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

Donald E. Craven, MD[a,b,*], Jana Hudcova, MD[b,c], Yuxiu Lei, PhD[a]

KEYWORDS

- Ventilator-associated pneumonia
- Ventilator-associated tracheobronchitis
- Ventilator-associated respiratory infection
- Microbiologic criteria for diagnosis • Endotracheal aspirates
- Bronchoalveolar lavage antibiotics
- Multidrug-resistant bacteria

Ventilator-associated respiratory infections (VARIs) may be manifested as tracheobronchitis (VAT) and ventilator-associated pneumonia (VAP).[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.[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).[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.[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.[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.[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

[a] Center for Infectious Disease & Prevention, Lahey Clinic Medical Center, 41 Mall Road, Burlington, MA 01805, USA
[b] Tufts University School of Medicine, 136 Harrison Avenue, Boston, MA 02110, USA
[c] Department of Critical Care & Surgery, Lahey Clinic Medical Center, 41 Mall Road, Burlington, MA 01805, USA
* Corresponding author. Centers for Infectious Diseases & Prevention, Lahey Clinic Medical Center, 41 Mall Road, Burlington, MA 01805.
E-mail address: donald.e.craven@lahey.org

Clin Chest Med 32 (2011) 547–557
doi:10.1016/j.ccm.2011.06.001

(B) or nonbronchoscopic (NB) BAL or PSB samples.[3,10,11] 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.[3,7,8,12]

EPIDEMIOLOGY

VAT and VAP are defined as infections that occur more than 48 hours after intubation.[1,3,4,7] 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 (**Table 1**). 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.[1,4,13] 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.[14]

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.[2] The incidence of VAT in Europe has ranged from 2.7% to 10%, depending on the population studied.[3] 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.[6] However, 32% of patients with VAT progressed to VAP.

Table 1
Pathogens associated with ventilator-associated respiratory infection

Antibiotic-Sensitive Pathogens	Multidrug-Resistant (MDR) Pathogens
Gram-Positive Cocci:	Gram-Positive Cocci:
Streptococcus pneumoniae (pneumococcus)	Methicillin-resistant *Staphylococcus aureus* (MRSA)
Methicillin-sensitive *Staphyloccus aureus (MSSA)*	
Gram-Negative Bacilli (GNB):	GNB:
Haemophilus influenzae	*Pseudomonas aeruginosa*
Escherichia coli	*E coli*[a]
Klebsiella pneumoniae	*K pneumoniae*[a,b]
Enterobacter aerogenes	*Enterobacter species*[a,b]
Proteus species	*Acinetobacter species*
	Stenotrophomonas maltophilia

[a] ESBL-positive (extended-spectrum β-lactamase).
[b] CRE (carbapenemase-resistant *Enterobacteriacaea*).

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.*[4] In addition, there has also been a dramatic increase in infections due to methicillin-resistant *Staphylococcus aureus* (MRSA) that is likely to continue.[3,4,15]

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 (**Fig. 1**).[1,4,7] Intubation with mechanical ventilation increases the risk of bacterial pneumonia sixfold to 20-fold.[1,4] 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 (**Fig. 2**).[1,2,4,7] Bacteria usually enter the lower respiratory tract by leakage around the ETT cuff or via the ETT lumen.[1,7,16] The inflated ETT cuff prevents the exit of bacteria and secretions from the lower airway, which increases the need for manual tracheabronchial suctioning of infected secretions. Furthermore, ETT biofilm-encased bacteria may also contribute to lower airway infection from biofilm emboli.[17,18]