There was no significant difference in the duration of MV and outcome of polymicrobial VAP and monomicrobial VAP. Combes et al also observed that the epidemiology and outcomes of patients with monomicrobial and polymicrobial VAP did not differ significantly.[13]

The duration of MV and outcome of early onset and late onset VAP also did not differ significantly. Late-onset VAP, caused by MDR pathogens is usually associated with increased morbidity and mortality.[14] In this study many of the early onset VAP cases had the risk factors for infection with MDR pathogens like prior antibiotic therapy and current hospitalisation for five days or more. That could be the reason for the almost similar outcome of late onset and early onset VAP. The ATS guidelines also support the same reasoning by suggesting that patients with early-onset VAP who have received prior antibiotics or who have had prior hospitalisation within the past 90 days behave similarly to patients with late-onset VAP.[14]

In this study, *Acinetobacter baumannii* was the most common VAP pathogen associated with mortality, accounting for 37.5% of deaths. However, no significant increase in the mortality rate was observed in patients infected by MDR pathogens compared to those infected by other pathogens. In two different studies *Pseudomonas* or *Acinetobacter* pneumonia was associated with high mortality rates of 65% and 87% which was significantly more compared with 31–55% for VAP due to other microbes.[4] Similarly in another study, methicillin-resistant *Staphylococcus aureus* (MRSA) was associated with 86% mortality directly attributable to pneumonia, compared to 12% mortality rate with methicillin-sensitive *Staphylococcus aureus* (MSSA).[15] The reason for the discordant results between our study and others could be the high mortality rate attributable to inappropriate therapy in patients infected with non-MDR pathogens in our study. However, we noted a significant increase in the duration of MV and hospital stay in patients infected by MDR pathogens. A recent study has shown that the increased mortality of VAP caused by MDR as compared with non-MDR pathogens was attributable to more severe comorbidity before VAP.[16]

Conclusion

To conclude, use of appropriate antibiotic therapy is a major prognostic factor for patients with VAP. Early administration of appropriate therapy, based on the antibiogram of the VAP pathogens identified by quantitative culture of endotracheal aspirate could lead to an improved outcome of patients with ventilator-associated pneumonia. Appropriate broad-spectrum antibiotics should be used for treatment of multi-drug resistant pathogens to reduce the mortality.

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CONFLICTS OF INTEREST

The authors declare that they have no competing interests.

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