Ventilator-Associated Tracheobronchitis: The Impact of Targeted Antibiotic Therapy on Patient Outcomes

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Nosocomial lower respiratory tract infections are a common cause of morbidity and mortality in ICU patients receiving mechanical ventilation. Many studies have investigated the management and prevention of ventilator-associated pneumonia (VAP), but few have focused on the role of ventilator-associated tracheobronchitis (VAT). The pathogenesis of lower respiratory tract infections often begins with tracheal colonization that may progress to VAT, and in selected patients to VAP. Since there is no well-established definition of VAT, discrimination between VAT and VAP can be challenging. VAT is a localized disease with clinical signs (fever, leukocytosis, and purulent sputum), microbiologic information (Gram stain with bacteria and leukocytes, with either a positive semiquantitative or a quantitative sputum culture), and the absence of a new infiltrate on chest radiograph. Monitoring endotracheal aspirates has been used to identify and quantify pathogens colonizing the lower airway, to diagnose VAT or VAP, and to initiate early, targeted antibiotic therapy. Recent data suggest that VAT appears to be an important risk factor for VAP and that targeted antibiotic therapy for VAT may be a new paradigm for VAP prevention and better patient outcomes.

Key words: aerosolized antibiotics; antibiotic therapy; methicillin-resistant Staphylococcus aureus; morbidity and mortality; prevention; Pseudomonas aeruginosa; ventilator-associated pneumonia; ventilator-associated tracheobronchitis

Abbreviations: ATS = American Thoracic Society; ETA = endotracheal aspirate; ETT = endotracheal tube; IDSA = Infectious Diseases Society of America; MRSA = methicillin-resistant Staphylococcus aureus; PMNL = polymorphonuclear leukocyte; PSB = protected specimen brush; VAP = ventilator-associated pneumonia; VAT = ventilator-associated tracheobronchitis

“In man’s mind, once stretched by a new idea, never regains its original dimension.”

Oliver Wendell Holmes

In comparison to ventilator-associated pneumonia (VAP), less data are available on ventilator-associated tracheobronchitis (VAT) and its management. VAT was not included in the 2005 American Thoracic Society (ATS)/Infectious Diseases Society of America (IDSA) guidelines for the management of hospital-acquired pneumonia, healthcare-associated pneumonia, and VAP, but two recent randomized, clinical trials of antibiotic therapy for VAT have stimulated interest.

VAT represents a spectrum of disease that has had different clinical definitions, and treatment options have been controversial. VAT should be suspected in intubated patients with clinical signs of lower respiratory tract infection (such as fever, leukocytosis, and purulent sputum) with a Gram stain demon-
strating microorganisms and polymorphonuclear leukocytes (PMNLs), with either semiquantitative or quantitative cultures suggesting infection in the absence of a new or progressive infiltrate on chest radiography. Existing studies on VAT report a crude incidence rate that may vary from 2.7 to 10%. Common pathogens for VAT include *Pseudomonas aeruginosa*, Acinetobacter spp, and methicillin-resistant *Staphylococcus aureus* (MRSA). This review summarizes current clinical data on the epidemiology, pathogenesis, and antibiotic management of VAT. A new paradigm for VAT treatment, VAP prevention, and improved outcomes in ICU patients receiving mechanical ventilation appears promising.

**Epidemiology and Etiology**

Several studies have looked at the incidence of VAT. A German multicenter study of 515 ICU patients found an incidence of 2.7%, among 161 multiple trauma patients in a single-center study in Spain the incidence was 3.7%, and it was 10% in a study of ICU patients receiving mechanical ventilation in France. The most frequent bacterial pathogens isolated have been *P aeruginosa*, followed by *Acinetobacter baumannii* and MRSA, *Streptococcus pneumoniae* (pneumococcus), *Haemophilus influenzae*, *Legionella pneumophila*, and methicillin-sensitive *S aureus*. Nonbacterial etiologies causing VAT are rare and also unlikely to cause VAP. Medical and surgical patients with VAT appear to have a significantly longer length of ICU stay and duration of mechanical ventilation. By comparison, higher crude mortality rates ranging from 20 to 50% have been reported for VAP, and health-care cost for these patients has been estimated at $40,000 per episode.

**Pathogenesis**

**Lower Respiratory Tract Colonization**

Intubation and mechanical ventilation increase the risk of VAP by sixfold to 20-fold. Long-term mechanical ventilation with high airway pressures promotes lung injury, ARDS, and increases the risk for lung infection. Placement of an endotracheal tube (ETT) offers bacteria in the nasopharynx a convenient, easy, one-way path into the lower respiratory tract that results in greater colonization and risk for VAT. The presence of the ETT cuff acts as a barrier for bacteria and secretions to exit the lower airways. In addition, risk is increased by routine sedation and limited ETT suctioning that is needed to replace spontaneous coughing.

Lower-airway colonization can also result from endotracheal suctioning, inadvertently flushing of contaminated tubing condensate into the airways, contaminated “in-line” medication nebulizers (aerosol), or emboli from biofilm formations in the ETT lumen. Over time, bacterial concentrations and inflammation increase, resulting in a greater risk of progression to VAT or VAP (Fig 1).

**Bacterial Risk Factors**

The complex interactions between the patient’s host defenses vs the quantity and virulence of the bacterial pathogen(s) entering the lower respiratory tract determines if colonization will progress to VAT, and in some cases to VAP (Fig 1). Bacterial virulence clearly varies between and within species. For example, infections caused by *P aeruginosa* isolates having exotoxin III are associated with a sevenfold-increased risk of death, when compared to other *P aeruginosa* isolates. Bacterial virulence also varies widely within Gram-positive species of MRSA.

**Host Lung Defenses**

Host defenses in the lung include three major groups: mechanical (cilia, mucous), cellular (PMNLs, macrophages, and their respective cytokines), and the humoral group (IgM, IgG, and IgA antibodies and complement). These marvelous defense systems are designed to contain or eliminate invading bacteria, and their efficacy will ultimately determine the clinical outcome of the patient.

**Potential Patient Outcomes**

If the outcome of this complex pathogen-host battle is favorable to the host, the infectious process will be halted, but tracheobronchial colonization can persist (Fig 2). If the host outcome is unfavorable, there may be increased numbers of lower respiratory tract pathogens and greater inflammation leading to purulent sputum as well as clinical signs and symptoms of infection and VAT, or possibly VAP may develop. VAP is usually associated with increased lung tissue damage, increased oxygenation demands, and a greater risk for complications such as empyema, lung abscess, secondary bacteremia, shock, and death. Therefore, the concept of halting the infectious progression to VAP at an earlier stage before tissue damage appears is an appealing strategy. Based on our current understanding of pathogenesis, appropriate treatment of VAT could represent such an opportunity.
Diagnosis and Definitions

As previously mentioned, there is no consensus on diagnostic criteria for VAT. This is unfortunate because it leads to difficulty distinguishing between VAT and VAP, comparing clinical studies, and establishing treatment directives for VAT. Several definitions exist, and they are primarily differing in the need for microscopic confirmation. Further complicating the diagnosis is that it may be difficult or impossible to tell if there is a new and progressive infiltrate on a chest radiograph or CT lung scan that would confirm the diagnosis of VAP, as discussed below. In our opinion, the use of quantitative endotracheal aspirates with a pathogen at concentration of either $10^5$–$10^6$ cfu/mL would be optimal to reduce confusion and controversy. In Table 1, we compare a proposed definition of VAT with the accepted definition of VAP by ATS/IDSA. Both are based on clinical signs and symptoms, microbiologic data, and radiographic findings.

Microbiologic Confirmation of VAT or VAP

Intubated patients have ready access to specimens for Gram stain and culture that may help establish a diagnosis of lower respiratory tract infection and may help discriminate between VAT and VAP. Smears (Gram stains) of the endotracheal aspirates help establish the presence of inflammation based on numbers of PMNLs. The Gram stain may also provide information on morphology of the invading bacteria and when present correlates with a culture with $\geq 10^5$ organisms per milliliter.

Semiquantitative cultures of the endotracheal aspirate (ETA) are performed in most hospital microbiology laboratories, and moderate-to-heavy growth of a pathogen(s) is usually considered significant. Other laboratories have used quantitative ETA in which significant growth of a pathogen usually corresponds to $\geq 10^5$–$10^6$ cfu/mL. We believe that microbiologic diagnosis of VAT and VAP is a “numbers game” and that quantitative criteria may provide a better standard for comparison and greater diagnostic specificity to discriminate between lower airway colonization and infection. However, the ETA will not help discriminate between VAT and VAP (Table 1). The diagnosis of VAP can be confirmed with quantitative samples, obtained from the distal airways using bronchoscopic or nonbronchoscopic BAL specimens or protected specimen brush (PSB) criteria as shown in Table 1.

Clinical signs and symptoms along with radiographic findings may be helpful for differentiating
lower respiratory tract colonization from infection. As shown in Table 2, quantitative microbiologic methods are also routinely used for processing urine cultures to help health-care providers discriminate between urinary tract colonization and infection (cystitis and pyelonephritis).

Biomarkers such as C-reactive protein, procalcitonin,19 soluble triggering receptor, elastin fiber, and BAL endotoxin have been used for the diagnosis of VAP and are summarized in a recent review article by Rea-Neto et al.20 These parameters offer an objective way to identify the presence of VAP.21 Povoa et al22 reported the identification of VAP as early as 4 days after the initiation of antibiotic treatment by repeatedly measuring C-reactive protein, there are no studies addressing the issue of biomarkers for VAT.

**Radiographic Evaluation for VAP**

In contrast to VAT, VAP requires the presence of a new or progressive infiltrate on chest radiograph or CT scan, which may be particularly difficult for the diagnosis of early VAP, which may not be identified on chest radiograph because pulmonary infiltrates are often the result of fluid, pus, or lung consolidation due to the host inflammatory response.23 In addition, the sensitivity and specificity for the diagnosis of VAP are limited in patients with preexisting infiltrates or concurrent disease due to congestive heart failure, atelectasis, prior pneumonia, or ARDS. For decades, it has been emphasized that use of the portable chest radiograph in critically ill ICU patients is often of poor quality and difficult to interpret.24,25 Nseir and coworkers2 reported that 38% of their ICU patients receiving mechanical ventilation had an abnormal chest radiograph finding at the time of admission to the ICU, and similar results have been reported by others.26

Interpretation of chest infiltrates on chest radiographs may be improved with the use of CT lung scans. There are data suggesting that CT scan is likely to be a more sensitive and specific tool for diagnosing VAP in critically ill patients,27 but availability is limited, more difficult to perform, and infiltrates suggestive of VAP may be difficult to confirm or find consensus among blinded readers, especially in patients with diffuse infiltrates, pleural effusions, prior surgery, or ARDS.28 Although CT scans would be more expensive, if used, they would likely improve diagnostic accuracy.

**Rationale for Antibiotic Therapy in VAT**

**Clinical Importance of VAT**

A’Court and coworkers29 studied the natural history of tracheal colonization in 150 patients receiving mechanical ventilation, using serial quantitative,
nonbronchoscopic, bronchial lavage samples. Increases in lower respiratory tract colonization occurred over time and appeared to peak approximately 2 days before the clinical signs of VAP, suggesting a window of opportunity for intervention.30

In a prospective, observational cohort study5 of medical and surgical ICU patients, VAT was associated with increased length of ICU stay, more mechanical ventilator days, and higher mortality in medical but not surgical ICU patients. Patients with COPD who had VAT, when compared to “matched” control subjects, had significantly greater median days of mechanical ventilation and more ICU days. In this study,31 antibiotic therapy did not protect against VAP; but in a later prospective, observational case-control study32 of VAT, patients who were treated with antibiotics had significantly fewer days of mechanical ventilation and ICU stay.

Recent Randomized Clinical Trials of Antibiotic Therapy for VAT

The use of antibiotic therapy for VAT has been evaluated in two recently conducted, randomized trials. The first trial, by Palmer et al.,3 was a double-blind, randomized, placebo-controlled study of medical and surgical ICU patients who received either targeted aerosolized antibiotic(s) treatment for 14 days or until extubation (n = 19) vs a saline solution placebo (n = 24). VAT was defined as the production ≥ 2 mL of purulent endotracheal secretions over a 4-h period with a Gram stain demonstrating bacteria. Aerosolized antibiotics included gentamicin sulfate if Gram-negative bacilli were present, vancomycin for Gram-positive bacteria, and both for those with mixed infections. Systemic antibiotics were administered at the discretion of treating physician, and were frequently prescribed in both groups. The aerosolized antibiotic group had significantly lower rates of clinical signs and symptoms of VAP, better weaning, reduced numbers of antibiotic-resistant organisms, and lower use of systemic antibiotics when compared to the placebo group (all end points, p < 0.05).3 Notable limitations of this study included the concerns over the definition of VAT without quantitative microbiologic evaluation of ETAs, high numbers of patients who had prior VAP, lack of data on radiographic signs of VAP, small numbers of patients studied, potential confounding by the use of systemic antibiotics, and possible risk of complications with the widespread or long-term use of aerosolized antibiotic therapy for 14 days.

The second study, by Nseir and coworkers,2 was a randomized, controlled, trial of patients who had monitored quantitative ETAs after intubation, to establish a diagnosis of VAT based on a pathogen in sputum (> 10^5 cfu/mL), who were then randomized to receive either targeted antibiotic therapy vs no therapy. The results demonstrated that the antibiotic-treated group had a significant decrease in VAP episodes (p < 0.02), more “mechanical ventilation-free days” (p < 0.001), and a lower ICU mortality (p < 0.05). Thus, serial monitoring of ETAs may provide an earlier diagnosis of VAT, and allow more timely, targeted antibiotic therapy that in turn reduces or prevents the evolution to VAP. This model may also reduce early VAP (too early for chest radiograph changes) or allow targeted antibiotic therapy for patients who may have VAP but cannot meet the diagnostic criteria of a new infiltrate due to a chest radiograph due to preexisting infiltrates (Fig 3). Additional benefits notable in this study include better patient outcomes in terms of reduced patient mortality and morbidity, which should translate into

Table 2—Comparison of Definitions for Lower Respiratory Tract and Urinary Tract Infections; Diagnoses Based on Clinical Spectrum and Microbiologic Definitions

<table>
<thead>
<tr>
<th>Diagnostic Criteria</th>
<th>Lower Respiratory Tract</th>
<th>Urinary Tract</th>
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<tr>
<td>Asymptomatic colonization</td>
<td>Tracheobronchial colonization: Gram stain = few or no PMNLs; quantitative ETA &lt; 10^5 cfu/mL; ETA = none or few colonies</td>
<td>Urine colonization: urinalysis: none or few PMNLs; urine culture = no growth or &lt; 10^5 cfu/mL</td>
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<td>Localized infection</td>
<td>VAT: fever, leukocytosis, purulent sputum; plus Gram stain: PMNLs with/without bacteria in sputum; semiquantitative ETA = moderate or heavy growth; quantitative ETA ≥ 10^5–6 cfu/mL; BAL &lt; 10^4 cfu/mL; PSB &lt; 10^3 cfu/mL</td>
<td>Cystitis: dysuria, frequency, urgency; plus Gram stain: PMNLs with/without bacteria in urine; urine culture ≥ 10^5 cfu/mL</td>
</tr>
<tr>
<td>Serious organ infection with/without secondary bacteremia</td>
<td>VAP: ETA Gram stain: PMNLs and bacteria; semiquantitative ETA: moderate-to-heavy growth; quantitative ETA &lt; 10^5–6 cfu/mL; BAL ≥ 10^3 cfu/mL; PSB ≥ 10^3 cfu/mL; plus fever, leukocytosis, purulent sputum; plus new or persistent infiltrate on chest radiograph/CT</td>
<td>Pyelonephritis: Gram stain/urine: many PMNLs; urine culture ≥ 10^5 cfu/mL; plus fever, chills, back pain, dysuria; plus kidney pathology on imaging</td>
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reduced health-care costs. Limitations of this study include low numbers of patients (increased risk of a statistical error); low study enrollment at several centers; an imbalance in the numbers of patients randomized by early discontinuation of some study participants; lack of an independent, blinded evaluation of end points and chest radiograph changes; and lack of routine CT scan evaluation. These data, however, are provocative, consistent with current concepts of VAP pathogenesis and prevention, but need confirmation by others.

VAT: a New Management Paradigm

The data from two, recent randomized clinical trials by Nseir and coworkers\(^2\) and Palmer et al\(^3\) underscore the importance of VAT and potential benefits of targeted antibiotic therapy to improve patient outcomes. Intuitively, reducing heavy bacterial colonization and associated inflammation in the lower respiratory tract also appears to be an important prevention strategy for VAP (Fig 3).\(^2\) Other prevention measures for VAP like oral decontamination with 2% chlorhexidine solution has proven to lower the incidence of VAP episodes supporting the colonization concept.\(^3\),\(^4\) In contrast to prevention strategies aimed at reducing oropharyngeal colonization with oral antiseptics or antibiotics, or specially designed ETTs that are used in all patients receiving mechanical ventilation, targeted antibiotic therapy for VAT would only be used in perhaps 5 to 10% of patients receiving mechanical ventilation.\(^1\),\(^2\),\(^3\),\(^17\),\(^35\) Advantages of a model for managing lower airway colonization and infection similar to that of Nseir et al\(^2\) are shown in Figure 4. The focus of this model is based on the use of serial ETAs to help discriminate between lower airway colonization and VAT. This would allow earlier, targeted antibiotic therapy as a strategy improves the outcomes of ICU patients receiving mechanical ventilation, and reduce or prevent VAP. The risk-benefit ratio for using antibiotic therapy for VAT needs confirmation and further evaluation in clinical trials, but should be cost-effective if available incidence data suggesting VAT rates of 2.7 to 10% are correct.\(^4\),\(^5\) The potential risks and advantages of VAT therapy include selection of multidrug-resistant pathogens and complications such as *Clostridium difficile* colitis, but these need further evaluation and appear to be unlikely.\(^3\)

The duration of targeted, antibiotic therapy for VAT has not been established, but VAT may respond to shorter courses of treatment because therapy is initiated early and before there is extensive tissue damage or when there are fewer bacteria. Singh and workers\(^36\) randomized 81 medical and surgical ICU patients with suspected pneumonia and a clinical pulmonary infection score \(\geq 6\) to a 3-day course of antibiotic therapy with ciprofloxacin compared to "routine care," which included combinations of antibiotics used for longer periods of treatment. The shorter-course group had significantly fewer superinfections and antibiotic-resistant pathogens (\(p < 0.01\)) and shorter ICU stay (\(p < 0.04\)), with a trend toward a lower 30-day mortality (\(p = 0.06\)). Shorter courses of antibiotic therapy (7 days) have been recommended for the treatment of uncompli-
ated health-care–associated pneumonia, hospital-associated pneumonia, and VAP. If confirmed effective, the use of aerosolized antibiotics for VAT may also decrease the need for systemic antibiotics and the development of antibiotic resistance.

Over the past 3 years, there has been greater emphasis directed at reducing health-care–associated infections by the Institute for Healthcare Improvement. Prevention of VAP has been a priority for hospitals that has achieved great success, but most critical care, infectious disease, and pulmonary providers do not believe that the use of the “VAP bundle” and checklists alone will produce a “zero-VAP infection” rate, especially in major referral hospitals caring for complicated patients. It is unlikely that all episodes of VAP can be prevented, eliminated, or considered a “medical error.” Our goal should be to reduce rates, change culture, and aim for “zero VAP.”

Several areas for future research on VAT have been identified, which include confirming these data, finding a common definition of VAT, a diagnostic threshold for quantitative endotracheal aspirates, and the duration of antibiotic therapy needed for VAT. We would also recommend a cost analysis of this strategy in comparison to other prevention strategies. In our opinion, this could be best achieved by the use of large, collaborative national and international networks for recruitment, with better designed clinical trials with independent data and statistical analysis. Such a network could save millions of dollars, provide more answers to our current questions, and provide a sound basis for future guidelines to manage lower respiratory tract infections.

Based on our current understanding of VAP pathogenesis, the use of serial quantitative ETAs should be a valuable thermometer to monitor the progress of the war between the invading host bacteria and host defenses as well as an intervention “flashpoint” for early, targeted antibiotic therapy for VAT. This model may have advantages over our current practice of early, empiric antibiotic therapy for VAT, followed by de-escalation and stopping antibiotics at 7 to 8 days. The benefits of using the VAT model as a strategy include a standard method and definition for benchmarking lower respiratory tract infection rates, a cost-effective alternative for VAP reduction and prevention, and several desired patient outcomes that include reduced antibiotic use and perhaps resistance, fewer days of mechanical ventilation, ICU stay, and reduced morbidity and mortality that should also decrease health-care costs. We believe that a paradigm targeting VAT has many attractive features, could improve our current management and prevention strategies, and is analogous to casting a stone into a still pond that creates ripples that will go on and on.

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