ICU-acquired pneumonia: is it time to use this term?

Antoni Torres

Ventilator-acquired pneumonia (VAP) is a major complication in intubated and mechanically ventilated patients. Its consequences include increases in length of stay, health costs, antibiotic consumption, and in crude and attributable mortality. Due to the systematic application of bundles to prevent VAP in recent years, its incidence has fallen below six cases per 1000 days of mechanical ventilation [1,2].

Nosocomial pneumonia in the ICU can be divided into VAP and hospital-acquired pneumonia (HAP). Most of our knowledge of HAP in nonintubated patients has been extrapolated from VAP, which has been thoroughly investigated; having focused so intensively on VAP for many years, we have probably neglected nonventilated HAP acquired or admitted to the ICU. Together, the two entities can be termed 'ICU-Acquired Pneumonia (ICUAP).' In a systematic prospective search of cases of ICUAP at six different ICUs at a university tertiary hospital, we found that VAP accounted for 60% of cases of ICUAP, and HAP 40% [3]. These figures emphasize the importance of nonventilated HAP [2] in the ICU. When nonventilated HAP requires mechanical ventilation, mortality is even higher than in VAP. In a docket document [4], the Food and Drug Administration (FDA) stressed the importance of HAP, HAP requiring ventilation and VAP. In fact, the 28-day mortality of these three different nosocomial categories varies: low for HAP, intermediate for VAP and the highest for HAP requiring mechanical ventilation. This information is likely to be of crucial importance for future RCTs.

The present issue of *Current Opinion of Critical Care* is devoted to the new concept of ICUAP. In the first chapter, the epidemiology of ICUAP is reviewed (MCC240512). As noted above, 30–40% of ICUAP are HAP and 50–60% VAP. With the increased use of noninvasive mechanical ventilation and high-flow oxygen systems, the number of intubated patients is falling. We now see more and more patients who are very sick but do not undergo intubation, and who frequently present risk factors for acquiring HAP.

The second (MCC240504) and third (MCC240509) chapters deal with microbial cause and its diagnosis, comparing HAP vs. VAP. The literature on this point is limited because of the difficulty of obtaining good quality respiratory samples in nonintuabted patients, but it seems that HAP in the ICU presents a similar microbiology to VAP. There is a need for good bronchoscopic studies in HAP patients to establish its microbial cause.

Conceptually, and according to the new guidelines [1,2], the different types of microorganisms that might cause HAP or VAP, and especially multi drug resistant microorganisms (MDR)/extended drug resistant microorganisms (XDR) or pan drug resistant microorganisms (PDR) microorganisms, are associated with a variety of clinical risk factors. In an era in which the majority of treatments for ICUAP are still empirical, precise information on the risk factors for MDR/XDR/PDR microorganisms is very important (MCC240514).

As mentioned above, the IDSA/ATS and International European Guidelines were published in 2016 and 2017, respectively [1,2]. The differences between the two sets of guidelines are reviewed in one of the chapters (MCC240510). The main differences lie in the sampling and culturing of respiratory secretions (distal quantitative vs. proximal qualitative), risk factors for MDR/XDR/PDR microorganisms, duration of antibiotic treatments, and the use of biomarkers.

One of the most important issues is antibiotic treatment (MCC240508). Overall, given the information available on HAP, there should not be many differences in the approach to the treatment of HAP and VAP in the ICU; the risk factors described for MDR/XDR/PDR microorganisms are the same for HAP as for VAP. However, studies that try to associate MDR/XDR/PDR microorganisms are much more frequent in VAP. Treatment duration, when the initial antibiotic is appropriate and when there are

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no complications of pneumonia, should not exceed 8–10 days. This is an important concept that has changed recently with the application of the stewardship programs. The international guidelines [2] propose an empirical treatment algorithm that is described in this chapter and is based on the presence or absence of two or more risk factors for MDR/XDR/PDR microorganisms, a probability of dying of more than 15% and the presence or absence of septic shock. In each of these situations dual or triple initial therapy (two antipseudomonal with anti MRSA) is recommended. This algorithm needs prospective validation.

Biomarkers, particularly C-reactive protein and Procalcitonin, are extensively used in the monitoring of treatment of severe infections in the ICU. However, the recent international guidelines [2] on HAP and VAP do not recommend their use in order to shorten antibiotic treatments when the initial treatment is appropriate and the patient presents good clinical evolution. However, there are situations in which biomarkers may guide the antibiotic duration, such as inappropriate initial treatment, immunosuppression, pulmonary abscess or empyema and the use of second-line antibiotics such as colistin, fosfomycin or tigecycline. All these issues are reviewed in depth in the chapter on biomarkers (MCC240505).

In the last 10 years, considerable efforts have been made to prevent VAP. The application of bundles (combination of effective methods of VAP prevention) has helped to reduce the incidence of VAP, as commented above. In HAP, on the other hand, the physiopathology, incidence and risk factors have not been well studied and its prevention has been neglected (MCC240501). A great deal remains to be done: probably, however, the use of very simple interventions such as raising the head from the bed, and the administration of special diets to avoid aspiration of gastric contents or food into the lower airways could reduce the incidence of HAP. There is a clear need for interventional studies in this field.

Finally, one of the chapters compares the views of the two main regulatory agencies [FDA and European Medicines Agency (EMA)] on the execution of Randomized Controlled Trials (RCTs) for antibiotics (MCC240503). The FDA is much more aware of the concept of ICU-acquired pneumonia than the EMA: the FDA's most recent recommendations [4], in which the main end-point is any cause 28-day mortality, recognize the differences in mortality between HAP, HAP requiring mechanical ventilation and VAP.

In summary, the concept of ICUAP (HAP and VAP) needs to be implemented in the control of respiratory infections in the ICU. Nosocomial pneumonia in the ICU does not only include VAP. Measures of quality control in the ICU should implement this new concept of ICUAP. In addition, future RCTs (especially those dealing with new antibiotics and prevention) need to include and stratify both entities.

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Epidemiology of ICU-acquired pneumonia

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Purpose of review
Review of the epidemiology of ICU-acquired pneumonia, including both ventilator-associated pneumonia (VAP) and hospital-acquired pneumonia (HAP) in nonventilated ICU patients, with critical review of the most recent literature in this setting.

Recent findings
The incidence of ICU-acquired pneumonia, mainly VAP has decrease significantly in recent years possibly due to the generalized implementation of preventive bundles. However, the exact incidence of VAP is difficult to establish due to the diagnostic limitations and the methods employed to report rates. Incidence rates greatly vary based on the studied populations. Data in the literature strongly support the relevance of intubation, not ventilatory support, in the development of HAP in ICU patients, but also that the incidence of HAP in nonintubated patients is not negligible. Despite the fact of a high crude mortality associated with the development of VAP, the overall attributable mortality of this complication was estimated in 13%, with higher mortality rates in surgical patients and those with mid-range severity scores at admission. Mortality is consistently greatest in patients with HAP who require intubation, slightly less in VAP, and least for nonventilated HAP. The economic burden of ICU acquired pneumonia, particularly VAP, is important. The increased costs are mainly related to the longer periods of ventilatory assistance and ICU and hospital stays required by these patients. However, the different impact of VAP on economic burden among countries is largely dependent on the different costs associated with heath care.

Summary
VAP has significant impact on mortality mainly in surgical patients and those with mid-range severity scores at admission. The economic burden on ICU-acquired pneumonia depends mainly on the increased length of stay of these patients.

Keywords
attributable mortality, ICU-acquired pneumonia, ventilator-associated pneumonia

INTRODUCTION

ICU-acquired pneumonia is defined as a pneumonia that develops in patients who have been admitted to an ICU for at least 48 h, regardless they are tracheally intubated and mechanically ventilated or not. Most studies on hospital-acquired pneumonia (HAP) are focused in ventilated patients, namely, ventilator-associated pneumonia (VAP), due to the higher incidence compared with in nonventilated patients, the elevated morbidity, and mortality, and the better availability of techniques to define the responsible microorganisms. However, a multicentre Spanish report showed that, among more than 10 000 ICU admissions, only 30% patients were mechanically ventilated for 48 h or more [1]. Therefore, there may be a likely bias when information on VAP is extrapolated to nonventilated patients with HAP. ICU-acquired pneumonia includes both VAP and HAP in nonventilated patients. In addition, nonventilated patients with HAP may require subsequent intubation and ventilation due to clinical worsening. Figure 1 shows a schematic definition of the different clinical presentations of ICU-acquired pneumonia.

Recently, the Centers for Disease Control and Prevention (CDC) convened a VAP surveillance definition working group [2]. This working group introduced a three-tier, adult surveillance definition algorithm for ventilator-associated events

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KEY POINTS

- The incidence of ICU-acquired pneumonia, including VAP and HAP has decrease in recent years possibly due to the implementation of preventive bundles. The incidence depends on the diagnostic methods employed. Patients with acute respiratory distress syndrome and those who receive those treated with venoarterial extracorporeal membrane oxygenation support have the highest risk for VAP.
- The mortality of patients with VAP subsequently intubated is greatest, slightly less in VAP, and least for nonventilated HAP.
- The overall attributable mortality of VAP is estimated in 13%, with higher mortality rates in surgical patients and those with mid-range severity scores at admission.
- The increased costs associated with the development of ICU-acquired pneumonia, particularly VAP, are mainly related to the increased length of stay, but this impact is largely dependent on the different costs associated with heath care among countries.

(VAE) to monitor complications in mechanically ventilated patients, using objective, readily available data elements and can identify a broad range of conditions and complications occurring in mechanically ventilated adult patients, including but not limited to VAP. The three tier definitions were named ventilator-associated condition, infection-related ventilator-associated complication (IVAC), and, depending on whether patients with IVAC also have laboratory and/or microbiological evidence of respiratory infection, possible and probable VAP. The VAE surveillance was implemented in January 2013 in the CDC's National Healthcare Safety Network.

Based on this algorithm, in a patient with an IVAC, possible and probable VAP are defined by signs of pulmonary infections (purulent secretions or a positive lower respiratory tract culture). In particular, probable VAP is defined by a positive lower respiratory tract culture, meeting-specific quantitative, or semiquantitative thresholds of pathogen growth (Fig. 2) [2].

INCIDENCE

Both HAP and VAP are frequent complications of hospital care, accounting for 22% of all hospital-acquired infections in a multistate point-prevalence survey [3]. VAP develops in approximately 10–40% of patients on mechanical ventilation for more than 2 days, with large variations among countries and ICU types [4–8].

In a 1-day point prevalence survey of 13 796 adult patients in 1265 ICUs of 75 countries, 51% patients were infected, of whom 64% (4503 patients) had an infection of the respiratory tract [9]. A total of 67.5% infected patients in this study, as compared with 44% noninfected patients, were mechanically ventilated at admission. As specific information on ventilated and nonventilated patients was not reported, these episodes could have been classified as either VAP or HAP in nonventilated patients. The incidence of pneumonia strongly depends on the time patients remain in critically ill condition. Therefore, this 1-day point prevalence survey may have overestimated the actual incidence of VAP or HAP among ICU patients, as patients with prolonged ICU stay are more likely to be represented

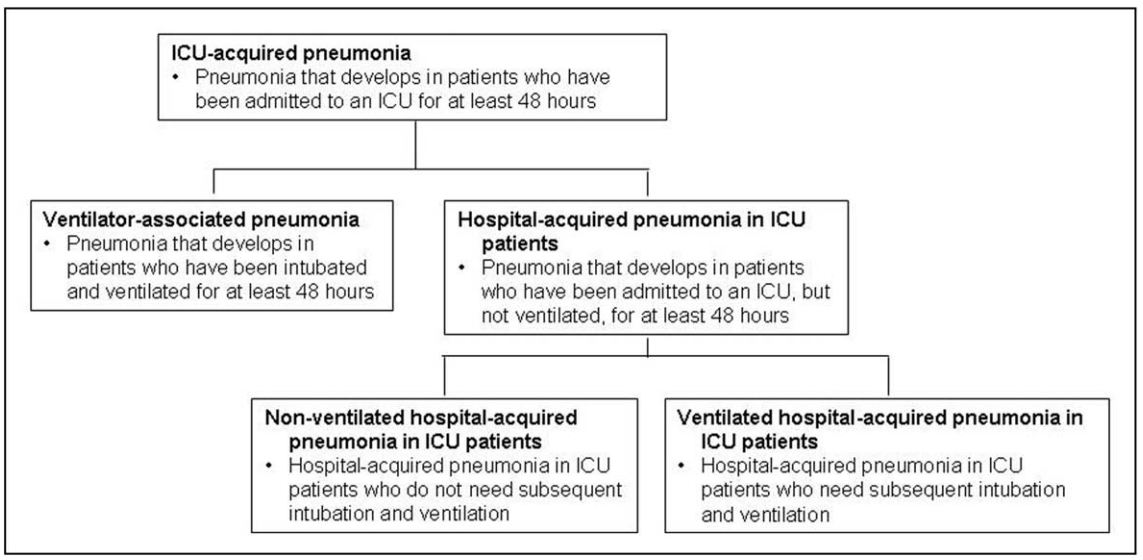

FIGURE 1. Schematic definition of the different type of pneumonia diagnosed in ICU patients.

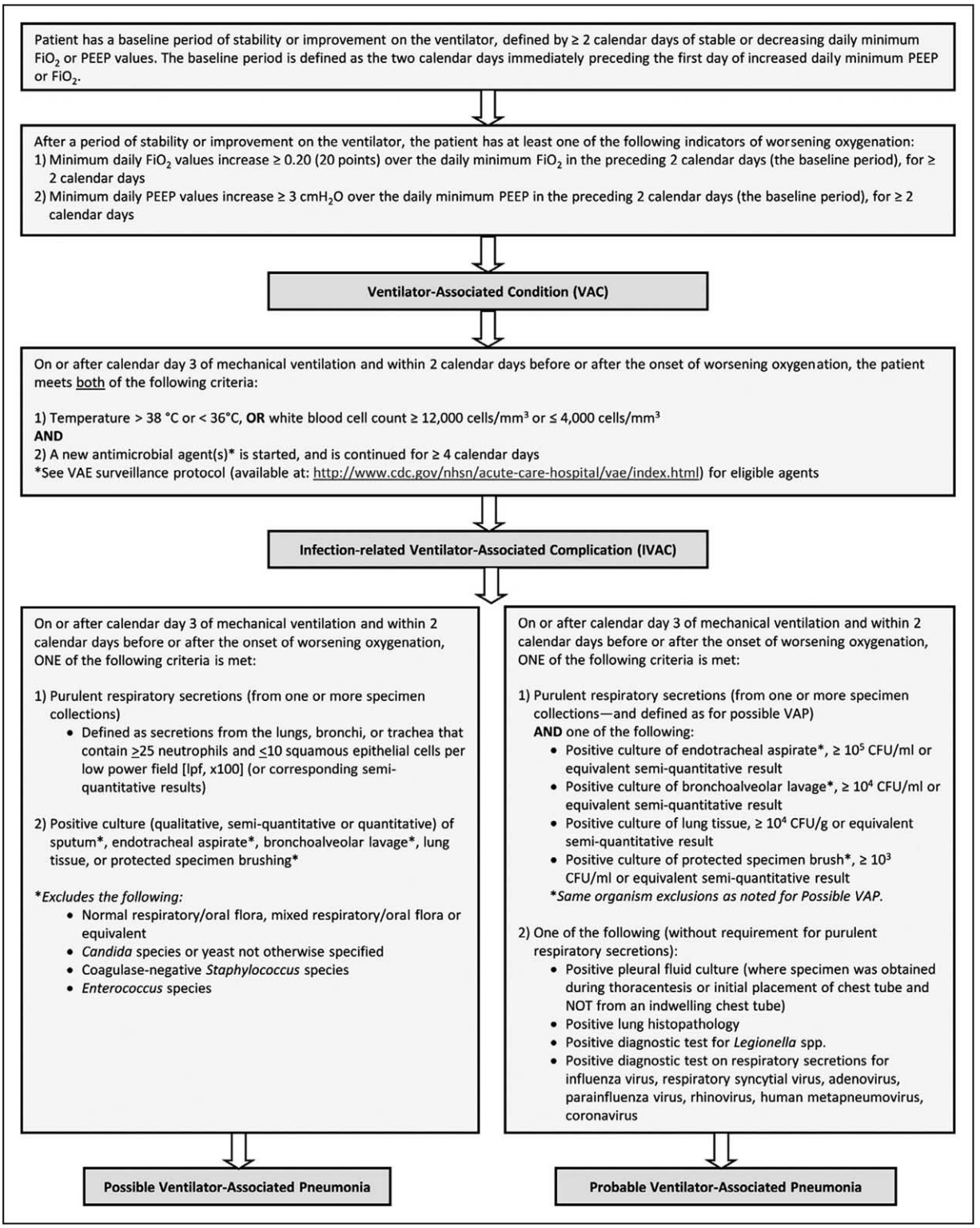

FIGURE 2. Ventilator-associated events surveillance definition algorithm. *Full ventilator-associated events surveillance protocol available at: http://www.cdc.gov/nhsn/acute-care-hospital/vae/index.html for eligible antimicrobials. CFU, colony-forming units; F_IO_2, fraction of inspired oxygen; PEEP, positive end-expiratory pressure; VAP, ventilator-associated pneumonia. Reproduced with permission [2].

in such surveys. Hence, reporting incidence density as cases per 1000 ventilator or ICU-days is an alternative method that reflects better the disease burden.

The exact incidence of VAP is difficult to establish due to the diagnostic limitations and the methods employed. In the latest report by the US National Healthcare Safety Network (NHSN) [10] mean VAP rates in North American institutions were as low as 1–2.5 cases per 1000 ventilator-days. This strongly differs compared with the higher rates reported in Europe [11,12], and suggests low diagnostic accuracy when VAP is detected through standard radiographic, pulmonary, and clinical signs of infection. Incidence rates greatly vary based on the studied population, for example, patients with acute respiratory distress syndrome have the highest risk for VAP, due to the severity of illness and the high requirement of sedatives [13].

From 2006 to 2012, the incidence of VAP reported to the CDC by the NHSN. In medical and surgical ICUs decreased in the USA [10,14], from 3.1 to 0.9 (71% decline) and 5.2 to 2.0 (62% decline) cases per 1000 ventilator-days, respectively. Whether the decrease was attributable to better care or stricter application of subjective surveillance criteria is unclear. For this reason, the USA Medicare Patient Safety Monitoring System (MPSMS) independently measured VAP rates since 2005, using a stable definition [15]. The trends in VAP rates, expressed as %, were further analyzed by the same authors in four 2-year periods [16▪], among a randomly selected sample of 1856 mechanically ventilated Medicare patients 65 years and older with principal diagnoses of acute myocardial infarction, heart failure, pneumonia, and selected major surgical procedures. These authors found that VAP rates were stable over time, with an observed rate of 9.7% during the whole period, and an adjusted average annual change of 0.00.

These data have limitations. The discordance between these findings and the significant declines in VAP rates reported by the NHSN [10,14] could in part be due to differences in MPSMS and NHSN measure definitions, hospitals, or patient groups, changes in characteristics of hospitals reporting to the NHSN over time, or preferential declines in VAP rates among hospitals reporting to the NHSN. Nonetheless, the dichotomy between VAP rates reported to the NHSN and measured in the MPSMS supports the concern that surveillance using traditional definitions may be unreliable. The ongoing risk to patient safety represented by VAP supports the NHSN decision to explore more objective surveillance targets [2].

Age does not appear to be particularly associated with a different risk to develop pneumonia. A European multicenter prospective cohort study investigated the epidemiology of VAP in elderly ICU patients [11]. The prevalence of VAP in cases/1000 ventilation days was 13.7 in middle-aged (45–64 years) patients, 16.6 in old patients (65–74 years), and 13.0 in very old patients (≥75 years). Logistic regression analysis could not demonstrate older age as a risk factor for VAP.

Among critically ill patients, those treated with venoarterial extracorporeal membrane oxygenation support (VA-ECMO) are at particularly high risk to develop VAP. A recent study in a surgical ICU about 150 patients assisted with VA-ECMO for more than 48 h during a 2-year period reported a 56% incidence of VAP confirmed microbiologically, for a rate of 60.6 per 1000 ECMO days [17▪]. This study highlighted that VAP in patients treated with VA-ECMO is associated with an increased morbidity and mortality.

Few studies have addressed HAP in nonventilated ICU patients. A previous study reported that more than 40% cases of ICU-acquired pneumonia occurred in patients who were not mechanically ventilated previously [18]. In this study, more that 50% cases of HAP in nonventilated patients required subsequent intubation, that is, ventilated-HAP. The positive etiologic diagnosis in this study was more frequent in VAP, as compared with nonventilated HAP, likely caused by more patients with lower respiratory tract samples cultured. However, in patients with defined cause only, the proportion of the most relevant pathogens was similar between patients with HAP and nonventilated HAP, suggesting that both types of patients might receive similar empiric antibiotic treatment.

Nonventilated ICU patients are at lower risk to develop pneumonia as compared with ventilated patients. An analysis of the German nosocomial infection surveillance system database on 400 ICUs with 779 500 admitted patients, 1068 472 invasive mechanical ventilation days and 101 569 noninvasive ventilation days reported 6869 cases of pneumonia between 2005 and 2007 [19]. The mean pneumonia incidence densities for patients with invasive and noninvasive ventilation were 5.44 and 1.58 cases per 1000 ventilation days, respectively, whereas the mean incidence density of HAP not associated with ventilation was lower with 0.58 cases per 1000 patient days without ventilation. These data strongly support the relevance of intubation, not ventilatory support, in the development of HAP in ICU patients, but also that the incidence of HAP in nonintubated patients is not negligible.

The incidence of HAP in non-ICU patients has also been less extensively addressed in the literature. Non-ICU HAP was prospectively studied for an 18-month period by active, bimonthly 1-week

surveillance [20]. Epidemiologic data, cause, and evolution of pneumonia were recorded, with blood and sputum cultures and *Legionella pneumophila* and *Streptococcus pneumoniae* urinary antigen tests were performed in this study. There authors reported a mean incidence of HAP of three cases/1000 hospital admissions, mostly in elderly patients from medical wards, with severe underlying diseases, and with a previous hospital stay more than 5 days. Clinical complications occurred in 52% of the cases, and mortality was 26% (13.9% attributed to pneumonia) in this study.

MORBIDITY AND MORTALITY

ICU-acquired pneumonia has major consequences and negatively impacts important patient outcomes. Although all-cause mortality associated with VAP has been reported to range from 20 to 50%, the mortality rates are inconsistent among studies, and the mortality directly related to VAP, that is, to what extent VAP increases the likelihood of death in ICUs, is debated.

The mortality associated with VAP has been traditionally considered higher than that of HAP in nonventilated patients [21]. However, these studies considered mainly noncritically ill HAP patients. When nonventilated HAP in ICU patients was compared with VAP, the crude mortality was similar, suggesting that factors related to the host, rather than previous intubation, are the main determinants of outcome [18].

A recent document focused on analyses of a total of 10 modern clinical trial datasets on patients with both VAP and HAP in ICU patients nonventilated previously [22▪]. The authors analyzed the relevance of the need for subsequent intubation due to pneumonia in those patients with HAP. The all-cause mortality was consistently greatest in ventilated HAP, likely because the need for intubation in this population is a marker of poor evolution of pneumonia, slightly less in VAP, and least for nonventilated HAP. Patient characteristics and mortality rates were considered sufficiently similar for VAP and ventilated HAP in this document. Therefore, nonventilated HAP patients appear sufficiently different from the other two groups in terms of outcomes. Additional predictors of increased mortality in nonventilated HAP include older age and elevated severity scores at admission.

Different methods have been used to calculate the attributable mortality of VAP, yielding estimates ranging from 0 to 60%. Most studies were observational, using cohorts of affected and nonaffected patients to calculate relative risks or odds ratios, or had extensive heterogeneity of studies [23]. Quantifying the effects of VAP on patient outcome is also hampered because of the time-dependent nature of the disease, which might include time-dependent bias and the fact that ICU mortality and discharge act as competing endpoints. To overcome these issues, innovative techniques such as multistate and competing risks models have been applied to estimate attributable mortality of VAP [24,25]. However, adjustment for confounding is still not possible because of the observational nature of the data. Randomization is the only procedure to exclude the effects of confounding, and therefore, studies in which patients have been randomly assigned to receive a preventive measure would allow a nonconfounded estimate of attributable mortality by analyzing the preventive effects on VAP and death. On the basis of a meta-analysis of aggregated data from 53 randomized prevention studies including 58 comparisons the attributable mortality of VAP was estimated to be 9% [26]. Yet, this approach was limited by the absence of individual patient data, which precluded subgroup analyses as well as applying any of the newer statistical methods that adjust for competing endpoints.

For this reason, an individual patient data meta-analysis of 6284 patients from 24 trials of VAP prevention was performed [27]. Predefined subgroups included surgical, trauma, and medical patients, and patients with different categories of severity of illness scores. The overall attributable mortality of VAP was 13% in this study, with higher mortality rates in surgical patients and patients with mid-range severity scores at admission. Attributable mortality was close to zero in trauma and medical patients, and in patients with low or high severity of illness scores. Competing risk analyses could be done for 5162 patients from 19 studies, and the overall daily hazard for ICU mortality after VAP was 1.13. The overall daily risk of discharge after VAP was 0.74, leading to an overall cumulative risk for dying in the ICU of 2.20. Highest cumulative risks for dying from VAP were noted for surgical patients (2.97) and patients with midrange severity scores at admission. Attributable mortality in this study is mainly caused by prolonged exposure to the risk of dying due to increased length of ICU stay.

On the contrary, similar studies on the attributable mortality of HAP in ICU patients are not available in the literature.

In addition to the importance of older age in the risk of death of patients with VAP [11], several variables have been proposed to predict adverse outcomes in these patients. The VAP Predisposition, Insult, Response, Organ dysfunction score was introduced to assess VAP severity, and predict ICU mortality rate [28]. Finally, we recently demonstrated

[29] in 335 patients with ICU-acquired pneumonia, including both VAP and HAP, that the lack of improvement in PaO_2/F_IO_2 and Sequential Organ Failure Assessment score within 5 days from the pneumonia diagnosis are strong predictors of mortality.

ECONOMIC IMPACT

There is little controversy regarding the tremendous resource use and prolonged hospital stay related to ICU-acquired pneumonia. Two recent studies estimated that VAP prolongs length of mechanical ventilation by 7.6–11.5 days and prolongs hospitalization by 11.5–13.1 days compared with similar patients without VAP [30,31]. The excess cost associated with VAP was estimated to be approximately 40 000 US dollars (USD) per patient [31]. Even in HAP outside the ICU, generally considered to be less severe than VAP, serious complications occur in approximately 50% of patients [20], including respiratory failure, pleural effusions, septic shock, renal failure, and empyema. This is particularly seen among patients who develop HAP in the ICU, where the mortality rate approaches that of patients with VAP [18,20].

The economic burden of ICU-acquired pneumonia, particularly VAP, is important. The patients often require longer periods of ventilatory assistance and have significantly longer ICU and hospital stays. On a per-case basis case VAP is associated with additional unadjusted hospital costs ranging between 40 000 and 49 000 USD in the USA [31–33]. This is mainly related to the longer ICU and hospital stay, the increased level of care, and the need for additional procedures and treatments. However, the attributable cost of VAP, controlling for other factors that may affect costs, was estimated to be substantially lower, 11 897 USD, in one study [32]. Thus, preventive measures are pivotal in reducing the burden of the disease.

The estimated impact of VAP on the economic cost is largely dependent on the characteristics of the health care system [31,32,34]. A recent report analyzed the impact of hospital acquired infections, specifically VAP, bloodstream infection, and urinary tract infections, on cost and outcome from ICUs in India [35▪]. Among 499 consecutive patients prospectively recruited for a 1-year period, there were 19.7 hospital acquired infections per 1000 ICU-days, including the three types of infection. As regards to VAP, 50 (10%) patients developed this infection. Occurrence of an episode of VAP was associated with a median attributable cost of nearly 1477 USD. Although ICU acquired infections increased the mean ICU length of stay in 7 days, it did not impact mortality. The attributable costs and the lack of impact on mortality were similar among the three types of infection. An important remark of this study is the different impact of VAP on economic burden in India as compared with those reported in USA or other countries with different costs associated with heath care.

As for mortality, information in the literature on the economic burden of HAP in ICU nonventilated patients is limited.

CONCLUSION

Although the overall incidence of ICU-acquired pneumonia has decreased in recent years, it largely depends on the diagnostic methods employed. The impact of VAP on mortality occurs mainly in surgical patients and those with mid-range severity scores at admission. The economic burden on ICU acquired pneumonia depends mainly on the increased length of stay of these patients. The epidemiologic information in the literature of HAP in ICU patients is limited.

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Conflicts of interest

There are no conflicts of interest.

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- ▪ of special interest
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The document proposed some considerations for clinical trial design for the study of hospital-acquired pneumonia and VAP. Patients with ventilated VAP were identified as those with the highest mortality and. Their characteristics and mortality rates were sufficiently similar to patients with VAP to permit these patients to be studied in the same trial.

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The study concluded that VAP in patients treated with VA-ECMO is associated with an increased morbidity and mortality. Renal replacement therapy and infection by Pseudomonas aeruginosa appear were strong risks factors of treatment failure.