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Ventilator-Associated Pneumonia Caused by High Risk Microorganisms

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Infection is a major problem in intensive care units (ICU) as it is the leading cause of death in non-cardiac ICUs around the world. Ventilator-Associated Pneumonia (VAP) presents a special challenge for intensivists, not only because of its high attributable mortality (up to 40% when high risk microorganisms are concerned), but also because of causing increased morbidity and cost. Emergence of multi-drug resistant microorganisms lead to frustration since very few treatment alternatives are available for them. Very recently, there have been reports of bacteria containing the New Delhi metallo-lactamase-1 (NDM-1) gene called “superbugs” which are resistant to all antibiotics.

Although VAP is a problem in every ICU, each country and even each institution face with different bugs. Well known EPIC I (Vincent et al. 1995) and EPIC II (Vincent et al. 2009) studies revealed the fact that the microbiologic profile differed among countries all over the world. For instance, according to the EPIC II study, methcillin resistant S aureus (MRSA) is a greater problem in North America compared to other regions, whereas Acinetobacter and Pseudomonas spp are more prevalant in Southeast Europe and in Asia. The EUVAP/CAP study (Koulenti et al. 2009) showed almost similar results, where high risk microorganisms i.e., MRSA, P aeruginosa, A baumannii and S maltophilia, accounted for more than 60% of isolates in late onset VAP.

Contributing to both EPIC II and EUVAP/CAP studies, Acinetobacter and Pseudomonas spp account for about three quarters of isolates in VAP in Turkey, and more than 60% of them are multi-drug resistant (resistant to at least two groups of antibiotics) (Korten et al. 2007). Colistin, which is the only effective antibiotic for these microorganisms is unfortunately not easily available in Turkey, therefore these reasons, we undertook a matched casecontrol study to determine the impact of high treatment of the patients infected with these microorganisms poses a great challenge. For these reasons, we undertook a matched casecontrol study to determine the impact of high these reasons, we undertook a matched casecontrol study to determine the impact of high microbiological evidence of VAP. Each case patient was matched to one control patient according to the duration of mechanical ventilation, (i.e., duration of mechanical ventilation risk microorganisms on mortality and morbidity (Aybar Turkoglu and Topeli Iskit 2008).

The Study Design

A matched cohort study was conducted in the medical ICU of Hacettepe University Hospital, Ankara. Patients ventilated for more than 48 hours were enrolled and patients who were admitted to the ICU after receiving mechanical ventilation for more than 48 hours in another place were excluded. For clinical diagnosis of VAP, standard criteria were used based on the presence of a new infiltrate on a chest xray with the presence of two of the criteria: Hypo- or hyperthermia, leukocytosis or leukopenia, purulent secretions and increase in hypoxemia. For the microbiologic diagnosis, quantitative endotracheal aspirate cultures these reasons, we undertook a matched casecontrol study to determine the impact of high microbiological evidence of VAP. Each case patient was matched to one control patient according to the duration of mechanical ventilation, (i.e., duration of mechanical ventilation were mostly used. Patients having positive quantitative culture results for high risk microorganisms including P aeruginosa, Acinetobacter spp, S maltophilia and/or MRSA, in addition to clinical findings were accepted as the case patients. Control patients were selected from the ventilated patients who had no clinical and microbiological evidence of VAP. Each case patient was matched to one control patient according to the duration of medical venti microbiological evidence of VAP. Each case patient was matched to one control patient according to the duration of mechanical ventilation, (i.e., duration of mechanical ventilation of the control patient was at least as long as the duration of mechanical ventilation prior to the onset of VAP for the case patient); APACHE II score and age (values for case and control patients were within ±8 and ±13 points, respectively); and date of admission of the case and the control patients was within 16 months.

Results

During the study period, 536 patients were admitted and stayed in the MICU for > 24 hours, among which 216 patients received mechanical ventilation with intubation. Sixty patients were excluded from the study. Of the remaining 156 patients 60 patients had developed VAP, microbiological evidence of VAP. Each case patient was matched to one control patient according to the duration of mechanical ventilation, (i.e.,

duration of mechanical ventilation 45 of whom with high risk microorganisms. Thirty five case patients could have been matched with 35 control patients. Baseline characteristics (age, APACHE II score, sex, admission diagnosis, type of underlying disease, sedative and steroid use, and use of enteral nutrition, type of stress ulcer prophylaxis, reintubation rate, prior antibiotic use) were similar in case and control patients. Median age and APACHE II score of case patients were 69 and 20, respectively and of control patients were 67 and 19, respectively. Duration of mechanical ventilation prior to the development of VAP in the case patients was 6 [3.5-9.5] (median [25th 75th percentile]) days and total duration of mechanical ventilation in control patients was 8 [6-11.5] days ($p< 0.01$).

In case patients, 43 high risk microorganisms were isolated. Acinetobacter spp were isolated in 15, P aeruginosa in 15, MRSA in 10 and S maltophilia in 3 patients. According to the resistance patterns appropriate antibiotics were prescribed in only 53% of patients. Isolated Acinetobacter or Pseudomonas spp in four patients were resistant to all aminoglycosides, carbapenems, third and fourth generation cephalosporins, piperacillin and quinolones and all of these patients died. Antibiotic resistance rate in Pseudomonas and Acinetobacter spp was very high. In P aeruginosa, resistance rate to carbepenems was 53%, tobramycin 93%, amikacin 67%, ceftazidim 87%, piperacillin 80%. In Acinetobacter spp, resistance rates for the above mentioned antibiotics were 73%, 13%,67%, 67% and 93%, respectively.

Although there was no difference between the case and the control patients in terms of the development of organ failures (acute renal failure, acute respiratory distress syndrome, shock requiring vasopressor therapy and disseminated intravascular coagulation) in this study, case patients were exposed to invasive procedures such as tracheostomy and central venous catheterisation more than the control patients.

ICU mortality rate was similar between case and control patients (80% and 71%, respectively, $p= 0.58$) as was hospital mortality rate (80% for both groups). However, length of ICU stay was longer in case patients than in control patients (20 [11-30] days and 13 [8-19] days, $p< 0.01$). Length of hospital stay was also longer in case patients than in control patients (29 [20-44] days and 22 [13-37] days, $p= 0.05$). In addition, duration of mechanical ventilation was longer in case patients than in control patients (18 [10- 25] days and 8 [6-11] days, $p< 0.01$). Therefore, VAP caused by high risk microorganisms resulted in an increase in length of ICU stay and hospital length of stay by seven days, and in duration of mechanical ventilation by 10 days.

When factors related with prolonged length of ICU stay, i.e., length of stay more than the median value (16 days), prolonged length of hospital stay (>26 days) and prolonged duration of mechanical ventilation (>11 days) found in bivariate analysis were put into a logistic regression model, VAP caused by high risk microorganisms was found to be an independent risk factor for increased length of ICU and hospital stay (OR 6 [CI 1.8-19.7] and OR 4 [CI 1.2-16.4], respectively) and increased duration of mechanical ventilation (OR 11 [CI 2.1-54.5]). Almost similar results were observed when outcome variables were evaluated separately for Pseudomonas, Acinetobacter spp and MRSA.

Discussion

VAP is believed to increase mortality rate, however it is important to differentiate the mortality due to the underlying disease process or the infection itself. Therefore there are conflicting results about attributable mortality rate in VAP and there are few studies mainly looking at the attributable mortality rate in VAP caused by high risk microorganisms. Most studies are subgroup analysis. Similar to our study, there are some studies which could not demonstrate an increased mortality caused by VAP (Garnacho et al. 2003). However, there are some which showed an attributable mortality rate of 43% when Pseudomonas or Acinetobacter spp were concerned (Fagon et al. 1993).

Although sample size is small due to being conducted in a single centre and due to the nature of the study design being a matched casecontrol study, the major findings were considerably increased length of ICU and hospital stay and duration of mechanical ventilation in VAP caused by high risk microorganisms. Similar to our results, in the literature, an increase in length of ICU stay attributable to VAP caused by high risk microorganisms ranges between 6 to 12 days (Heyland et al. 1999). In addition to these findings, we have also shown that development of VAP due to high risk microorganisms was an independent risk factor for prolonged length of ICU and hospital stay, and duration of mechanical ventilation. There are also conflicting results in the literature about whether high risk microorganisms increase development of organ failures.

Reasons for the finding of insignificant difference in mortality rate between case and control patients could be the small sample size and presence of similar frequencies of organ failures and similar disease severities observed in our case and the control patients. Still, the mortality rate in our control patients was relatively higher in that period. Since then, observed ICU mortality rate decreased in time reaching down to 24% despite APACHE II score remaining around 21, due to various reasons such as adapting a closed ICU organisation (Topeli et al. 2005), improvement in the physical properties of the ICU and the hospital, increase in number of experienced nurses and physicians, continuous medical education and implementing various protocols for severe sepsis, sedation, weaning, etc. and bundles especially for VAP. In addition, although antibiotic resistance rates to all antibiotic groups including carbapenems (excluding colistin increased in time up to almost 90% in Acinetobacter spp in year 2009), rate of VAP decreased from 17.5/1000 ventilator days in 2001 to 8.1/1000 ventilator days in 2009 in our institution (from Cetinkaya-Sardan. Reports of the Infection Control Committee of Hacettepe University Hospital, Ankara).

Appropriate empiric antibiotics were started in about 50% of patients, which is a very low rate increasing mortality and morbidity. The difficulties in finding colistin timely in Turkey is one of the reasons for that.

After completion of this study, we conducted another descriptive study (unpublished yet) where we looked at appropriate empiric antibiotic use, antibiotic resistance patterns and prognosis in VAP and primary bacteremias caused by Acinetobacter spp between January 2004- August 2009. Accordingly, in 64 patients, VAP caused by Acinetobacter spp developed on the 12th day [6-25] of mechanical ventilation. ICU and hospital mortality rates in these patients were 52% and 64%, respectively. Lengths of ICU and hospital stay were very long being 37 [15-60] and 49 days [33-91] respectively. Of these isolates, 69% were considered to be multi-drug resistant. Resistance respectively. Of these isolates, 69% were

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rates to carbapenems were 83%, aminoglycosides 52%, sulbactam-cefaperazone 80% and piperacillin-tazobactam 99%. As seen in Figure 1, resistance rates increased over time.

Conclusion

We believe this study is important, since it is one of very few matched case-control studies investigating the attributable mortality and morbidity of VAP caused by high risk microorganisms. It revealed that VAP caused by high risk microorganisms had not increased mortality, however, it independently increased ICU and hospital length of stay and duration respectively. Of these isolates, 69% were considered to be multi-drug resistant. Resistance of mechanical ventilation. Finally, although pan-resistance is a great problem in Turkey especially for Acinetobacter spp, VAP rates could stil be lowered with implementing protocols and bundles.

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