SUPPLEMENT ARTICLE

Mortality, Attributable Mortality, and Clinical Events as End Points for Clinical Trials of Ventilator-Associated Pneumonia and Hospital-Acquired Pneumonia

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Appropriate end points are crucial for the successful interpretation of clinical trials. Choosing end points for therapeutic trials of ventilator-associated pneumonia (VAP) and hospital-acquired pneumonia (HAP) requires careful consideration, because they are complications of critical illness. It may be difficult to distinguish the consequences of VAP and HAP from manifestations of the underlying illnesses, and it is important to determine their incremental magnitude, to plan for possible treatment effects and, thus, sample size calculations. In this article, we discuss mortality, attributable mortality, and time to clinical events as possible end points for HAP and/or VAP trials. Because of the paucity of evidence on HAP, we focus predominantly on VAP. In a systematic review of applicable trials, VAP appears to have slight intensive care unit and low hospital-attributable mortality. VAP is associated with prolonged durations of intensive care unit stay, hospital stay, and mechanical ventilation. Because of these findings, superiority trials of VAP treatment that use mortality as a primary end point are not possible. Equivalency studies are possible, but there are sample size implications. The use of time to clinical event end points, especially when combined with mortality, may be the best option for trial in the future.

Clinical trials are indispensable tools to generate new knowledge and to test therapeutic options for the care of critically ill patients. Trial design is a crucial factor in determining whether these goals are to be achieved, and one of the most important aspects of trial design is choosing an appropriate end point. This is exemplified by the difficulties in designing clinical trials involving ventilator-associated pneumonia (VAP) and hospital-acquired pneumonia (HAP). HAP and VAP continue to be the cause of nosocomial morbidity, and new, evidence-based, preventive, diagnostic, and treatment strategies are needed. In particular, with the increasing prevalence of multidrug-resistant pathogens, new therapeutic options are required. The evaluation of these new treatments will require properly designed clinical trials with appropriate end points. In this context, what is a suitable end point for a VAP and/or HAP trial? In this article, we examine the suitability of mortality, attributable mortality, and time to clinical event analysis as possible end points for VAP treatment trials. We will focus on VAP, because the applicable literature for HAP is sparse, although the principles are the same for both of these diseases.

An ideal end point has the following characteristics [1]. First, the end point should be objective, and there should be little subjectivity between observers. Subjective outcomes introduce unnecessary noise, which may impair the ability to detect a treatment effect. Second, the end point chosen should be easily and reproducibly measured. It would be difficult to conduct a trial if an end point could only be intermittently measured or not measured by all the institutions conducting the trial. Third, the end point should have internal validity. That

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is, it should be directly linked to the disease being studied, and treatment for the disease, if effective, should be able to influence the outcome. Lastly, the end point chosen should have external validity or generalize outside the study and be clinically important. In this manner, conducting a trial with an end point that is not important to populations outside the limited study population may yield a successful trial, but it would not meet the goal of being able to guide therapy for patients outside the study.

CONCEPT OF ATTRIBUTABLE MORTALITY

Mortality at a predefined time after enrollment has been traditionally regarded as the primary end point of choice in many or most critical care trials. Mortality is easy to ascertain, involves no subjectivity, is a common occurrence in critical illness, and is of broad importance to patients and the critical care community. Because of these characteristics, it fits many of the criteria for an ideal end point and is widely used. However, it may not be appropriate for some critical care studies [2]. More specifically, as we explain below, it may not be appropriate for studies of complications of critical illness, such as nosocomial infections and, in particular, nosocomial pneumonia.

Nosocomial pneumonia occurs in hospitalized patients who have a wide spectrum of illnesses as a reason for their underlying hospitalization. The underlying disease or critical illness has an associated mortality dependent on the disease process and the severity of illness. Any mortality associated with nosocomial pneumonia will be in addition to the mortality associated with the underlying disease process, and attributable mortality arises. Attributable mortality is defined as the total mortality minus the mortality associated with the underlying disease process. The absolute attributable mortality of VAP or HAP would be the total mortality in the study population minus the mortality in the population without VAP and/or HAP [3]. For a treatment trial of VAP and/or HAP to have an effect on total mortality, the absolute attributable mortality must be reduced. Other ways of describing attributable mortality are the relative risk of VAP- and/or HAP-associated mortality, defined as mortality among patients with VAP and/or HAP divided by the mortality among patients without VAP and/or HAP. In accordance with this, for a given amount of absolute attributable mortality, the relative risk is dependent on the mortality in the underlying population, and relative risk may not generalize between populations. Lastly, the other common method of describing the mortality associated with nosocomial pneumonia is the odds ratio (OR). An OR for VAP and/or HAP would be obtained by dividing the odds of mortality in a population with VAP and/or HAP by the odds of mortality in a population without VAP and/or HAP. Similarly, ORs are affected by the underlying population mortality for a given absolute attributable mortality; the lower the underlying mortality, the higher the relative risk and OR are for a given attributable mortality. Furthermore, from the viewpoint of designing a treatment trial, if the attributable mortality of VAP and/or HAP is only a small fraction of the mortality associated with the critical illness that the diseases complicate, it may be difficult to ascertain whether a signal is present in a treatment trial. Moreover, the sample size implications are enormous if the treatment effect is submerged in the noise characteristics of the underlying study population.

ATTRIBUTABLE MORTALITY OF VAP

Many reports about VAP indicate that VAP is associated with significant morbidity and mortality. Where does this idea come from, and is it true? The first consideration is that all studies of VAP-associated mortality include patients treated with antibiotics with varying degrees of adequacy and timeliness. These are important determinants of outcome and, for obvious reasons, there are no studies on outcomes of untreated VAP. Therefore, when the attributable mortality of VAP is discussed, implicit in the discussion is the quality of the therapy administered.

To determine VAP mortality, researchers compare mortality in groups of critically ill patients who develop or acquire VAP with that in groups who do not, and the difference in outcomes is reported as those attributable or not attributable to VAP. The difficulty arises in knowing whether the groups with and without VAP are otherwise identical. Because some of the risk factors for VAP are associated with worse outcomes from critical illness, it is difficult to dissociate the worse outcome from the underlying disease process or VAP. For example, acquired brain injury is associated with both worsened intensive care unit (ICU) outcome independent of VAP and increased risk of developing VAP [4]. Moreover, if ICU outcomes are used and if VAP increases the duration of hospital stay and mechanical ventilation, the risk of death during the period of observation is higher, and this may lead to a time-at-risk bias. For these reasons, unmatched observational trials of VAP-attributable mortality tend to overestimate excess mortality and should not be considered [5]. However, unmatched reports of VAP-associated mortality are useful to determine the baseline mortality in populations with VAP. Case-control studies attempt to avoid systematic bias by matching the patients with VAP with patients without VAP by using criteria, such as severity of illness, underlying disease process, and time to development of VAP. Although not all the factors that affect outcome may be matched in case-control studies, their estimates of excess mortality associated with VAP are more likely to be realistic.

To determine the baseline mortality in populations in which VAP occurs, we conducted a literature search of all unmatched trials reporting on VAP-associated mortality since 2000. We did not extend our search farther back because we wanted mortality

to more accurately reflect the current therapeutic environment. We found a total of 15 unmatched trials that compared mortality among patients with VAP with mortality among patients without VAP (Table 1). The mean baseline mortality among critically ill patients without VAP in these trials was 16% (range, 10%–47%). The mortality among patients with VAP in unmatched trials was 33%. In 2 large trials (one of which included only patients with VAP [6] and one of which included patients with suspected VAP [7]) and a systematic review of VAP treatment that included only patients with VAP [8], the mortality was ~20% in both groups. Overall, the mortality rate among critically patients with VAP is high and needs to be considered when planning VAP trials.

To estimate the effect of VAP on mortality we conducted a review of all trials that used a case-control methodology since 1990. We found a total of 14 trials (Table 2) and 1 systematic review [5]. Matching criteria were variable but usually included severity of illness, time to development of VAP, and diagnosis at hospital admission. The trials were abstracted for the outcomes of ICU mortality, hospital mortality, and duration of ICU stay, hospital stay, and mechanical ventilation.

Two trials reported both hospital and ICU mortality (Table 2). Seven trials reported ICU mortality only, and 5 trials reported hospital mortality only. Only trauma patients were enrolled in 6 of the trials, medical-surgical patients were enrolled in 6 trials, and only medical patients were enrolled in 2 of the trials. It was not otherwise possible to distinguish between medical and surgical patients. In a meta-analysis of the 9 trials that reported ICU mortality, using a random effects model, the OR of ICU mortality associated with VAP was 1.94 (95% confidence interval [CI], 1.24–3.03). On aggregate, the mortality rate among patients without VAP was 22%, with an absolute attributable mortality of VAP of 13.5% (95% CI, 4%–23%). There was significant heterogeneity among the trials (I^2, 69%; 95% CI, 37%–84%).

In a meta-analysis using a random effects model, of the 7 trials that reported hospital mortality, the effect on attributable mortality disappeared with an OR for hospital mortality of 1.03 (95% CI, 0.89–1.21). The aggregate mortality among patients without VAP was 31%, with an absolute attributable mortality of VAP of 1.1% (95% CI, 2%–5%). The heterogeneity was less (I^2, 12%; 95% CI, 0%–74%). On analysis of the 4 studies that reported on trauma patients, the aggregate overall mortality among patients without VAP was 19%. There was little attributable mortality of VAP (OR 1.28; [95% CI, 0.7–2.33]; I^2, 48% [95% CI, 0%–83%]) and an absolute attributable mortality of 4% (95% CI, 6%–14%).

TIME-TO-EVENT ANALYSIS

Among the 14 case-control studies, data on duration of ICU stay were available for 8, on duration of hospital stay for 4, and on duration of mechanical ventilation for 7 (Table 2). In contrast to studies reporting mortality, in the studies that reported either duration of hospital stay, ICU stay, or mechanical ventilation, there was a similar effect for all 3. In a meta-analysis of the studies that reported duration of ICU stay, the attributable prolongation of stay attributable to VAP was 8.74 days (95% CI, 4.51–12.97; $P < .01$), and hospital stay was prolonged by 11.45 days (95% CI, 9.86–13.04; $P < .01$). In the studies that reported on durations of ICU and hospital stays, there was significant heterogeneity in the studies of duration of ICU stay

Table 1. Mortality Associated with Ventilator-Associated Pneumonia (VAP) in Unmatched Studies

Study (year)	No. of patients	Population	Mortality in group without VAP, no (%)	Mortality in group with VAP, no. (%)
Ibrahim et al [11] (2001)	880	Medical-surgical	283 (32.2)	400 (45.5)
Tejada et al [12] (2001)	103	Trauma	19 (18.8)	45 (43.5)
Moine et al [13] (2002)	764	Medical-surgical	168 (22.0)	359 (47.0)
Kanafani et al [14] (2003)	70	Medical-surgical	21 (30.0)	27 (39.0)
Warren et al [15] (2003)	819	Medical-surgical	278 (34.0)	410 (50.0)
Alp et al [16] (2004)	2402	Medical-surgical	288 (12.0)	1561 (65.0)
Myny et al [17] (2005)	287	Medical-surgical	57 (20.0)	89 (31.0)
Noor et al [18] (2005)	250	Medical-surgical	80 (32.0)	143 (57.1)
Moreno et al [19] (2006)	2172	Medical-surgical	391 (18.0)	760 (35.0)
Hyllienmark et al [20] (2007)	221	Medical-surgical	35 (16.0)	73 (33.0)
Suka et al [21] (2007)	8892	Medical-surgical	889 (10.0)	1823 (20.5)
Valles et al [22] (2007)	101	Medical-surgical	27 (27.0)	45 (45.0)
Van Der Kooi et al [23] (2007)	1533	Medical-surgical	353 (23.0)	399 (26.0)
Cuellar et al [24] (2008)	1290	Medical-surgical	181 (14.0)	497 (38.5)
da Rocha et al [25] (2008)	275	Medical-surgical	128 (46.5)	88 (32.1)
Total	20,059	…	3200 (16.0)	6719 (33.5)

Table 2. Case Control Studies of Ventilator-Asscoiated Pneumonia (VAP) Outcomes Since 1990

Study (year)	Patient population	Data abstracted
Fagon et al [26] (1993)	Medical-surgical	ICU mortality
Baker et al [27] (1996)	Trauma	ICU mortality
Papazian et al [28] (1996)	Medical-surgical	ICU mortality, hospital mortality, ICU LOS, hospital LOS, duration of MV
Leroy et al [29] (1999)	Medical	ICU mortality
Heyland et al [30] (1999)	Medical-surgical	ICU mortality
Bercault et al [31] (2001)	Medical-surgical	ICU mortality, ICU LOS
Rello et al [32] (2002)	Medical-surgical, Trauma	Hospital mortality, ICU LOS, hospital LOS, duration of MV
Leone et al [33] (2002)	Trauma	Hospital mortality, ICU LOC, duration of MV
Rincon et al [34] (2004)	Trauma	Hospital mortality
Cocanour et al [35] (2005)	Trauma	ICU mortality, ICU LOS, duration of MV
Nseir et al [36] (2005)	Medical	ICU mortality, ICU LOS, duration of MV
Kallel et al [37] (2005)	Trauma	Hospital mortality, ICU LOS, hospital LOS, duration of MV
Cavalcanti et al [38] (2006)	Trauma	ICU mortality, hospital mortality, ICU LOS, hospital LOS, duration of MV
Tejerina et al [39] (2007)	Medical-surgical	Hospital mortality

NOTE. ICU, intensive care unit; LOS, length of stay; MV, mechanical ventilation.

(I^2, 98%; 95% CI, 98%–99%) but no heterogeneity in the studies of duration of hospital stay (I^2, 0; 95% CI, 0%–85%). In the 7 studies in which the duration of mechanical ventilation was obtainable, mechanical ventilation was prolonged by 7.57 days (95% CI, 3.09–12.04; $P < .01$; I^2, 99%; 95% CI, 99%–99%).

SUMMARY

On the basis of the current evidence, the association between VAP and mortality does not appear to be clear cut. Although there is significant heterogeneity among the reported studies, there appears to be low ICU mortality and no hospital mortality. The discrepancy between hospital and ICU mortality may be secondary to the time-at-risk bias. That is, although VAP increases durations of both hospital and ICU stay, the majority of the increased duration of stay is in the ICU. Furthermore, VAP prolongs the need for mechanical ventilation, which may keep patients with a poor prognosis from their underlying comorbidities in the ICU. Both of these factors would increase the probability of death in the ICU among patients who develop VAP.

It should be emphasized that the attributable mortality rates calculated are for patients with VAP who were receiving the therapeutic regimens that were in place at the time of study conduct. The adequacy and timeliness of VAP treatment are important determinants of VAP outcome [9]; however, few studies of attributable mortality report this, and it may account for some but not all of the heterogeneity observed among studies. Other possible causes of the variability in mortality rates among studies include the inclusion of a heterogeneous group of patients secondary to the lack of a reference standard for VAP, the inclusion of VAP caused by pathogens of variable virulence and drug resistance, and the inclusion of patients with a spectrum of comorbidities and severity of illness. Overall, because of the number of potential determinants of the impact of VAP on mortality, it is not surprising that heterogeneity was observed. In spite of these, the association between VAP and clinical outcomes, such as duration of ICU stay, hospital stay, and mechanical ventilation, appears to be more robust, because the direction of effect was the same among all 3 parameters.

IMPLICATION FOR STUDY DESIGN

The possibility that treated VAP may have low attributable mortality has profound implications for study design on the use of mortality as an end point. Two types of study designs are possible when considering treatment trials: superiority studies and equivalency studies. A superiority study would not be feasible if there is low or no attributable mortality of VAP with current treatment. Taking into consideration a treatment trial with 2 different therapies (a new one, compared with standard therapy), as long as the new treatment is equal or superior to standard therapy, a reduction in total mortality would not be observed; all that would be seen is the baseline mortality in the study population in both arms.

With use of mortality, the only type of trial design that would be feasible is an equivalency study. In this type of study, the mortality observed would be the underlying mortality in the population with VAP if the treatments were equivalent. If the comparator therapy was worse, a higher mortality rate in the comparator group would be observed, and in this manner, a signal of lack of effect would be observed. However, in populations with a high baseline mortality, clinically important increases in VAP-associated mortality could be hidden unless

large sample sizes were used. For example, taking into consideration the ability to detect an increase in VAP-associated mortality by 5% clinically important and if the baseline mortality was 30%, to detect a mortality increase from 30% to 35%, ~1400 patients per group would be needed to achieve 80% power at a 2-sided α of 0.05. Similarly, if the baseline mortality of the population studied was 20%, ~1100 patients in each group would be required.

Moreover, if mortality was used as a primary end point, the time of ascertainment would be very important. There may be a difference between ICU and hospital mortality, and using ICU mortality only may lead to erroneous conclusions regarding treatment effect. Similarly, use of arbitrary timelines for the determination of mortality, such as 14 day, 28 day, or longer (60 or 90 day), poses significant questions. In particular, it is not known whether VAP mortality occurs only near the time of the VAP event or whether VAP has an effect on long-term mortality. It is likely that mortality occurs at both times, similar to other critical care diseases [10], and any trial of VAP-associated mortality needs to consider this.

Time to clinical events, such as duration of ICU stay, hospital stay, and mechanical ventilation, appears to be more consistently influenced by VAP and is clinically important to patients and clinicians. Because of the consistent effect on these parameters in spite of treatment, both superiority and equivalence trials of the treatment of VAP would be possible. Although it is possible that the magnitude of the effect of VAP on these parameters may be overestimated in straightforward comparisons between patients with and without VAP, even after controlling for important confounders, the effect is still likely to be significant. Using a more sophisticated analytical approach, Beyersmann et al [40] used nosocomial pneumonia in the ICU as a time-dependent covariate in a proportional hazards model and found that there was still a large effect on prolongation of ICU stay (mean $\pm$ standard deviation, 6.2 $\pm$ 2.5 days).

Although time to clinical events could be influenced by factors other than the clinical status of the patients, it is possible to mitigate their influence with proper procedures, protocols, and clinical trial design, such as randomization and blinding (eg, duration of mechanical ventilation has been used frequently in trials on mechanical ventilation). In addition, these measures, such as survival and ventilator-free days or survival and discharge from hospital, could be combined with mortality to increase their robustness.

In conclusion, VAP and HAP are diseases that occur in a diverse group of patients without a common underlying pathophysiology who are cohorted because of the requirement for either mechanical ventilation or hospitalization. It is likely that VAP has varying effects on mortality and clinical outcomes, depending on the underlying disease process and patient population. However, because of limitations in the current literature, we are not able to discern this level of detail, and on aggregate, VAP has little effect on hospital mortality but proportionately has greater impact on duration of hospital stay and mechanical ventilation. Improved methods of studying VAP (and HAP) are needed, so that patients grouped in observational trials on the effects of VAP and VAP treatment trials are more homogenous. Until these results are available, because of the limitations of the current understanding of the impact of VAP on outcome, the use of mortality as a primary end point in VAP treatment trials is problematic and would require large sample sizes. Clinical outcomes combined with mortality, such as survival and ventilator-free days or survival and ICU-free days, are possible end points that would have fewer of these drawbacks and should be considered.

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