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The Severity of ICU-Acquired Pneumonia

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Abstract Much controversy exists about pneumonia in intensive care—especially, ventilator-associated pneumonia (VAP)—about its diagnosis and its attributable mortality. A better consensus exists about its prevention and its treatment. VAP occurs in already critically ill patients, and the relationship between preexisting organ dysfunction or failures and the severity of VAP has been recently highlighted. The role of the underlying disease should be considered as dominant, and this fact explains the paradox that exists between the high mortality of VAP and the relative minor effect of prevention measures on mortality.

Keywords Ventilator associated pneumonia · Intensive care unit · Attributable mortality · Severity of illness · SOFA score

Introduction

Pneumonia—especially, ventilation-associated pneumonia (VAP)—is the most frequent nosocomial infection occurring in the intensive care unit (ICU) [1]. Although its incidence is decreasing following the implementation of several prevention measures, it remains astonishing that these measures have little impact on length of ventilation, length of stay, and mortality [2].

Epidemiology of VAP

One of the best reviews about VAP's epidemiology, diagnosis, and treatment remains the paper of Chastre and Fagon published in 2002 [3••]. In this paper, it was reported that the crude ICU mortality rate associated with VAP was between 24 % and 76 % and that VAP itself increased the risk ratio of mortality by a factor of 2.2–4. It was also emphasized by these authors that VAP provoked by potentially resistant organisms like *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, or Methicillin-resistant *Staphylococcus aureus* had a considerably higher mortality. More recently, the systematic review of observational and randomized trials on the incidence of VAP done by Sadfar et al. in 2005 [4] concluded that patients who develop VAP appear to be twice as likely to die, as compared with similar patients without VAP; thus, the mortality rate was a little less than that in the review of Chastre and Fagon [2] but still was substantially impressive.

However, the real worsening of the clinical status provoked by VAP in a patient who, by definition, is already in the ICU for a reason other than VAP has been poorly described. Since the review of Chastre and Fagon, several large epidemiological studies on infection in the ICU have been published. The EPIC II study involved 13,796 patients from 1,265 participating ICUs in 75 countries [1]. Fifty-one percent of patients were considered infected the day of this point prevalence study. The infection was of respiratory origin in 64 % of the infected patients. Interestingly, the infection rate was related to disease severity, as expressed by the simple acute physiologic score (SAPS) and the degree of organ failure. However, the episodes were not classified between infections already present on admission and infections occurring during the ICU stay. In the same way, the temporal relationship between organ failure and infection could not be established. Obviously, organ failures preceding the ICU-acquired infections (IAIs) could not be attributed to these infections. The SOAP study about sepsis in European ICUs could have answered this question [5]. This cohort, multicenter, observational study differentiated sepsis on admission and sepsis occurring during ICU stay. Among 3,147 patients, 37 % had sepsis; two thirds of these had sepsis on admission. Again, the lung was the most common site of infection (68 %), and patients with sepsis had more severe organ dysfunction and a higher mortality rate than did patients without sepsis. Unfortunately, regarding the ICU-acquired sepsis, the temporal relationship between organ

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failure and sepsis was not evaluated. In this study, Pseudomonas species was the only microorganism independently associated with increased mortality.

In another large multicenter epidemiological study about sepsis and infection in ICU patients involving 14,364 patients, Alberti et al. reported that 15.3 %–31.4 % of ICU patients developed an IAI, depending on the fact that they were infected or not at entry in the ICU [6]. Among these IAIs, 75.6 % were pneumonia. Interestingly, the authors specified that severe sepsis or septic shock occurred in 56.2 % of these IAIs. It must indeed be acknowledged that severe sepsis or septic shock involves new organ dysfunctions or failures and that these failures can be the cause of an increased rate of mortality. The same authors went further in the analysis of sepsis in critically ill patients, showing that the first stage of sepsis had similar outcomes as infection without signs of sepsis, emphasizing the role of organ dysfunction or shock in the prognostic significance [7]. In a third paper, Alberti et al. interestingly looked for the risk factors for worsening sepsis in infected patients [8]. Unfortunately, the study enrolled patients who were diagnosed as having sepsis and did not analyze the period preceding the infection.

Impact of the Prevention Studies

To further analyze the relationship between VAP and mortality, it is worth taking into account the studies about prevention. It has indeed been demonstrated during the last decade that the implementation of one or a bundle of prevention procedures substantially and successfully reduces the incidence of VAP [9, 10, 11•], from about 10 episodes/1,000 ventilation days to almost zero in the United States [12] and from 25 or more to about 12 episodes/1,000 ventilation days in Europe [13–16]. Besides the strange difference between the United States and Europe regarding the incidence of VAP, it is worth noting that no studies with a successful decrease in VAP incidence could demonstrate a similar reduction in mortality. In a recent paper, indeed, Melsen et al. reviewed 58 randomized studies on VAP prevention, including studies about selective digestive decontamination, stress ulcer prophylaxis, selective oral decontamination, ventilator circuit management, closed suction, enteral feeding, subglottic secretion suctioning, probiotics, endotracheal tubes, and body positioning [17•]. Melsen et al. concluded that mortality attributable to VAP was estimated to be only 9 %, despite the fact that none of the 58 comparisons showed a statistically significant relative risk reduction.

The absence of an effect on mortality was also addressed by Klompas, who argued that this paradox should largely be attributable to lack of specificity in the VAP definition [2, 18•, 19]. Objective surveillance definitions for VAP are now looked for [20, 21], and a new concept is emerging: the ventilator-associated complication, which appears to be a simple, objective measure of respiratory deterioration based on the increases in the fraction of inspired oxygen or positive end-expiratory pressure lasting at least 2 days after at least 2 days of stability [22]. It must be acknowledged that we need an objective tool for meaningful internal or external benchmarking and for improvement of the quality of care for ventilated patients. However, in order to explain the paradox raised by Klompas [17•], we may wonder whether there is not another explanation.

Evaluation of the Severity of VAP

The reason for the striking discrepancy in mortality rate estimation between epidemiological studies and prevention studies may be found in an already old paper from E Girou et al. published in 1998 [23]. In this study, the authors tried to define the risk factors and outcomes of nosocomial infections by a matched case–control study of ICU patients. Patients with IAI were matched with patients without IAI on the basis of age, the same APACHE II score on ICU admission, and a length of ICU stay at least equal to the interval for cases from admission to the occurrence of IAI. The particular interest of this study was that the authors gave the evolution of severity scores (APACHE II, SAPS, and Therapeutic Interventions Scoring System [TISS]) during 7 days before the occurrence of IAI. Although these scores were of the same magnitude for both groups on admission, their evolutions were totally different, rapidly decreasing in control patients but remaining high in cases until the occurrence of infection. That means that the medical or surgical problems of patients who developed IAI were not cured as easily as in the control patients, before occurrence of IAI. Therefore, the differences in the evolution between cases and controls could not be attributed solely to the IAI but might also have depended on the underlying disease prior to IAI. Curiously, the authors inadequately attributed the difference in mortality solely to IAI, in a proportion as high as 40 %. It was, however, clear that the underlying disease was part of the problem.

Now, using the Sequential Organ Failure Assessment (SOFA) score [24], we have the possibility of estimating daily the number and the severity of organ dysfunction or failure in ICU patients. The $SOFA_{max}$ is a score derived from the SOFA score and is the sum of all the organ dysfunctions or failures encountered by patients during the total ICU stay. It characterizes the ICU stay and is well correlated with ICU mortality [25]. In the same way and in order to define what was going on in patients before the occurrence of IAI or VAP, we defined the $SOFA_{preinf}$, which is the sum of all the organ dysfunctions or failures occurring before the occurrence of IAI that may be a VAP [26]. $SOFA_{preinf}$, measured in 625 patients developing an IAI among 2,423 patients hospitalized for more than 48 h in a 26-bed ICU during 4 years, represented as much as 83 %

of the $SOFA_{max}$, which reached 11.7. The $SOFA_{preinf}$ (9.7) was higher than the $SOFA_{max}$ (7.3) of the 1,523 patients without IAI. The $SOFA_{preinf}$ corresponded to a mean number of 2.2 organ failure defined by a partial SOFA score of 3 or 4. Interestingly, patients who suffered from septic shock provoked by IAI had a $SOFA_{preinf}$ (11.3) significantly higher than the $SOFA_{preinf}$ of patients who developed only sepsis or who did not develop signs of sepsis (8.9). Patients with severe sepsis had a $SOFA_{preinf}$ in between (Fig. 1). That means that the severity of sepsis could also depend on the severity of the underlying disease. By multivariate analysis, both the severity of sepsis and the $SOFA_{preinf}$ were significantly associated with mortality.

Regarding VAP, this type of infection was encountered in 453 patients [27]. These patients were classified according to the microorganisms responsible for VAP into seven groups: patients infected by third-generation cephalosporin-resistant nonfermenting Gram-negative bacilli (n=31), patients infected by third-generation cephalosporin-sensitive nonfermenting Gram-negative bacilli (n=92), patients infected by methicillin-resistant *Staphylococcus aureus* (n=27), patients infected by methicillin-sensitive *Staphylococcus aureus* (n=68), patients infected by extended spectrum betalactamase-producing *Enterobacteriaceae* (n=36), patients infected by *Enterobacteriaceae* not producing extended spectrum of betalactamase (n=162), and lastly, patients infected by *Streptococcus pneumoniae* or *Haemophilus influenzae* (n=37) [14]. In doing so, it was confirmed that nonfermenting Gram-negative bacilli provoked a septic shock more often than did the other groups (30 % vs. 18.8 %, respectively; p=.01) and that they were associated with a higher ICU mortality (39 % vs. 25.8 %; p=.007). However, the occurrence of severe sepsis or septic shock between groups was almost completely related to the magnitude of $SOFA_{preinf}$, the determination coefficient R^2 reaching .84. For all the VAPs, the new organ dysfunctions or failures occurring during VAP and attributable to them represented only 11 % of $SOFA_{max}$, despite the fact that septic shock occurred in 21 % of the episodes. Interestingly, the type of bacteria was not a risk factor for the occurrence of septic shock or for mortality. Age and $SOFA_{preinf}$ were risk factors for sepsis severity, and the latter was a risk factor for ICU mortality. VAP provoked a minor part of organ dysfunction or failures as evaluated by $SOFA_{max}$. It was not surprising, therefore, that in our series, the appropriateness of the first treatment was not kept as a risk factor for mortality by the multivariate analysis.

Confirmatory Studies About the Role of the Underlying Disease

VAP occurred in already critically ill patients. The high number of organ failures preexisting the most severe episode may explain why the prevention procedures had little impact on mortality. Preexisting organ failures have been also pointed out by Depuydt et al. in a recent study in which the authors analyzed the risk factors for mortality in patients suffering

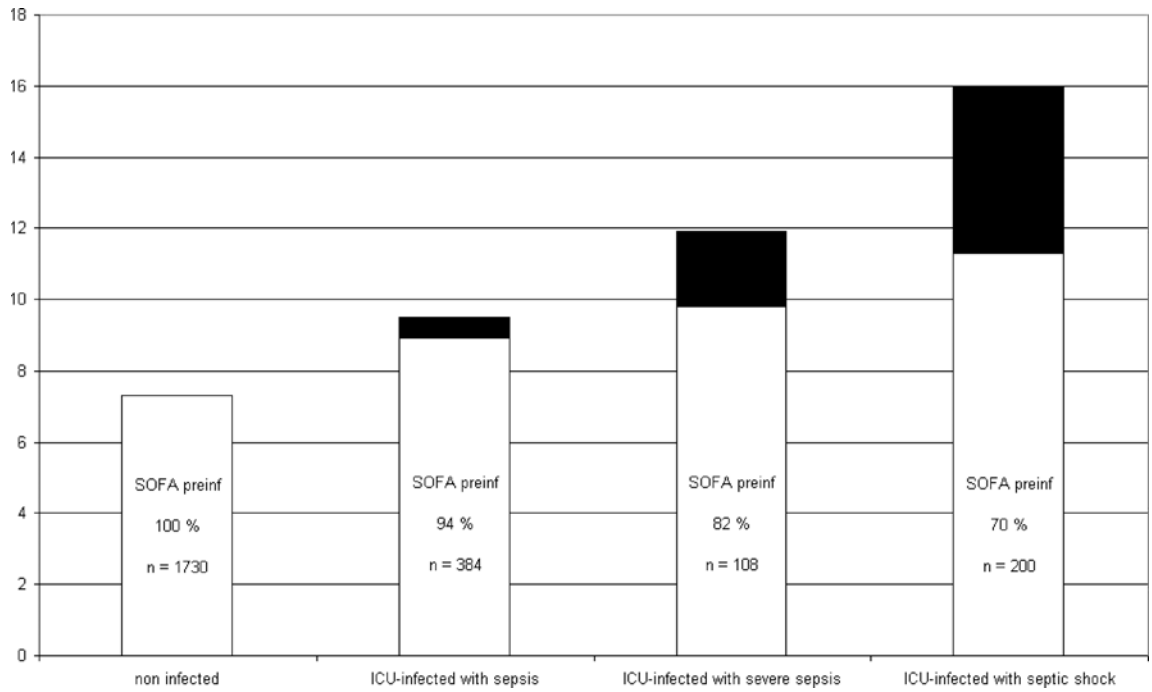

Fig. 1 Partition of $SOFA_{max}$ according to the severity of infection. $SOFA_{max}$ is the sum of all the organ dysfunctions or failures during the ICU stay. $SOFA_{preinf}$ is the sum of all the organ dysfunctions or failures before the occurrence of ICU-acquired infection

from VAP [28]. They also found that neither the type of bacteria—in particular, their resistance patterns—nor the appropriateness of treatment was related to mortality, in contrast with presence of shock, ARDS, or renal failure before the occurrence of VAP. All of these failures are taken into account in the $SOFA_{preinf}$. Finally, using a new statistical method from the field of causal inference, taking into account the evolution of risk and the occurrence of organ dysfunction during the ICU stay, Bekaert et al. were able to analyze in depth the outcome for 4,479 patients from the longitudinal prospective French multicenter Outcomerea database [29••]. This study found that 4.4 % of the deaths in the ICU on day 30 were attributable to VAP. With an observed ICU mortality of 23.3 % on day 30, this corresponded to an ICU mortality attributable to VAP of about 1 % on day 30. This emphasizes the actual low effect on mortality provoked by VAP, as already discussed by Muscedere in 2010 [30].

If the underlying disease appears to play a major role in the outcome for patients with VAP, it is interesting to look at the outcome for patients with usually low comorbidities and few organ dysfunctions, such as trauma patients, who may be ventilated for a long period of time. Magret et al. recently observed that VAP in trauma patients was indeed associated with lower mortality [31]. In the same way, Josephson et al. found no increase in mortality in their neurological critically ill patients [32].

Before concluding, we should welcome efforts such as those mentioned in Grgurich et al.'s recent review [33] in order to define a gold standard for proper definition of VAP—hence, the one that best fits our daily clinical practice.

Conclusion

In conclusion, the severity of VAP depends on the underlying disease's severity in ICU patients. The more sick the patient is, the more prompt he or she is to become infected, and the more severe this infection will be. This explains why patients developing VAP have a high mortality, as compared with patients who do not, and also why prevention measures have little impact on the outcome. This is the end of the seemingly paradox.

Compliance with Ethics Guidelines

Conflict of Interest Hugues Marechal, Nathalie Layios, and Pierre Damas declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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