Antibiotic Use and the Risk of Pneumonia: 20 Years of Studies, but Where Are We Now?

Emili Diaz,1 Jordi Rello,1 and Jordi Valles2

1Critical Care Department, University Hospital Joan XXIII, University Rovira & Virgili, Tarragona, and 2Critical Care Department, Hospital de Sabadell, Sabadell, Barcelona, Spain

(See the article by Bornstain et al. on pages 1401–8)

Since 1986, when Craven et al. [1] published their pioneering multivariate analysis of risk factors for developing ventilator-associated pneumonia (VAP), many studies of the issue have been conducted. Some of these have been multicenter studies, and the results have identified different risk factors. However, the greatest confounding factor is that variables reported to be particularly influential by some researchers have been found to be negligible by others or, in some cases, even to protect against disease. After 20 years of study, it is time to assess the current situation.

Key areas in VAP research are the effect of the selection of the variables to be explored in the database, the case-mix of the population, and the relationship between antibiotic use and VAP over time. Clinical researchers cannot study all potential risk factors, because a database designed for this purpose would be extremely difficult to analyze. When researchers design a prospective study, variables to be recorded and analyzed should be selected on the basis of clinical experience or on the basis of a review of prior literature. Two studies provide good examples: Kollef et al. [2] reported that transfer from the intensive care unit (ICU) during mechanical ventilation was a risk factor for VAP, and a study by Valles et al. [3] demonstrated that continuous aspiration of subglottic secretions (CASS) was an independent factor that decreased the rate of VAP. However, the study by Kollef et al. [2] did not evaluate the effect of CASS. In turn, study by Valles et al. [3] was not able to explore the effect of transportation out of the ICU, because this variable was not included in the database. In addition, the capacity of retrospective studies to find an association between variables is limited because the database is already closed.

One of the limitations of most clinical investigations is that their results cannot be generalized. The first issue to be analyzed is the use of different prophylactic strategies to prevent nosocomial infection. Two recent studies emphasized that the degree of adherence to evidence-based prophylactic measures against VAP may vary widely among health care workers [4, 5]. For instance, limitation of stress-ulcer prophylaxis to high-risk patients—a grade B recommendation—was followed by 66.7% of health care workers, whereas selective digestive decontamination—a grade A recommendation—was applied by only 15.5% of experts. This low level of adherence was independent of the degree of evidence. Barriers to implementation of these measures for nurses were based on patient considerations, and many physicians expressed concerns about the interpretation of study results. The effectiveness of a particular strategy depends on its applicability. In the study by Bornstain et al. [6], heavy sedation and sucralfate therapy were used for only 27% and 17% of patients, respectively; a significant reduction in use of heavy sedation or sucralfate therapy would have a low impact on the overall rate of VAP. In addition, interactions between sucralfate therapy, enteral nutrition, and semirecumbent position are significant [7, 8]; however, this aspect is not detailed by Bornstain et al. [6].

It has been reported that the presence of coma was an independent risk factor for the development of VAP [9]. In fact, patients who are admitted to the ICU for coma or trauma have a high rate of early-onset VAP, reaching 50%–60% of patients in some series. Moreover, Sirvent et al. [10] reported an incidence of VAP of ∼50% in patients admitted to the hospital with structural coma, intracerebral hemorrhage, or head injury. Therefore, the case-mix is a factor to be considered when...
analyzing the results and their relevance in the clinical setting.

However, the case-mix is not the only factor that may cause differences between studies. Another limitation of all studies of risk factors is geographical variability. In 1999, a study compared the etiology of VAP in 4 sites (Barcelona, Spain; Seville, Spain; Paris; and Montevideo, Uruguay) and found large differences [11], although 3 of the 4 ICUs had similar case-mixes. The etiologic microorganisms most frequently isolated were *Pseudomonas aeruginosa*, oxacillin-resistant *Staphylococcus aureus*, Acinetobacter baumannii, and *Stenotrophomonas maltophilia*. Most episodes were due to *P. aeruginosa* (>95%) at one site, whereas episodes at the other sites were caused by *P. aeruginosa* and oxacillin-resistant *S. aureus* (37% and 63%, respectively). This variability should have an important effect on the design therapeutic guidelines [12]. Obviously, the effect of preventive measures may also present great variability between different sites. Similarly, there is high variability of practices and opinions among nurses and other health care workers at different sites [5].

Particularly noticeable is the relationship between antibiotic use and VAP. The majority of antibiotics used in the ICUs are active against the normal oropharyngeal flora (*Haemophilus influenzae*, *Streptococcus pneumoniae*, and methicillin-susceptible *S. aureus*). Given that the aspiration of contaminated secretions is the main pathogenic mechanism for the development of VAP [13], the efficacy of antibiotics to reduce the inoculum during the first days of intubation and to diminish the rate of VAP is easy to explain. Antibiotic use was useful as preemptive therapy for early-onset pneumonia in patients who were admitted to the hospital with coma [10], but it was associated with an increase in pneumonia due to antibiotic-resistant microorganisms in patients admitted because of trauma [14]. The effect of time on this dual action needs to be clarified. Two articles from the 1990s evaluated the dynamic pattern of risk factors over time [15, 16]. In 1999, we reported a cohort study that focused on episodes of pneumonia developed within the first 48 h after commencement of intubation. Of interest, the administration of antibiotics had a significant protective effect (OR, 0.29), although antibiotic exposure was associated with a significantly increased risk of pneumonia after 1 week of intubation (OR, 1.42) [14]. In a multicenter study, Cook et al. [15] analyzed the role of several risk factors, finding a protective factor for VAP in patients in the overall population who received antibiotic therapy (OR, 0.37; 95% CI, 0.27–0.51). This protection decreased over time during receipt of mechanical ventilation. In the study by Cook et al. [15], at day 5, patients had an OR for VAP of 0.3 (95% CI, 0.17–0.52), but, by day 20, the OR had increased to 0.89 (95% CI, 0.25–3.13). These studies confirm earlier reports suggesting that, although antibiotic therapy can decrease the overall rate of VAP as a result of a substantial reduction in the bacterial load during the first days of therapy, its use can increase late-onset VAP episodes due to antibiotic-resistant microorganisms [17], which are associated with high mortality rates [18].

In this issue of *Clinical Infectious Diseases*, Bornstain et al. [6] explore the association between a large number of variables and early-onset VAP in a mostly medical population. However, they do not assess other potentially associated variables, such as transportation out of the ICU or the effect of continuous sedation or continuous muscle-relaxing agents, as independent variables. In agreement with previous reports in the medical literature, they find a protective effect of antibiotic use in this period, but they do not analyze the effect of antibiotic therapy on the patients who continue to receive mechanical ventilatory support after 1 week of intubation. In fact, the authors report similarities between early-onset and late-onset cases of VAP (80 vs. 78), whereas other studies have found that the risk for VAP during the first week of mechanical ventilation is 2 or 3 times that during the rest of the mechanical ventilation period [14]. The incidence of tracheostomy is not reported, even though this procedure affects the incidence of VAP [19]. Besides, late-onset VAP can be affected by prior antibiotic administration [17].

The study by Bornstain et al. [6] provides a detailed description of risk factors that can be improved in our daily practice. Their findings suggest that it is possible to improve sedation policy and to emphasize ulcer prophylaxis without changing bacterial ecology. However, we believe that they do not provide convincing arguments in favor of use of antibiotics as systemic prophylaxis or preemptive therapy. Although antibiotic exposure may reduce the rate of early-onset pneumonia, we need to look forward and to assess the effect of antibiotics on delayed nosocomial infection (especially pneumonia), and length of stay, and mortality rate. An increase in the use of antibiotics to prevent early-onset VAP may increase the rate of late-onset VAP due to multiresistant bacteria. At this time, the association between antibiotic exposure and reduction in early-onset VAP seems to be clear, as does the association between antibiotic use and late-onset VAP. Presently, prophylactic administration of antibiotics for prevention of VAP in all patients is based on expert opinion, but more evidence is lacking. Therefore, we cannot recommend prophylactic administration of antibiotics for all patients during the first days of mechanical ventilation. Randomized, controlled trials of a single dose of a large half-life agent (compared with placebo) that use the incidence of VAP, the prevalence of long-term resistance, length of hospital stay, and mortality rates as end points should be performed now.

Acknowledgment

We thank Dr. Loreto Vidaur for insightful critique of the manuscript.
References