CHEST Special Feature

Ventilator-Associated Tracheobronchitis*

The Impact of Targeted Antibiotic Therapy on Patient Outcomes

Donald E. Craven, MD; Alexandra Chroneou, MD; Nikolaos Zias, MD, PhD; and Karin I. Hjalmarson, MD

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. ***(CHEST 2009; 135:521–528)***

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

"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,[1] but two recent randomized, clinical trials[2,3] 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.[2–4] VAT should be suspected

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in intubated patients with clinical signs of lower respiratory tract infection (such as fever, leukocytosis, and purulent sputum) with a Gram stain demon-

*From the Departments of Infectious Diseases (Drs. Craven and Hjalmarson) and Critical Care Medicine (Drs. Chroneou and Zias), Lahey Clinic Medical Center, Burlington, MA.
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Correspondence to: Donald E. Craven, MD, Chair, Department of Infectious Diseases, Lahey Clinic Medical Center, 41 Mall Rd, Burlington, MA 01805; e-mail: donald.e.craven@lahey.org
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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.[3,5] Existing studies[5–7] 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).[5,7,8]

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.[2,3,9]

Epidemiology and Etiology

Several studies have looked at the incidence of VAT. A German multicenter study[6] of 515 ICU patients found an incidence of 2.7%, among 161 multiple trauma patients in a single-center study[7] in Spain the incidence was 3.7%, and it was 10% in a study[5] 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 influenza*, *Legionella pneumophila*, and methicillin-sensitive *S aureus*.[5] Nonbacterial etiologies causing VAT are rare and also unlikely to cause VAP.[10]

Medical and surgical patients with VAT appear to have a significantly longer length of ICU stay and duration of mechanical ventilation.[5] 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.[1,11,12]

Pathogenesis

Lower Respiratory Tract Colonization

Intubation and mechanical ventilation increase the risk of VAP by sixfold to 20-fold.[1,11] Long-term mechanical ventilation with high airway pressures promotes lung injury, ARDS, and increases the risk for lung infection.[13] 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.[11,14] 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.[14] 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).[1,11,14] 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.[15] Bacterial virulence also varies widely within Gram-positive species of MRSA.[16]

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.[1,11,17,18]

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.[11] 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.