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Articoli originali

Original articles

Cost analysis of ventilator-associated pneumonia in Turkish medical-surgical intensive care units

Analisi dei costi della polmonite associata a ventilazione in Unità di Terapia Intensiva medico-chirurgiche in Turchia

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INTRODUCTION

Ventilator-associated pneumonia (VAP) is the most frequent nosocomial infection in intensive care units (ICUs), and occurs at least 48 hours after intubation in a mechanically ventilated patient. The risk of this complication in the ICU ranges from 8% to 25%, with an incidence of 5 to 10 cases per 1000 ventilator days [1-4]. This complication leads to increased hospital length of stay and cost, and may have an attributable mortality of up to 27% [5-9].

Risk factors include mechanical ventilation for >48 hours, re-intubation, inappropriate use of antibacterial agents, stay in an ICU, duration of ICU or hospital stay, severity of underlying illness, and presence of comorbidities, obvious aspiration and the use of muscle relaxants, low cuff pressure in the endotracheal tube and a supine position [10-14].

VAP is often divided into early-onset (developing in the first 5 to 7 days of mechanical ventilation) and late-onset forms (developing after 5 to 7 days of mechanical ventilation) [8]. While early-onset pneumonia is usually caused by microaspiration of bacteria colonizing the oropharynx (gram-positive cocci and *Haemophilus influenzae*), late-onset pneumonia is usually caused by nosocomial organisms (*Pseudomonas aeruginosa*, *Stenotrophomonas maltophilia*, *Acinetobacter* species, and methicillin-resistant *Staphylococcus aureus* [5, 15].

The clinical and economic consequences of VAP are unclear, with a broad range of values reported in the literature. Unfortunately, studies of patients with VAP have often provided contradictory results, making it challenging to provide an overall estimate of the clinical and economic consequences of VAP [16]. The greatest number of reports on VAP in ICUs is published from USA, and reports from Turkey are scarce [11]. Mertens et al. emphasized that international comparisons of results of infection surveillance data for prevention of nosocomial infections are important [17]. Thus we aimed to assess the length of stay in ICUs, mortality and attributable costs of VAP in Turkey.

PATIENTS AND METHODS

This study was conducted with approval from the institutional ethic committee at the Medical Faculty of Akdeniz University; consent was

waived because the protocol was observational. This prospective case control study was performed in the Anaesthesiology Intensive Care Units (n=2) in Akdeniz University Hospital between October 2004 and October 2005. The one-year data collected in this study consisted of 162 (81 intubated patients with VAP and 81 controls) adult ICU patients. Multiple nosocomial infections were excluded from the study because we aimed to detect costs for only VAP. Eighty-one mechanically ventilated control cases who stayed in the ICU for more than 48 hours and did not develop VAP were matched with respect to similarity of age (±5 years), gender and underlying disease with the VAP group.

The two central ICUs served the medical and surgical patients of the hospital. The first ICU was an eight-bed unit with one isolated 1-patient room and one 7-patient room. The second ICU was with three isolated 3-patient rooms, one 13-patient room and one isolated 1-burned patient room. The units was staffed by 10 physicians (four lecturers and six residents specialized in Anaesthesiology and Intensive Care) and 25 nurses. An infectious diseases physician consulted the patients daily. An infection control nurse collected data daily on standard surveillance charts. Haematological and biochemical tests (daily), chest radiographs (daily) and microbiological cultures from blood, nasopharynx, tracheal aspirate, urine and wounds (on admission, or when necessary) were performed routinely. The decision of VAP or colonization was made according to the laboratory and clinical findings. Appropriate antimicrobial therapy was given to the patients when necessary. Education on infection control procedures is performed twice a year for all ICU staff. Infection control measures and guidelines on prevention of nosocomial infections are applied according to CDC [18].

All data including gender, age, admission and discharge date, admission diagnosis and the Acute Physiology and Chronic Health Evaluation II (APACHE II) score at patient's admission to the ICU were recorded. The other data consisting of the length of intubation and ventilation, if there were re-intubation and tracheotomies, usage of antibiotics, bacterial growth in the ETA and BAL cultures were recorded in a patient's follow-up chart.

Criteria for defining VAP were those recommended by CDC [18]. A diagnosis of VAP was considered when radiological evidence of new and persistent (>48 hours) pulmonary infiltrates were detected together with at least two of the following features: temperature higher than 38°C or lower than 35°C, peripheral leukocytosis, (5000 per mm^3 or a 25% increase in the circulating leukocytes from the baseline), or a leukocyte recount lower than 4000 per mm^3 purulent respiratory secretions, and appearance or worsening of respiratory insufficiency.

Table 1 - Characteristics of patients admitted and mechanically ventilated in the ICUs.

Characteristics	*VAP group n (%)*	*Control group n (%)*	*P value*
Gender			NS
Female	29 (35.8)	29 (35.8)	
Male	52 (64.2)	52 (64.2)	
Age	43.8±19.7	43.3±19.8	NS
LOS (days)	15.7±9.1	4.9±4.9	<0.0001
Duration of MV (days)	12.8±7.9	3.6±4.2	<0.0001
Underlying disease			NS
Multiple trauma	55 (50)	55 (50.5)	
Cerebrovascular disease	34 (30.9)	34 (31.1)	
Cardiac insufficiency	6 (5.5)	5 (4.6)	
Intoxication	5 (4.5)	5 (4.6)	
COPD	4 (3.6)	4 (3.6)	
Burn injury	3 (2.7)	3 (2.8)	
Malignancy	3 (2.7)	3 (2.8)	

MV: mechanical ventilation, LOS: length of stay, COPD: chronic obstructive pulmonary disease. The patients had more than one underlying disease. Numbers in parentheses are percentages.

Moreover, the presence of significant growth on quantitative cultures of the bronchoscopic protected specimen brush ($\geq 10^3$ colony forming units [cfu]/ml) was required to accept the pneumonia as microbiologically proven. Patients were followed daily until discharge from the ICU or death. Risk of mortality for each group based on their APACHE II scores was analyzed. In all cases, if there was a clinical suspicion of VAP, specimens of endotracheal aspirates (ETA) were taken. To confirm VAP diagnosis, bronchoscopy was done and specimens of bronchoalveolar lavage (BAL) were taken, and then quantitative cultures were obtained. The VAP patients were followed up even if they were transported to their own ward, and control patients were followed up until they were discharged from the ICUs.

The costs of laboratory and radiological studies, antibiotics, other drugs and medical materials, as well as the costs of patient care, operations and ICU beds, were recorded in a separate form for each patient.

Statistical analysis was performed using SPSS 13.0 (SPSS Inc., Chicago, USA). All *p*-values less than 0.05 were considered significant. Descriptive analyses were performed by using chi-square and Studentís t-tests.

RESULTS

Of all 641 hospitalized adult patients 162 patients (81 patients with VAP, and 81 patients without) who underwent mechanical ventilation during the study period for more than 48 hours were prospectively enrolled in the study. Of the 162 patients, in each group there were 29 females (35.8%) and 52 males (64.2%). Thus there was no difference in gender split between the two groups. The VAP patients were aged between 14 and 81 years (43.8±19.7), and the control patients were aged between 13 and 81 years (43.3±19.8), with ages being similar in the two groups.

Length of stay (LOS) in the ICUs was 15.7±9.1 (4-46) days in the VAP group and 4.9±4.9 (2-43) days in the control group, and there were statistical difference in LOS between the two groups ($p<0.0001$). Mechanical ventilation lasted 12.8±7.9 (3-46) days in the VAP group and 3.6±4.2 (2-36) days in the control group, and

Table 2 - Distribution of microbial pathogens in early-onset or late onset VAP patients*.

Causative pathogen	*Early-onset VAP Number of cases (%)*	*Late-onset VAP Number of cases (%)*
Staphylococcus aureus (MS)	6 (22.3)	3 (4.9)
Staphylococcus aureus (MR)	0	2 (3.3)
Streptococcus pneumoniae	1 (3.7)	1 (1.6)
Haemophilus influenzae	3 (11.1)	1 (1.6)
Moraxella catarrhalis	1 (3.7)	2 (3.3)
Klebsiella pneumoniae	4 (14.8)	5 (8.2)
Klebsiella oxytoca	1 (3.7)	3 (4.9)
Pseudomonas aeruginosa	2 (7.4)	25 (41.1)
Acinetobacter baumannii	3 (11.1)	11 (18.1)
Acinetobacter sp	1 (3.7)	1 (1.6)
Escherichia coli	3 (11.1)	3 (4.9)
Citrobacter coseri	1 (3.7)	0
Citrobacter sp	0	1 (1.6)
Proteus mirabilis	1 (3.7)	0
Enterobacter cloacae	0	3 (4.9)
Total 27 (100) 61 (100) *Two of the early-onset VAP pathogens were polymicrobial, and five of the late-onset VAP were polymicrobial.		

Table 3 - Costs in the VAP and control groups (US Dollars).

Costs	*Costs of VAP Group ± SD (min-max)*	*Costs of Control Group ± SD (min-max)*	*P value*
Bed	1193.7±679.8 (176-3140)	381.0±382.2 (154-3320)	<0.0001
Antibiotics	837.1±472.9 (40-2140)	8.5±11.0 (0-40)	<0.0001
Drugs and medical materials	2305.0±1347.6 (330-8143)	816.7±645.9 (125-4125)	<0.0001
Laboratory	1647.0±1004.5 (248-8068)	546.4±442.4 (34-2335)	<0.0001
Radiology	269.9±222.1 (36-1683)	156.8±160.9 (16-806)	<0.0001
Operation	628.2±1190.1 (0-7280)	302.4±535.3 (0-2523)	<0.05
Intervention	1024.6±973.8 (135-7794)	254.3±271.7 (43-1579)	<0.0001
Care	696.7±613.1 (72-3753)	155.4±192.8 (23-1524)	<0.0001
Total	8602.7±5045.5 (1879-39422)	2621.9±2053.3 (658-14305)	<0.0001

SD: Standard deviation, min: minimum, max: maximum.

there were statistical differences in duration of mechanical ventilation between the two groups (p<0.0001). Onset of VAP development occurred 6.4±3.0 (3-16) days after admission in the ICUs. Of these VAP patients, 25 patients (30.9%) were classified as early-onset VAP and 56 patients (69.1%) were classified as late-onset (Table 2). Causative microorganisms for early-onset VAP were monobacterial in 23 cases and polymicrobial in 2 cases. By contrast, causative microorganisms for late-onset VAP were monobacterial in 51 cases and polymicrobial in 5 cases. While MSSA was the most common causative bacteria (22.3%) for early-onset VAP patients, *P. aeruginosa* was the most common causative bacteria (41.1%) for the late-onset VAP patients (Table 2).

The mortality rate was 32.0% (26/81) in the VAP group and 19.7% (16/81) in the control group; there were statistical differences in the mortality rates between the two groups (p<0.05). APACHE II scores were 18.2±4.7 (10-28) in VAP and 16.7±5.0 (9-30) in the control, with no statistical differences between the two groups. Total cost amounted to 8602.7±5045.5 (1879-39422) US Dollars in the VAP group and 2621.9±2053.3 (658-14305) US Dollars in the control group, with the costs being higher in the VAP group (p<0.0001). The cost components are shown in Table 3. The distribution of the total cost in the VAP group is also shown in Figure 1.

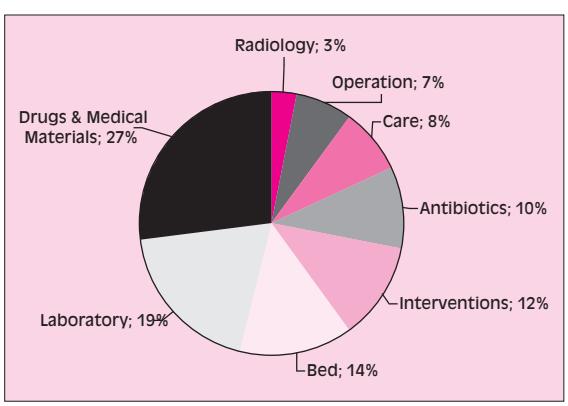

Figure 1 - Distribution of costs in the VAP group.

DISCUSSION

Ventilator-associated pneumonia still remains an important cause of death and increases costs of ICU care despite use of broad spectrum antibiotics and protective measures for nosocomial infections [11, 16, 19, 20]. However, diagnostic criteria that define VAP remain controversial. Minei et al. demonstrated that in a surgical ICU, the candidate definitions of pneumonia have little agreement [21]. Diagnosis of VAP cannot be established definitively with clinical criteria which include the appearance of a new or progressive pulmonary infiltrate, fever, leukocytosis, and purulent tracheobronchial secretions because such criteria are non-specific [22-24]. Also, cultures of tracheal aspirates are not very useful in establishing the cause of VAP [22]. Although such cultures are highly sensi-

tive, their specificity is low even when they are cultured quantitatively [25]. More specific signs such as air bronchograms or rapid cavitation have been rarely seen. Also, even the combination of clinical and radiological findings is not reliable for the diagnosis of VAP. Wunderink et al. demonstrated that in an autopsy study on VAP patients, all radiological signs had a diagnostic efficiency of ≤68%, and the addition of clinical signs and microbiological culture results of sputum to the radiological signs led to only a slight increase in the prediction of pneumonia diagnosis (72%) [23]. Invasive diagnostic tests such as protected brush catheter (PBC) and bronchoalveolar lavage (BAL) may increase physician confidence in the diagnosis and management of VAP and allow for greater capacity to limit or discontinue antibiotic treatment and reduce organ dysfunctions and the mortality rate [26, 27]. Hence we used clinical, radiological and laboratory values and also invasive diagnostic tests to define VAP.

In this study, mean duration of mechanical ventilation was 12.8 days in the VAP group and 3.6 days in the control group ($p<0.0001$). Generally, length of stay in ICU, and the duration of mechanical ventilation increase the risk of pneumonia [11, 28]. Cocanour et al. reported a significant increase in ICU length of stay (21.6 versus 6.4 days) and the number of ventilator days (17.7 versus 5.8) in VAP patients when compared to control patients [29]. In our study, the mean length of stay was longer in the VAP cases than controls (15.7 versus 4.9 days), and the additional length of stay attributable to VAP was estimated at 10.8 days. Our results were generally in accordance with findings elsewhere.

Dasta et al. demonstrated that ICU costs were higher during the first two days of admission, stabilizing at a lower level thereafter [30]. Mechanical ventilation is associated with significantly higher daily costs for patients treated in the ICU throughout their entire ICU stay. It was calculated that the daily cost of ICU care in mechanically ventilated patients was USD 10794, contrasting with USD 6667 in patients who received no mechanical ventilation therapy. On the second day, the cost of ICU care in mechanically ventilated patients was USD 4796, while in those who received no mechanical ventilation it was USD 3496.

In this study, we observed that reintubation was an important risk factor for development of VAP. The patients were reintubated in 61.7% in VAP cases and 17.3% in controls. The American Thoracic Society has advised practitioners to avoid reintubation to reduce the risk of VAP development [9].

In our study, mean (SD) duration of tracheostomy was less in VAP patients than controls (7.5 versus 0.6 days, $p<0.0001$). In the literature, the frequency of VAP increases 7.4 times with reintubation, 5.3 times with gastric content aspiration, 3 times with tracheostomy, 2.7 times respiratory failure and 2.4 times mechanical ventilation [16].

In this study, pathogen bacteria of early-onset VAP were monomicrobial in 92 percent of cases, and polymicrobial in 8 percent. The most common nosocomial pathogen of early-onset VAP was MSSA (22.3%) followed by *Klebsiella pneumoniae* (14.8%), *H. influenzae* (11.1%), *Escherichia coli* (11.1%) and *Acinetobacter baumannii* (11.1%). Pathogen bacteria of late-onset VAP were monomicrobial in 91 percent of cases, and polymicrobial in 9 percent. The most common nosocomial pathogen of late-onset VAP was *P. aeruginosa* (41.1%), followed by *A. baumannii* (18.1%) and *K. pneumoniae* (8.2%). Generally, most common pathogen bacteria in early-onset VAP are *H. influenzae*, *Streptococcus pneumoniae*, methicillin-sensitive *S. aureus* (MSSA), and they are called "primary endogen". In late-onset VAP, most common pathogen bacteria are Gram-negative bacilli. They may be seconder endogen or exogen bacteria, and they are usually resistant to antibacterial agents (16). In our study, the incidence of MRSA was low as 3.3 percent.

The important factors for cost increases in hospital-acquired infections are prolonged length of stay in the ICU, increase in use of antibiotics and other drugs and other health care costs. On the other hand, there are some factors that not very well defined such as the impact of cost on hospital activities, legal aspects and morbidity and mortality [16, 31-33]. Hospital-acquired infections may also affect indirect individual costs, loss of work for family or society. In this study, we calculated only the direct costs of VAP, and indirect costs, such as lost days from work and disability associated with VAP, were not included in our cost calculations. LOS is the easiest calculated parameter, but cost calculations of additional LOS are somewhat complex. To calculate additional LOS, VAP patients should be compared with the patients without VAP who have similar age, gender and illness to the VAP patients [16]. For this reason, we

chose 81 VAP patients from 641 mechanically ventilated patients, and for the control group chose 81 patients without VAP who had similar characteristics to the VAP patients. In our study, LOS was 15.7 days in the VAP group and 4.9 days in the control group, and additional LOS was 10.8 days. Rosenthal et al. reported that additional LOS was 8.9 days [34]. In other studies, additional LOS was reported as 10.1 [25] and 5.5 days [11, 16].

Additional cost of hospital care is an important factor for economic analysis of hospital-acquired infections [16]. Additional cost of hospital care is reported in the range of USD 1,000 to 4,500 from different countries [31, 32]. In this study, additional cost was found as USD 5,980, which was higher than findings elsewhere. We thought that the reasons for higher cost may be due to antibiotics, other drugs, and other healthcare materials (e.g. urinary catheters, tracheal aspiration catheters etc.), Indeed, such drugs and materials amount to 37 percent of total additional cost and, are expensive in Turkey because they are imported from foreign countries. Rosenthal et al. reported that additional cost in VAP patients was USD 2255 [34]. Warren et al. reported that total hospital cost in VAP patients was USD 70,568 and in control patients was USD 21,620 and the attributable cost of VAP was USD 11,897 [35]. Cocanour et al. reported that total hospital cost in VAP patients was USD 82,195, contrasting with USD 25,037 in control patients [29]. Some authors reported that the most important factor of additional cost is bed cost, but others estimated this factor to be antibiotics [31]. We calculated that 10 percent of total cost was spent on antibiotics, and 27 percent on other drugs and medical materials. One of the rare studies from Turkey concerning the cost of VAP found that 20% of total cost was spent on antibiotics [11]. Another study from Turkey [32] reported that antibiotics accounted for 52% of total cost of hospital-acquired infections, attributable to both the high price of foreign-imported antibiotics and to their inappropriate usage. Rosenthal et al. reported that 34% of total cost was on antibiotics for nosocomial pneumonia patients in ICUs [34]. In our study, the mean expenditure of laboratory studies was USD 1647 in the VAP group, as compared with USD 546 in the control group. Further, in the VAP group, 19% of total cost went on laboratory studies. In the study by Erbay et al., the mean expenditure of laboratory studies was USD 435 in VAP group and USD 112 in the control group, and in the VAP group, laboratory studies accounted for 15% of total cost [11].

We found that the mortality rate was 32% in the VAP group, compared with 19.7% in the control group ($p<0.05$). In the literature, the mortality rate of VAP was stated in the range of 23% to 70%, but not all deaths were related to VAP [36]. The mortality due directly to VAP was only 1/3 to 1/2 of all deaths. Mortality rates may be higher in situations of bacteraemia if the pathogen microorganisms are resistant gram-negative bacilli such as *P. aeruginosa, Acinetobacter* spp. or MRSA [36].

Older age, late-onset pneumonia, pneumonia due to resistant bacteria and severity of underlying disease may increase the mortality rate [26]. It has been shown that the mortality rate was higher in the VAP cases that have multi-resistant bacteria (6, 14). Also, da Rocha et al. stated that the practice of de-escalation therapy appears to be urgently needed in order to improve the situation (14). Hugonnet et al. found that the mortality rate was 32% in VAP cases in ICU [33]. In this study, mean APACHE II scores were 18.2 compared with 16.7 in the control group, and there was no statistical difference between the groups. In both groups 60% of patients had multiple trauma patients. Hence we thought that there was no difference between the groups.

Constant education for ICU staff is an important factor for preventing the nosocomial infections [19]. Salahuddin et al. reported that 13.2±1.2 VAP cases were seen per 1000 ICU days in an untrained staff group, compared with 6.5±1.5 VAP cases after staff had been given training [37]. They stated that if multidisciplinary education programmes were applied properly, there could be a decrease in VAP cases in ICUs.

CONCLUSION

VAP is an important hospital-acquired infection which may increase morbidity and mortality rates, the length of stay in ICUs and health care costs. Appliance of strict infection control programmes may reduce morbidity and mortality rates as well as the length of stay in ICUs.

Key words: VAP, costs, ICU, Turkey.

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SUMMARY

A study was carried out to assess treatment success and the overall costs of patients with ventilator-associated pneumonia (VAP). In a prospective case control study, data were collected from 25 intensive care unit (ICU) beds. A total of 162 ICU patients who required mechanical ventilation were assessed. Of these, 81 patients were diagnosed with VAP and the other 81 were controls (without VAP). Risk of mortality was analyzed and total cost of care was recorded.

Age, sex and underlying disease were similar between the groups. The mean length of stay (LOS) in the ICUs in the VAP cases (15.7±9.1 days) exceeded that of the controls (4.9±4.9 days) ($p<0.0001$), and the additional LOS attributable to VAP was estimated at 10.8 days. In the VAP group, 25 patients had early-onset VAP, and the other 56 patients had late-onset VAP.

Mortality rates were higher in VAP patients (32%) than controls (19.7%) $p<0.05$). Total costs were USD 8602.7±5045.5 in the VAP group and USD 2621.9±2053.3 in controls. The additional cost for VAP was found to be USD 5980 per patient. These data suggest that morbidity, mortality, ICU length of stay and costs increase with VAP. The additional costs for VAP are especially based on the use of novel and expensive antibiotics, other drugs, and medical material.

RIASSUNTO

Premessa: *In questo articolo gli autori hanno valutato alcuni aspetti correlati alla polmonite associata a ventilazione meccanica (VAP) in Unità di Terapia Intensiva (UTI) medico-chirurgiche in Turchia: durata della degenza, mortalità e costi.*

Pazienti e metodi: *Nello studio, prospettico e caso-controllo, sono stati raccolti i dati relativi a pazienti degenti in UTI (25 posti letto). Complessivamente, sono stati valutati 162 pazienti che necessitavano di ventilazione meccanica, di cui 81 affetti da VAP; i pazienti rimanenti hanno costituito il gruppo di controllo. È stato analizzato il rischio di mortalità ed è stato registrato il costo totale dell'assistenza.*

Risultati: *L'età, il sesso e le malattie di base dei pazienti sono risultati simili in entrambi i gruppi. La durata media di degenza in UTI per i soggetti affetti da VAP (15,7±9,1 giorni) è risultata maggiore rispetto a quella dei pazienti di controllo (4,9±4,9 giorni) ($p<0,0001$), e la degenza supplementare attribuibile alla VAP è stata pari a 10,8 giorni. Nel gruppo di pazienti con VAP, la malattia aveva avuto un esordio precoce in 25 pazienti e tardivo nei rimanenti 56. Il tasso di mortalità è risultato più elevato nei pazienti affetti da VAP (32%) che nei controlli (19,7%) $p<0,05$). I costi totali ammontavano a USD 8602,7±5045,5 nel gruppo di pazienti affetti da VAP e a USD 2621,9±2053,3 nel gruppo di pazienti di controllo. Il costo aggiuntivo attribuibile alla VAP è stato pari a USD 5980 per paziente.*

Conclusioni: *I dati da noi riscontrati indicano che la VAP determina un aumento di morbilità, mortalità, durata di degenza in UTI e costi. I costi aggiuntivi determinati dalla VAP sono ascrivibili soprattutto all'uso di nuovi e costosi antibiotici, alla necessità di altri farmaci, e a materiale sanitario in genere.*

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