

REVIEW

Ventilator associated pneumonia (VAP): An Impossible Diagnosis? Call for a pragmatic approach

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ABSTRACT

Many years after the introduction of the protected specimen brush (PSB) by Wimberley *et al.* as a tool to diagnose ventilator associated pneumonia (VAP), new sampling techniques have increased the controversy concerning the diagnosis of VAP. Agreement exists only on the high sensibility and low specificity of the clinical symptoms combined with imaging data. However, sampling methods, qualitative/quantitative microbiological evaluation and the value of "markers" still appear to be unresolved issues. Because a proven diagnosis is very rare, a more pragmatic approach to VAP diagnosis seems necessary. More specifically, the questions we must focus on include the following: "Which patients with possible pneumonia or lower respiratory infection require antibiotic treatment?" and "In which patients with possible/suspected VAP is empiric treatment not immediately necessary and for which of these patients can empiric treatment be limited or discontinued?". (*Minerva Anestesiol* 2009;75:584-90)

Key words: Pneumonia, ventilator-associated - Cross infection - Diagnosis - Treatment.

Although 30 years have passed since the publication by Wimberley *et al.*^{1,2} of a method to collect uncontaminated samples by a protected telescopic brush through the working channel of a fiberoptic bronchoscope, the diagnostic procedures utilized in cases of suspected ventilator-associated pneumonia (VAP) is controversial, as is the definition of VAP itself. It is almost universally accepted that determining the microbiological diagnosis, at least in difficult cases, and establishing whether the pneumonia arises from a multidrug-resistant bacteria, is fundamental. However, there is still much debate as to what the most reliable sampling method is (Table I). Sampling methods range the gamut, from methods that are simple, safe and inexpensive such as using unprotected tracheal aspirate (TA) to those that are more sophisticated, possibly more specific, but more invasive such as the use of a fiberoptic broncho-

scope in combination with a quantitative culture method (e.g., the protected specimen brush, PSB, or bronchoalveolar lavage, BAL).

When discussing how to diagnose VAP in our Intensive Care Unit (ICU) patients, we have found that the best solution is to start from what everybody can agree upon. Pneumonia and/or lower respiratory tract infections (LRTIs) are, at least in Italian ICUs, the most frequently diagnosed infections³ and are, therefore, the primary reason for administering antimicrobials.

Furthermore, our usual "clinical" criteria for VAP (i.e., clinical history, fever, physical examination, increased sputum production, purulence of tracheobronchial secretions, worsening oxygenation, chest X-rays or even computed tomography scan with new or evolving opacities) are the most important early contributions to the diagnosis of VAP. These "clinical" criteria trigger empiric

TABLE I.— VAP: Diagnostic procedures. "Invasive" versus "non-invasive" sampling methods.

Invasive sampling methods	Non-invasive sampling methods
Optimal identification of the sampling site.	Easy and cheap to perform.
Minimal risk of contamination from the upper airways.	Well tolerated by almost all patients (precautions as for tracheal suctioning).
Best validated both for diagnosis of VAP and for identification of responsible pathogens.	Very high sensitivity: nearly no false negative results.
Results obtained allow optimal targeted and de-escalation therapy.	

ic-broad spectrum antimicrobial treatment in many cases and in others these criteria are used as the basis for increased clinical suspicion and, thus, lead to further diagnostic, mainly microbiological, investigations. The "clinical" criteria, albeit highly sensitive, are not sufficiently specific. Based on these criteria alone, VAP is probably over-diagnosed and, therefore, over-treated. A prospective, multi-center, randomized clinical trial⁴ used an approach based on the Center for Disease Control and Prevention diagnostic criteria of VAP^{5, 6} treatment rather than one based on clinical criteria, followed by quantitative microbiology on distal samples and targeted antibiotics. This study demonstrated that utilizing the clinical criteria led to more diagnoses of VAP and a subsequent increase in the use of antibiotics in patients who may or may not have had pneumonia, hence requiring the use of more antibiotics for each patient without survival benefit. Moreover, a quantitative culture result from a distal sample does not necessarily result in reduced antibiotic use;⁷ however, an optimal microbiological diagnosis is required for the use of limited spectrum antibiotics.⁸

An optimal microbiological diagnosis may be necessary, or at least very useful, for optimal treatment. To date, there is convincing evidence that appropriate treatment of VAP increases survival and shortens length of respiratory support.⁹⁻¹¹ However, appropriate treatment is possible without a precise diagnosis when early and very broad spectrum antimicrobial therapy is prescribed. Nevertheless, appropriate treatment of VAP with limited spectrum drugs requires the best available and sometimes even repeated diagnostic investigation.

There is a general agreement on many, but not all, interpretations of microbiological culture results. They are as follows:

1) A sample collected from the tracheobronchial tree before starting an antimicrobial treatment can allow a clinician to detect pathogen or pathogens with high probability.

2) A result of "no bacterial growth" on samples collected under the same conditions from unprotected TA or even from distal, protected or unprotected samples, will exclude pneumonia caused by the most common "VAP pathogens." This criterion, however, is not applicable to infections due to micro-organisms requiring special detection methods, such as viruses, *Mycobacteria sp*, *Legionella pn.*, *Mycoplasma pn.*, *Chlamydia pn.*, molds, etc..., which cannot, therefore, be excluded on the basis of usual routine procedures.

3) A high density of micro-organisms growing in a sample (TA, PSB, BAL, etc.) of a patient in whom our "clinical" criteria suggest a new episode of VAP is indicative of bacterial pneumonia caused by that micro-organism. A concordant positive blood culture is the optimal, albeit rare, diagnostic criterion.

4) The growth of more than one bacterial species may reflect polymicrobial infection or oropharyngeal contamination due to inadequate sampling. In a patient with clinical suspicion of pneumonia, micro-organisms cultured from distal samples (PSB or BAL) are more likely to represent the causative micro-organisms rather than contaminating flora from the upper airways.

5) In the case of low, or "below threshold," concentrations of micro-organisms in the sample, it is difficult to discriminate between bacterial colonization of the airways and infection. Most of the

controversy concerning the diagnosis of VAP dwells in this specific subset.

Despite many interesting data on markers of “sepsis” or “infection,” no specific marker has enough data to support its use as a cornerstone in the diagnosis of VAP. C-reactive protein, soluble triggering receptor expressed on myeloid cells,^{12, 13} and procalcitonin,¹⁴⁻¹⁸ have been extensively investigated but have proved useful only for specific purposes. To date, none of these markers significantly increases our ability to discriminate between patients who may or may not have VAP.

The value of VAP in the ICU, as well as the importance of microbiological data for the treatment of VAP in order to determine the most appropriate use of antimicrobials are both excellent reasons for the more than 25 years of studies and discussions that the topic has stimulated. So why is it challenging that a percentage of patients are considered to have “suspected VAP”? And why has VAP recently been considered problematic or even an inappropriate quality measure for use as a benchmark?^{19, 20}

As far as community-acquired pneumonia (CAP) is concerned, there is almost no discussion regarding the diagnostic criteria, even when microbiological data are seldom available. The IDSA/ATS Guidelines for CAP in Adults²¹ state “*In addition to a constellation of suggestive clinical features, a demonstrable infiltrate by chest radiograph or other imaging technique, with or without supporting microbiological data, is required for the diagnosis of pneumonia. (Moderate recommendation; level III evidence.)*”. On the other hand, when VAP is suspected, microbiological data are the hinges upon which the door of diagnosis and treatment open and close. All intensivists are aware that “a constellation of suggestive clinical features, a demonstrable infiltrate by chest radiograph or other imaging technique” in a ventilated patient is common and may or may not be pneumonia-related.

Very important research has been done to find a gold standard for the diagnosis of VAP and to calibrate, thereafter, the different proposed diagnostic approaches. Wimberley's² (1982) gold standard to establish the cut off value of 10^3 cfu/mL, was “*patients with pneumonia (clinical criteria and response to antibiotics), lung abscess, necrotizing*

pneumonia, and non-bacterial lung disease (fever and infiltrates, initially suspected of being bacterial pneumonia, with a final diagnosis other than bacterial lung disease, established by other diagnostic means)”. In Wimberley's sample, none of the subjects had VAP.

As a start, we must accept that VAP is a non-homogeneous, multifocal, and evolving disease.²²⁻²⁵ The aspiration of bacteria from the oropharynx is its prevalent pathogenetic mechanism, to which all lung segments are exposed, albeit not at the same risk. Lung tissue cultures have frequently been found to be polymicrobial, when investigated.^{22, 24} The dependent parts of the right lower lobe are the most frequently involved in the supine ventilated patient,²² however also local defense mechanisms and pre-existing, non-infectious lesions may play a major role. Furthermore, each single focus of infection has its own evolution. Depending on the competence of the patient's defense mechanisms, a local inflammatory response to bacteria, with leukocytes surrounding a small bronchiolus, can increase in dimensions and become an abscess, or can result in a clearing of the infection.²⁶ Initial, active or even worsening disease may be found close to an area where infection/inflammation is resolving. In these cases, the histology is similar, but the bacterial load and, therefore, the prognosis, are not!

Non-homogeneous distribution of bacterial burden and inflammatory lesions in the lung tissue may explain the many divergent results when sample methods for the microbiological VAP diagnosis are compared to a “gold standard” such as histology and microbiology of the lung tissue after early autopsy.^{22-25, 27-33} As always, the study hypothesis and the patients chosen for such a difficult study influence the results. If we want to investigate the model in its simplest shape, we need to increase homogeneity of the samples and limit the evolution of the disease as well as the interval between clinical diagnosis, bronchoscopic investigation and tissue sampling. The ideal patients for such a study are those with very poor prognosis on admission, a short ICU stay and no antibiotic treatment. On the contrary, the validity of the distal approach with quantitative microbiology, can be brought into question, and even be rejected, when patients with the most confounding condi-

TABLE II.—*Studies comparing 28-day mortality based on the type of diagnostic sample collection from the airways.*

Invasive sampling methods	Non-invasive sampling methods
Specific equipment, training and skill are necessary.	High risk of sampling micro-organisms that colonize the trachea or of sampling material aspirated from the oropharynx.
More side effects (e.g., transient hypoxia, sepsis-like syndrome, pneumothorax, bleeding, etc.) are reported.	With qualitative analysis or with low threshold (<104 cfu mm-3) quantitative culture, the specificity is low and many false positives result, which may lead to excessive antibiotic treatment.
More expensive.	With qualitative analysis or with high threshold (>105 cfu mm-3) quantitative culture, the specificity is high but the sensitivity is low.
Advantage for patients not clearly demonstrated.	

tions are investigated. These conditions include a longer ICU stay with multiple previous and concomitant infectious episodes, a recent change in antibiotic treatment (expected to reduce bacterial burden much earlier than histological changes appear), and a longer interval between sampling and autopsy. These differences in design, patient inclusion and underlying hypothesis may largely explain the different results found in sensitivity and specificity of TA, PSB, and BAL for the diagnosis of VAP in the different post-mortem studies on ICU patients. One fundamental message clearly arises from these studies—VAP is a very non-homogeneous disease. Thus, lung biopsies and histology are not helpful in all cases and diagnostic approaches must be individually tailored. Additionally, the interpretation of the diagnostic results must take into account many data and the specific condition that the patient is in. In more complicated, long-term ventilated ICU patients it would be impossible to make a clear delineation between the presence and absence of pneumonia, even if lung tissue were available for microbiological and histological examination. One could conclude that all severely ill, long-term ventilated ICU patients probably always have some degree of inflammation or infection in their lungs, less if they are improving and more if they are worsening.

The lack of an accepted and acceptable “gold standard” severely hampers all evidence based and systematic reviews³⁴⁻³⁸ on the diagnostic value of sample methods. Schurink *et al.*³⁹ and Klompas⁴⁰ report an interesting Bayesian approach for diagnosing VAP. Unfortunately, these are just first

attempts and the underlying information (the definition of a true VAP) is insufficient for optimal input in the system.

Furthermore, outcome-studies of ventilated patients in whom VAP is investigated by bronchoscopic sample methods or by quantitative and non-quantitative TA, could be seen as an indirect way to learn whether one approach leads to a more reliable diagnosis of VAP than the other. Once again, there is no clear answer regarding mortality and antibiotic use from the five randomized studies^{4, 7, 41-43} summarized in Table II. Besides possible pitfalls in the study design,⁴⁴ these results also suggest that the impact of the sampling method on the outcome of population based studies is actually quite weak.³⁸ As a matter of fact, this is not so difficult to understand. In many patients, the diagnosis of VAP is easy and micro-organisms can be isolated from TA as well, so more invasive procedures do not add any particular benefit. A more precise diagnosis of VAP will help in avoiding over treatment, but over treatment is seldom an immediate hazard for the individual patient. Thus, once again no specific benefit is evidenced in the study. Finally, the difficult cases, where a “high-quality” diagnosis could make the difference, are hard to define and to investigate separately as a specific cohort.

Difficult cases exist in all ICUs. They represent anywhere from 10% to 20% of all patients with suspected pneumonia who are on respiratory support. What makes them difficult? Most of these patients are severely ill and on admission have complex diseases which resolve very slowly or do not resolve at all. In particular, the lungs are fre-

TABLE III.—CIPIS (Singh *et al.* 2000⁴⁶), modified from Pugin *et al.* (1991).

1) *Temperature (°C)	≥36.5 or ≤38.4	0 point
	≥38.5 or ≤38.9	1 point
	≥39.0 or ≤36.0	2 points
2) *Blood leucocytes (/mm ³)	≥4000 or ≤11000	0 point
	<4000 or >11000 + band forms?50%	1 point
	+band forms ≥50%	add 1 point
3)* Tracheal secretions	Absence of tracheal secretions	0 point
	Nonpurulent tracheal secretions	1 point
	Purulent tracheal secretions	2 points
4)*Oxygenation: PaO ₂ /FiO ₂	≥240 or ARDS (ARDS defined as PaO ₂ /FiO ₂ ≤200, pulmonary arterial wedge pressure ≤18 mmHg and acute, bilateral infiltrates)	0 point
	≤200 and no ARDS	2 points
5)*Pulmonary radiography	No infiltrate	0 point
	Diffuse (or patchy) infiltrate	1 point
	Localized infiltrate	2 points
Consider also at the evaluation at day 3:		
6) Progression of pulmonary infiltrate	No radiographic progression	0 point
	Radiographic progression (after CHF and ARDS excluded)	2 points
7)*Culture of tracheal aspirate	Pathogenic bacteria cultured in rare or light quantity or no growth	0 points
	Pathogenic bacteria cultured in moderate or heavy quantity	1 point
	Same pathogenic bacteria seen on Gram stain	add 1 point

ARDS: acute respiratory distress syndrome; CHF: chronic heart failure; PaO₂/FiO₂: ratio of arterial oxygen pressure to fraction of inspired oxygen. CIPIS at baseline (day 1) is assessed on the basis of the first 5 variables; CIPIS at day 3 is calculated based on all 7 variables. A score of >6 at baseline or at day 3 is suggestive for pneumonia.

Modified from Singh *et al.* 2000;⁴⁶ *items earlier proposed as CIPIS by Pugin *et al.* 1991.⁴⁵

quently damaged by chronic lung diseases, heart failure, direct lesions or systemic diseases. In a long term ventilated patient, imaging is of little help, since there are many evolving opacities. Additionally, the signs of local and systemic inflammation are not specific enough, the trachea is most certainly colonized with bacteria, and previous antimicrobial treatments may have already selected for multi drug resistant micro-organisms. In such non-standard patients a very specific diagnostic investigation, carried out with appropriate skill and knowledge, might make a difference. However, such patients are not very frequent and specific outcome-studies on such patients seem rather impossible to perform.

If the sophisticated diagnostic methods of VAP are cumbersome and without evidence of superiority, what about the simplest approaches to the diagnosis of VAP?

The Clinical Pulmonary Infection Score (CIPIS) has been proposed as an objective basis for the clinical criteria used in our everyday bedside approach.^{18, 45-49} Fever, white blood cell count, absence or presence of tracheal secretions and their

characteristics, oxygenation, chest X-ray results, and findings from microbiological examination of the tracheal aspirate are taken into account (Table III). Although the diagnostic sensitivity and specificity are not significantly higher than that of the clinical criteria, the ability to quantify the clinical criteria with a number has allowed for the design of several interesting studies.

Singh *et al.*⁴⁶ adopted a 3-day, empiric antibiotic treatment schedule in suspected Hospital Acquired Pneumonia/VAP and used repeated CIPIS scores. A second value below the threshold of 6, supported early withdrawal of empiric treatment, with a subsequent decrease in antibiotics being prescribed and no worse outcome.

Luyt *et al.*⁴⁷ applied the modified CIPIS concept with repeated computation of the score to 201 patients from the data base of an earlier study⁴ and were able to calculate CIPIS operating characteristics to identify patients with VAP, using microbiologically proven pneumonia (quantitative culture results from BAL or PSB samples as the reference test. The sensitivity of CIPIS >6 points to identify patients with VAP was 89%, the

specificity was 47%, the positive predictive value was 57% and the negative predictive value was 84%. Discrimination between the presence and absence of VAP was possible only by taking into account the values of the second scoring on day three. Patients with VAP had a score of 8.7 ± 1.8 vs. 71.9 in patients without VAP, $P < 0.0001$.

Conclusions

The diagnosis of VAP, in spite of numerous investigations, remains challenging to define. Paradoxically, it seems easier to agree on the diagnosis of VAP at the bedside of a patient than to agree on the definition of VAP itself. This is a major issue in VAP-studies and hence for treatment recommendations. The best available evidence based approach⁶ is not clearly in favor of either of these diagnostic strategies. Different approaches lead to different frequencies of the diagnosis of VAP⁴; however, to date, we have been unable to identify more reliable criteria. This is related to the fact that most ventilated patients have inflammation or infection in their lungs, sometimes more, sometimes less, leading to the conclusion that VAP is not a disease which is either present or absent, but nearly always present with a variety of clinical presentations.

In clinical practice, a reliable definition of VAP is less important than reliable criteria to decide when to treat and when to withhold antimicrobials.⁵⁰ Such criteria would allow clinicians to manage rapidly evolving infections (severe sepsis, and septic shock), without unnecessarily treating patients who are not in need of antimicrobial care. Luyt *et al.*⁴⁷ and Singh *et al.*⁴⁶, both in a theoretical and practical fashion, demonstrated the importance of an early second evaluation. It is useful to see the diagnosis of VAP as a clinical pathway that begins with a suspicion, proceeds to a first evaluation, and which may or may not end in immediate treatment, followed by a re-evaluation of the patient after a short interval of time. Of course, if new information collected on a patient over time is not incorporated into an evolving treatment strategy, it is still possible that the advantages gained by adhering to a clinical pathway, so far as administering appropriate treatments and avoiding unnecessary medication, may be missed.

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