Review: Clinical Trial Methodology

CLINICAL INVESTIGATION

Considerations in the design of clinical trials of antibacterial agents for ventilator-associated pneumonia

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Ventilator-associated pneumonia (VAP) remains a cause of additional morbidity, mortality and increased healthcare costs in mechanically ventilated patients. The pathogens responsible for VAP are becoming increasingly resistant to currently available antibiotics and new antibacterial agents are required to maintain an effective therapeutic armamentarium. Clinical trials are necessary to evaluate the effectiveness of antibacterial agents. However, VAP occurs in complex critically ill patients, is difficult to diagnose and its resolution is difficult to ascertain. These clinical characteristics must be considered in the design of clinical trials evaluating antibacterial agents in VAP. Failure to do so will make trial completion difficult and may render the data obtained uninterpretable. Herein we discuss the specific elements that are unique to the design of antibiotic trials for VAP.

Keywords: attributable mortality • non-inferiority trial • study end point • ventilator-associated pneumonia

Ventilator-associated pneumonia (VAP) remains a cause of morbidity and increased healthcare costs in critically ill patients [1]. In spite of efforts to eradicate it, VAP continues to occur significantly and when it does occur, it increases duration of intensive care unit (ICU) stay and duration of mechanical ventilation [2,3]. VAP attributable mortality is controversial but may be significant if therapy is inadequate or delayed or if it occurs in high risk populations [4]. With aging populations in the developed world, the incidence of patients requiring mechanical ventilation is expected to rise and with this associated nosocomial infections such as VAP will continue to be of concern [5]. Moreover, the pathogens causing VAP are becoming increasingly resistant to currently available antibiotics and as a consequence VAP has become much more difficult to treat and will become increasingly so in the future [6]. In spite of the burden of illness posed by VAP and the threat of increasing bacterial resistance, recently approved antibacterial agents indicated for the treatment of VAP have been few and it is imperative that new antibacterial agents be added to the therapeutic options available to clinicians. However, for an antibacterial agent to be approved for use in clinical practice it must be rigorously evaluated in clinical trials designed to demonstrate its effectiveness and safety.

To examine the issues regarding the design and conduct of trials evaluating antibacterial treatment for VAP and hospital-acquired pneumonia both regulatory and professional societies have recently convened workshops and symposia. The results of a workshop convened in 2009 by the Infectious Disease Society of America and the US FDA were recently published [7] including a position paper endorsed by multiple societies [8]. A similar workshop, discussing many of the same issues on the design of clinical trials for antibacterials was also convened by the

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European Medicines Agency and the results have also been made available [101]. The FDA recently released a draft guidance document [102]; however, many of the recommendations are controversial and remain under consideration as the final document has not yet been released.

Ventilator-associated pneumonia has clinical characteristics that if not addressed in the design of clinical trials may make trial conduct difficult or render the data obtained uninterpretable. Specifically, despite extensive research, VAP remains difficult to diagnose, optimal treatment for VAP remains unknown and it is difficult to ascertain the resolution of VAP. Further, VAP is not a primary illness but rather it occurs on a background of a wide spectrum of critical illnesses rendering its biological behavior less predictable. It is these factors that pose many unique challenges to the design of antibacterial trials for the treatment of VAP and these will be the focus of this manuscript.

Inclusion criteria & diagnosis of VAP

In order to conduct a successful therapeutic trial for any disease, it is critically important that patients with the disease in question be enrolled in the trial. Although this seems obvious, enrolling appropriate patients poses a unique challenge to the design of trials for VAP. VAP is difficult to diagnose and is suspected in mechanically ventilated patients using a combination of clinical, radiological and microbiological criteria. The reference standard for the diagnosis of VAP remains the histopathologic examination and culture of lung tissue [9,10]. Such a technique is invasive, must be performed by clinicians with specialized training, is associated with significant morbidity and mortality, and is not suitable for both clinical use and as an entry criterion for a clinical trial. As a result of the absence of a readily available reference standard, treatment in clinical practice is based on a clinical suspicion of VAP and antibiotic therapy is guided by respiratory tract cultures. Further, it is known that delays in the initiation of antibiotic therapy and inappropriate or inadequate antibiotic therapy are associated with worsened clinical outcomes and increased mortality [11]. To prevent delays in the initiation of adequate antibiotic therapy, it is recommended that empiric antibiotic therapy be initiated at the time VAP is suspected [12]. The time of VAP suspicion may be influenced by factors external to the patient, such as clinician and institutional factors which can lead to variability between the true onset of infection and suspicion time. Although this may impact on outcome, it is unknown how to deal with this in the context of a clinical trial since surveillance for early VAP may lead to increased enrolment of patients who may not have the disease. Moreover, since culture results are not available at the time of VAP suspicion and due to the high prevalence of multidrug-resistant pathogens in the ICU, broad spectrum antibiotic coverage is required when empiric antibiotics are initiated [13].

Although the practice of initiating broad spectrum antibiotic therapy for VAP at the time of clinical suspicion is based on the best available current evidence, it may not be optimal for the conduct of a clinical trial. A clinical suspicion of VAP is usually based on the presence of new or persistent radiographic features suggestive of pneumonia and various combinations of: fever >38°C or <36°C, leukocytosis (>11.0 × 10^9/l) or neutropenia (<3.5 × 0^9/l), purulent endotracheal aspirates (ETA) secretions, isolation of pathogenic bacteria from an ETA, and increasing oxygen requirements. However, these elements are not specific to VAP and may also arise from other common conditions in the critically ill. As examples, pulmonary infiltrates may be secondary to pulmonary edema, atelectasis or pleural disease, alterations in white blood cell count may be secondary to a systemic inflammatory response syndrome [14] or other nonpulmonary infection, worsening hypoxemia may be secondary to other disease processes and there are many causes of fever in the critically ill [15]. Moreover, the relationship between positive cultures and infection in mechanically ventilated patients is unclear since positive cultures may represent colonization rather than infection. Due to the need to initiate antibiotic therapy when VAP is suspected, a significant percentage of patients will turn out to have other disease processes other than VAP [16].

Further complicating the diagnosis of VAP is the recently described entity of ventilator-associated tracheobronchitis (VAT) [17]. VAT is diagnosed on the basis of clinical criteria including the isolation of pathogens in respiratory secretions in the absence of infiltrates on a chest radiograph [18]. This condition is likely a precursor of VAP but given the nonspecificity of chest x-rays in critically ill patients, the spectrum of VAT and VAP overlap. Since VAT may be associated with significant morbidity including increased duration of ICU length of stay and duration of mechanical ventilation [19], treatment is likely to be initiated. Some of these patients may have VAP or have gone on to have VAP thereby reducing the number of patients eligible for trial participation.

For the diagnosis of VAP, variable clinical criteria such as those of the CDC/National Healthcare Safety Network [20] and the American College of Chest Physicians [21] and scoring systems such as the clinical pulmonary infection score (CPIS) [22] are utilized in practice. However, studies comparing clinical criteria

for VAP and histological evidence of VAP have yielded variable results. A recent study by Tejerina *et al.* found that clinical criteria (including loose and rigorous definitions) and CPIS were nonspecific [23]. They found that the loose definition (chest x-ray findings plus two of three: temperature <35.5°C or >38.0°C, white blood cell count >10,000/µl or <4000/µl, purulent respiratory secretions) had a sensitivity of 65% and a specificity of 36% while the rigorous definition (chest x-ray findings plus three of three of the clinical signs above) had a sensitivity of 15.5% and a specificity of 91%. Similarly the CPIS also performed poorly with a sensitivity of 46% and specificity of 60%. With the isolation of microorganisms in tracheal aspirates the specificities of both clinical definitions increased to 91 and 100%, respectively. From a trial perspective, enrolling patients on the basis of clinical criteria alone may lead to a significant number of patients not having the disease in question with no hope that the antimicrobial agent would contribute to the end point chosen. As is evident, it is important to obtain microbiological confirmation of VAP but this poses its own unique challenges.

The most commonly used methods for the microbiological confirmation of VAP are bronchoscopy with broncho–alveolar lavage (BAL), protected specimen brush or ETA all with or without quantification. Despite considerable research, there is no consensus regarding the optimal strategy [24–26] and the method of microbiological sampling likely does not influence outcomes [27]. Bronchoscopy with BAL is invasive and operator dependant, while ETA is much quicker, safer, does not require a specialized skill set and is for the most part better tolerated. There has been much debate and controversy over which method is superior. Heyland *et al.* studied if BAL with quantitative culture compared with ETA with nonquantitative bacterial cultures affected patient outcomes [28]. They found that while patients with BAL had slightly more positive cultures versus ETA (59.7 vs 51.9%; $p = 0.03$) and antibiotic administration was slightly delayed in patients who underwent BAL (8 vs 6.8 h; $p < 0.001$) there was no difference in 28 day mortality or other clinical outcomes. In regards to the correlation between invasive cultures and histological confirmation of VAP, again this is variable [29].

Overall the diagnosis of VAP remains challenging and as a result determining the inclusion criteria for clinical trials of VAP is also problematic. Irrespective of the inclusion criteria chosen it is likely that some patients enrolled will not have VAP and that these patients will not contribute to the end point. When determining sample size this should be considered. To minimize this, radiologic plus rigorous clinical criteria should be included in the inclusion criteria combined with microbiological confirmation. The method of microbiological sampling could include both ETA or BAL. Current evidence does not favor one or the other. Since invasive techniques have not been shown to improve clinical outcomes when used in practice, require personnel with specialized skills and equipment and cost more, they are used less and less in clinical practice. These factors may pose significant barriers to the conduct of trials of VAP in which BAL is a requirement for enrolment since the required personnel may not be available around the clock and there may be reluctance to conduct an invasive investigation solely for study purposes. Given these factors along with the ease of obtaining samples, patient safety considerations would favor ETA as the preferred method for obtaining microbiological samples.

A concern with either BAL or ETA is the length of time required to culture pathogens since patients would be enrolled at the time of VAP suspicion when, in most patients, culture results would not be available. A significant percentage of these patients will turn out to have negative cultures and in studies this has ranged from 15–50% [28,30]. In this regard, the main issue is how to analyze these patients at the completion of the study. Some of these patients will have been suspected of VAP but never had the disease while others will have VAP but for a variety of reasons such as inadequate sampling, culture techniques or prior antibiotic use will have negative cultures. As will be discussed later, the impact on overall study interpretation will depend on study design. If these patients are included in the overall patient population in an intention-to-treat (ITT) analysis, then in a superiority study this is the most conservative analysis. In an equivalency study, ITT is not the most conservative analysis and the group who are microbiologically evaluable or have positive cultures may be given greater weight in the study's conclusions. This will need to be explicitly defined *a priori* and the impact on sample size will need to be considered.

To increase the likelihood that patients being considered for enrolment in VAP trials have the disease in question or have positive cultures, new technologies may be of use. Particularly, molecular techniques are independent of culture results and may readily identify the pathogen present at the time of enrolment [31,32]. Furthermore, rapid sensitivity testing may identify patients where the antibiotics in the control or experimental group are not adequate [33]. Procalcitonin (PCT) also holds promise in the ability to identify patients with higher likelihood of bacterial infection or to monitor therapy throughout the trial [34] and remains a topic of intensive investigation with multiple trials underway

or soon to be reported. Unfortunately, although these techniques hold great promise, they require further investigation as is the case with PCT or the tests may not be widely available.

Finally, in spite of the difficulties with the diagnosis of VAP, it is increasingly being used as a measure of quality of care, rates are publically reported and some jurisdictions are considering withholding reimbursement for the diagnosis of VAP. This leads to the reluctance to make the diagnosis of VAP or the institution of therapy under other guises such as VAT and may lead to difficulties with patient recruitment for VAP trials. To the extent that this occurs, it may lead to selective enrolment based on nonclinical factors and lead to difficulties with study completion and poor study generalizability.

Study design

Randomized clinical trials (RCTs) remain the standard for trials of antibacterial agents and will likely remain so for the foreseeable future. The two main considerations for the design of VAP studies are the study goal and the end points for the study.

Study goal

Randomized clinical trials for treatment can be structured as superiority or non-inferiority trials. Superiority trials are designed to demonstrate that one treatment is more effective than another. Due to their design, superiority studies are usually felt to be more robust, are interpretable without further assumptions and the most conservative analysis is ITT. Non-inferiority trials are designed to confirm the absence of a meaningful difference between treatments. The margin of clinical equivalence is chosen beforehand based on the effect of the active arm in historical placebo-controlled trials or the largest clinically acceptable difference. Non-inferiority studies are usually done when a placebo-controlled trial is considered unethical. A major limitation of non-inferiority trials is that they are inherently 'biased towards the null' – that is poor study quality can lead to an incorrect finding of noninferiority [35]. Consider a trial comparing two treatments for a particular condition, one of which in reality is inferior and in which a significant number of patients who did not have the condition are enrolled. The patients who did not have the condition would not be affected by the study therapies (effective or not), have similar outcomes and result in both groups in the RCT having similar outcomes leading to an erroneous conclusion of non-inferiority. For this reason, in a non-inferiority trial, ITT is non-conservative. This is particularly important in VAP, where depending on the inclusion criteria and the difficulty in diagnosing VAP, some patients enrolled may not have VAP and therefore may not be sensitive to the antibiotic therapy chosen, biasing the trial towards non-inferiority irrespective of the activity of study agents.

Most antibiotic trials utilize non-inferiority trials since a placebo-controlled trial for an infectious process would be considered unethical and sample sizes in comparison to superiority trials are typically smaller. Further, although a new antibacterial agent may be demonstrated to be 'equivalent' there may be other considerations other than the end point in the study that make it advantageous to use the newer, such as changing microbial resistance, allergies or intolerance to older agents, ease of use factors such dosing frequency and cost [36]. However, given some of the inherent difficulties in non-inferiority trials, strict attention to study conduct and quality are required for the conclusions to be valid.

Study end point

An appropriate end point is crucial for the successful interpretation of a clinical trial and a good end point has the following characteristics:

- It must be objective (little variability in measurement between observers);
- It must be easy to measure;
- It must have internal validity (related to the disease process being studied);
- It must have external validity (valid to target populations outside the study) [37].

In the context of a trial of an antibacterial agent for VAP, it is illuminating to examine the various possible end points (Box 1) and examine whether they meet the above characteristics.

Mortality

In critical care trials, mortality is the end point that is traditionally used. It fits all the criteria for an ideal end point in that it is objective, easy to measure, related to critically ill patients and is valid to other populations. However, for it to be interpretable it is necessary to define additional parameters such as time of ascertainment. For VAP is it unclear as to what the most discriminative time point is. Possibilities include mortality at a time point around the episode of VAP (14-day mortality) or longer intervals such as mortality at 28 days, 90 days or further out. As an example, a critically ill patient who develops VAP and

whose hospitalization is thus prolonged, may survive the initial episode of VAP but succumb at some later point because of complications from the prolonged hospitalization. In this instance, where mortality is ascertained may lead to different conclusions as to the efficacy of the antibacterial agent being studied. Since time of mortality ascertainment is usually reported as either ICU or hospital mortality [38] for VAP there is little information on long-term outcomes. However, from the sepsis literature, which should be broadly applicable to VAP given that a significant number of patients with VAP will develop sepsis, mortality continues to accrue over the long term and it is likely that mortality out to a minimum of 90 days should be studied [39]. A second consideration when mortality is chosen as an end point in critically ill patients is whether it is all cause or cause specific mortality. This is particularly important in the context of critically ill patients with VAP where the mortality conferred by VAP or attributable VAP mortality is in addition to the baseline mortality of the critical illness. In this regard, it is important to know the baseline mortality of the population in which the VAP studied is being planned since this has important considerations for sample size. Complicating this is that the groups in which VAP occurs are very heterogeneous populations defined solely by the need for mechanical ventilation rather than common underlying pathophysiology. As a result, mortality rates may vary between studies, institutions and over time depending on the underlying study population enrolled. Further, the effect of VAP may be vastly different again depending on the group. Moreover, since VAP attributable mortality may be only a small fraction of all cause mortality, the total mortality is more dependent on the underlying critical illness than VAP. In treatment trials of VAP, total mortality is approximately 20% (range 10–45%). The evidence for this comes from two large RCTs of treatment and diagnosis [28,40], a meta-analysis of antibiotic treatment for VAP [41] and a meta-analysis of all cause mortality in VAP trials [42].

Attributable VAP mortality is defined as total mortality (with VAP) minus the mortality of underlying population in which VAP occurs. In order to have an idea of possible treatment effect it is necessary to know what VAP attributable mortality is. For a superiority study, it is necessary to know what attributable VAP mortality is using current standards of treatment to which the new agent will be compared. For non-inferiority studies, it is necessary to know what attributable VAP mortality is for untreated VAP; this information does not exist directly and can only be inferred by examining data from published studies in which patients receive either inadvertent inadequate or delayed antibiotic therapy.

Box 1. Possible end points for an antibacterial treatment trial for ventilator-associated pneumonia.

Morality
- All cause mortality
- Attributable hospital-acquired pneumonia/VAP mortality

Time-to-event analysis
- Duration of mechanical ventilation
- ICU length of stay
- Hospital length of stay
- Resolution of pulmonary dysfunction

Resolution of pneumonia
- Clinical cure
- Microbiological cure

ICU: Intensive care unit; VAP: Ventilator-associated pneumonia.

Studies examining the question of attributable VAP mortality are all observational and are either comparisons of unmatched or matched cohorts of patients with and without VAP. Matching criteria vary but usually include baseline characteristics or risk factors for VAP. Melsen *et al.*, in a meta-analysis of attributable VAP mortality using unmatched studies, found it to be highly heterogeneous with no mortality in trauma and acute respiratory distress syndrome patients [38]. One of the confounders of unmatched studies is that patients with a higher severity of illness may be more prone to VAP. To account for this, we conducted a meta-analysis of recent trials in which baseline characteristics were matched and we found that VAP had little or no attributable mortality [4]. It should be emphasized that in all these trials patients were treated with the usual antibiotic regimens in use where the study was done although adequacy of antibiotic therapy was not usually reported. However, given the results of both of these meta-analyses, it is likely that given current therapies, VAP has little or no attributable mortality. The major implication of this is that a superiority antibiotic trial using mortality as an end point would not be possible. In other words, if VAP did not confer additional mortality, no matter how effective the new treatment was, all that would be seen is the mortality of the underlying population as long as the comparator was also effective. However, if the control therapy had limited effectiveness, such may found in VAP caused by multidrug-resistant bacteria, then superiority trials would be feasible [43].

Although VAP may have little attributable mortality given current therapy, to determine if a non-inferiority trial could serve as suitable evaluation with mortality as an end point, it is necessary to examine the attributable mortality of untreated or placebo treated VAP. Theoretically, if VAP did not have mortality,

irrespective of treatment, then a non-inferiority trial using mortality as an end point would always demonstrate equivalency irrespective of the activity of the agents studied. This concept is termed historical evidence of sensitivity to drug effect and further assumes that there are no major differences in other practices, treatments and patients between historical trials and future trials (constancy assumption) which may be problematic in critical care given the rapidly changing field [44]. Placebo-controlled trials of VAP treatment are non-existent for obvious reasons and to infer treatment effect, it is necessary to examine reports of VAP treatment where antibiotic therapy was inadvertently delayed or inappropriate. Sorbello *et al.*, in a review of available literature arrived at an all cause mortality of 20% (95% CI: 18–23%) in the active control group and a mortality of 62% (95% CI: 52 –71%) in the group that received inadequate therapy, yielding a difference of 29% which was arbitrarily discounted to 7% because of the uncertainty in the estimates [42]. In the draft FDA guidance, the difference of 29% was discounted by 30% yielding a treatment difference of 20% and the non-inferiority margins were set at 50% of this or 10% [102]. Discounting the treatment effect was used to conservatively adjust for the uncertainty in treatment effect due to lack of placebo-controlled studies but is arbitrary and the appropriate degree of discounting is unknown. Non-inferiority margins of 7–10%, would preserve most of the treatment effect but, for example, on the background of 20% mortality, the mortality of the experimental group may fall within a range of 20–27% or 20–30% and still be considered non-inferior. Whether such large margins are clinically acceptable or should be reduced remains to be determined. Setting the non-inferiority margin lower would have enormous sample size implications and lead to feasibility issues in conducting the actual trial. For example, again assuming a baseline mortality of 20% and a non-inferiority margin of 7% the sample size for each arm of a RCT would be approximately 400 patients or a total of 800 patients, for a non-inferiority margin of 5% the total sample size rises to approximately 1600 patients and for a non-inferiority margin of 3%, it rises to approximately 4400 patients. In contrast, with a non-inferiority margin of 10% the total sample size would be 400 patients.

Time-to-event analysis

Other than mortality, VAP has been shown to have deleterious effects on ICU length of stay and duration of mechanical ventilation. In a review of 14 case control studies, data for ICU length of stay was available in eight studies, data for hospital length of stay in four studies, and duration of mechanical ventilation was available in seven studies [4]. In meta-analysis of ICU length of stay, the attributable prolongation of length of stay from VAP was 8.74 days ($p < 0.01$, 95% CI: 4.51–12.97, $I^2 = 98\%$) and hospital stay was prolonged by 11.45 days ($p < 0.01$, 95% CI: 9.86–13.04, $I^2 = 0$). The duration of mechanical ventilation was prolonged by 7.57 days ($p < 0.01$, 95% CI: 3.09–12.04, $I^2 = 99\%$). Given the effect of VAP on these outcomes, in any VAP trial it should be possible to demonstrate an effect on these parameters. In contrast to attributable mortality, it would be possible to conduct both superiority and non-inferiority studies based on these parameters. The feasibility of influencing these parameters in VAP antibiotic trials was demonstrated recently by Kollef *et al.* who found that doripenem was associated with a reduction in duration of mechanical ventilation, hospitalization and a trend towards reduced ICU length of stay in spite of similar overall mortality [45]. Concerns that these parameters are controlled by clinicians or that these parameters are influenced by factors other than biology can be mitigated by having specific criterion in place. The duration of mechanical ventilation can be standardized by having weaning protocols in place and standardized criteria for termination of mechanical ventilation. However, even with protocols in place, it is crucial to blind the studies in order to remove the influence of clinician bias on these outcomes.

Resolution of symptoms as test of cure

For pneumonia trials clinical cure is usually defined as a complete resolution of all the signs and symptoms of pneumonia with stable or improved radiological findings at the test of cure assessment which usually occurs anywhere between 7 and 21 days after enrolment. Unfortunately, in critically ill patients, it is difficult to determine when the resolution of signs and symptoms occurs and for the most part this becomes a judgement call on the part of the physician. For example, even if a patient is appropriately treated for VAP there may be other causes of worsening radiological abnormalities [46], fever [47], clinical or laboratory indications of possible infection [48]. Up until the present the majority of registration trials for antibacterial agents for hospital-acquired pneumonia have used clinical response rate (cure, indeterminate, failure) at the test of cure visit, which was at variable time points after the administration of antibacterial agents [49]. Given that there may be many causes of a suspicion of infection in the critically ill, which may be both infectious and non-infectious, the difficulty in diagnosing pneumonia and the reliance on equivalency studies for antibiotic trials in VAP, resolution of symptoms as a test of cure should be secondary end points.

Microbiological response

The eradication of the causal pathogens has been commonly used as a measure of efficacy in pneumonia trials. Although attractive on superficial examination, it is only applicable to a subset of patients with pneumonia since, as discussed previously, up to 50% of patients enrolled in VAP trials will have negative enrolment cultures, irrespective of whether they are obtained by ETA or with invasive techniques [28]. If the sample size calculation is based on those that are microbiologically confirmed then it would mean that up to twice the total number of patients would have to be enrolled. In addition, the eradication of pathogens in patients who are instrumented with an endotracheal tube or tracheostomy may not be possible because of the development of chronic airway colonization or the presence of a biofilm on the artificial surfaces. Further, the persistence of bacteria appears to be pathogen specific and will vary depending on the target population [50]. As such, in these patients persistence of pathogens may not be reflective of antibiotic efficacy. An additional consideration is whether to repeat the method of microbiological confirmation done at study enrolment specifically, if invasive techniques are utilized. For example, many clinicians will be reluctant to repeat a bronchoscopy with BAL if the patient has responded to treatment. The timing of assessment is important since if delayed, patients may be extubated and it may be difficult to obtain samples of respiratory secretions; if done too early there may be persistence of the pathogen because the antibiotic has not had time to achieve its effect.

For these reasons microbiological end points cannot be used as the primary outcomes of VAP studies. Rather, these end points can used for subgroup analysis and if this is contemplated, this should be specified prior to study initiation.

Biomarkers

There has been an increasing amount of interest on the utility of biomarkers both for the diagnosis of and to guide therapy for VAP. Some of the biomarkers studied include CRP, IL-6, sTREM-1 and PCT. Of these, the most studied has been PCT; both as a guide for the initiation and discontinuation of antibiotic therapy. Recent meta-analyses have demonstrated aggregate reduction in antibiotic duration when PCT is used in this manner [51]. However, in these studies significant potential harm could not be ruled out and clinicians chose to ignore PCT-guided recommendations in a large proportion of patients. Further research is required to resolve these issues before PCT could be utilized in new antibiotic trials for VAP. If these issues can be resolved, PCT has the potential to serve as an objective guide for the duration of antibiotic therapy in both arms of a RCT; if a new antibiotic had greater efficacy, normalization of PCT levels could occur earlier and time of therapy could serve as an end point. In contrast, the other biomarkers for VAP require even more study before they can be considered for inclusion into diagnostic or therapeutic algorithms in VAP trials.

Antibiotic therapy

■ Empiric antibiotic therapy

The spectrum of pathogens responsible for VAP varies widely between ICUs, between regions, between countries and is dependent on a wide variety of patient factors [52]. Given that inadequate or delays in empiric therapy are associated with increased mortality, enrolment must occur at the time of VAP suspicion and the empiric therapy in both the control and experimental groups must be adequate to cover all suspected pathogens. In order to plan the trial, it is ideal to know the resistance patterns of the commonly isolated pathogens in the ICUs to be studied. The pathogens that pose the greatest difficulty are methicillin-resistant *Staphylococcus aureus* (MRSA), *Pseudomonas* sp. and multidrug-resistant Gram negatives. If these pathogens are endemic in the ICUs participating in the study, then the empiric therapy chosen must have activity against them. For the experimental antibiotic, adjunctive therapy will depend on its spectrum of coverage to achieve the desired degree of expanded coverage. For the control therapy, none of the commonly available antibiotics for VAP have both anti-*Pseudomonal* and anti-MRSA coverage. To achieve this spectrum of activity, adjunctive therapy may need to be added with the narrowest possible spectrum to achieve the desired coverage. For MRSA, this may mean a drug such as vancomycin and for *Pseudomonas* a drug such as aztreonam. In ICUs where MRSA or *Pseudomonas* are not common or clinicians do not routinely add anti-MRSA or anti-*Pseudomonal* coverage then it may be ethical to withhold such coverage. The addition of antibiotics to widen the spectrum such that multidrug-resistant Gram-negative pathogens are covered may be required in some instances but may be problematic if they are used in the experimental arm since they may interfere with the interpretation of trial results. Combination therapy in which two drugs have activity against one pathogen likely provides minimal clinical benefit and should be avoided in the context of a clinical trial [53].

Given that delays in the initiation of antibiotic therapy when VAP is suspected are associated with adverse outcomes [11], antibiotic therapy should be initiated as soon as possible. However, enrolment in a clinical trial is associated with significant delays such as ensuring that enrolment criteria are met, locating the substitute

decision maker, obtaining informed consent, discussion with the sponsor (if required), randomization and obtaining study drug/placebo. Since these delays can be significant it may be necessary to start nonstudy antibiotics prior to study antibiotics. Prohibiting potential study patients from receiving any nonstudy antibiotics prior to enrolment, although methodologically sound, will jeopardize enrolment and potentially compromise patient safety. Clear specification of allowed antibiotics and number of doses prior to enrolment is required. Allowing one or two doses of nonstudy antibiotics prior to enrolment will be unlikely to jeopardize study results, ensure patient safety and increase the likelihood that the study can be completed.

In summary, for patient safety in the context of a clinical trial, it is important that empiric antibiotic therapy be started in a timely manner, is adequate and achieved with the fewest antibiotics possible to aid in the interpretation of the trial results. In the future, the ability to identify or exclude pathogens such as MRSA at enrolment with molecular techniques such as PCR, may simplify this [32].

Duration of therapy

The duration of protocolized antibiotic therapy that should be mandated in a clinical trial is not clear. If the duration is too short then the likelihood of treatment failure increases while longer durations increase trial costs, difficulties in carrying out the study, potential for antibiotic related side effects and may not provide incremental benefit. Also fixed treatment durations of antibiotics do not allow for early discontinuation of an antibiotic which may be particularly effective. Although VAP has been traditionally treated for 14 days there is little evidence to support this practice, and there is evidence that for most cases of VAP, 8 days of therapy are adequate [40]. The exception to this may be for VAP caused by nonfermenting Gram-negative bacteria such as *Pseudomonas* sp. which may require longer duration of therapy. Given current evidence, the duration of therapy planned in the trial protocol, in both the control and experimental groups should be 8 days with prolonged therapy of 15 days in patients where nonfermenting Gram-negative pathogens are isolated. As discussed previously, PCT levels may allow for earlier discontinuation of antibiotic therapy but further research is required in this regard [51].

Future perspective

The number of patients requiring mechanical ventilation has increased in the past decade and is expected to increase further in the future [54]. Although individual rates of VAP have fallen with the increasing utilization of VAP preventive measures, VAP is unlikely to be completely eradicated and when combined with increased rates of mechanical ventilation, it will continue to be a significant source of morbidity, mortality and increased healthcare costs for the foreseeable future. This must be balanced against the perception that VAP can be completely eradicated thereby reducing the incentive to study VAP or that it is impossible to study because of the rarity of its occurrence. In reality, it is highly unlikely that VAP can be completely eradicated [55] and that surveillance significantly underreports VAP rates [56,57]. The perception that VAP is no longer a problem is one of the greatest threats to future conduct of VAP research since funders; both academic and industry may not be willing to invest the necessary resources in such research.

The microbiology of VAP continues to evolve and the bacterial pathogens causing VAP will become increasingly resistant to currently available antibiotics [58]. The development of new antibiotics is necessary and their evaluation through clinical trials will be paramount. The conduct of antibacterial trials for the treatment of VAP poses many unique challenges that need to be addressed for their successful completion. The utilization of newer techniques such as nonculture-based identification of microbial pathogens and biomarkers to stratify for patient severity and monitor response will become of increasing importance. It is likely that regulatory agencies will increasingly require that VAP antibacterial trials be powered for the primary end point of mortality rather than the currently utilized end points of clinical response and pathogen eradication. However, new end points such as the combination of clinical data with pharmacodynamics and pharmacokinetics may become available in the future once they have the necessary research evidence and validation. With the decreasing incidence of VAP, more patients will need to be screened thereby increasing trial duration and cost. The risk for the future is that with the complexity and costs of antibacterial trials for VAP, they may become prohibitively expensive. This may lead to the development of fewer new antibiotics for the indication of VAP at time where they are increasingly needed.

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Executive summary

- The number of patients requiring mechanical ventilation is increasing and will continue to do so. Ventilator-associated pneumonia (VAP), a complication of mechanical ventilation, is a cause of morbidity, mortality and increased healthcare costs in these patients.
- The bacterial pathogens that cause VAP are becomingly increasingly resistant to presently available antibiotics and new therapeutic options will be increasingly required. Clinical trials are required to evaluate the effectiveness of new antibiotic therapies for VAP.
- Trials of antibacterial agents for VAP pose many unique challenges.
- It is difficult to diagnose VAP. Clinical diagnostic criteria are nonspecific and do not correlate well with pathology findings. Microbiologic confirmation of VAP can be done invasively by bronchoscopic methods or non-invasively with endotracheal aspirates. Clinical studies have not been able to demonstrate the advantage of one over the other and given the ease of use and lack of requirement for specialized personnel and equipment, endotracheal aspirates are preferred.
- The end point of antibacterial trials for VAP remains controversial. Possible end points include mortality, attributable mortality, time to clinical event and clinical or microbiological response.
- Appropriately treated VAP likely has little or no attributable mortality while there is significant morbidity and mortality if therapy is delayed or inadequate. For these reasons, using mortality as an end point, superiority trials of antibacterial therapy for VAP are not possible unless therapy in the control arm is inadequate as may occur with multidrugresistant pathogens. Equivalency trials using mortality are possible but the equivalency margins need to be established.
- VAP increases length of intensive care unit stay, duration of mechanical ventilation and hospital stay. Using these as end points would be possible but since they may be influenced by clinician or environmental factors, rigorous blinding and protocols for care are required.
- Clinical resolution of VAP is difficult to ascertain in critically ill patients and likely should not be used as a primary end point for VAP trials but may serve as a secondary end point.
- Microbiological resolution is difficult to evaluate in patients with VAP since a significant proportion will have negative cultures and in those with positive cultures it is difficult to distinguish colonization from infection.
- Nonculture-based methods for the detection of bacterial pathogens and the utilization of biomarkers for severity stratification and monitoring of response to therapy hold promise for the conduct of VAP trials.

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