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## Defining ventilator-associated pneumonia: a (de) construction concept

*Definindo pneumonia associada à ventilação mecânica: um conceito em (des)construção*

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### “DEFINING” VENTILATOR-ASSOCIATED PNEUMONIA

Ventilator-associated pneumonia (VAP) is the most common nosocomial infection in the intensive care unit (ICU) setting. It has variable prevalence rates, ranging from 6 to 50 cases per 100 admissions to the ICU.<sup>(1,2)</sup> Such variability comes mainly from two aspects: the presence of case-mix differences among the different units evaluated in the literature and the lack of accurate diagnostic criteria that allow for an accurate functional diagnosis, making subjectivity an important aspect of definitive diagnosis and treatment decisions.<sup>(3)</sup> Several studies show that the incidence of this infection increases with the length of time on mechanical ventilation and show a rate of infection of approximately 3% per day during the first five days of mechanical ventilation.<sup>(2,4)</sup> The development of nosocomial pneumonia in an intensive care setting, especially of VAP, has significant morbidity, prolonging the duration of mechanical ventilation as well as the length of stay in the ICU with all the costs associated with that extended stay.<sup>(4-6)</sup>

Beside VAP diagnosis takes into consideration a combination of clinical, radiological and laboratory findings. Microbiological data are used as an attempt to refine diagnostic accuracy given the low specificity of clinical criteria alone. These criteria include the following: presence of a new or progressive, persistent infiltrate OR consolidation OR cavitation; AND at least two of these criteria: fever (axillary temperature above 38°C), without any other etiology OR leukopenia (<4,000 cells/mm<sup>3</sup>) or leukocytosis (>12,000 cells/mm<sup>3</sup>) OR emergence of purulent secretions OR change in secretion characteristics OR increased secretions.

Additional factors to consider include the presence of functional impairment, hypoxemia with worsening PO<sub>2</sub>/FiO<sub>2</sub> (relative partial pressure of oxygen/fraction of inspired oxygen), increased biomarkers, altered mental status or the appearance of severe sepsis/septic shock.

Ventilator-associated pneumonia is considered to have microbiological confirmation if at least one of the following laboratory criteria is present: positive blood culture without any other apparent source of infection OR positive pleural fluid culture OR bronchoalveolar lavage culture ≥10<sup>4</sup> UFC/mL or tracheal aspirate culture ≥10<sup>6</sup> UFC/mL OR histopathology exam with evidence of lung infection OR urinary antigen or culture for *Legionella spp.* OR other positive laboratory tests for respiratory pathogens (serology, direct visualization and culture). In the absence of any of these microbiological criteria, VAP is diagnosed clinically.

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The widely used clinical definition has limited accuracy. Several clinical conditions can mimic VAP. In a systematic review of 14 studies that evaluated clinical and microbiological criteria for VAP against autopsy results, Klompas,<sup>(7)</sup> observed important variations from 23 to 92% agreement between criteria and confirmed cases (average prevalence of 47%, CI 95%: 35%-59%). The sensitivity and specificity varied greatly according to the criteria used in the studies and how rigorous the need was for the use of definitive criteria. Furthermore, the separate evaluation of clinical, radiological and microbiological criteria resulted in variable but consistently low accuracy; up to 50% of the patients who met the criteria for VAP had an alternative diagnosis. Further, radiological findings could not exclude the possibility of VAP; rather, it only decreased its diagnostic probability, even when VAP was absent. The limited accuracy of diagnostic criteria was mainly due to the extreme subjectivity inherent in the evaluation of important components of clinical diagnosis such as radiological findings and secretion characteristics. An attempt to make the diagnostic approach less subjective has generated a tool to assist in VAP diagnosis: Clinical Pulmonary Infection Score (CPIS), which assigns points for clinical, laboratory, radiological and microbiological criteria.<sup>(8)</sup> A score above 6 points is suggestive of pneumonia. However, this approach has not been sufficient to target the diagnosis because radiological and secretion aspects, which have significant subjective variability, are present in the score.

The absence of a gold standard for VAP diagnosis complicates the adequate evaluation of different case definitions as well as any systematic approach to its confirmation. The variable sensitivity and specificity of available clinical criteria make diagnostic evaluation complex.

This complexity limits the possibility of comparing different studies and the creation of clinical benchmarks based on the use of VAP rates as a marker of quality care.<sup>(9-11)</sup> Given this difficulty in diagnosis, confirmation of these episodes is largely uncertain, and diagnosis will be invariably probabilistic. Even the use of quantitative cultures does not have the power to absolutely define the presence of VAP, limiting diagnostic confirmation to the realm of probabilities.<sup>(3,12)</sup>

### THE IMPACT OF PREVENTION STRATEGIES ON VAP RATES: RATE "ZERO"

Several risk factors for VAP are modifiable such that different interventions have been proposed to prevent it, and numerous isolated preventive measures have

been shown to impact VAP rates.<sup>(13-16)</sup> The development of prevention strategies occurred with the idea that a group of interventions implemented together could increase adherence to these measures and their impact on prevention (bundles).<sup>(13-16)</sup> With the application of this bundle concept, some studies have shown positive results, with significant reduction in the rates of preventable nosocomial infections<sup>(13)</sup> and VAP.<sup>(14-16)</sup> However, from a positive finding (a reduction in VAP rates obtained with the implementation of bundles), a false assumption was made: that every pneumonia episode that occurred in a patient on mechanical ventilation is a preventable adverse event. Important differences in the evaluated populations were ignored as well as physio-pathogenic characteristics of VAP which make it intrinsically different from other nosocomial infections such as bloodstream infections associated with catheters. The concept that nosocomial infections are entirely preventable was spread, and their incidence was used as an indicator of quality and performance in an ICU and, consequently, as benchmarks of success.<sup>(9-12)</sup> In some centers, a requirement of "zero rates" became a reality, and VAP, along with other nosocomial infections, became non-refundable by insurances or other payers. However, there is a series of limitations for the use of VAP as a quality indicator, especially as a benchmark of success<sup>(12)</sup> (Table 1).

**Table 1** - Controversies in the use of ventilator-associated pneumonia as an indicator of quality and benchmarks

Diagnostic inaccuracy
Absence of gold standard
Difference between clinical and surveillance definitions
Different case-mix between institutions
Subjectivity of the criteria contributing to handling fees

The main limitation is in the inaccuracy of its own diagnosis, which occurs in the clinical setting and is purely probabilistic. An operational definition has not been developed that allows for objective diagnosis that is measurable and comparable. VAP diagnosis is based on clinical, radiological and laboratory data that are unspecific and common to other diagnoses and frequent complications in critically ill patients on mechanical ventilation (MV), as discussed previously.<sup>(3,12,17)</sup> Several studies show that although defined criteria are used, VAP diagnosis is subject to great variability among observers and that the rates recorded by epidemiologic surveillance are substantially inferior to those indicated by ICU assistance teams.<sup>(18)</sup> Furthermore, the subjective components present

in the definition allow for manipulation of the rates, and the emergence of new entities, such as tracheobronchitis associated with MV or nonspecific respiratory infection in intubated patients, is becoming increasingly prevalent. Additionally, an inconsistency present in most studies reporting “too good to be true” reductions in VAP rates is the absence of a significant reduction in the consumption of antimicrobials in “zero VAP” units.

## IN SEARCH OF AN IDEAL MODEL

With this concern, several studies were published that sought to build a new model for defining VAP that was more objective, enabled comparisons and did not allow for such great variability.<sup>(9-11,17-19)</sup> Klompas et al. reported that VAP prevalence defined by clinical criteria varied in a mathematical model that only depends on the presence of acute respiratory distress syndrome (ARDS) or pulmonary edema.<sup>(17)</sup> Skrupky et al. found low concordance between the two surveillance strategies for VAP: one based on clinical criteria from the American College of Chest Physicians and another based on surveillance criteria from the National Healthcare Safety Network.<sup>(18)</sup> This discrepancy reflects the subjectivity and inconsistency of the classically used criteria. In addition, it demonstrates the fallacy that may derive from the use of this measure as an indicator of quality of care. The first glimpse of change came in 2011 with a seminal study published in PLOS One where Klompas et al. described a new concept of complications associated with MV (CAMV). Within this concept the focus is changed from etiology to clinical consequence.<sup>(20)</sup> The cause becomes less important given functional impairment derived from this complication because functional impairment is something objective, definable and comparable. The initial definition included the need to increase positive end-expiratory pressure (PEEP) by at least 2.5 cmH<sub>2</sub>O or an increase in FiO<sub>2</sub> of at least 15% that was sustainable for at least 2 days. The use of CAMV compared to VAP showed that CAMV was significantly associated with worse clinical outcomes, such as duration of MV, time spent in ICU and hospital mortality, whereas the classical VAP criteria was not associated with differences in mortality.<sup>(20)</sup> Furthermore, in the group with clinical VAP criteria, 33% of the patients had confirmed pneumonia versus 25% in the CAMV group. Subsequently, another study from the Center for Disease Control and Prevention (CDC), in which variables likely to be accessed objectively were chosen for different proposals of VAP definition, has shown that

definitions for which objective measures of functional decline were included after a period of stability had an association with worse outcomes.<sup>(21)</sup> Additionally, Hayashi et al. described that while surveillance and the classical definition of VAP demand more time and work, with high risk of inaccuracy, the use of the CAMV concept, besides being more objective and easily identified, is correlated to clinical outcomes and the consumption of broad spectrum antibiotics.<sup>(22)</sup>

## NEW STRATEGY FOR MONITORING VAP: TOWARD A NEW DEFINITION

The publication of new guidelines for the surveillance of events associated with MV<sup>(23)</sup> by the CDC in April 2013 radically changed the criteria for monitoring patients on mechanical ventilation, which used to consider only pneumonia and now consider, more broadly, complications associated with mechanical ventilation (Table 2).

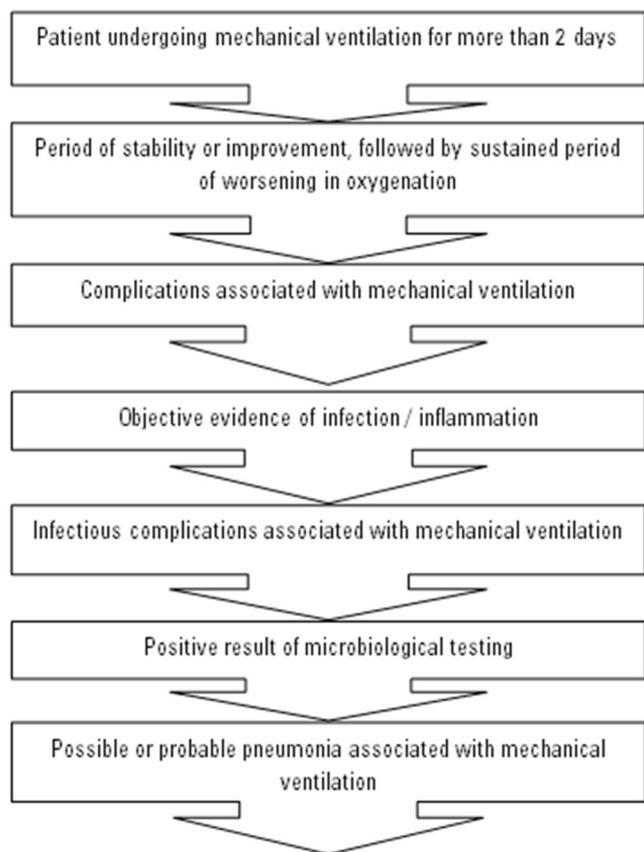
This approach, based on the data discussed above, aimed to minimize the subjectivity of the criteria previously used. Data such as radiographic criteria for pneumonia and specific signs and symptoms (for example: change in pulmonary secretion pattern) show great variability in interpretation, description and recording, which makes it difficult to use in programs that measure quality of care, and limits comparison between institutions and set benchmarks.

The current algorithm is based on objective criteria, simplified and potentially automatic, which try to identify a wide range of complications in adult patients undergoing mechanical ventilation. These are easily implemented criteria, capable of identifying elements that impact length of hospital stay, morbidity and mortality of patients. The algorithm includes surveillance in hierarchal levels (Figure 1). The first step is called VAC (ventilator-associated condition) and identifies patients whose respiratory performance deteriorated after a period of stability or improvement of at least 2 days. In this case, it is considered a significant worsening of function that requires an increase in PEEP and FiO<sub>2</sub> with sustained alterations for 2 days. Thus, all pulmonary complications and non-pulmonary complications capable of causing sustained alterations in a patient's ventilation can be covered. Because some of these events are unpredictable consequences or not necessarily preventable 100% of the time, a “zero” seems to be a more difficult goal to achieve. Furthermore, variability in registration and detection is significantly reduced, minimizing the risk of manipulation of rates.

**Table 2 - New concepts in surveillance of patients on mechanical ventilation** <sup>(23)</sup>

Concept	Name	Definition
New functional respiratory deterioration	ventilator-associated condition (VAC)	≥2 days with reduction or stabilization of the low PEEP or FiO2 followed by an increase in PEEP of ≥3 cm of water or increase in FiO2 of >20 points sustained for 2 days
New functional respiratory deterioration with evidence of infection	infection-related ventilator-associated complication (IVAC)	VAC associated with a temperature <36 °C or >38 °C or leukocyte count ≤4,000 or ≥12,000 mm <sup>3</sup> with one or more new antibiotics, maintained for at least 4 days in a period of 2 days prior to or after the onset of VAC, excluding the first 2 days of mechanical ventilation
New functional respiratory deterioration with possible evidence of lung infection	Possible pneumonia	IVAC associated with Gram stain of tracheal aspirate or bronchoalveolar lavage with neutrophils ≥25 and ≤10 epithelial cells per field of view, or positive culture with potentially pathogenic organism in a period of 2 days before or after the onset of VAC, excluding the first 2 days of mechanical ventilation
New functional respiratory deterioration with probable evidence of lung infection	Probable pneumonia	IVAC associated with Gram stain of tracheal aspirate or bronchoalveolar lavage with neutrophils ≥25 and ≤10 epithelial cells per field of view AND endotracheal aspirate with ≥10 <sup>5</sup> CFU/mL or culture of bronchoalveolar lavage with ≥10 <sup>4</sup> CFU/mL, or endotracheal aspirate or equivalent semiquantitative bronchoalveolar lavage for a period of 2 days before or after the onset of VAC, excluding the first 2 days of mechanical ventilation

VAC - ventilator-associated condition; IVAC - infection-related ventilator associated complication; PEEP - positive end-expiratory pressure.



**Figure 1 - Algorithm for evaluation of complications associated with mechanical ventilation in critically ill patients.**

When the possibility of infection caused by VAC is considered, IVAC (infection-related ventilator-associated complication) is defined; a deterioration in respiratory function and sustained functional impairment associated with temperature changes, WBC count and prescription of a new antibiotic capable of treating the respiratory tract infection.

For the definition of probable or possible pneumonia, the next step in the algorithm adds the identification of a pathogenic organism in respiratory secretions via Gram stain or another culture method. Probable pneumonia can also be defined by pulmonary histopathology that is suggestive of infection, positive culture of pleural fluid, as well as positive diagnostic test for *Legionella spp.* and viruses.

With these new concepts, it is possible to identify a large number of patients with serious complications from mechanical ventilation that are not exclusively pneumonia and, thus, can be included in programs for improvement of care. By including the data on antibiotic prescription, programs for infection control gain a tool to facilitate the comparison of antimicrobial use between institutions, reinforcing the ability to design and compare strategies and policies for the rational use of these drugs.

## CLINICAL IMPACT OF THE NEW DEFINITIONS

From the described characteristics, it is clear that operational definitions are designed primarily for surveillance. The standardization, objectification and comparability that come with the new criteria are fundamental for the construction of clear prevention policies that are effective and allow for management strategies to be designed in a more accurate way. These definitions of the CDC aim to improve surveillance of adverse effects and assist with the implementation of general policies of improvement of care. They should not be used as criteria for diagnostic definition and therapy of individual patients because it is not reasonable to delay treatment of a patient by 2 days to verify if functional impairment is in fact sustained as required by the new criteria.

However, we can infer some clear insights from the data that generated the new definitions with potential hypotheses to be considered in management strategies. The correlation between functional impairment, antimicrobial use and clinical outcome should not be dismissed. Frequently, we see patients where the MV parameters and ventilatory support have been removed or where the  $PO_2/FiO_2$  ratio has improved after having been mistakenly diagnosed as having VAP, taking advantage of the inaccuracy of the finding classically associated with this diagnosis. Therefore, to use the absence of functional impairment and sustained respiratory deterioration - based on the necessity of PEEP and  $FiO_2$  increase - in the reevaluation of patients with clinical suspicion of VAC after 72 to 96 hours of treatment along with biomarkers<sup>(24)</sup> and criteria for clinical resolution<sup>(25)</sup> can be a valuable strategy allowing for the identification of patients with a lower risk of unfavorable outcome and potential to consider alternative diagnosis and/or discontinuation of treatment.

Certainly this is a hypothesis to be evaluated prospectively and appropriately before it can be recommended in a clinical setting, but it constitutes a plausible evolution derived from new strategies and definitions of surveillance of events related to MV. Thus, through the (de)construction of the surveillance model, a higher concordance between expected clinical impact and that observed in patients with clinical suspicion of VAP is possible, contributing perhaps to the solution of a crucial question in the care of critical patients, which involves the mortality attributed to patients suspected of presenting with this clinical syndrome.

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