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Diagnosis of Ventilator-Associated Respiratory Infections (VARIs): Microbiologic Clues for Tracheobronchitis (VAT) and Pneumonia (VAP)

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Ventilator-associated respiratory infections (VARIs) may be manifested as tracheobronchitis (VAT) and ventilator-associated pneumonia (VAP).\textsuperscript{1–6} VARI is usually caused by bacteria colonizing the patient’s oropharynx or stomach that enter the lower respiratory tract around the endotracheal tube cuff or through the lumen.\textsuperscript{1,3,4} Initial antibiotic management of VARI is complicated by delays in identification and antibiotic sensitivity data for a wide spectrum of potential pathogens that are increasingly multidrug-resistant (MDR).\textsuperscript{4}

Placement of an endotracheal tube facilitates bacterial entry into the lower respiratory tract, impairs bacterial clearance by host defenses, and increases the risk of VAP 6-fold to 20-fold.\textsuperscript{1} The differentiation between VARI and colonization is initially based on the presence of clinical signs and symptoms suggesting infection, such as fever, purulent sputum, and elevated peripheral leukocyte counts. Microbiologic data are also critical, but specific criteria vary with the sampling method and type of sample. For example, endotracheal aspirates (EAs) are readily available in intubated patients and bronchoalveolar lavage (BAL) or protected specimen brush (PSB) technique.\textsuperscript{1,4,7–10} Gram-stained EA might assist diagnosis of VARI and is employed in many hospitals and intensive care units. The presence of polymorphonuclear leukocytes (PMNL) indicates possible inflammation or infection, whereas information about bacterial morphology may suggest likely pathogens. Culture of the EA either by a quantitative (Q-EA) or semiquantitative methods (SQ-EA) is used to distinguish colonization from VARI.\textsuperscript{2,4,7} Identification and sensitivity data are usually available within 48 to 72 hours.

Lack of standardized definitions for the diagnosis of VAT and VAP based on EA samples has created confusion for clinicians using either Q-EA or SQ-EA methods versus bronchoscopic

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(B) or nonbronchoscopic (NB) BAL or PSB samples. The purpose of this article is to highlight the epidemiology, pathogenesis, diagnosis, and management strategies for VARI. The authors’ primary aim is to clarify current diagnostic criteria to diagnose VAT and VAP versus tracheal colonization and to underscore specific clinical and microbiologic clues that could lead to earlier, appropriate antibiotic treatment of VARI.

**EPIDEMIOLOGY**

VAT and VAP are defined as infections that occur more than 48 hours after intubation. Early VAP occurs within the first 5 days of intubation. Late-onset VAP occurs after 5 days, is more commonly caused by MDR pathogens, and carries higher morbidity and mortality. The reported crude mortality rate for VAP ranges from 20% to 50%, and health care costs are estimated to be $15,000 to $40,000 per episode. In a recent study of outcomes of 126 intensive care unit (ICU) patients who received long-term ventilation in 5 ICUs at Duke University, the survival rate at 1 year was 56%, and only 9% of the patients were not in dependent care. Many patients had multiple admissions to a spectrum of transitional care facilities, with an estimated cost of $3.4 million dollars per patient.

Medical and surgical patients diagnosed with VAT also experience a significantly longer length of ICU stay and duration of mechanical ventilation with possible progression to VAP. The incidence of VAT in Europe has ranged from 2.7% to 10%, depending on the population studied. A recent study in the United States, using a different model and definitions, reported an incidence of VAT of 1.4%, compared with a 4.0% incidence of VAP. However, 32% of patients with VAT progressed to VAP.

**BACTERIAL PATHOGENS**

The most frequent pathogens isolated from patients with VAT and VAP are shown in Table 1. Over the past 20 years, there has been an increased incidence of infections due to MDR gram-negative pathogens, such as *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, *Stenotrophomonas maltophilia*, or *Enterobacteriaceae*, such as *Escherichia coli* and *Klebsiella pneumonia*. In addition, there has also been a dramatic increase in infections due to methicillin-resistant *Staphylococcus aureus* (MRSA) that is likely to continue. VARI may rarely be caused by pathogens that are not regularly identified by routine EA and BAL cultures or Gram stains, such as *Legionella pneumophila*, anaerobic bacteria, coagulase-negative staphylococci; viruses such as influenza A and B, respiratory syncytial virus, herpes simplex virus, coronavirus, or cytomegalovirus. Reactivation of *Mycobacterium tuberculosis* is rare, as are fungal pathogens such as *Cryptococcus neoformans*, *Aspergillus fumigatus*, and *Candida* species, which occur rarely, except in immunocompromised patients.

**PATHOGENESIS**

Understanding the pathogenesis of VAT and VAP is essential for establishing principles and strategies for therapy and prevention. Intubation with mechanical ventilation increases the risk of bacterial pneumonia sixfold to 20-fold. The endotracheal tube (ETT) and oro/nasogastric tube (OG/NT) facilitate bacterial entry into the lower respiratory tract and tracheal colonization, which may progress in some intubated patients to VAT or VAP. Bacteria usually enter the lower respiratory tract by leakage around the ETT cuff or via the ETT lumen. The inflated ETT cuff prevents the exit of bacteria and secretions from the lower airway, which increases the need for manual tracheobronchial suctioning of infected secretions. Furthermore, ETT biofilm-encased bacteria may also contribute to lower airway infection from biofilm emboli.
Fig. 1. Pathogenesis of ventilator-associated respiration infections (VARI). Bacteria enter the lower respiratory tract from the oropharynx by leakage around the endotracheal tube (ETT) cuff or from intraluminal biofilm. The black arrows represent the battle between the entering bacterial pathogen(s) and host defenses. The circles correspond to either colonization or VARI, manifest as either tracheobronchitis (VAT), pneumonia (VAP), or both.

Fig. 2. Schematic view of the intubated patient with orogastric tube (OGT) and endotracheal tube (ETT). High levels of bacteria are present in the oropharyngeal secretions that may collect in the subglottic space above the ETT cuff. Bacteria-encased biofilm in the ETT lumen may colonize or embolize into the distal airways. Ventilator-associated respiratory infection (VARI) includes tracheobronchitis (VAT) or pneumonia (VAP) or both. Endotracheal aspirates (EA) examined by quantitative methods (Q-EA) or semiquantitative methods (SQ-EA) are used to distinguish infection versus colonization, and bronchoalveolar lavage (BAL) and protected specimen brush (PSB) are used to define VAP versus VAT or colonization.
The numbers, type, and virulence of bacterial pathogen(s) entering the trachea, as well as host defenses, are important factors in disease progression. In addition to a wide spectrum of potential pathogens, bacterial virulence may vary within the same bacterial species.\textsuperscript{19,20} Mechanical host defenses (mucus and cilia), polymorphonuclear leukocytes (PMNLs), and macrophages with their respective cytokines, work in conjunction with humoral antibodies (eg, immunoglobulin M [IgM], IgG, and IgA) and complement to prevent progression of colonization to VAT or VAP.\textsuperscript{4,21}

**DIAGNOSIS AND DEFINITIONS**

Similarities and differences in diagnostic criteria for VAT and VAP are summarized in Table 2 and Fig. 3. Note that there is a considerable overlap in clinical definitions in terms of fever, leukocytosis, purulent sputum, and change in oxygenation.\textsuperscript{22} Some clinicians and investigators have relied on a combination of these factors that are included in the clinical pulmonary infection score (CPIS).\textsuperscript{23–26} A score of at least 6 has been suggested as a marker of VAP. Clinical differentiation between VAT and VAP can be difficult due to current

### Table 2

**Diagnostic criteria used for the diagnosis of ventilator-associated respiratory infection that includes pneumonia and tracheobronchitis**

|                      | VAT                                      | VAP                                      |
|----------------------|------------------------------------------|------------------------------------------|
| **Clinical Signs**   | At least one of these                   |                                          |
| and Symptoms         | Temperature (>38°C or 100.4°F)           |                                          |
|                      | Or                                       |                                          |
|                      | Leukocyte count >12,000/mm³ or leukopenia <4000/mm³ |                                          |
|                      | Plus                                     |                                          |
|                      | One of these                             |                                          |
|                      | New onset of purulent secretions or change in suctioning requirements |                                          |
|                      | Or                                       |                                          |
|                      | Worsening oxygen requirements (increasing FiO₂ or PaO₂/FiO₂ ratio) |                                          |
|                      | Or                                       |                                          |
|                      | CPIS Score ≥6                            |                                          |
| **Radiologic Signs** | Chest radiograph or CT scan:             | Chest radiograph or CT scan:             |
|                      | New or persistent infiltrate,            | No new infiltrate                        |
|                      | consolidation or cavitation              | Findings consistent with diagnosis       |
|                      |                                          | of atelectasis, ARDS, CHF                |
| **Microbiologic**    | Endotracheal aspirate (EA)               |                                          |
| **Criteria**         | Gram stain:                              |                                          |
|                      | Many polymorphonuclear leukocytes (PMNL) |                                          |
|                      | Many bacteria (morphology: cocci vs bacilli) |                                          |
|                      | Bacterial culture:                       |                                          |
|                      | SQ-EA = many/++++ growth correlates with Q-EA = 10⁶ cfu/mL |                                          |
|                      | Or                                       |                                          |
|                      | SQ-EA = moderate/+++ growth correlates with Q-EA = 10⁵ cfu/mL |                                          |
|                      | Bronchoscopic B-BAL/PSB                 | Bronchoscopic B-BAL/PSB:                 |
|                      | Cytospin: many PMNL & bacteria           | Cytospin: few PMNL, no bacteria          |
|                      | B-BAL ≥ 10⁴ cfu/mL                      | B-BAL < 10⁴ cfu/mL                      |
|                      | Or                                       |                                          |
|                      | PSB ≥ 10³ cfu/mL                        | PSB < 10³ cfu/mL                        |
|                      | Or                                       |                                          |
|                      | Nonbronchoscopic N-BAL:                  | Nonbronchoscopic N-BAL:                  |
|                      | Cytospin: many PMNL & bacteria           | Cytospin: few PMNL, no bacteria          |
|                      | N-BAL ≥ 10³ cfu/mL                      | N-BAL < 10³ cfu/mL                      |

Note the overlapping microbiologic criteria when endotracheal aspirates are used for diagnosis in contrast to different criteria when bronchoalveolar lavage or protected specimen brush are used.

**Abbreviations:** ARDS, acute respiratory distress syndrome; BAL, bronchoalveolar lavage; CHF, congestive heart failure; CT, computerized tomography; FiO₂, inspired oxygen concentration; PaO₂, partial pressure of oxygen in arterial blood; PMNL, polymorphonuclear leukocytes; PSB, protected specimen brush; VAP, ventilator-associated pneumonia; VARI, ventilator-associated respiratory infection; VAT, ventilator-associated tracheobronchitis.
definitions and overlap between these infections when EAs are used for the microbiologic diagnosis.7

In contrast to VAT, VAP requires radiographic evidence of a new infiltrate, which may be difficult to assess, especially in patients with pre-existing infiltrates, severe congestive heart failure, or acute respiratory distress syndrome (ARDS) (Fig. 4).4,27–29 Unfortunately, portable chest radiographs are often of poor quality that can reduce sensitivity, and there are concerns about specificity as well, particularly in patients with pre-existing pulmonary infiltrates due to non-infectious causes.27,28 Nseir and colleagues10 reported that 38% of their ventilated study patients had an abnormal chest radiograph at the time of admission to the ICU. Similar problems with chest radiograph interpretation and specificity have been noted by others.27,30,31 Data suggest that computerized tomography (CT) lung scans provide better resolution, but also have limitations, and are not readily available in many ICUs. Interpretation of chest infiltrates in critically ill patients could be improved with the use of CT lung scans, but this may be impractical for many ICU patients. In addition, the dose of radiation exposure is high and is equivalent to greater than 100 portable chest radiographs.32,33 Based on these clinical and radiological reservations, microbiologic criteria become the cornerstone for the diagnosis of VAT or VAP due to aerobic bacterial pathogens (see Table 2).

**QUANTITATIVE MICROBIOLOGY**

Standardized criteria for the microbiological diagnosis of VAP exist for B-BAL (>10^4 cfu/mL) and NB-BAL (>10^3 cfu/mL), as well as B-PSB (>10^3 cfu/mL) techniques (see Fig. 3, Table 2; Table 3). Smears from EAs and cytopsins of BAL or PSB specimens can be examined for PMNL and bacteria. Many PMNLs, along with bacteria,
suggest infection and the presence of bacteria on Gram stain of EA corresponds to a bacterial colony count of greater than $10^5$ colony forming units (cfu)/mL. Gram stain provides clues about bacterial morphology (cocci or bacilli), morphologic arrangement (clusters vs pairs or chains) and whether the bacteria belong to the gram-positive or gram-negative group. Absence of PMNL reduces the likelihood of bacterial infection, and the presence of many is suggestive of VARI. No bacteria on the smear, in the absence of recent treatment with antibiotics, suggests noninfectious or nonbacterial causes.

There has been more confusion and less standardization for quantitative culture assessment of EA samples. Many microbiology laboratories use SQ-EA methods, and report the growth of the bacterial pathogen(s) isolated as: rare (+), few (++), moderate (+++), or many (++++) as shown in Fig. 5. Cultures with + or ++ growth usually represent colonization, and the presence of +++ or ++++ growth is more consistent with VARI (VAT or VAP). Other laboratories have used Q-EA and report results as a number of cfu/mL of specimen. There is no clear-cut value for diagnosis of VARI, and different providers use different thresholds (eg, $10^5$ vs $10^6$ cfu/mL). Quantitative cultures less than these values suggest colonization.

Several combinations of clinical and microbiologic criteria exist for the diagnosis of VAT and VAP, which vary considerably, and the merits of each have been debated for decades.1,3,4,7,12,27,31,34,35 For the diagnosis of VAT and VAP, Q-EA $>10^6$ cfu/mL has been proposed by French investigators, which corresponds well with moderate or many (+++++) growth by SQ-EA and many bacteria on Gram stain. Dallas and colleagues6 have suggested a threshold of Q-EA greater than or equal to $10^5$ cfu/mL. SQ-EA with moderate (++) or many (+++++) growth also correlated with few-to-moderate bacteria present on Gram-stained smears of EA.7,10,35 El-Ebiary and colleagues8 reported that although Q-EA at greater than $10^5$ cfu/mL had good sensitivity and specificity, Q-EA was less specific than PSB and BAL for diagnosing VAP. Nseir used a Q-EA result of greater than $10^6$ cfu/mL for the diagnosis of VAT, because it had better specificity than $10^5$ cfu/mL.12

The lack of accepted universal definitions and microbiological benchmarks for assessing Q-EA and SQ-EA is unfortunate as it is often based on the sensitivity and specificity of the criteria compared with a gold standard that remains elusive. Specific definitions are critical, not only for patient care, but also for surveillance, assessing the efficacy of prevention strategies, public...
The EA Gram-stain and culture data will enable distinction between colonization and infection, facilitate earlier appropriate antibiotic therapy, and improve patient outcome (Fig. 6).

Three studies have examined the use of serial, respiratory surveillance cultures collected at different times. Michel and colleagues obtained Q-EA twice weekly in an intubated cohort, and when compared with a culture from BAL performed at the time of VAP, the causative organism was identified by prior Q-EA in 83% of study patients. VAP was most commonly late-onset, and the offending organism was P aeruginosa. Deputdt and colleagues used weekly Q-EA to detect VAP due to MDR pathogens, and found that VAP was due to MDR pathogens in 69% of the episodes. Surveillance cultures led to the appropriate antibiotic therapy in 96% of the patients. In a similar study with BAL confirmed VAP, Hayon and colleagues reported that Q-EA surveillance cultures identified at least one of the pathogens isolated by BAL, with the highest predictive value of cultures obtained within 72 hours of the VAP diagnosis. Finally, Yang and colleagues used daily Q-EA cultures to identify patients with MDR P aeruginosa, and reported that colonized patients were more likely to develop VAP. Further studies are clearly needed to expand and confirm these results in different patient populations. There is also a need to look for optimal intervals between surveillance cultures to provide appropriate and timely therapy and improve patient outcome (see Fig. 6).

RATIONAL FOR TREATING VAT

VAT may be a precursor to or overlap with VAP. Treatment provides an opportunity for earlier intervention and targeted rather than empiric antibiotic therapy. Several observation and randomized VAT studies have been published and are summarized.

A’Court and colleagues studied tracheal colonization in 150 mechanically ventilated patients, using serial quantitative, nonbronchoscopic BAL samples and reported increases in lower respiratory tract colonization over time that appeared to peak about 2 days before the onset of clinical signs of VAP. In a prospective, observational cohort of medical and surgical patients by Nseir and colleagues, VAT was associated with increased length of ICU stay, more mechanical ventilator days, and higher mortality in medical but not surgical ICU patients. In a later study of
patients with chronic obstructive pulmonary disease (COPD), the same authors reported that patients with VAT, when compared with matched controls, had significantly lower median days of mechanical ventilation and more ICU days, but antibiotic therapy did not appear to protect against VAP. In a later prospective, observational case–control study of patients with VAT, patients who were treated with antibiotics had significantly fewer days of mechanical ventilation and ICU stay, but no difference was noted in mortality rates.

Two randomized studies of antibiotic therapy for VAT have recently been conducted, but the study populations, definitions of VAT, and interventions were different. Nseir and colleagues reported results from a controlled, unblinded trial of 58 patients with a clinical diagnosis of VAT. VAT was defined by a Q-EA greater than $10^6$ cfu/mL and no infiltrate on chest radiograph. Patients were randomized to receive targeted intravenous antibiotic therapy versus no or delayed therapy. The antibiotic-treated group displayed better outcomes: more mechanical ventilation-free days (median 12 vs 2 days, $P<.001$), a lower ICU mortality (18% vs 47%, $P<.05$), and a significant decrease in VAP (47% vs 14%, $P<.02$). The same bacterial pathogens were identified in each study group, supporting the concept that VAT appeared to progress to VAP in some patients.

Fig. 5. Patient “MJ” had clinical signs of ventilator-associated respiratory infection (VARI). Her semiquantitative endotracheal aspirate (SQ-EA) showed many/++++ bacterial growth (A), and a simultaneous Q-EA demonstrated $>10^6$ cfu/mL of *Pseudomonas aeruginosa* on blood agar plates (B), consistent with the diagnosis of ventilator-associated tracheobronchitis (VAT) or pneumonia (VAP). Patient “YL” had clinical signs of VARI; an SQ-EA showed few/++ bacterial growth (C) and Q-EA<$10^4$ cfu/mL of *Escherichia coli* (D), consistent with endotracheal colonization.
Important limitations of this study included low numbers of patients, an imbalance in the numbers of patients randomized to each group, and lack of an independent, blinded evaluation of endpoints such as interpretation of chest radiographs to exclude early VAP.

Palmer and colleagues performed a double-blind, randomized, placebo-controlled study of medical ICU (MICU) and surgical ICU (SICU) patients, comparing aerosolized antibiotic treatment (gentamicin every 8 hours if gram-negative bacilli were present, vancomycin every 8 hours if gram-positive bacteria were detected, or both for those with mixed infections) for 14 days or until extubation (n = 19) versus a saline placebo (n = 24). VAT was defined as the production of at least 2 mL of purulent EA over a 4-hour period with a Gram stain demonstrating bacteria. Systemic antibiotics were given at the discretion of treating physician and frequently prescribed in both groups. Compared with the placebo group, the aerosolized antibiotic group had significantly better outcomes, manifested as lower rates of clinical signs and symptoms of VAP, faster weaning of the ventilator, reduced numbers of MDR pathogens, and lower use of systemic antibiotic, with all endpoints, \( P < 0.05 \). Notable limitations of this study included the definition of VAT, lack of Q-EA, high numbers of patients who had prior VAP, lack of data on radiographic signs of VAP, small numbers of study patients, and potential confounding effect by the use of systemic antibiotics.

Different results were reported by Dallas and colleagues in a retrospective study of VAT and VAP in medical and surgical ICU patients. Dallas and colleagues reported that VAT occurs less commonly than VAP when using an EA cutoff of \( 10^5 \) cfu/mL. Most patients had MDR pathogens; patients diagnosed with VAT frequently progressed to VAP and VAT, and VAP patients had similar mortality (19% vs 21%). These conclusions may have been related to the definitions used for VAT and VAP, the well-known limitations of portable chest radiograph interpretation to define VAP, lack of surveillance cultures, and retrospective chart review.

**VARI: A NEW PARADIGM FOR CLINICAL MANAGEMENT**

Diagnosis of VAT or VAP by B-BAL/N-BAL/PSB has been clearly delineated. However, when EAs are used for diagnosis, discrimination between VAP and VAT is almost impossible, because of low sensitivity and specificity of clinical and radiologic findings and overlapping microbiologic criteria. However, quantitative and semiquantitative EAs can discriminate between colonization
and infection. 4 VARI is a term that clearly discriminates between colonization and infection due to VAT, VAP, or both.

Due to the limited availability of B-BAL/N-BAL/PSB in many ICUs, EAs are commonly used for the diagnosis VAP. The authors emphasize the importance of quantitative and semiquantitative EA criteria for assessing for VARI and as a trigger point to consider initiating early, appropriate antibiotic therapy. For example + or ++ growth of Klebsiella species on SQ-EA or Q-EA less than 10^5 most likely represents colonization that likely does not require treatment with antibiotics. However, at least 3 caveats apply to these recommendations:

The patient is not critically ill (eg, shock)
- No cultures have been performed within 24 to 48 hours
- Patients have not received antibiotics within 24 hours before the cultures were obtained.

In addition, these recommendations pertain to the bacterial pathogens associated with VARI that are summarized in Table 1.

Early, appropriate antibiotic therapy, as emphasized in the 2005 American Thoracic Society/Infectious Diseases Society of America guidelines, is associated with improved patient outcomes.4 These guidelines recommend broad-spectrum, empiric antibiotic therapy until culture and antibiotic sensitivity data are available, and then de-escalation of antibiotics based on the microbiologic data. However, for intubated patients, the use surveillance EA may provide earlier information on colonization with MDR pathogens that could be used for targeted antibiotic therapy. This approach could reduce inappropriate antibiotic therapy, reduce overuse of antibiotics that can result in selection of MDR pathogens, improve clinical outcomes, and reduce health care costs.

SUMMARY

The clinical definitions for the diagnosis of VAT and VAP lack specificity, and differentiating between them may be difficult. These definitions are important to guide clinicians on when antibiotic treatment should be initiated and which antibiotics should be used. VARI is a term that indicates infection that deserves consideration for antibiotic therapy. Surveillance cultures will identify pathogens and help clinicians to initiate earlier targeted antibiotic therapy. The purpose of this communication is to highlight the importance of microbiologic clues to aid clinicians in distinguishing between infection and colonization. The authors’ goal is to drive down rates of VARI and to emphasize prevention strategies to decrease rates or VAT or VAP. Strategies to improve outcomes include early identification of infection, avoiding intubation, removing endotracheal tubes as soon as possible, use of sedation vacation, treating infections early, and limiting inappropriate antibiotic use.

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