# The Pathogenesis of Ventilator-Associated Pneumonia: Its Relevance to Developing Effective Strategies for Prevention

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Ventilator-associated pneumonia (VAP) is the most common nosocomial infection in the intensive care unit and is associated with major morbidity and attributable mortality. Strategies to prevent VAP are likely to be successful only if based upon a sound understanding of pathogenesis and epidemiology. The major route for acquiring endemic VAP is oropharyngeal colonization by the endogenous flora or by pathogens acquired exogenously from the intensive care unit environment, especially the hands or apparel of health-care workers, contaminated respiratory equipment, hospital water, or air. The stomach represents a potential site of secondary colonization and reservoir of nosocomial Gram-negative bacilli. Endotracheal-tube biofilm formation may play a contributory role in sustaining tracheal colonization and also have an important role in late-onset VAP caused by resistant organisms. Aspiration of microbe-laden oropharyngeal, gastric, or tracheal secretions around the cuffed endotracheal tube into the normally sterile lower respiratory tract results in most cases of endemic VAP. In contrast, epidemic VAP is most often caused by contamination of respiratory therapy equipment, bronchoscopes, medical aerosols, water (eg, *Legionella*) or air (eg, *Aspergillus* or the severe acute respiratory syndrome virus). Strategies to eradicate oropharyngeal and/or intestinal microbial colonization, such as with chlorhexidine oral care, prophylactic aerosolization of antimicrobials, selective aerodigestive mucosal antimicrobial decontamination, or the use of sucralfate rather than $H_2$ antagonists for stress ulcer prophylaxis, and measures to prevent aspiration, such as semirecumbent positioning or continuous subglottic suctioning, have all been shown to reduce the risk of VAP. Measures to prevent epidemic VAP include rigorous disinfection of respiratory equipment and bronchoscopes, and infection-control measures to prevent contamination of medical aerosols. Hospital water should be *Legionella*-free, and high-risk patients, espe-

**cially those with prolonged granulocytopenia or organ transplants, should be cared for in hospital units with high-efficiency-particulate-arrestor (HEPA) filtered air. Routine surveillance of VAP, to track endemic VAPs and facilitate early detection of outbreaks, is mandatory.** *Key words: cross-infection, ventilator-associated pneumonia, mechanical ventilation, microbiology, nosocomial, bacteria, antibiotic, antibiotic-resistant.* [Respir Care 2005;50(6):725–739. © 2005 Daedalus Enterprises]

## Introduction

Mechanical ventilation is an essential feature of modern intensive care unit (ICU) care. Unfortunately, mechanical ventilation is associated with a substantial risk of ventilator-associated pneumonia (VAP). VAP is the most common nosocomial infection in the ICU, with an incidence ranging from 9% to 40%,[1–3] and is associated with prolonged hospitalization,[4–6] increased health care costs,[7] and a 15–45% attributable mortality.[8–10] Understanding the pathogenesis of VAP is essential to devising strategies for prevention of these infections.[11] Advances in our understanding of pathogenesis have led to the development of specific measures that can greatly reduce the risk of VAP.[12–15] This review focuses on the pathogenesis and epidemiology of VAP and implications for prevention.

## Defense Mechanisms for Prevention of Respiratory Infection in the Normal Host

In the normal nonsmoking host, multiple host defense mechanisms play an essential role in prevention of pneumonia (Table 1).[16,17] The aerodigestive tract above the vocal cords is normally heavily colonized by bacteria; however, unless the person has chronic bronchitis or has had respiratory tract instrumentation, the lower respiratory tract is normally sterile. Normal adults aspirate frequently during sleep; yet the lower airways and pulmonary parenchyma of healthy, nonsmoking persons without lung disease are remarkably free of microbial colonization.[18,19]

The major defense mechanisms include anatomic airway barriers, cough reflexes, mucus,[20] and mucociliary clearance (Table 1).[21] The ciliated mucosa of the upper respiratory tract has a major role in removing particulate matter and microbes that have gained access to the bronchial tree. Mucociliary clearance is a complex process, the integrity of which depends upon the composition of airway secretions, an effective mucociliary reflex, and an effective cough.[21]

Below the terminal bronchioles, the cellular and humoral immune systems are essential components of host defense.[22] Alveolar macrophages and leukocytes remove particulate matter as well as potential pathogens, elaborate cytokines that activate the systemic cellular immune response, and act as antigen-presenting cells to the humoral arm of immunity.[23] Immunoglobulins and complement inactivate and opsonize bacteria and bacterial products within the respiratory tract, facilitating phagocytosis.

In the mechanically ventilated patient, a number of factors conspire to compromise host defenses: critical illness, comorbidities,[24] and malnutrition impair the immune system,[25] and, most importantly, endotracheal intubation thwarts the cough reflex,[26] compromises mucociliary clearance,[27] injures the tracheal epithelial surface,[28] and provides a direct conduit for rapid access of bacteria from above into the lower respiratory tract.[29,30] It would probably be more accurate pathogenetically to rename VAP as "endotracheal-intubation-related pneumonia." Invasive devices and procedures and antimicrobial therapy create a favorable milieu for antimicrobial-resistant nosocomial pathogens to colonize the aerodigestive tract.[31]

This combination of impaired host defenses and continuous exposure of the lower respiratory tract to large numbers of potential pathogens through the endotracheal tube (ETT) (Fig. 1) puts the mechanically ventilated patient at great jeopardy of developing VAP.

## Noninvasive Ventilation

Avoidance of intubation and mechanical ventilation is the first defense against VAP. In a matched case-control study of 100 patients admitted to a medical ICU with respiratory failure, Girou et al found that rates of nosocomial pneumonia and all nosocomial infections were much lower in patients supported with noninvasive ventilation than those intubated and ventilated mechanically (8% vs

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Table 1. Normal Host Defenses for Prevention of Pneumonia

| |
|---|
| Anatomy of airways |
| Cough reflex |
| Mucus |
| Mucociliary clearance |
| Alveolar macrophages |
| Leukocytes |
| Immunoglobulins |
| Complement |
| Lactoferrin |
| Basement membrane |

22%, 18% vs 60%, p = 0.04, and p < 0.001, respectively). Moreover, the proportion of patients receiving antibiotics for nosocomial infection (8% vs 26%, p = 0.01), length of ICU stay (9 vs 15 d, p = 0.02), and crude mortality (4% vs 26%, p = 0.002) were all far lower among patients receiving noninvasive ventilation.[32] Randomized trials have found similar results,[33–35] and a recent meta-analysis showed that patients with exacerbations of chronic obstructive pulmonary disease supported by noninvasive ventilation had a 62% reduction in mortality, compared with patients who were intubated and mechanically ventilated.[36]

## Routes of Development of VAP

In order for microorganisms to cause VAP, they must first gain access to the normally sterile lower respiratory tract, where they can adhere to the mucosa and produce sustained infection. Microorganisms gain access by one of 4 mechanisms (see Fig. 1): (1) by aspiration of microbe-laden secretions, either from the oropharynx directly or, secondarily, by reflux from the stomach into the oropharynx, then into the lower respiratory tract;[37–39] (2) by direct extension of a contiguous infection, such as a pleural-space infection;[40] (3) through inhalation of contaminated air or medical aerosols;[41] or (4) by hematogenous carriage of microorganisms to the lung from remote sites of local infection, such as vascular or urinary catheter-related bloodstream infection.[42–44]

## Epidemic VAP

Outbreaks of VAP due to contamination of respiratory therapy equipment, bronchoscopes, and endoscopes have been well described (Table 2).[41,45–148] For example, Takigawa et al reported 16 episodes of hospital-acquired pneumonia due to *Burkholderia cepacia* caused by contamination of inhaled medication nebulizer reservoirs.[50] Srinivasan et al reported 28 episodes of pneumonia caused by *Pseudomonas aeruginosa* linked epidemiologically to contaminated bronchoscopes with defective biopsy-port

caps;[102] the outbreak occurred despite adherence to disinfection and sterilization guidelines.[108]

Since the first reports of large outbreaks of severe acute respiratory syndrome (SARS) in 2003, in which more than 8,000 persons in China, Hong Kong, Singapore, Vietnam, Taiwan, and Canada ultimately became infected and 9.6% died,[118] major advances have been made in our understanding of the epidemiology and modes of transmission of this remarkably virulent new human coronavirus.[119] SARS spreads almost exclusively in respiratory droplets from person to person, rarely by distant airborne spread or contact. The risk of acquiring SARS is far higher in the hospital than in the community, and nearly one half of the early cases involved health care workers or hospitalized patients infected secondarily after admission.[119,120] Although SARS has been contained for now, if it returns it will pose an ongoing threat to patients and health care workers as a cause of severe nosocomial pneumonia.

Outbreaks of other respiratory pathogens, such as *Legionella pneumophila*, influenza A, or respiratory syncytial virus, are well described in health care institutional settings (Table 2).[121–127]

In the mid-1980s, tuberculosis rates in the United States rose after a half-century of decline, and many nosocomial outbreaks with multiple-drug-resistant strains were documented. In one such outbreak investigated by the Centers for Disease Control, 6 cases of tuberculosis occurred following exposure to a source patient who had spent several weeks in the hospital before being placed in respiratory isolation.[128] Transmission of tuberculosis through contaminated bronchoscopes and respiratory equipment has also been reported.[53,104]

Although pseudo-outbreaks with nontuberculous mycobacteria far outnumber epidemics of true disease, nosocomial outbreaks caused by these ubiquitous environmental organisms are well described, most often in association with contaminated hospital water (Table 2).[68,69]

## Endemic VAP

For most endemic VAPs, the most important mechanism of infection is gross or micro-aspiration of oropharyngeal organisms into the distal bronchi, followed by bacterial proliferation and parenchymal invasion. Inflammation of the bronchiole wall involves the alveolar septi and air spaces, leading to bronchopneumonia.

Pathogens causing VAP may be part of the host's endogenous flora at the time of hospitalization or may be acquired exogenously after admission to the health care institution, from the hands, apparel, or equipment of health care workers, hospital environment, and use of invasive devices (see Fig. 1).

Although most epidemics of VAP have stemmed from direct infection of the lower airway by exogenous organ-
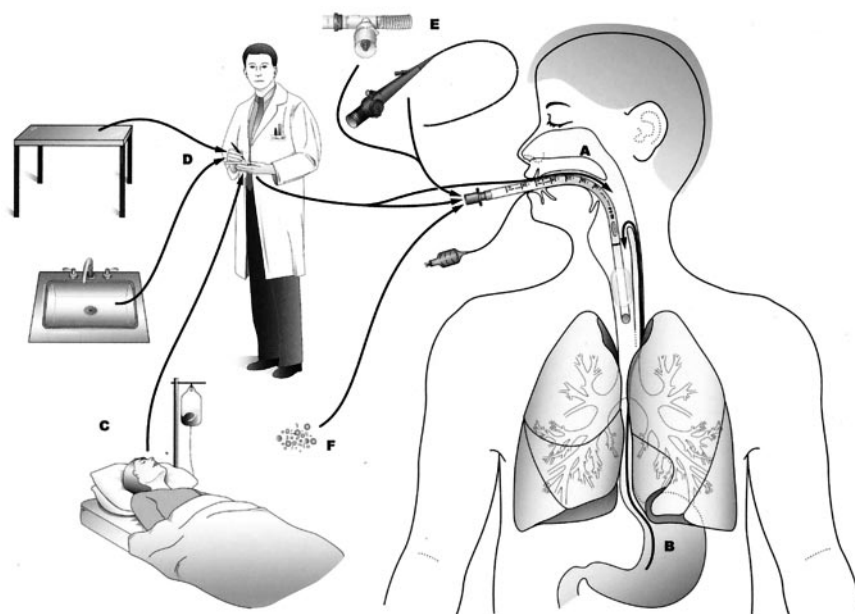
Fig. 1. Routes of colonization/infection in mechanically ventilated patients. Colonization of the aerodigestive tract may occur endogenously (A and B) or exogenously (C through F). Exogenous colonization may result in primary colonization of the oropharynx or may be the result of direct inoculation into the lower respiratory tract during manipulations of respiratory equipment (D), during using of respiratory devices (E), or from contaminated aerosols (F).

isms such as Gram-negative bacilli, *Legionella*, or *Aspergillus*, epidemics can also be insidious, with colonization of the upper airway and cases of VAP occurring only days or even weeks later.

## The Sequence of Oropharyngeal Colonization and VAP

The normal flora of the oropharynx in the nonintubated patient without critical illness is composed predominantly of viridans streptococci, *Haemophilus* species, and anaerobes. Salivary flow and content (immunoglobulin, fibronectin) are the major host factors maintaining the normal flora of the mouth (and dental plaque). Aerobic Gram-negative bacilli are rarely recovered from the oral secretions of healthy patients.[149] During critical illness, especially in ICU patients, the oral flora shifts dramatically to a predominance of aerobic Gram-negative bacilli and *Staphylococcus aureus*.[150] Bacterial adherence to the orotracheal mucosa of the mechanically ventilated patient is facilitated by reduced mucosal immunoglobin A and increased protease production, exposed and denuded mucous membranes, elevated airway pH, and increased numbers of airway receptors for bacteria, due to acute illness and antimicrobial use.

Numerous studies show that colonization of the oropharynx by aerobic Gram-negative and Gram-positive pathogens, such as *S. aureus,* is a near-universal occurrence in critically ill patients receiving mechanical venti-

lation.[151–154] In a study of 80 ventilated patients, de la Torre et al found that in 19 patients with secondary tracheal colonization, 46% of the microorganisms isolated from the trachea had previously been isolated from the pharynx.[37] In a more recent study of 48 trauma patients, Ewig et al found that, upon admission to the ICU, patients were colonized mainly with *S. aureus*, *Haemophilus influenzae,* and *Streptococcus pneumoniae*; however, follow-up cultures showed rapid replacement of the normal oropharyngeal flora by enteric Gram-negative bacilli and *P. aeruginosa*. Oropharyngeal colonization was a powerful independent predictor of subsequent tracheobronchial colonization (odds ratio 23.9, 95% confidence interval 3.8 – 153.3).[38] George et al reported similar findings: 42% of the pathogens isolated from 26 patients with VAP were previously recovered from the oropharynx.[39]

Aspiration of oropharyngeal contents containing a large bacterial inoculum overwhelms host defenses already compromised by critical illness and the presence of an ETT, thus leading to the development of VAP.

Understanding this sequence of pathophysiologic events, it would seem logical that reducing concentrations of oral microorganisms should have a beneficial effect for prevention of VAP (Table 3). Four studies have evaluated the use of scheduled oral care with a chlorhexidine antiseptic solution for prevention of VAP;[155–158] chlorhexidine oral care reduced the incidence of oral microbial colonization *and* VAP. The use of chlorhexidine for oral antisepsis warrants further study and consideration for application in clin-

Table 2.  Reported Outbreaks of Ventilator-Associated Pneumonia Traced to Environmental Sources

| Source of Outbreak | Reference(s) | Organisms |
|---|---|---|
| Reusable electronic ventilator probes and sensors | 54–56 | *Burkholderia cepacia* |
| | | *Stenotrophomonas maltophilia* |
| Nebulized medication | 41, 45–53 | *Burkholderia cepacia* |
| | | *Pseudomonas aeruginosa* |
| | | *Mycobacterium tuberculosis* |
| Ventilator circuits and equipment, humidifiers, and respirometers | 57–66 | *Acinetobacter calcoaceticus* |
| | | *Burkholderia cereus* |
| | | *Pseudomonas aeruginosa* |
| Ice and water | 67–99 | *Legionella pneumophila* |
| | | *Pseudomonas aeruginosa* |
| | | Nontuberculous mycobacteria |
| Bronchoscopes | 100–108 | *Pseudomonas aeruginosa* |
| | | *Mycobacterium tuberculosis* |
| | | Nontuberculous mycobacteria |
| Fingernails and hands of health care workers | 109–112 | *Pseudomonas aeruginosa* |
| | | *Klebsiella pneumoniae* |
| Miscellaneous | | |
|   Milk bank pasteurizer | 113 | *Pseudomonas aeruginosa* |
|   Blood-gas analyzer | 114 | *Pseudomonas aeruginosa* |
|   Mouthwash | 115 | *Burkholderia cepacia* |
|   Food coloring dye | 116, 117 | *Pseudomonas aeruginosa* |
| | | *Burkholderia cepacia* |
| Infected patients or health-care workers | 118–133 | SARS human coronavirus |
| | | Influenza A, respiratory syncytial virus |
| | | *Mycobacterium tuberculosis* |
| | | Methicillin-resistant *Staphylococcus aureus* |
| Ambient air | 134–148 | Aspergillus, zygomycetes |

ical practice. The use of aerosolized antimicrobials and the topical application of antimicrobial combinations to the aero-digestive mucosa for prevention of VAP are discussed below.

## Gastric Colonization and Aspiration

The stomach has been posited to be an important reservoir of organisms that cause VAP (see Fig. 1).[37] In healthy persons, few bacteria entering the stomach survive in the presence of gastric acid. Conditions that reduce the gastric pH, such as achlorhydria, treatment with $H_2$ antagonists or proton-pump inhibitors, or enteral nutrition, predispose to bacterial proliferation in the stomach.[159–162] Studies have shown a powerful relationship between a high gastric pH and massive overgrowth of gastric bacteria.[159–162] Gastric microorganisms can reflux up the esophagus, abetted by recumbency and the ever-present naso- or oro-gastric tube, and are aspirated into the trachea. Direct and indirect evidence exists to implicate the stomach as a potential reservoir of bacteria causing VAP.[163–165] Numerous studies have shown that gastric contents can be aspirated into the lower airways, despite the presence of an endotracheal cuff.[166,167] However, recent studies suggest that the stomach, although often heavily colonized by enteric Gram-

negative bacilli, is not the primary source for lower-airway colonization with nosocomial pathogens, and the gastropulmonary route is not a major pathogenetic route for development of VAP.[168]

In a prospective, randomized, double-blind study in ICU patients, Bonten et al compared antacids and sucralfate and measured intragastric acidity. Colonization by *Enterobacteriaceae* occurred in the stomach, trachea, and oropharynx; however, intragastric acidity did not appear to influence the development of VAP.[169] In another analysis of the same study, the same group of investigators showed that oropharyngeal colonization by *Enterobacteriaceae* was an important independent risk factor for VAP; in contrast, gastric colonization by *Enterobacteriaceae* was not found to increase the risk of VAP.[170]

## Prophylactic Antimicrobials for Prevention of VAP

### Aerosolized Antimicrobials

The delivery of antimicrobials through aerosol administration allows for the deposition of antimicrobial agents directly at the site of infection, in concentrations not achievable with systemic administration. The adjunctive use of

Table 3.    Measures for Prevention of Ventilator-Associated Pneumonia Based on Our Understanding of Pathogenesis and Epidemiology

| Source of VAP Pathogen | Prevention Goal | Specific Measures |
| --- | --- | --- |
| Aerodigestive colonization | Prevent colonization by exogenous routes | Hand hygiene<br>Microbial surveillance and targeted barrier isolation<br>Preemptive barriers:<br>    Routine gloving<br>    Routine gowning<br>    Dedicated equipment |
| | Suppress oropharyngeal mucosal colonization | Oral decontamination with chlorhexidine<br>Selective digestive tract antimicrobial decontamination<br>Aerosolized antimicrobials<br>Sucralfate instead of $H_2$-blockers |
| | Prevent aspiration | Noninvasive ventilation<br>Semirecumbent positioning<br>Novel endotracheal tube permitting continuous subglottic suctioning |
| Contaminated respiratory therapy equipment and medical aerosols | Safe equipment and medical aerosols | Procedures for reprocessing bronchoscopes and reused respiratory therapy equipment<br>Training and education of reprocessing staff and respiratory therapists<br>Procedures for use of aerosolized medications |
| | Reducing contamination of ventilator circuit | Heat-and-moisture exchanger<br>Periodically drain condensate from circuit<br>Sterile water for bubble-through humidifiers<br>Aseptic procedures for suctioning of ventilated patients |
| Contaminated tap water (*Legionella* species, *Pseudomonas aeruginosa*) | Safe water | Sterile water for:<br>    Cleaning respiratory therapy equipment<br>    Rinsing bronchoscopes<br>    Aerosolized medications<br>Hospital surveillance for cases of nosocomial legionellosis<br>Microbial surveillance of hospital water for contamination by legionellae<br>Engineering controls for contaminated water:<br>    Superheat and flush<br>    Ultraviolet light<br>    Hyperchlorination<br>    Silver-copper ionization<br>    Ozonation |
| Contaminated ambient air (filamentous fungi, *Mycobacterium tuberculosis*, SARS coronavirus | Safe air | Procedures for minimizing communicable airborne infections:<br>    Disease recognition<br>    Administrative controls<br>    Engineering controls<br>Procedures for minimizing risk to immunocompromised patients:<br>    High-efficiency particulate arrester (HEPA)-filtered rooms<br>    N95 masks for intrahospital transports<br>Policies and procedures for management during periods of construction and renovation |

VAP = ventilator-associated pneumonia
SARS = severe acute respiratory syndrome

aerosolized antimicrobial agents has become widely practiced in the treatment of patients with cystic fibrosis,[171] and has gained much interest for treatment of VAP, especially with the rapid emergence of nosocomial microorganisms resistant to multiple systemic antimicrobials in many ICUs. Anecdotally, aerosolized colistin[172] and poly-

myxin B[173] have been used to successfully treat infections caused by a variety of multi-resistant Gram-negative bacteria, such as *P. aeruginosa* or *Acinetobacter* species, resistant to most or all available antimicrobial drugs that can be administered systemically. Moreover, a prospective randomized controlled trial has shown that adjunctive use of

aerosolized tobramycin, in addition to systemic therapy, controls respiratory-tract infections caused by Gram-negative bacilli more rapidly than systemic therapy alone, although survival did not differ between the 2 groups.[174]

Given the early successes of aerosolized antimicrobials in the treatment of VAP, interest has also grown in using aerosolized antimicrobials for prevention, given the fundamental role of airway colonization in the pathogenesis of VAP (see Table 3). A large prospective trial more than 30 years ago showed that aerosolized polymyxin B significantly reduced airway colonization (1.6% vs 9.7%, $p < 0.01$) and VAP caused by *P. aeruginosa* (0.8% vs 4.6%, $p < 0.01$), although overall mortality from VAP was unchanged.[175] The authors of this study rightly pointed out the concerns of promoting antimicrobial resistance through the use of prophylactic antimicrobial agents, and we believe that further studies are needed before aerosolized antimicrobial agents can be endorsed for *prevention* of VAP. Notably, the heavy prophylactic use of aerosolized colistin in patients with cystic fibrosis in one center recently resulted in the very unusual emergence of a strain of *P. aeruginosa* resistant to colistin, which spread to other patients in the unit.[176]

### Selective Aerodigestive Mucosal Antimicrobial Decontamination

The use of topically-applied nonabsorbable oral antibiotics to eradicate or at least reduce aerodigestive mucosal colonization by pathogenic microorganisms (see Table 3), a process widely termed selective digestive decontamination, has been extensively studied.[177,178] A short course of parenteral antimicrobials with a prolonged duration of topical antimicrobials has been used in most studies evaluating the efficacy of selective digestive decontamination for the prevention of VAP. More than 40 randomized controlled trials[179,180] and 8 meta-analyses[181–185] have undertaken to determine the efficacy of selective digestive decontamination for reducing the incidence of VAP; most, but not all, have found a beneficial effect in VAP but an inconsistent effect on ICU mortality. Regardless of efficacy, a very real concern relates to the potential for promoting antimicrobial resistance with long-term use of selective digestive decontamination.[186,187] Recent studies have justified this concern and further dampened enthusiasm for this approach in U.S. centers.

Most of the studies were not designed to assess the relative effect of the 2 major components of selective digestive decontamination (topical *and* systemic agents) on the prevention of VAP. Future studies especially need to more clearly evaluate antimicrobial resistance as a major end point, incorporating the use of selective media for surveillance cultures to enhance recovery of antibiotic-resistant nosocomial pathogens.

Randomized controlled trials have shown that simple strategies to prevent aspiration, such as semirecumbent (rather than supine) positioning,[188] and continuous suctioning of subglottic secretions,[189–192] can greatly reduce the incidence of VAP (see Table 3), and are far more attractive ecologically than the heavy use of prophylactic antimicrobials.

### Biofilms of the Endotracheal Tube

The ETT has also been posited as a reservoir for infecting microorganisms, which adhere to the surface of the foreign body,[193] producing a biofilm. Biofilms are highly resistant to the effects of antibiotics and host defenses and may represent a site of cumulative and persistent colonization by antibiotic-resistant nosocomial pathogens.[194] In a prospective study of 40 patients with VAP, Adair et al found that 70% of patients with VAP had identical pathogens isolated from both endotracheal biofilm and tracheal secretions.[194] In another prospective study, Feldman et al obtained cultures from oropharyngeal, gastric, respiratory tract, and ETT twice daily for 5 days, and noted the following sequence of colonization in patients undergoing mechanical ventilation: the oropharynx (36 h), the stomach (36–60 h), the lower respiratory tract (60–84 h), and, thereafter, the ETT (60–96 h). Nosocomial pneumonia occurred in 13 patients, and in 8 cases identical organisms were recovered from lower-respiratory-tract specimens and from material lining the interior of the ETT.[195]

This discovery has led to the development of novel antiseptic-impregnated ETTs. In a laboratory model, the effect of ETTs impregnated with chlorhexidine and silver carbonate was tested *in vitro* against *S. aureus*, methicillin-resistant *S. aureus, P. aeruginosa*, *Acinetobacter baumannii*, and *Enterobacter aerogenes*. After 5 days of incubation, bacterial colony counts on all ETT segments, both antiseptic-impregnated and control ETTs were measured. There was a significant reduction in colony counts of organisms recovered from the antiseptic-impregnated ETTs (1–100 colony-forming units per tube, compared with $10^6$ colony-forming units per tube from control ETTs).[196] An in vivo study in 12 dogs, comparing a silver-coated ETT to a standard ETT, found significantly reduced lower-respiratory-tract colonization with the silver-coated tube.[197] A multicenter trial to ascertain the efficacy of the chlorhexidine-silver carbonate-impregnated tube is currently underway.

### Sinusitis and Pneumonia

In a prospective study of sinusitis, Holzapfel et al found that bacterial paranasal sinusitis was associated with an almost 3-fold increased risk for pneumonia (risk ratio 2.29, 95% confidence interval 1.10–4.74).[198] Other investiga-

tors have found similar results.[199,200] However, it is unclear whether sinus infection precedes and then predisposes to the development of VAP or is a noncausal epiphenomenon. Further studies are needed before a systematic search for sinusitis can be recommended in every patient with VAP.

Microbiologic analysis of a sinus aspirate in a patient with suspected sinusitis and VAP may serve to assist in the diagnosis of VAP, as the pathogens causing VAP and nosocomial sinusitis are virtually identical. In a prospective study, Souweine et al found that in patients with VAP and sinusitis the same pathogens were recovered in cultures from both sites of infection.[200]

### The Role of Respiratory Equipment in Causing VAP

Condensates of ventilator circuits can also be a potential source of microorganisms; numerous studies have shown that manipulation of circuits can increase the risk of VAP.[201,202] Goularte et al found that changing circuits every 48 hours instead of every 24 hours decreased the incidence of VAP.[202] In a randomized trial, Kollef et al found that eliminating routine changes of ventilator circuits altogether did not result in an increased incidence of VAP and resulted in substantial cost savings.[201] Closed tracheal suctioning has been associated with an increased risk of colonization; however, the risk of VAP was not increased.[203] Table 2 shows major outbreaks of VAP related to contaminated respiratory equipment or transfer of microorganisms from health-care workers or other patients to susceptible patients; most outbreaks were caused by *P. aeruginosa* and *B. cepacia.*

### Hospital Water

A variety of organisms, including bacteria, mycobacteria, fungi, and parasites, are isolated from hospital water systems and have been implicated in endemic and epidemic nosocomial infections.[70] Many of these outbreaks were caused by bacteria typically thought of as "water" organisms such as *P. aeruginosa*,[72–74] *Stenotrophomonas maltophilia*,[75] and *A. baumannii*;[76–79] however, the hospital water organisms most commonly implicated in epidemic nosocomial pneumonia are the *Legionella* species (see Table 2).[80]

The first reports describing *Legionella* species as human pathogens were published in 1976. The genus *Legionella* is composed of 48 different species and 70 different serotypes, although *L. pneumophila* accounts for the vast majority of human infections (> 90%), with other species, such as *Legionella longbeachae*, *Legionella bozmanii*, and *Legionella micdadei*, being isolated far less commonly.[81] Nosocomial legionellosis was first described in 1979,[82] and it is estimated that 25–45% of all cases of legionel-

losis are acquired in the health-care setting,[82] with a mortality that approaches 30%.[83] Legionella contamination of hospital potable water remains underappreciated, despite studies showing that *Legionella* species can be recovered from 12–70% of hospital water systems,[84] and studies have demonstrated an uncovering of unrecognized cases when aggressive diagnostic and surveillance methods are employed.[86,87] Characteristics of water systems that enhance legionella contamination of hospital water include plumbing with dead-ends that produce water stagnation, large-volume water heaters that result in inefficient heating of hospital water, water sediment build-up, heated-water temperatures $\leq 60°C$, tap-water temperatures $\leq 50°C$, water pH $\leq 8$, and municipal water not treated with monochloramine.[88–89]

### Hospital Air

Filamentous fungi and molds are the primary microorganisms routinely found in ambient air, including hospital air, and more than 2 decades ago infections caused by these organisms were considered a curiosity. The enormous increase in immunocompromised patients as a result of greatly increased bone-marrow and solid-organ transplantation and the epidemic of acquired immune deficiency syndrome has changed this view,[134] and numerous outbreaks of filamentous fungal infection have now been reported (see Table 2), most linked to new construction or renovation or to breakdowns in air-handling systems.[135] Pegues et al reported an unusual outbreak of invasive pulmonary aspergillosis among orthotopic liver-transplant recipients, traced to massive aerosolization of spores following wound dressing changes in a patient with a surgical wound infection caused by *Aspergillus fumigatus*.[135]

Routine high-efficiency-particulate-arrestor (HEPA) filtration of intake air in units with patients at risk can greatly reduce the risk of invasive fungal infection (see Table 3),[136,137] although outbreaks of infections caused by filamentous fungi have continued to be reported during periods of construction, when ambient levels of fungi rise sharply and overwhelm engineering controls.[138,148]

The spread of the SARS virus was effectively contained by stringent respiratory isolation precautions designed to prevent airborne transmission. Routine use of high-quality filtration masks, ideally N-95 masks, but even surgical masks,[130] combined with full barrier precautions in a single room was highly effective in preventing spread to other patients and health care workers where it was most carefully studied, in Hong Kong, Singapore, and Canada.[131] Persons exposed to SARS must be quarantined; however, there is no need to extend the period of quarantine of exposed persons beyond 10 days, as very few persons develop clinical SARS more than 10 days after exposure.[132]

The prevention of nosocomial transmission of community-acquired respiratory viral infections, such as influenza, also deserves mention, given the numerous institutional outbreaks reported (see Table 2).[133] Infection control practices to prevent nosocomial spread of respiratory viral infections include: (1) a high level of immunization of patients and staff against influenza; (2) prevention of patient contact with persons (friends, family, and health-care staff) who have active respiratory symptoms; (3) use of rapid diagnostic tests to quickly identify symptomatic patients with potentially transmissible viral pathogens, to facilitate early implementation of isolation precautions; (4) cohorting patients with confirmed infection when single rooms are not available; and (5) placement of patients with suspected community-acquired respiratory viral infections in droplet isolation precautions. The use of more aggressive isolation procedures, such as contact and airborne isolation precautions, with or without the use of prophylactic antiviral agents, deserves consideration with outbreaks among very-high-risk patients.[15]

## Summary

In sum, the major route of pulmonary infection in *endemic* VAP is aspiration of oropharyngeal secretions colonized by nosocomial organisms, especially enteric Gram-negative bacilli or *S. aureus*. The stomach and/or the intestine may play a secondary role as a reservoir of nosocomial organisms; however, the digestive tract does not appear to be the *initial* site of colonization in most cases of VAP. ETT biofilm may contribute to sustaining colonization, creating an increased risk of infection, and further studies are needed to determine the exact role that ETT biofilm plays in facilitating infection and sustaining it. With *epidemic* VAP, contaminated respiratory equipment and medical aerosols are the major sources; however, contaminated hospital air (*Aspergillus*) and water (*Legionella*) are also important causes of nosocomial pneumonia deriving from environmental reservoirs. Future research needs to focus on delineating more clearly the sequence of aero-digestive-tract colonization, including the relative importance of the various sites of potential early colonization: the oropharynx, stomach, and trachea. Better understanding of pathogenesis and epidemiology is essential to devising more effective strategies for prevention of VAP.

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## Discussion

**MacIntyre:** What is your take on Gerry Smaldone's idea that maybe you should aerosolize these antibiotics into the airway as a preventive measure to prevent colonization?

**Maki:** I will talk about that this afternoon.

**Solomkin:** Do you think that solid-organ-transplant patients should be managed the same way as other high-risk ICU patients?

**Maki:** I'll tell you about that this afternoon, but, in a nutshell, the answer to your question, I think, is yes, because they're much more vulnerable to colonization and infection by resistant organisms. That is the greatest challenge of these patients. If you do liver transplantation, you're going to have a lot more VRE [vancomycin-resistant enterococcus], a lot more beta-lactamase-producing Gram-negative rods, and more MRSA [methicillin-resistant *Staphylococcus aureus*] in your unit or in your hospital. I think you have to accommodate this in your preventive strategies.

**Solomkin:** Do you think those differences are because of physiologic changes in the host?

**Maki:** No. Do you know what the greatest risk factor is for picking up MRSA in the hospital, or VRE? It's how long you're hospitalized. Length of stay is such a powerful risk factor that when we do multivariable mod-

eling with large databases, if we leave it in the model, it's hard to find other risk factors. The longer you are in the hospital, the more likely you are to pick up a resistant organism.

We're now about 600 patients into a prospective study that's been going on for 2 years, in which we are culturing for 5 resistant organisms when a patient enters the hospital and every 5 days thereafter until the patient goes home, and length of stay is a huge risk factor. Liver transplant patients have a length of stay that is 3 times the average of other patients. They've often already spent time in other hospitals and other ICUs, getting their liver disease and gastrointestinal bleeding treated, so they often arrive colonized by resistant organisms, but they acquire even more nosocomial organisms in your hospital following the transplant.

**Kollef:** I want to echo that. I participated in a study, with Linda Mundy, looking at our ICU gowning practices in regard to VRE colonization, and we basically found that in the multivariable analysis there was a compound effect: that the gowning had its greatest effect in preventing VRE colonization with patients who spent more than 10 days in the ICU.[1,2] The problem, I think, from an infection-control perspective is that people are looking for that quick fix in terms of where it's going to have an impact and not recognizing that it may be a very specific population in the ICU—often the more compromised patients who do spend longer time in the ICU.

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**Maki:** I think it's feasible to target high-risk patients for special interventions.

**Kollef:** In regard to oral decontamination with either antimicrobial agents or antiseptic agents, when you look at the chlorhexidine data, there *are* some issues with those studies.[1,2] They have tended to be small, they haven't been blinded, and one thing they didn't look at was VAP-free survival, and they really weren't powered to look at VAP in the survivors. Even the studies that have been done, including Mark Bonten's study[3]—and I've talked to him about this a number of times—they're not truly randomized double-blinded studies in that regard, and I'm a little worried, because there is a trend going on now in terms of just using chlorhexidine and assuming that it may fix many of the problems for us. Part of the reason I raise this concern is that when we recently finished this oral decontamination study using this antimicrobial peptide, we found that the signal was very small. The only place we found a signal was in the trauma population.

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**Maki:** I think you are absolutely right. I don't think the use of chlorhexidine topically in the oropharynx is a done deal. It's a work in progress. It's very interesting and promising. What's attractive about it is that it's unlikely to select for resistance, and it's simple. It's going to be relatively nontoxic and safe; it shouldn't be terribly expensive. But it's not been studied sufficiently so that we can conclude it's a Category 1A recommendation. It would benefit greatly from a multicenter trial, ideally, a blinded trial.

**Kollef:** Do you think that maybe we're going to be looking at combinations of preventive approaches? Maybe using something like chlorhexidine, maybe having something that prevents a biofilm in place? This afternoon I think you are going to be overwhelmed, because the reality of life is that if we don't have a multifaceted approach to prevention, we're in big trouble. We have to have multifaceted approaches.

Ventilator-associated pneumonia, in my opinion, is the most formidable of all the infections we deal with. It's relatively simple to prevent line sepsis. It's relatively simple to reduce the risk of surgical-site infection with specific strategies. The urinary tract and respiratory tract are still *very* formidable problems, because you have a tube passing through a very heavily colonized surface, and there is the possibility of mass transport. I mean if a bolus of $10^6$ organisms goes zipping down the tube, I don't think anything you do on the surface or in the urinary tract is going to do anything about that, and you need to have a multifaceted approach to deal with that, as well as stuff seeping along the side, where biofilms may play a role.

**Niederman:** I think you stated that most pathogenesis begins with oropharyngeal colonization, and I think that that isn't necessarily true—at least it hasn't been in some of the things that I've been involved with. I think you have to make a distinction in whether it's an early pneumonia or late pneumonia and specifically what the pathogen is. I think an important pathogen where that may not always be true is pseudomonas, about which a number of studies[1–4] show that you can get primary tracheal colonization without preceding oropharyngeal colonization.

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**Maki:** I'm convinced that most of those probably come from condensate.

**Niederman:** Whether it's condensate, the environment, or the hands of the staff, consistently the subglottic secretion drainage studies show that they're not very effective at both late pneumonia and pseudomonas pneumonia.

**Maki:** Let me comment on a shortcoming of a lot of the studies of looking at the linkage between oropharyngeal colonization and VAP. First, if you really want to be able to detect low-level colonization by target pathogens such as MRSA, you should probably culture daily. Second, you should use selective media. If you don't use selective media, it's hard to detect small populations that may be there.

**Niederman:** But I think that, at least conceptually, even if the methodology of those serial culture studies isn't perfect, the subglottic secretion-drainage tubes don't work great for late-onset pneumonia or pseudomonal pneumonia, and that may be the explanation. With regard to biofilm, as I think you were describing it and as many people have conceptualized it, this is material that is produced primarily by the bacteria, but the other important component in this system, which I don't think is addressed by any of these prophylactic strategies, is the mucus in the airway. I think that may be one of the reasons why the antibacterial approach may not work: because even if you have a completely sterile biofilm, mucus will bind to the endotracheal tube very effectively, and bacteria will stick to the mucus, probably better than they will stick to anything else. That's why mucus is there. Mucus is effective at removing bacteria because it binds them so well. But if you happen to have stagnation and sticking of that mucus to the endotracheal tube, then it's a bridge to colonization and infection. So I do think that unless we can combine an antibacterial approach with some-

thing that would prevent mucus from binding to the tube, it's probably not going to be effective.

**Maki:** I think your point's well taken.

**Hess:** A question of semantics. If the problem is the endotracheal tube, why do we keep calling it *ventilator-associated* pneumonia?

**Maki:** That's a very legitimate point.

I think a patient who has just had a tracheostomy but is not necessarily on a ventilator, has many of the same vulnerabilities. It would probably be more appropriate to call it *endotracheal-tube*-associated pneumonia.



Pneumonia ward, U.S. Army
Camp Hospital, Humes, France, 1918
Courtesy National Library of Medicine