Critical Care and Resuscitation 25 (2023) 159–160

Contents lists available at ScienceDirect

Critical Care and Resuscitation

journal homepage: www.elsevier.com/locate/ccrj

Editorial

Ventilator-associated pneumonia: A problematic outcome for clinical trials

Keywords:
Ventilator associated pneumonia
Ventilator associated tracheobronchitis
Clinical trial design
Intensive care
Critical care

Ventilator-associated pneumonia (VAP) occurs commonly in intensive care unit (ICU) patients.[1] Although it is used as a quality of care metric, its use is controversial.[2] A number of randomised clinical trials have reported that prophylactic antibiotics may reduce VAP in patients with acute brain injuries in the ICU.[3–6] However, understanding the implications of these trials for clinical practice requires careful consideration of the potential shortcomings of VAP as a clinical trial outcome. Such considerations are also relevant when designing clinical trials where VAP is a potential outcome measure.

From a pathophysiological perspective, the point when VAP occurs is not black and white. Instead, there is a continuum between airway colonisation and pneumonia.[1] Ventilator-associated tracheobronchitis is increasingly recognised as an intermediate on the spectrum between airway colonisation and VAP.[7,8] It is characterised by the same microbiology as pneumonia[8] and has an overlapping inflammatory biomarker profile.[9] While there is little doubt that ventilator-associated tracheobronchitis can clinically consequential,[8] the point on the continuum where an infection is consequential may differ depending on the clinical context.

In patients with acute brain injuries, fevers due to ventilator-associated tracheobronchitis may contribute to secondary brain injury.[10] In this group of patients, where airway reflexes are often impaired, production of purulent sputum may delay extubation and worsen outcomes.[11] Accordingly, lower respiratory tract infections that fall short of the diagnosis of VAP may be clinically important in patients with brain injuries. On the other hand, sometimes VAP may not have important clinical consequences. Often VAP is diagnosed and antibiotics are started and then stopped soon after because additional information becomes available or the progress of the patient makes it clear an important infection is not present. In part, this is because differentiating VAP from conditions like mucous plugging, atelectasis, and fluid overload can be difficult. In clinical practice, a patient who seems highly likely to have pneumonia at one point in time can seem unlikely to have ever had it a day later. Measuring and verifying an outcome like VAP poses substantial logistic challenges. The measured occurrence of the outcome is likely to differ depending on when it is ascertained.

A diagnosis of VAP requires clinical signs of an infection (e.g. production of purulent sputum) and radiographic evidence that the lower respiratory tract is the focus of that infection in a patient who has been invasively mechanically ventilated for 48 h or more.[12] Often microbiological data are incorporated into the definition.[12] All elements of this definition can be problematic when VAP is used as an outcome in a clinical trial.

The presence or absence of purulent sputum is not readily captured in the medical records. This means that verifying clinical trial data against source material (i.e. the medical records) may not be possible. Even where the presence of purulent sputum is documented, the characterisation of secretions as purulent, and the reproducibility and interrater reliability of assessment of secretion purulence are unclear.[13]

Determining if a patient has a new, persistent or progressive radiological infiltrate without obvious cause other than infection requires a subjective assessment. This and other issues have led many investigators to adjudicate VAP events. Such adjudication adds complexity and cost to a clinical trial. Moreover, in a blinded trial it is uncertain that such adjudication is desirable. While it may be considered to demonstrate methodological rigour, adjudication reduces generalisability because it means that captured events are not concordant with clinical diagnoses. An additional issue is that adjudication, which is limited to events that have been identified by investigators, disregards the possibility that some events may have been incorrectly categorised by investigators as not being due to VAP.

The use of microbiological data can be problematic as the respiratory tract is not sterile and the isolation of an organism from the respiratory tract can occur without a clinical syndrome of infection.[14] Even when microbiological data are not included in the definition, it is probable such data will affect diagnoses. For example, a pulmonary infiltrate that occurs in a patient who has *Streptococcus pneumoniae* in the blood will almost certainly be considered more likely to constitute radiographic evidence of an infection than a similar infiltrate occurring in a patient without such positive microbiology. While the *Streptococcus pneumonia*-positive blood culture offers a striking example, it is likely that various factors influence whether microbiological specimens are even sent to the lab. These include protocols for surveillance cultures, nursing practice, and clinical gestalt. The quality of specimens may vary, but findings from all such specimens likely influence VAP diagnosis to some extent. When antibiotics are the intervention being tested, their suppression of growth of bacteria has the potential to uncouple the measured occurrence of VAP from patient-important outcomes. In particular, in this situation, because growth of bacteria in the laboratory lends support to a diagnosis of infection and specimens that

https://doi.org/10.1016/j.ccrj.2023.10.005

contain antibiotics are less likely to grow bacteria in the lab, there is an inherent risk of detection bias for both clinicians and adjudicators.

Sometime definitions of VAP incorporate a requirement for a respiratory deterioration.[12] However, no guidance is provided as to what constitutes such a deterioration, and no consideration is given to fact that alternative causes of respiratory deterioration can clearly co-exist with a lower respiratory tract infection.

The *Clinical Pulmonary Infection Score* uses components of the VAP definition as a scoring system to determine the likelihood of VAP. Unfortunately, this score also has low sensitivity, specificity, and interrater reliability.[15]

Overall, we consider that VAP is a problematic clinical trial outcome. Whatever, definition is employed in a clinical trial is likely to lack both sensitivity and specificity. Ultimately, for interventions that are worthwhile investigating, clinical trials need to focus on patient-important outcomes like mortality and functional recovery. However, even for phase two trials, the physiological consequences of VAP such as fevers, hypoxia, and increased minute ventilation are easily captured in routine clinical information and provide a more direct mechanistic link to patient-important outcomes than measurement of VAP does. For interventions that are likely to suppress the growth of bacteria the potential for interventions to uncouple diagnosis of VAP diagnosis from the clinical consequences of VAP means that findings in relation to this outcome have a high chance of misleading clinicians. In this context, we recommend against using VAP as an outcome.

Conflict of interest

The authors declare the following financial interests/personal relationships that may be considered as potential competing interests: Prof Young serves as an Associate Editor for Critical Care and Resuscitation.

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17 October 2023