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Incidence and risk factors for ventilator-associated pneumonia in a developing country: Where is the difference? ☆

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Summary
Background: Latin America exhibits a wide range of differences, compared to developed nations, in genetic background, health services, and clinical research development. It is valid to hypothesize that the incidence and risk factors for ventilator-associated pneumonia (VAP) in our setting may be substantially different of those reported elsewhere. We conducted a study to determine the incidence and risk factors for VAP in a University Hospital from Medellin, Colombia.
Methods: Prospective cohort study in three intensive care units (ICU) (surgical/trauma, medical, cardiovascular) in a 550-bed University Hospital. Critically ill patients ($n = 270$) who required at least 48 h of mechanical ventilation (MV) between June 2002 and October 2003 were followed until ICU discharge, VAP diagnosis or death.
Results: Sixty patients (22.2%) developed VAP 5.9 ± 3.6 days after admission. The overall incidence of VAP was 29 cases per 1000 ventilator-days. The daily hazard for developing VAP increased until day 8, and then decreased over the duration of stay in the ICU. The only statistically significant factor after multivariable analysis was gender, with being female reducing 57% the risk of pneumonia (hazard ratios (HR): 0.43; 95% confidence intervals (CI): 0.19–0.96).
Conclusions: The epidemiologic profile of VAP in terms of incidence, length of stay and clinical course resembles the general pattern described everywhere. Surprisingly, we could not identify any potentially modifiable risk factor for VAP. A comprehensive multicenter

Abbreviations: VAP, ventilator-associated pneumonia; ICU, intensive care unit; CRF, chronic renal failure; CHF, chronic heart failure; COPD, chronic obstructive pulmonary disease; HIV, human immune deficiency virus; APACHE, acute physiology and chronic health evaluation; MV, mechanical ventilation; WBC, white blood cells; CFU, colony-forming units

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study is warranted. It should provide deep insight about the specific microbiological, genetic and clinic features of VAP in our setting.

Introduction

Ventilator-associated pneumonia (VAP) is the most common infection in intensive care units (ICUs), with frequencies ranging between 15% and 45%.[1] VAP prolongs the duration of hospitalization for an average of 7–9 days per patient, and it is associated with increased health care costs.[2] The crude mortality rate for VAP has been cited to be as high as 70%, but there is wide recognition that not all deaths among affected patients are the direct result of infection, but, rather, that the infection seems a marker for severity of illness.[3]

Appropriate identification of high risk patients and of potential modifiable factors may define preventive strategies or institutional policies to halt the infection. Although several studies have addressed the issue of risk factors for VAP, some results have been controversial or nonreproducible.[4–9] On the other side, we are not aware of investigations regarding this problem in developing countries. Furthermore, Latin America apparently exhibits a wide range of differences, compared to developed nations, in genetic background, cultural heritage, health services, and clinical research development.[10] Moreover, we showed that in the setting of nosocomial bacteremia in a University Hospital, our population was significantly younger, healthier, and more susceptible than those patients described in studies worldwide.[11] Although there are no studies specifically regarding Latin American ICUs and their infectious profiles, it is valid to hypothesize that the incidence and risk factors for VAP in a Latin American country may be substantially different of those reported elsewhere.

Accordingly, we conducted a prospective cohort study to determine the incidence and risk factors for VAP in three ICUs at the Hospital Universitario San Vicente de Paúl (HUSVP, Medellin, Colombia).

Materials and methods

Study location and patients

The study was performed at three ICUs: surgical/trauma (12 beds), medical (12 beds) and cardiovascular (six beds), all of them located in the HUSVP. This is a 550-bed University Hospital that is a referral center for a region with approximately 3 million habitants. Inclusion criteria were age 16 years or older and requirement of mechanical ventilation (MV) for at least 48 h. Exclusion criteria were death within 24 h after study recruitment, and pneumonia as admission diagnosis to ICU or detected within the first 24 h. The research protocol was approved by the local institutional review board. Routine strategies for MV at the institution include: semi-recumbent positioning with a goal of 45°, enteral feeding within 24 h of admission with a caloric goal of 25 kcal/kg/day and change from gastric to jejunal route according to the patient's tolerance, stress ulcer prophylaxis with ranitidine, daily antiseptic oral rinse with clorhexidine, heat and moisture exchangers in patients without contraindications, as well as close endotracheal suctioning systems which are changed weekly or as clinically indicated. Analgesia and sedation strategies, as well as the weaning plan, are conducted according to the physicians' preferences without any specific protocol.

Design and data management

Prospective cohort study conducted between June 2002 and October 2003. Patients were recruited consecutively and were followed until VAP diagnosis, death or discharge from ICU. Data collection and follow-up were done by research assistants (medical students) and supervised daily by the investigators, and the relevant information was recorded in specific pre-designed case report forms. Admission diagnosis to ICU was classified by general system: cardiovascular diseases, respiratory disease, neurological disease, gastrointestinal disease, trauma, and non-emergency surgery. As comorbid conditions, taken from the medical records of the patients, were defined chronic heart failure (CHF), chronic obstructive pulmonary disease (COPD), chronic renal failure (CRF), diabetes, alcoholism, immunocompromised status (use of immunosuppressant chemotherapy during the previous 3 months or use of systemic corticosteroids for at least 1 month), cancer, and cirrhosis. VAP potential related factors, based on an extensive literature review, were age, gender, previous use of antibiotics (less versus higher than 48 h before MV), Glasgow Coma Scale at admission, acute physiology and chronic health evaluation (APACHE) II at admission, thoracic or major abdominal surgery 24 h before MV, type of enteral nutrition (jejunal versus gastric route), type of ICU (surgical versus other), requirement of paralytic agents, tracheostomy, or reintubation, aspiration of gastric content, and comorbid conditions. Comorbid conditions were grouped and analyzed according to their capability to disturb directly the immune system. Doing so, we could explore more efficiently their effect on the incidence of VAP.

VAP was considered in presence of new or progressive and persistent radiographic infiltrate, plus at least two of the following criteria.[12]

Temperature $\geqslant 38.3\,^{\circ}C$ or $< 36\,^{\circ}C$.

Purulent tracheal secretions

Leukopenia (< 4000 white blood cells (WBC)/mm^3) or leukocytosis ($> 12{,}000$ WBC/mm^3).

In patients who met the previous definition plus worsening gas exchange ($PaO_2/FiO_2 < 300$), an additional microbiologic criterion was required: at least 10^3 colony-forming units (CFU) on protected specimen brushing, 10^4 CFU on bronchoalveolar lavage, or 10^5 CFU on nonbronchoscopically tracheal secretions. Radiographic findings were defined by

trained radiologists blinded to the study objectives. Only the first VAP episode was considered in the analysis. This case definition was verified independently by at least two investigators, and any disagreement was resolved by consensus with a third investigator.

Statistical analysis

We expressed continuous variables as the mean ± standard deviation (SD) or median and interquartile range (IQR) according to data distribution. The cumulative risk of VAP was estimated with the Kaplan–Meier product-limit estimator, and the hazard function for the event rate per day was smoothed with a Kernel density estimator.[13] We used locally weighted regression to explore graphically the association between continuous variables and the log odds of VAP.[14] Doing so, we could estimate optimal cut-off points for age and APACHE II score. These categorized variables are more clear and useful from a clinical point of view. Then, we performed both univariable and multivariable Cox proportional hazards regression analysis with the same variables to evaluate potential risk factors for VAP. We checked this analysis with both a backward and a forward stepwise selection method. Factors were considered significant if the *P*-value was less than 0.05 in the multivariable analysis. We calculated hazard ratios (HR) and 95% confidence intervals (95% CIs) for all predictors of VAP in the univariable and multivariable analysis. We tested for all pairwise interactions between risk factors in the multivariable model using the likelihood ratio statistic with a *P*-value <0.1.[15] We investigated the possibility that the effects of risk factors may vary over the duration of stay in the ICU (i.e., proportional hazard assumptions). This was done by using a nonproportional Cox model testing the interaction of each variable, in the final model, with time.

Results

Of 271 patients enrolled in the study, one was excluded because he had pneumonia in the first 24 h after MV, leaving 270 patients ventilated for 48 h or more who were free of pneumonia at admission to the ICUs. Table 1 shows the general characteristics of the cohort. Of these patients, 60 (22.2%) developed VAP 5.9 ± 3.6 days after admission. The total duration of MV among patients with VAP was 13.9 ± 8.2 days compared with 9.6 ± 16.7 days in patients without the infection ($P<0.0001$). Among the 60 patients with VAP, 35 (58.3%) had microbiological confirmation by bronchoscopic testing with bronchoalveolar lavage, protected specimen brush, blood cultures or nonbronchoscopically tracheal secretions. Organism isolated were *Staphylococcus aureus* (10), *Klebsiella pneumoniae* (seven), *Haemophilus influenzae* (four), *Enterobacter cloacae* (four), *Pseudomonas aeruginosa* (three), *Stenotrophomonas maltophilia* (two), *Serratia marcecsens* (two), *Acinetobacter baumannii* (two), and *Citrobacter freundii* (one).

Patients in the following admitting diagnostic categories had VAP: trauma (29 of 134 patients [21.6%]), respiratory disease (eight of 35 patients [22.9%]), thoracic or abdominal surgery (six of 32 patients [18.8%]), gastrointestinal disease (10 of 26 patients [38.5%]), central nervous system disease (four of 21 patients [19.1%]), metabolic or other disease (two of 12 patients [16.7%]), and cardiovascular disease (one of 10 patients [10%]) ($P = 0.583$ for difference across groups). The cumulative risk for developing VAP over successive days in the ICU is shown in Fig. 1. The overall incidence of VAP was 29 cases per 1000 ventilator-days. The hazard function represents the conditional probability of VAP in the next day, given that a patient is event free (i.e., without pneumonia). Therefore, estimation of the hazard function shows the event rate per day over the duration of ventilation. The daily hazard for developing VAP increased until day 8, and then decreased over the duration of stay in the ICU (Fig. 2). The mortality rate among patients with VAP (18%, $n = 11$) was similar to the overall ICU mortality.

Factors potentially related with VAP in the univariable and multivariable analysis are shown in Table 2. The only

Table 1 General characteristics of 270 mechanically ventilated patients at Medellín, Colombia.

Variable	Value
Type of intensive care unit, *n* (%)	
Surgical	151 (56%)
Medical	101 (37%)
Cardiovascular	18 (7%)
Age, median (IQR)	41 (26–55)
Gender (female/male)	73/197
APACHE II score, median (IQR)	17 (13–22)
Previous use of antibiotics, *n* (%)	
Less than 48 h	27 (10%)
Higher than 48 h	99 (36.6%)
Comorbidities, *n* (%)	
Immunosuppressive state	26 (9.6%)
Chronic renal failure	16 (6%)
Chronic obstructive pulmonary disease	15 (5.5%)
Diabetes	15 (5.5%)
Alcoholism	13 (5%)
Cancer	11 (4%)
Chronic heart failure	11 (4%)
Cirrhosis	6 (2%)
ICU mortality, *n* (%)	50 (18.5%)

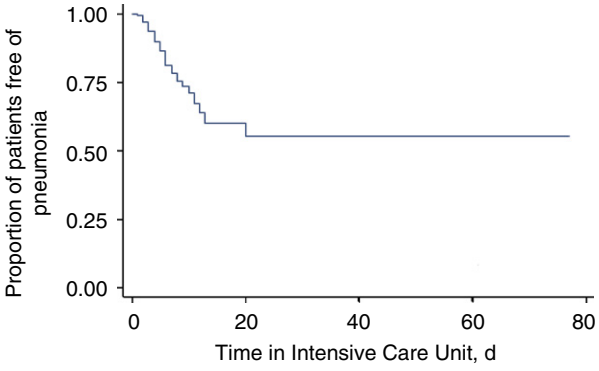

Figure 1 Proportion of patients free of pneumonia during their stay in the intensive care unit (Kaplan–Meier product-limit estimator).

statistically significant factor after multivariable analysis was gender, with being female reducing 57% the risk of pneumonia (HR: 0.43; 95% CI: 0.19–0.96). We considered the possibility of survival bias. This means that those patients more severely ill at admission might die early and, consequently, not being exposed to develop VAP. Accordingly, we performed univariable and multivariable analysis considering only survivors. These new models did not show any significant difference with the original results (data no shown). Similarly, we fitted a new model considering only VAP cases with microbiological confirmation ($n = 35$), and none of the potential independent predictors was significantly associated with the outcome. No interactions were seen between the potential risk factors in either analysis. Evaluation of risk factors in the nonproportional hazards model demonstrated no statistically significant changes over time.

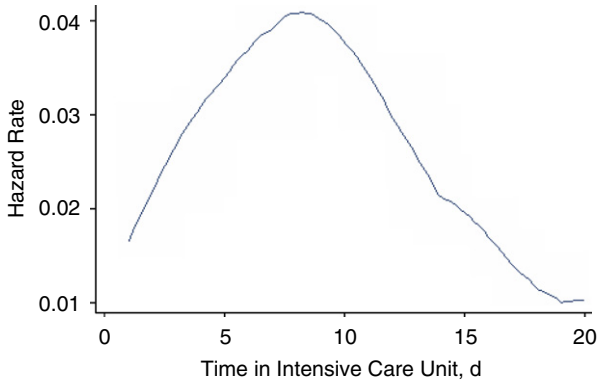

Figure 2 Hazard rate for ventilator-associated pneumonia during the stay in the intensive care unit.

Discussion

We examined the incidence of and risk factors for VAP in a cohort of 270 mechanically ventilated patients. We found an overall rate of 29 cases per 1000 ventilator-days and a frequency of 22.2% among the total cohort. These figures are among those reported in the literature: Cook et al. described an incidence of 14.8 cases per 1000 ventilator-days in a cohort with 1014 patients in 16 ICUs in Canada four; and Eggimann et al.[16] reported a rate of 35.7 cases per 1000 ventilator-days in 1049 patients followed in Switzerland. Studies from middle-income countries as Greece and from Middle East countries as Saudi Arabia and Lebanon, showed similar frequencies of VAP in multidisciplinary ICUs: 32–33.8% in the formers,[17,18] and 25.2–47% in the later.[19,20] We also demonstrated that the risk for developing VAP increased cumulatively until day 8 and then decreased evenly. Such a decreasing hazard reflects the high risk for early VAP and suggests that long-term survivors are patients at lower intrinsic risk for this outcome. These findings confirm those reported by Cook et al.[4] in which the risk per day was approximately 3.3% at day 5, 2.3% at day 10, and 1.3% at day 15. Furthermore, like other investigators,[3,21] we confirmed that a VAP diagnosis prolongs the time for MV adding an average of 4.3 days over the duration of MV in patients without the infection. Thus, we can infer that the epidemiologic pattern of the problem in our setting seems very similar to the general profile described worldwide.

Our results about risk factors, instead, showed striking differences compared to those commonly reported in the literature.[4,7,9,17–19,22–33] After multivariable analysis, only female sex remained as a significant variable reducing the risk of VAP (HR: 0.43; 95% CI: 0.19–0.96). Surprisingly, our data suggested a "protective" but not statistically significant effect for comorbidity (HR: 0.52; 95% CI: 0.16–1.63) and APACHE II score higher than 17 (HR: 0.66; 95% CI:

Table 2 Potential risk factors for ventilator-associated pneumonia.

Risk factor	Univariable hazard ratio (95% CI)	Multivariable hazard ratio (95% CI)
Age ⩾40 years	0.84 (0.47–1.50)	1.28 (0.63–2.57)
Gender (female vs. male)	0.41 (0.20–0.83)	0.43 (0.19–0.96)
Previous use of antibiotics (less than 48 h vs. non-use)	1.10 (0.29–4.14)	1.01 (0.24–4.26)
Previous use of antibiotics (higher than 48 h vs. non-use)	0.69 (0.16–1.34)	0.89 (0.42–1.87)
Glasgow Coma Scale (1 point)	1.01 (0.95–1.08)	1.00 (0.91–1.10)
APACHE II score ⩾17	0.58 (0.32–1.07)	0.66 (0.30–1.44)
Thoracic or mayor abdominal surgery before ICU admission	0.81 (0.41–1.59)	0.72 (0.33–1.55)
Type of enteral nutrition (jejunal vs. gastric)	1.02 (0.44–2.34)	1.18 (0.49–2.85)
Type of ICU (surgical vs. others)	1.12 (0.62–2.01)	1.11 (0.57–2.18)
Requirement of paralytic agents	0.93 (0.39–2.24)	0.90 (0.35–2.32)
Requirement of tracheostomy	0.93 (0.46–1.89)	1.06 (0.48–2.31)
Requirement of reintubation	0.86 (0.37–1.95)	1.12 (0.39–3.16)
Aspiration of gastric content	1.65 (0.50–5.36)	1.60 (0.42–6.04)
Comorbidity related to the immune system[a]	0.33 (0.11–0.95)	0.52 (0.16–1.63)
Comorbidity non-related to the immune system[b]	0.62 (0.26–1.44)	0.67 (0.24–1.84)

[a]Any of cancer, chronic renal failure, cirrhosis or immunocompromised status (see Materials and methods).
[b]Any of chronic heart failure, chronic obstructive pulmonary disease, diabetes or alcoholism.

0.30–1.44). Our clinical definition of VAP merits attention, as this may produce a non-differential misclassification of the outcome. This means that the "wide" definition may consider eventually some non-microbiological-confirmed cases as infected and, less likely, some VAP cases also may be undetected by clinical criteria. Consequently with the concept that this information bias might move the results toward the null, a new model with only microbiologically confirmed VAP cases did not show any significant VAP predictor. A clinically useful VAP definition, however, remains as a critical challenge for daily practice, and we set our full analyses based on the easier and more reproducible definition.

Several reasons may explain this lack of independent factors for developing VAP. First, in prospective cohort designs that require multivariable analysis as logistic or Cox regression, a common rule of thumb suggest at least 10 outcomes per each independent variable considered in the model.[34] Therefore, since our study population included 60 patients with VAP, we would not be able to analyze more than six factors simultaneously. This drawback might affect the stability of the coefficients in the full model and introduce random error in their estimation. However, the univariable analysis, which is not subject to the same considerations regarding sample size, showed similar findings in the direction, magnitude and precision of the hazard ratios. The issue of precision is remarkable, as the wide of confidence intervals was overly similar in both univariable and multivariable analysis. Moreover, several recent studies with smaller sample sizes were able to detect risk factors for VAP.[17–19] Therefore, small sample size seems not enough explanation for our findings.

Second, there are some biases that are particular to cohort studies, namely immortal time bias and confounding by time-dependant covariates.[35] Immortal time bias refers to cohort studies with follow-up time during which a subject cannot, by definition, incur the outcome event under study. The inappropriate consideration of such immortal person-time may produce biased estimates of the effect measures.[36] In our cohort, patients with less than 48 h of MV were not included, but in patients included we considered date of starting MV as the "zero time" in the analysis. Furthermore, our population also may be considered with early-onset VAP as they developed it 5.9 ± 3.6 days after admission. In fact, 12 out of 60 patients (20%) developed VAP between 48 and 72 h of starting MV. Therefore, we performed two additional different analyses: a Cox regression considering an at-risk period after 48 h of MV, and a Cox regression excluding those subjects who developed VAP between 48 and 72 h of MV. Both models confirmed gender as the only one significant independent predictor. On the other hand, an outstanding feature of longitudinal studies is their capability to explore both exposures and outcomes that change over the time.[35] An individual may not be exposed until certain time of the following period, and then turn out exposed once the time-dependant covariate changes its status.[37] This time-dependant nature of some risk factors may also generate biased estimates of the effect measures. We analyzed three independent variables not necessarily present at the starting of MV: requirement of paralytic agents, reintubation, or tracheostomy. However, they were recorded certainly before VAP diagnosis and most of them occurred within the first 10 days of MV. Additionally, these factors were present in less than 20% of the cohort: requirement of paralytic agents in 45 patients (17%), requirement of tracheostomy in 39 patients (14%), and requirement of reintubation in 25 patients (9%); and their hazard ratios were close to one and non significant in both univariable and multivariable analyses. Therefore, neither immortal time bias nor confounding by time-dependant covariates appeared to be major determinants in our results.

Third, there are several aspects to our study population that merit attention. Most of patients were in the surgical/trauma ICU (56%) and the main reason for admission was trauma in 134 patients (50%). The median age was 41 years, and 71% of the patients ($n = 193$) were free of any comorbidity. This is the youngest and healthiest population at risk of VAP ever reported. Indeed, the overall ICU mortality was 18.5%; which is lower than the 25% predicted by the median APACHE score of 17.[38] It is interesting to speculate regarding an intrinsic difference in susceptibility to infections; and probably also differences in health care services and methods of patient care. As a matter of fact, in a previous study we analyzed risk factors for nosocomial bacteremia in our institution.[11] Despite a young and healthy study population; we found a rate of almost 20% of positive blood cultures, most of them (56%) caused by Gram-negative bacteria and fungi. Additionally, we identified four clinical variables associated with positive blood cultures but with substantially low values as cut points for the outcome. These microbiological and clinical findings also were significantly different of those reported worldwide.[39,40] Thus, the issue of the particular characteristics of our population may be instrumental in the comprehension of our findings.

Finally, we cannot discard completely the role of chance or residual confounding. In absence of random allocation, as expected in an observational study, the likelihood of imbalance in known or unknown prognostic factors increases. Furthermore, although we considered the most relevant potential factors, unmeasured variables as pharyngeal colonization could have some impact in the incidence of VAP.

In summary, VAP represents a common problem in our country. Its epidemiologic profile in terms of incidence, length of stay and clinical course resembles the general pattern described everywhere. However, we could not identify any potentially modifiable risk factor for VAP. A comprehensive multicenter study is warranted, as it should provide deep insight about the specific microbiological, genetic and clinic features of VAP in our setting.

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References

1. Vincent JL, Bihari DJ, Suter PM, et al. The prevalence of nosocomial infection in intensive care units in Europe. Results

of the European Prevalence of Infection in Intensive Care (EPIC) Study. EPIC International Advisory Committee. *JAMA* 1995;**274**: 639–44.
2. Byers JF, Sole ML. Analysis of factors related to the development of ventilator-associated pneumonia: use of existing databases. *Am J Crit Care* 2000;**9**:344–9.
3. Heyland D, Cook D, Griffith L, Keenan S, Bun-buisson C. The attributable morbidity and mortality of ventilator-associated pneumonia in the critically ill patient. *Am J Respir Crit Care Med* 1999;**159**:1249–56.
4. Cook DJ, Walter SD, Cook RJ, et al. Incidence of and risk factors for ventilator-associated pneumonia in critically ill patients. *Ann Intern Med* 1998;**129**:433–40.
5. Kollef MH. Ventilator-associated pneumonia. A multivariate analysis. *JAMA* 1993;**270**:1965–70.
6. Bonten MJ, Bergmans DC, Ambergen AW, et al. Risk factors for pneumonia, and colonization of respiratory tract and stomach in mechanically ventilated ICU patients. *Am J Respir Crit Care Med* 1996;**154**:1339–46.
7. Craven DE, Kunches LM, Kilinsky V, Lichtenberg DA, Make BJ, McCabe WR. Risk factors for pneumonia and fatality in patients receiving continuous mechanical ventilation. *Am Rev Respir Dis* 1986;**133**:792–6.
8. Torres A, Serra-Batlles J, Ros E, et al. Pulmonary aspiration of gastric contents in patients receiving mechanical ventilation: the effect of body position. *Ann Intern Med* 1992;**116**:540–3.
9. Chevret S, Hemmer M, Carlet J, Langer M. Incidence and risk factors of pneumonia acquired in intensive care units. Results from a multicenter prospective study on 996 patients. European Cooperative Group on nosocomial pneumonia. *Intens Care Med* 1993;**19**:256–64.
10. Jaimes F. A literature review of the epidemiology of sepsis in Latin America. *Rev Panam Salud Publica* 2005;**18**:163–71.
11. Jaimes F, Arango C, Ruiz G, et al. Predicting bacteremia at the bedside. *Clin Infect Dis* 2004;**38**:357–62.
12. Garner JS, Jarvis WR, Emori TG, Horan TC, Hughes JM. CDC definitions of nosocomial infections. In: Olmsted RN, editor. *APIC Infection Control and Applied Epidemiology: Principles and Practice*. St. Louis: Mosby; 1996. p. A-1–A-20.
13. Hougaard P. *Analysis of multivariate survival data*. New York: Springer; 2000. p. 1–542.
14. Loader C. Local regression and likelihood. New York, 1999. p. 1–308.
15. Hamilton LC. *Statistics with Stata (updated for version 7)*. Belmont, CA: Duxbury Press; 2003.
16. Eggimann P, Hugonnet S, Sax H, Touveneau S, Chevrolet JC, Pittet D. Ventilator-associated pneumonia: caveats for benchmarking. *Intens Care Med* 2003;**29**:2086–9.
17. Sofianou DC, Constandinidis TC, Yannacou M, Anastasiou H, Sofianos E. Analysis of risk factors for ventilator-associated pneumonia in a multidisciplinary intensive care unit. *Eur J Clin Microbiol Infect Dis* 2000;**19**:460–3.
18. Apostolopoulou E, Bakakos P, Katostaras T, Gregorakos L. Incidence and risk factors for ventilator-associated pneumonia in 4 multidisciplinary intensive care units in Athens, Greece. *Respir Care* 2003;**48**:681–8.
19. Memish ZA, Cunningham G, Oni GA, Djazmati W. The incidence and risk factors of ventilator-associated pneumonia in a Riyadh hospital. *Infect Control Hosp Epidemiol* 2000;**21**:271–3.
20. Kanafani ZA, Kara L, Hayek S, Kanj SS. Ventilator-associated pneumonia at a tertiary-care center in a developing country: incidence, microbiology, and susceptibility patterns of isolated microorganisms. *Infect Control Hosp Epidemiol* 2003;**24**:864–9.
21. Ibrahim EH, Tracy L, Hill C, Fraser VJ, Kollef MH. The occurrence of ventilator-associated pneumonia in a community hospital: risk factors and clinical outcomes. *Chest* 2001;**120**: 555–61.
22. Apostolopoulou E, Sparos L, Soumilas A, Mantas I. Determinative factors in nosocomial pneumonia in patients with mechanical ventilation in the respiratory care unit. *Noseleutike* 1990;**29**:113–22.
23. Appelgren P, Hellstrom I, Weitzberg E, Soderlund V, Bindslev L, Ransjo U. Risk factors for nosocomial intensive care infection: a long-term prospective analysis. *Acta Anaesthesiol Scand* 2001; **45**:710–9.
24. Bauer TT, Ferrer R, Angrill J, Schultze-Werninghaus G, Torres A. Ventilator-associated pneumonia: incidence, risk factors, and microbiology. *Semin Respir Infect* 2000;**15**:272–9.
25. Beck-Sague CM, Sinkowitz RL, Chinn RY, Vargo J, Kaler W, Jarvis WR. Risk factors for ventilator-associated pneumonia in surgical intensive-care-unit patients. *Infect Control Hosp Epidemiol* 1996;**17**:374–6.
26. Bonten MJ, Kollef MH, Hall JB. Risk factors for ventilator-associated pneumonia: from epidemiology to patient management. *Clin Infect Dis* 2004;**38**:1141–9.
27. Cunnion KM, Weber DJ, Broadhead WE, Hanson LC, Pieper CF, Rutala WA. Risk factors for nosocomial pneumonia: comparing adult critical-care populations. *Am J Respir Crit Care Med* 1996;**153**:158–62.
28. Girou E, Stephan F, Novara A, Safar M, Fagon JY. Risk factors and outcome of nosocomial infections: results of a matched case-control study of ICU patients. *Am J Respir Crit Care Med* 1998;**157**:1151–8.
29. He L, Chen X, Pan J. Incidence, risk and prognostic factors of pneumonia acquired at intensive care units. *Zhonghua Jie He He Hu Xi Za Zhi* 1998;**21**:532–4.
30. Konrad F, Wiedeck H, Kilian J, Deller A. Risk factors in nosocomial pneumonia in intensive care patients. A prospective study to identify high-risk patients. *Anaesthesist* 1991;**40**: 483–90.
31. Noor A, Hussain SF. Risk factors associated with development of ventilator associated pneumonia. *J Coll Physicians Surg Pak* 2005;**15**:92–5.
32. Tejada AA, Bello DS, Chacon VE, et al. Risk factors for nosocomial pneumonia in critically ill trauma patients. *Crit Care Med* 2001;**29**:304–9.
33. Torres A, Aznar R, Gatell JM, et al. Incidence, risk, and prognosis factors of nosocomial pneumonia in mechanically ventilated patients. *Am Rev Respir Dis* 1990;**142**:523–8.
34. Concato J, Feinstein AR, Holford TR. The risk of determining risk with multivariable models. *Ann Intern Med* 1993;**118**: 201–10.
35. Rothman KJ, Greenland S. *Modern epidemiology,* 2nd ed. Philadelphia: Lippincott Williams & Wilkins; 1998.
36. Suissa S. Effectiveness of inhaled corticosteroids in chronic obstructive pulmonary disease: immortal time bias in observational studies. *Am J Respir Crit Care Med* 2003;**168**:49–53.
37. Altman DG, De Stavola BL. Practical problems in fitting a proportional hazards model to data with updated measurements of the covariates. *Stat Med* 1994;**13**:301–41.
38. Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. *Crit Care Med* 1985; **913**:818–29.
39. Bates DW, Sands K, Miller E, et al. Predicting bacteremia in patients with sepsis syndrome. Academic Medical Center Consortium Sepsis Project Working Group. *J Infect Dis* 1997; **176**:1538–51.
40. Martin GS, Mannino DM, Eaton S, Moss M. The epidemiology of sepsis in the United States from 1979 through 2000. *N Engl J Med* 2003;**348**:1546–54.