

# The Microbiology of Ventilator-Associated Pneumonia

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Ventilator-associated pneumonia (VAP) is a common complication of ventilatory support for patients with acute respiratory failure and is associated with increased morbidity, mortality, and costs. Awareness of the microbiology of VAP is essential for selecting optimal antibiotic therapy and improving these outcomes. The specific microbial causes of VAP are many and varied. Most cases of VAP are caused by bacterial pathogens that normally colonize the oropharynx and gut, or that are acquired via transmission by health-care workers from environmental surfaces or from other patients. Common pathogens include *Pseudomonas* species and other highly resistant Gram-negative bacilli, staphylococci, the *Enterobacteriaceae*, streptococci, and *Haemophilus* species. Antibiotic-

resistant pathogens such as *Pseudomonas* and *Acinetobacter* species and methicillin-resistant strains of *Staphylococcus aureus* are much more common after prior antibiotic treatment or prolonged hospitalization or mechanical ventilation, and when other risk factors are present. The bacterial pathogens responsible for VAP also vary depending on patient characteristics and in certain clinical circumstances, such as in acute respiratory distress syndrome or following tracheostomy, traumatic injuries, or burns. But these differences appear to be due primarily to the duration of mechanical ventilation and/or degree of prior antibiotic exposure of these patients. The causes of VAP can vary considerably by geographic location (even between units in the same hospital), emphasizing the importance of local epidemiological and microbiological data. Atypical bacteria, viruses, and fungi also have been implicated as causes of VAP, but these pathogens have not been studied systematically and their role is presently unclear. In conclusion, information about the microbiology of VAP serves to guide optimal antibiotic therapy. The risk of antibiotic-resistant pathogens can be estimated using simple clinical features and awareness of local microbiology patterns. The roles of atypical bacterial and nonbacterial pathogens in VAP are incompletely understood and should be investigated further. *Key words:* ventilator-associated pneumonia, mechanical ventilation, microbiology, nosocomial, pathogen, pneumonia, bacteria, antibiotic, antibiotic-resistant. [Respir Care 2005; 50(6):742–763. © 2005 Daedalus Enterprises]

### Introduction to the Microbiology of Ventilator-Associated Pneumonia

Ventilator-associated pneumonia (VAP) is defined as pneumonia that develops while a patient is receiving mechanical ventilation, usually positive-pressure ventilation delivered via an endotracheal tube for support during acute respiratory failure. VAP is distinguished from severe community-acquired pneumonia that results in acute respiratory failure, and from nosocomial pneumonia occurring among hospitalized patients not receiving mechanical ventilation. The diagnosis of VAP is usually based on clinical, radiographic, and microbiologic criteria and will be covered elsewhere. So why should busy clinicians learn about the microbiology of VAP?

First of all, awareness of the potential microbial causes of VAP and confirmation of the specific cause in an individual patient are essential to guide optimal antibiotic therapy. This is arguably the single most important management decision in the care of these patients, because inadequate initial antibiotic therapy leads to excess mor-

tality,<sup>1,2</sup> and excessive antibiotic therapy increases treatment-related complications and costs and leads to increased prevalence of antibiotic resistance.<sup>2,3</sup> Attention to the microbiology of VAP has many additional benefits: it may inform the prognosis of individual patients, can allow clinicians to track trends in local antimicrobial resistance patterns, can provide insights into the pathogenesis of VAP, can aid the prompt recognition of local VAP outbreaks, and can suggest locally relevant infection-control and VAP-prevention efforts.

Challenges to defining the microbiology of VAP from the existing literature include heterogeneous patient populations and varying use of prior antibiotic treatment, prevention and screening practices, and diagnostic approaches and criteria. In much of the VAP literature, the unit of analysis is blurred between individual patient, VAP episode, type of specimen, and individual bacterial isolate. Finally, not all patients with suspected VAP actually have VAP, or any other infection. VAP is typically confirmed in fewer than half of suspected cases,<sup>4</sup> and many other infectious and noninfectious conditions may account for the clinical manifestations of suspected VAP.<sup>5</sup>

The goals of this paper are 4-fold: First, to review the taxonomy and microbiology of potential VAP pathogens. Second, to describe common bacterial causes of VAP and the clinical variables that help to predict when antibiotic-resistant bacteria may be involved in individual patients. Third, to discuss evidence that other microbes may be involved in some cases of VAP. And, fourth, to describe the microbiology of VAP in unique and important clinical circumstances. In a subsequent paper I will discuss the implications of these factors for the antibiotic treatment of patients with VAP.<sup>5a</sup>

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## Medical Microbiology of VAP

### Overview of VAP Pathogenesis and Changes in Microbial Flora of Hospitalized Patients

The microbial causes of VAP are many and varied. Each of the microbes known to cause VAP shares an ability to exploit some defect in the patient's lung defenses, resulting from the pulmonary and systemic effects of critical illness and medical therapy, the alteration of the normal host microbial flora by illness and antibiotic therapy, and the interference with normal airway protection and clearance mechanisms due to altered consciousness and airway devices.

Details of the pathogenesis of VAP are beyond the scope of this review, but VAP usually results from the aspiration of oropharyngeal secretions past the endotracheal tube cuff,<sup>6,7</sup> or from inoculation directly into the airway.<sup>8-11</sup> Accordingly, colonization of the oropharynx, of the ventilator circuit, and of the lower airways are critical determinants of the causes of subsequent episodes of VAP.<sup>12-14</sup> It has been known for decades that the microbial flora of hospitalized and critically ill patients becomes drastically altered within days after admission,<sup>15,16</sup> particularly when antibiotics have been administered.<sup>17,18</sup> The usual mixed flora of the oropharynx and anaerobic flora of the colon typically have low virulence. In critically ill patients these organisms become overgrown by endogenous aerobic Gram-negative bacilli, which can then colonize the airway and lead to lung infection. In addition, exogenous transmission can lead to colonization and infection with nosocomial bacterial pathogens that are either acquired from environmental sources or passed by health-care workers from one patient to another.<sup>12-14</sup> As will be illustrated, the most common microbial causes of VAP reflect these changes in the normal host flora and the acquisition of antibiotic-resistant exogenous nosocomial bacterial strains.

First, however, I will review the taxonomy and unique features of important microbial pathogens that may cause VAP. Most cases are caused by standard bacterial pathogens, but atypical bacteria and even commensal bacteria may play a role.<sup>2,4,19</sup> Viruses, fungi, and other miscellaneous causes are uncommon but potentially important VAP pathogens, particularly in immunocompromised patients. Each of the microbes commonly associated with VAP are listed in Table 1. The bacterial pathogens are grouped on the basis of Gram-stain characteristics and, for the Gram-negative pathogens, by their ability to ferment sugars. This is often the order in which results emerge from the microbiology laboratory. The Gram-stain of lower respiratory secretions should be available within minutes to hours, depending on the circumstances. This can be tremendously helpful information because the Gram-stain of respiratory specimens can help the clinician to anticipate pathogens

that may not have been suspected otherwise and that might require different antibiotic treatment. For instance, the visualization of Gram-positive cocci in clusters in respiratory secretions is highly suggestive of *Staphylococcus aureus* infection and warrants the inclusion of anti-staphylococcal antibiotic therapy in the empiric regimen. Visualization of Gram-negative rods indicates the importance of a different empiric treatment regimen. Initial growth of bacterial cultures may be evident within the first 24 hours of incubation. At that time, before final identification and susceptibility testing can be completed, a simple biochemical test for lactose fermentation can suggest whether the organisms are likely to be relatively antibiotic-susceptible enteric bacilli (lactose fermenters) or highly resistant *Pseudomonas* or *Acinetobacter* species (nonfermenters).

### Features of Specific Common VAP Pathogens

Certain VAP pathogens occur commonly enough that typical circumstances of infection and risk factors for infection can be described (Table 2). The unique microbiological features of these organisms are described in the following paragraphs. I have included brief discussions of important virulence factors expressed by these organisms. Details about the prevalence and mechanisms of antibiotic resistance will be presented in a subsequent review of the antibiotic treatment of VAP.<sup>5a</sup>

***Streptococcus pneumoniae.*** *Streptococcus pneumoniae* is a Gram-positive diplococcus that is protected from opsonization and phagocytosis by a polysaccharide capsule. It colonizes the upper respiratory tract and invades the lung after microaspiration of oropharyngeal secretions. This pathogen is notorious as the most common cause of community-acquired pneumonia.<sup>20</sup> Although pneumococcal antibiotic resistance is a growing problem,<sup>21,22</sup> most *S. pneumoniae* isolates remain susceptible to achievable concentrations of traditional  $\beta$ -lactam antibiotics.<sup>23,24</sup> The importance of pneumococcal antibiotic resistance during nosocomial infections is less well understood.<sup>25</sup> *S. pneumoniae* causes VAP predominantly in the early days after intubation and is rapidly cleared after beginning antibiotic therapy.<sup>26</sup> The main risk factors for VAP caused by this pathogen are smoking, chronic obstructive pulmonary disease (COPD), and the absence of prior antibiotic therapy.<sup>4,27</sup>

***Haemophilus influenzae.*** *Haemophilus influenzae* is a small pleomorphic Gram-negative coccobacillus.<sup>28</sup> The Gram-stain appearance can be sufficiently characteristic that the diagnosis can sometimes be made on that basis alone, although caution must be taken to avoid confusion

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Table 1. Known and Suspected Microbiologic Causes of VAP

Gram-positive cocci	Anaerobic bacteria
<i>Staphylococcus aureus</i>	Bacilli
<i>Streptococcus pneumoniae</i>	<i>Bacteroides</i> species
Other streptococci	<i>Fusobacterium</i> species
Coagulase-negative staphylococci	<i>Prevotella</i> species
Enterococci	<i>Actinomyces</i> species
Gram-positive rods	Cocci
<i>Corynebacterium</i> species (diphtheroids)	<i>Veillonella</i> species
<i>Listeria monocytogenes</i>	Peptostreptococci
<i>Nocardia</i> species	“Atypical bacteria”
Aerobic Gram-negative bacilli	<i>Legionella</i> species
<i>Haemophilus influenzae</i>	<i>Legionella</i> -like amoebal pathogens
Lactose fermenting Gram-negative bacilli	<i>Mycoplasma pneumoniae</i>
<i>Enterobacteriaceae</i> or Enteric Gram-negative bacilli	<i>Chlamydia pneumoniae</i>
<i>Escherichia coli</i>	Fungi
<i>Klebsiella</i> species	<i>Candida</i> species and other yeasts
<i>Enterobacter</i> species	<i>Aspergillus</i> species and other molds
<i>Proteus</i> species	<i>Pneumocystis carinii</i>
<i>Serratia</i> species	Viruses
<i>Citrobacter</i> species	Influenza and other respiratory viruses
<i>Hafnia alvei</i>	Herpes simplex virus
Non-lactose fermenting Gram-negative bacilli	Cytomegalovirus
<i>Pseudomonas aeruginosa</i>	Miscellaneous causes
<i>Acinetobacter calcoaceticus</i> and <i>baumannii</i>	<i>Mycobacterium tuberculosis</i>
<i>Stenotrophomonas maltophilia</i>	<i>Strongyloides stercoralis</i>
<i>Burkholderia cepacia</i>	Others
Gram-negative cocci	
<i>Neisseria</i> species	
<i>Moraxella</i> species	

with *Acinetobacter* species. Like *S. pneumoniae*, *H. influenzae* is fastidious, easily eradicated by antibiotic therapy,<sup>26</sup> and causes VAP most often early after the initiation of mechanical ventilation. Risk factors for *H. influenzae* as a cause of VAP include COPD and the absence of prior antibiotic therapy.<sup>29</sup>

***Staphylococcus aureus.*** *Staphylococcus aureus* is a Gram-positive coccus that frequently colonizes the anterior nares and is consistently one of the most important causes of nosocomial infection and of VAP.<sup>4,30</sup> Staphylococci cause VAP throughout the course of critical illness. Traditionally, most strains have been susceptible to penicillinase-resistant  $\beta$ -lactam antibiotics (methicillin-sensitive *S. aureus*), but the prevalence of methicillin-resistant *S. aureus* (MRSA) strains is increasing, even in community isolates.<sup>31</sup> Proven risk factors for VAP caused by methicillin-sensitive *S. aureus* include younger age, traumatic coma, and neurosurgical problems.<sup>32–35</sup> Risk factors for VAP caused by MRSA include COPD, longer duration of mechanical ventilation, prior antibiotic therapy, prior

steroid treatment, and prior bronchoscopy.<sup>35,36</sup> Prior bronchoscopy is presumably a marker of some other lung condition or treatment rather than an indication of cross-contamination between patients. The likelihood that VAP due to *S. aureus* will be methicillin-resistant becomes nearly certain if the patient has received antibiotic treatment and the onset of VAP is later in the hospital course.<sup>36</sup>

*S. aureus* possesses a number of important virulence factors.<sup>37–39</sup> A particularly ominous development in staphylococcal microbiology has been the emerging incidence of strains bearing the Panton-Valentine leukocidin gene.<sup>40</sup> Panton-Valentine leukocidin gene is a 2-component extracellular secreted staphylococcal toxin that has been associated with aggressive virulent skin and soft-tissue infections and severe necrotizing pneumonia.<sup>41–43</sup> Panton-Valentine leukocidin-gene-bearing staphylococci are usually methicillin-resistant too, and lung infection by these strains is associated with tissue destruction, cavitation, hemoptysis, and lethality.<sup>41–43</sup> Most cases have been community-acquired,<sup>40,44</sup> but the potential for spread to hospital units and lethal nosocomial outbreaks is real.

Table 2. Risk Factors for Specific VAP Pathogens\*

Pathogen	Risk Factor(s)
<i>Streptococcus pneumoniae</i>	Smoking COPD Absence of antibiotic therapy
<i>Haemophilus influenzae</i>	Smoking COPD Absence of antibiotic therapy
<i>Staphylococcus aureus</i> (MSSA)	Younger age Traumatic coma Neurosurgery
<i>Staphylococcus aureus</i> (MRSA)	COPD Steroid therapy Longer duration of mechanical ventilation Prior antibiotic therapy Prior bronchoscopy
<i>Pseudomonas aeruginosa</i>	COPD Steroid therapy Longer duration of mechanical ventilation Prior antibiotic therapy
<i>Acinetobacter</i> species	ARDS Head trauma Neurosurgery Gross aspiration Prior cephalosporin therapy

VAP = ventilator-associated pneumonia

\*Associations shown in case-control studies of patients with ventilator-associated pneumonia.

See text for explanation and references.

COPD = chronic obstructive pulmonary disease

MSSA = methicillin-sensitive *Staphylococcus aureus*

MRSA = methicillin-resistant *Staphylococcus aureus*

ARDS = acute respiratory distress syndrome.

**Enterobacteriaceae.** The *Enterobacteriaceae*, or enteric Gram-negative bacilli, are a group of aerobic lactose-fermenting Gram-negative bacilli that normally reside in the lower gastrointestinal tract. Antibiotic therapy and critical illness can suppress the normal bacterial flora and lead to an overgrowth of *Enterobacteriaceae* in the gut and colonization of the skin and the upper gastrointestinal and respiratory tracts. Individual members of this genus have unique intrinsic antimicrobial susceptibility patterns, but the most concerning development has been the acquisition of extended-spectrum  $\beta$  lactamases that render the bacterial resistant to penicillin and cephalosporin antibiotics.<sup>45-47</sup> This has implications mainly for antibiotic therapy and will be discussed in a subsequent review of antibiotic therapy of VAP.<sup>5a</sup>

***Pseudomonas aeruginosa.*** *Pseudomonas aeruginosa* is an aerobic nonfermenting Gram-negative bacillus and is intrinsically resistant to many classes of antibiotics. It is the most common antibiotic-resistant pathogen causing

VAP,<sup>4</sup> and the most common cause of fatal episodes of VAP.<sup>27</sup> Unlike many other causes of VAP, *Pseudomonas* is consistently associated with a measurable attributable mortality.<sup>27,48-52</sup> *Pseudomonas* VAP is unusual early in the hospital course in previously healthy patients. It typically occurs only if risk factors are present, including COPD, prolonged duration of mechanical ventilation, and prior antibiotic therapy.<sup>27,53</sup> *Pseudomonas* is difficult to eradicate from the airways.<sup>26</sup> Persistent or recurrent episodes of pneumonia are common,<sup>51,54</sup> especially in patients with acute respiratory distress syndrome (ARDS).<sup>54</sup> However, not all series have found this association.<sup>55</sup>

*Pseudomonas* has numerous virulence factors, including many that appear to facilitate lung infection.<sup>56</sup> The most important are a family of secreted exotoxins (ExoS, ExoT, ExoU [PepA], and ExoY) that are injected directly into the cytoplasm of host cells, using the so-called type III secretion system.<sup>57</sup> The presence of type III exotoxins was detected in 72-77% of *Pseudomonas* isolates causing VAP in 2 series and was associated with higher mortality rates.<sup>58,59</sup> When 35 of these isolates were tested using in vitro cytotoxicity assays and in a mouse model of pneumonia, the strains expressing ExoU appeared to have the greatest virulence, as measured by lysis of alveolar epithelial and macrophage-like cell lines and by lethality in the mice.<sup>60</sup> The importance of these findings for patients with VAP is not yet clear, but conceivably these factors may be potential targets for novel therapies.<sup>61</sup>

***Acinetobacter* species.** *Acinetobacter* species (predominantly *baumannii* and *calcoaceticus*) are aerobic nonfermenting Gram-negative bacilli that are widely distributed in soil and fresh-water sources. *Acinetobacter* species have traditionally been felt to have low virulence, and clinical isolates have often been considered to represent colonization rather than infection.<sup>62</sup> Recently there has been increasing recognition of *Acinetobacter* species as important causes of nosocomial infection, particularly in critically ill intensive care unit patients.<sup>62-67</sup> A retrospective case-control study in Spain found no attributable mortality due to *Acinetobacter*-associated VAP, compared with a closely matched control group of patients with non-acinetobacter VAP.<sup>68</sup> The authors of this study and of the accompanying editorial conclude that *Acinetobacter* VAP does not contribute to excess mortality.<sup>68,69</sup> I would interpret the results differently, to suggest that *Acinetobacter* VAP is at least as deleterious as the other forms of late-onset VAP that characterized their control group. *Acinetobacter* are particularly important as causes of outbreaks and are readily spread from one patient to another. This appears to be due to their ability to survive on health-care workers' hands and inanimate environmental surfaces<sup>70-73</sup> and their intrinsic resistance to many common antibiotics,<sup>74-77</sup> rather than any potent virulence factors aimed at host defenses. Risk fac-

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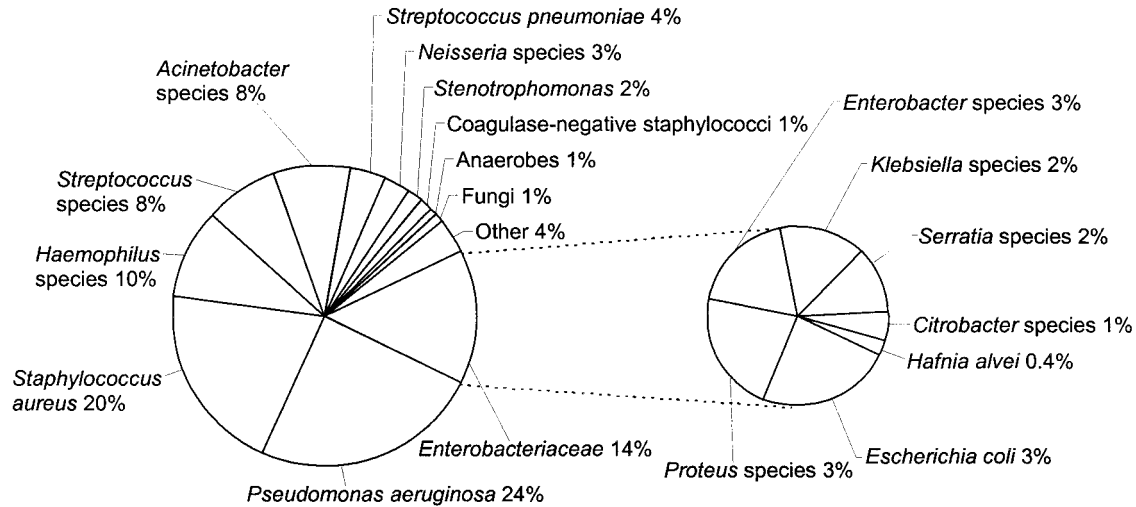


Fig. 1. Causes of ventilator-associated pneumonia. The relative proportions of common causes of ventilator-associated pneumonia are shown from 1,689 bronchoscopically-confirmed cases involving 2,490 individual isolates reported in 24 published studies. (Data from Reference 4.)

tors for VAP due to *Acinetobacter* included neurosurgery, ARDS, head trauma, and gross aspiration in one series,<sup>78</sup> and prior ceftazidime therapy and poor hand-washing in another.<sup>79</sup>

### The Relative Clinical Importance of Various Bacterial Causes of VAP

#### The Prevalence of Routine Bacterial Pathogens in VAP

The relative prevalence of specific pathogens responsible for VAP vary considerably, depending on the characteristics of the patient population, the duration of hospitalization and mechanical ventilation prior to the onset of pneumonia, prior exposure to antibiotic therapy, and the methods and criteria used for diagnosis.<sup>4</sup> Taking the latter point first, the use of bronchoscopic sampling methods and quantitative culture techniques remains somewhat controversial in clinical practice, but most authorities agree that this approach yields the most specific microbiology results. Organisms identified by this means are likely to be true VAP pathogens and not merely colonizing the airways. In their state-of-the-art review, Chastre and Fagon compiled microbiology data from 24 published studies that used such bronchoscopic diagnostic methods to confirm 1,689 episodes of VAP involving 2,490 isolates of pathogens.<sup>4</sup> These pooled data represent the most common causes of VAP across varying patient populations, hospitals, units, geographic areas, and time periods. Overall, aerobic Gram-negative bacilli represented 58% of isolates, and Gram-positive cocci made up another 35%. Importantly, since most of the source studies have focused on routine bacte-

rial pathogens only, this compilation did not include atypical pathogens such as *Legionella* species that require special diagnostic techniques.

The specific bacterial causes of VAP, as reported by Chastre and Fagon, are depicted in Figure 1.<sup>4</sup> The single most common pathogen was *P. aeruginosa*, accounting for 24% of isolates. Next most common was *S. aureus*, accounting for another 20% of isolates. Of these *S. aureus* isolates, 56% were methicillin-resistant strains. The *Enterobacteriaceae*, or enteric Gram-negative bacilli, made up the third most common group of pathogens. Collectively, they accounted for 14% of isolates. This group included roughly equal numbers of *Escherichia coli*, *Proteus* species, *Enterobacter* species, and *Klebsiella* species, and smaller numbers of *Citrobacter* and *Hafnia* species. *Haemophilus* species (9.8%) were the next most common isolates, followed by nonpneumococcal streptococci (8.0%), *Acinetobacter* species (7.9%), *S. pneumoniae* (4.1%), *Neisseria* species (2.6%), *Stenotrophomonas maltophilia* (1.7%), coagulase-negative staphylococci (1.4%), and various other organisms (< 1% each), including anaerobic bacteria, fungi, *Corynebacterium* species, *Moraxella* species, and enterococci.

Another important feature of the microbiology of VAP is that, in many instances, it is a polymicrobial infection. This fact is often obscured when isolates are reported as a percentage of the total number of isolates, as opposed to episodes of pneumonia. Combes and colleagues have reported a series of VAP cases using the first episode of VAP as the unit of analysis. Nearly half (48%) of their 124 cases were polymicrobial, with up to 4 separate important isolates from individual patients. Interestingly, the clinical features and outcomes and the prevalence of specific in-

dividual pathogens in the polymicrobial cases did not appear to differ from the monomicrobial cases.<sup>80</sup>

**Multidrug-Resistant VAP Pathogens**

Many of the organisms that cause VAP, such as *Pseudomonas*, *Acinetobacter*, and *Stenotrophomonas* species, and MRSA typically display high levels of antibiotic resistance. These organisms, and enteric Gram-negative bacilli expressing extended-spectrum  $\beta$ -lactamases, have been termed “potentially drug-resistant” pathogens<sup>81</sup> or “multidrug resistant” pathogens.<sup>2</sup> In order to ensure adequate initial antibiotic therapy when these multidrug-resistant pathogens are likely to be present, the empiric antibiotic regimen must include multiple agents with an extremely broad spectrum of activity.<sup>81</sup> However, unnecessarily broad antibiotic coverage can have adverse consequences, including encouraging the development of more resistant bacterial strains, higher rates of antibiotic-related complications, and increased costs.<sup>3</sup> A major goal of VAP management is to minimize the unnecessary use of antibiotics, but it is essential to be able to predict when antibiotic coverage for multiple-drug-resistant pathogens is necessary, in order to avoid under-treatment of these serious infections.<sup>2,82,83</sup>

The single most important determinant of the microbiological cause(s) of VAP and of the likelihood of multiple-drug-resistant pathogens appears to be the duration of mechanical ventilation prior to the onset of pneumonia. VAP is customarily categorized as either “early-onset” VAP if it occurs within 4–7 days after intubation, or “late-onset” VAP if it occurs after ventilation for more than 4–7 days. Early-onset VAP is typically caused by *Haemophilus* species, streptococci including *S. pneumoniae*, methicillin-sensitive *S. aureus*, and susceptible strains of *Enterobacteriaceae*. These pathogens also may cause late-onset VAP, but multiple-drug-resistant pathogens are much more common in the late-onset VAP period.<sup>2</sup> These temporal relationships are depicted in Figure 2.

The distinction between microbial causes of early-onset and late-onset VAP has been recognized for some time.<sup>84</sup> Numerous reports have described an association between potentially drug-resistant pathogens and late VAP.<sup>11,35,49,53,81,85–91</sup> In some studies the early/late onset distinction is quite clear-cut; all 11 potentially drug-resistant pathogens (out of a total of 40) occurred in the late VAP period (after 5 d) in one series.<sup>86</sup> However, the appearances of unexpected multiple-drug-resistant pathogens in the early VAP period mandate careful consideration of other risk factors for these infections in individual patients.<sup>88</sup>

Prolonged hospitalization prior to the onset of mechanical ventilation is probably an underappreciated risk factor for multidrug-resistant infections in patients still

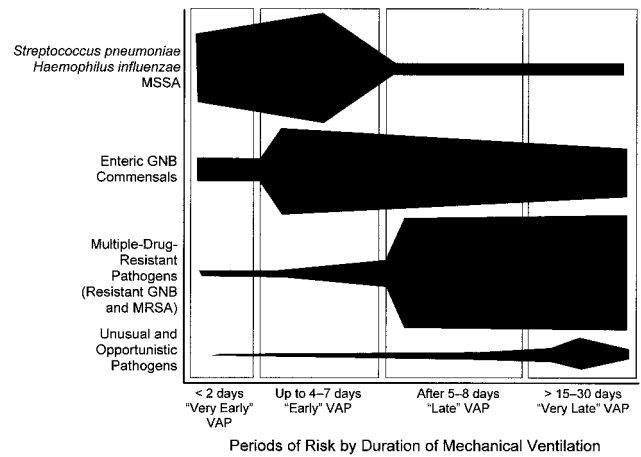


Fig. 2. Periods of risk for various microbial causes of ventilator-associated pneumonia (VAP), according to the duration of mechanical ventilation. Stages of increasing duration of mechanical ventilation are listed in sequence across the horizontal axis. The relative importance of the common bacterial pathogens on the left is indicated by the thickness of the bars as they progress through each stage from left to right. MSSA = methicillin-sensitive *Staphylococcus aureus*. GNB = Gram-negative bacilli. MRSA = methicillin-resistant *Staphylococcus aureus*.

in the “early” VAP period, in terms of days of mechanical ventilation.<sup>2,87,92</sup> Pre-existing medical illnesses, including human immunodeficiency virus infection, cancer, and COPD, and pre-hospital endotracheal intubation predicted infection with multidrug-resistant pathogens in one series of trauma patients.<sup>91</sup> In another multidisciplinary ICU population, conditions at the time of intubation, including emergency intubation, aspiration, and altered consciousness, predicted infection with multidrug-resistant pathogens in VAP occurring within the first 5 days of mechanical ventilation.<sup>89</sup> Prior antibiotic therapy appears to have an interesting dual effect. It may lessen the risk for early VAP due to antibiotic susceptible Gram-positive cocci and *H. influenzae*, but it increases the risk of VAP due to *Pseudomonas*, MRSA, and other multidrug-resistant pathogens, usually later in the hospital course.<sup>27,48,53,81,86,87,90,93</sup>

In one of few studies to focus on the prediction of resistant VAP pathogens, Trouillet et al prospectively and specifically evaluated risk factors for infection with potentially drug-resistant pathogens in 135 consecutive cases of bronchoscopically confirmed VAP.<sup>81</sup> Overall, potentially drug-resistant isolates were involved in 77 (57%) cases. Multivariate analysis identified 3 variables independently associated with infection by a potentially drug-resistant pathogen: duration of mechanical ventilation > 7 days (odds ratio 6.0), prior antibiotic use (odds ratio 13.5), and prior broad-spectrum antibiotic use (odds ratio 4.1).<sup>81</sup> Reassuringly, no potentially drug-resistant isolates were identified in the 22 cases of VAP that occurred within the

first 7 days of mechanical ventilation in patients who had not received prior antibiotic therapy (group 1), whereas potentially drug-resistant pathogens were found in 6 out of 12 cases diagnosed within 7 days in patients who had received antibiotic treatment (group 2). Potentially drug-resistant pathogens accounted for only 4 out of the 17 cases of VAP diagnosed after 7 days of mechanical ventilation in patients who had not received antibiotics (group 3). However, when VAP occurred after 7 days of mechanical ventilation in antibiotic-treated patients (group 4), 89 potentially drug-resistant isolates were recovered from 84 patients.<sup>81</sup>

Not surprisingly, these findings translate into major implications for empiric antibiotic selection choices. The antimicrobial susceptibility patterns of the isolates recovered from these groups became increasingly resistant with increased duration of mechanical ventilation and with prior exposure to antibiotics. For instance, isolates from group 1 patients were 90–100% susceptible to common antibiotics routinely used in ICUs (eg, amoxicillin-clavulanic acid, piperacillin-tazobactam, ceftazidime, and imipenem), whereas the rate of susceptibility to these drugs of isolates from group-4 patients was only 32–64%.<sup>81</sup>

### Variability of Bacterial Causes of VAP

Unfortunately for the clinician caring for patients with VAP, the simple scheme for predicting antibiotic resistant infections outlined above may not be generalizable to other settings. Rello and colleagues tested this hypothesis by comparing the rates of potentially drug-resistant pathogens causing VAP in patients categorized exactly as reported in the French study<sup>81</sup> from 3 sites in Barcelona and Seville, Spain, and Montevideo, Uruguay.<sup>87</sup> In contrast to the data from Paris, 10% of group-1 patients (ventilated < 7 d and not exposed to antibiotics) pooled from these other sites had multiple-drug-resistant pathogens. In addition, there was considerable variability in the frequency of individual bacteria isolated at each of the different sites. Whether this variation was due to the different geographic locations, to the differing patient populations, or to other factors is unknown.<sup>87</sup>

The causes of VAP appear to differ even between different hospitals within the same city and between ICUs within a single hospital. Babcock and colleagues compared causes of VAP in an academic teaching hospital, a community hospital, and a university-affiliated pediatric hospital, all located in St Louis, Missouri.<sup>94</sup> In 753 first episodes of VAP they found similar rates of isolation of *Pseudomonas* and *Acinetobacter* species and staphylococci across the 3 sites, but marked differences in the rates of methicillin-resistant *S. aureus* (most common at the community hospital and least common at the pediatric hospital) and enteric Gram-negative bacilli (seen predominantly

Table 3. Risk Factors for Multidrug-Resistant VAP Pathogens\*

Duration of current hospitalization 5 days or longer
Recent antimicrobial therapy (in the preceding 90 days)
Recent hospitalization (for 2 days or more in the preceding 90 days)
High frequency of antibiotic resistance in the community or in the specific hospital unit
Residence in a nursing home or extended-care facility
Home infusion therapy
Chronic dialysis (within 30 days)
Home wound care
Family member with a multidrug-resistant pathogen
Immunosuppressive disease or therapy

\*Multidrug-resistant pathogens include *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, *Stenotrophomonas maltophilia*, and methicillin-resistant *Staphylococcus aureus*. (Adapted from Reference 2.)

at the pediatric hospital). Within the adult hospitals there were significant differences in the distribution of VAP pathogens between the surgical, neurosurgical, medical, and cardiothoracic units.<sup>94</sup> An important additional finding of this study, confirming the experience of Rello and co-workers,<sup>87</sup> was that a substantial minority (31%) of isolates found in early-onset VAP cases (within 4 d of intubation) were potentially drug-resistant pathogens.

The practical implications of these data are that empiric antibiotic treatment decisions for patients with VAP must take into account local microbiology and antimicrobial susceptibility data: preferably VAP-specific data.<sup>87,94,95</sup> Antibiotic choices based on published data from other centers or generalized recommendations and guidelines may be ineffective if the local microbiology patterns vary from the published reports. The new joint American Thoracic Society/Infectious Diseases Society of America VAP guidelines acknowledge this limitation of generic antibiotic treatment recommendations and encourage customization of treatment algorithms based on local data.<sup>2</sup> Nevertheless, the guidelines do list general risk factors for multidrug-resistant pathogens. These factors are listed in Table 3 and include antimicrobial therapy in the preceding 90 days, current hospitalization duration of 5 days or longer, a high frequency of antibiotic resistance in the community or in the specific hospital unit, hospitalization for 2 days or more in the preceding 90 days, residence in a nursing home or extended care facility, home infusion therapy, chronic dialysis within 30 days, home wound care, a family member with a multidrug-resistant pathogen, and immunosuppressive disease or therapy.<sup>2</sup>

### Evaluation of Routine Bacterial VAP Pathogens at a Local Institution

One example of how local VAP microbiology data can be gathered and analyzed to facilitate VAP management



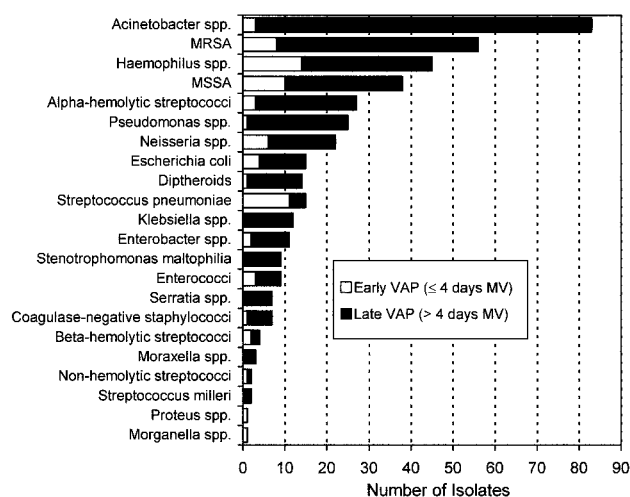


Fig. 3. Bacterial causes of early-onset and late-onset ventilator-associated pneumonia (VAP). The bars show the frequency of bacterial causes of VAP from 267 bronchoscopically-confirmed cases seen at Harborview Medical Center, in Seattle, Washington. Isolates from early-onset VAP cases (occurring within 4 d of beginning mechanical ventilation) are represented by the white portions of the bars. Isolates from late-onset cases (occurring after 4 d of mechanical ventilation) are represented by the black portions of the bars. All of the 11 early-onset cases with multiple-drug-resistant isolates had other risk factors for these infections (see text for explanation). MRSA = methicillin-resistant *Staphylococcus aureus*. MSSA = methicillin-sensitive *Staphylococcus aureus*. MV = mechanical ventilation. (Data courtesy of Timothy Dellit MD and Jeannie Chan PharmD, Harborview Medical Center, Seattle, Washington.)<sup>96a</sup>

comes from my own institution: Harborview Medical Center, in Seattle, Washington. Harborview is an urban city/county hospital and regional level-1 trauma center and major referral center for patients with burns and neurological injuries. It is a major clinical training and research affiliate of the University of Washington and has served as the clinical site for a specialized center of a research program studying patients with ARDS for over 2 decades. To address the problem of VAP-related morbidity and costs, and rising antibiotic resistance rates, the hospital established a VAP Task Force to implement evidence-based VAP-prevention interventions in 2003. Coincidentally, we began systematically to evaluate patients with suspected VAP, using quantitative cultures of samples collected by bronchoalveolar lavage (BAL) and/or protected-specimen-brush techniques. Between June 2003 and November 2004, 568 patients underwent bronchoscopy because of suspected VAP: 267 (47%) were "positive" for at least one isolate present in amounts greater than 10,000 colony-forming units (CFU)/mL for BAL specimens or 1,000 CFU/mL for protected-brush specimens, as described by Fagon et al.<sup>96</sup> The microbiology results from these patients are presented in Figure 3. The isolates are grouped into early-onset and late-onset VAP categories, depending on the whether the

duration of mechanical ventilation before the episode of VAP was  $\leq 4$  days (47 cases) or  $> 4$  days (220 cases), respectively. *Staphylococcus aureus* was the single most common isolate overall, with most of these being methicillin-resistant strains. The next most common isolates were *Acinetobacter* species, the *Enterobacteriaceae*, *Haemophilus* species, alpha-hemolytic streptococci, *P. aeruginosa*, *Neisseria* species, *S. pneumoniae*, *S. maltophilia*, and others.

*S. pneumoniae*, *Haemophilus* species, and methicillin-sensitive *S. aureus* were the most common isolates in the early-onset VAP cases, but 11 out of 72 (15%) of the early VAP isolates were potentially drug-resistant strains. These included 7 isolates of methicillin-resistant *S. aureus*, 3 of *Acinetobacter baumannii*, and 1 of *P. aeruginosa*. Upon further inquiry, each of these patients had additional risk factors for infection with an antibiotic-resistant pathogen. Five of the MRSA cases had been in the hospital for at least a week before being intubated and 2 were injection drug users. One of the *Acinetobacter* cases had been hospitalized for more than a week before intubation and 2 were chronically ill and known to be colonized. The *Pseudomonas* case had been hospitalized for more than a week before intubation. Data on previous antibiotic treatment in these cases and on actual antibiotic susceptibilities of these isolates have not yet been analyzed. Nevertheless, these local data have helped to guide our empiric antibiotic treatment of suspected VAP, by prompting coverage for methicillin-resistant *S. aureus* and *Acinetobacter* species in patients with late-onset VAP or with other risks factors, and by supporting narrower antibiotic coverage for early-onset cases without other risk factors. These data were presented by Timothy Dellit at the annual meeting of the Infectious Diseases Society of America in 2004 in Boston, Massachusetts.<sup>96a</sup>

### Summary of Routine Bacteria in VAP

In summary, antibiotic-susceptible routine bacterial pathogens can be expected in previously healthy patients on no antibiotic therapy who develop VAP within 5–7 days after admission or initiation of mechanical ventilation. Potentially antibiotic-resistant pathogens should be anticipated in patients who develop VAP at any time after receiving antibiotic therapy or after being hospitalized or intubated for more than 5–7 days. There may be gray areas and exceptions to these broad generalizations. In the Trouillet study, onset of VAP caused by multidrug-resistant pathogens was generally delayed well beyond the first week of mechanical ventilation, as long as no prior antibiotic therapy had been given.<sup>81</sup> Additional research is needed to define important risk factors for infection with multidrug-resistant pathogens in the early-onset VAP period, and to identify patients in the late-onset VAP

period who are unlikely to have a multidrug-resistant infection.

### The Importance of Other Bacteria in VAP

#### Anaerobic Bacteria in VAP

VAP is thought to result primarily from the aspiration of oropharyngeal contents past the endotracheal tube cuff and into the lungs. Accordingly, it has been assumed that anaerobic bacteria from the oropharynx must play an important role in VAP, as has been reported in aspiration pneumonia in nonintubated patients.<sup>97,98</sup> In support of this notion, anaerobic bacteria are reported to colonize the lower respiratory tract in intubated patients. A prospective surveillance study found that 22 of 26 consecutive mechanically ventilated patients developed bacterial colonization of the lower respiratory tract. Of these, 15 patients became colonized by 28 different anaerobic strains.<sup>99</sup> A report of 130 patients diagnosed with VAP using the protected-specimen brush found substantial quantities (> 1,000 CFU/mL) of anaerobic bacteria in 30 (23%) patients, albeit always in association with additional aerobic bacteria.<sup>100</sup> Altered level of consciousness, greater severity of illness, and admission to a medical ICU were independently associated with the isolation of anaerobic organisms.<sup>100</sup> Further supporting a pathogenic role for anaerobic bacteria, patients with VAP and *Prevotella* species isolated from protected-specimen-brush samples also developed specific humoral responses against these organisms.<sup>101</sup> Finally, antibiotic therapy active against anaerobic bacteria appears to improve short-term outcomes in VAP patients with anaerobic isolates.<sup>102</sup>

However, the data regarding the role of anaerobic bacteria in VAP are conflicting. Despite careful anaerobic handling techniques, not a single anaerobic isolate was recovered from protected-specimen-brush or mini-BAL specimens from a series of 185 episodes of suspected VAP reported by Marik and Careau.<sup>103</sup> The reasons for these discrepant results are not clear. Although an antibiotic with activity against anaerobic bacteria had been given prior to the sample collection in 35% of episodes in the latter study, this seems unlikely to account for the complete absence of positive anaerobic cultures.<sup>103</sup> Furthering doubt about the role of anaerobes, 2 independent teams of investigators were unable to isolate anaerobic bacteria from the lungs of even patients with gross aspiration pneumonia.<sup>103,104</sup> This led Marik and Careau to speculate that the role of anaerobes in aspiration pneumonia has been greatly overestimated and that earlier studies of aspiration pneumonia (based largely on transtracheal aspirate cultures) may have been flawed by false positive cultures because of tracheal colonization or because of airway contamination during the procedure.<sup>103</sup> In my mind, the role of anaer-

obes in VAP is unclear. I can't adequately explain the discrepancies between the published reports. It is somewhat reassuring that most broad-spectrum antibiotics used in the treatment of VAP have some activity against oropharyngeal anaerobic bacteria.

#### Commensal Bacteria in VAP

Commensal bacteria of the oropharynx and skin (such as non- $\beta$ -hemolytic streptococci, *Neisseria* species, *Corynebacterium* species, *Haemophilus* species other than *influenzae*, and coagulase-negative staphylococci) are generally believed to have low virulence for causing pneumonia. Yet these organisms are reported in most of the published VAP case series.<sup>4</sup> Whether a "positive" quantitative culture yielding a commensal organism has the same import as a culture growing a more virulent pathogen is unknown. In fact, some clinicians ignore cultures growing only commensal organisms. In an effort to clarify the importance of these isolates, Lambotte and coworkers retrospectively analyzed their experience with 369 episodes of bronchoscopically-confirmed VAP in 292 patients over a 10-year period.<sup>105</sup> In 77 episodes, commensal isolates were accompanied by positive cultures for other VAP pathogens. In 29 additional episodes (8% of all VAP episodes), commensal organisms were the only isolates present in substantial quantities. Ten of these 29 episodes occurred within the first 5 days of mechanical ventilation. Supporting their assertion that the commensal isolates represented true pathogens, the authors noted that these patients developed typical clinical features of VAP and had large quantities of the organisms in their lungs. Furthermore, the culture results were supported by findings of intracellular bacteria in greater than 5% of cells in over half of the cases. Pneumonia was confirmed by post-mortem examination in both of the patients who died before resolution of their clinical pneumonia while on treatment. Finally, the 7 patients who did not receive treatment effective against the commensal isolates did poorly: 3 died and 2 developed lung abscesses.<sup>105</sup> Based on the limited available data, it seems prudent to consider isolates of commensal organisms as potential VAP pathogens, particularly when the commensal organisms are the only isolate present.

#### Atypical Bacteria as VAP Pathogens

##### *Legionella* Species

Legionnaires' disease, caused by *Legionella pneumophila* and related species, has become recognized as an important cause of both epidemic and sporadic cases of hospital-acquired pneumonia.<sup>106-110</sup> Nosocomial cases accounted for 35% of the cases of Legionnaires' disease reported to the Centers for Disease Control between 1980

and 1998.<sup>111</sup> Risk factors include immunosuppression, smoking, alcoholism, chronic lung disease, and chronic renal failure.<sup>110</sup>

There is evidence that the rate of Legionnaires' disease varies considerably by geographic location, but this may be due, in part, to varying efforts to identify cases. A Spanish multicenter study found that awareness of environmental contamination by *Legionella* species varied markedly among 20 hospitals in the Catalonia region.<sup>112</sup> Most of these hospitals performed no environmental surveillance, and only 2 of 20 had detected cases of Legionnaires' disease in the preceding 4 years. After recognition of *Legionella* species in the water supply of 17 hospitals, 2 things happened: water purification and decontamination efforts were begun, and clinicians began to test for Legionnaires' disease in patients with nosocomial pneumonia. In the subsequent 5 years, despite improved control of water-supply contamination, Legionnaires' disease cases were detected in 11 of the hospitals (55% of all hospitals and 65% of hospitals with an initially contaminated water supply).<sup>112</sup> This and other data suggest that Legionnaires' disease is a more common cause of nosocomial pneumonia than is usually appreciated. Increased suspicion and testing will uncover unsuspected cases, particularly if culture techniques are used that can detect the presence of all strains, not solely *L. pneumophila* serogroup 1, as detected by urinary antigen testing.<sup>112-115</sup>

Interestingly, *Legionella* species appear to be unusual causes of pneumonia (VAP) in patients already receiving mechanical ventilation. In a 5-year prospective study of 300 episodes of nosocomial pneumonia in Barcelona, Spain, *L. pneumophila* was implicated in 36 (12%) episodes.<sup>116</sup> Risk factors identified by multivariate analysis in this cohort included cytotoxic chemotherapy and corticosteroid treatment. However, despite the fact that many ventilated patients were at risk, none of the 36 patients diagnosed with Legionnaires' disease had been intubated prior to developing pneumonia. A South African group reported a series of 12 cases of Legionnaires' disease that occurred as a community and nosocomial outbreak. In this small series, mechanical ventilation was strongly associated with acquiring *Legionella* infection, but the authors were later unable to recover *Legionella* from cultures of the ventilators, the humidifier water, or the compressed air source.<sup>117</sup> In several cases, an apparent nosocomial case occurred in a patient ventilated with a machine previously used to ventilate a community-acquired case, so it is conceivable but unproved that short-term contamination of the respiratory care equipment was responsible for transmission.<sup>117</sup>

I wonder if the uncommon occurrence of Legionnaires' disease as a cause of VAP may be because patients on mechanical ventilation are protected from exposure to contaminated tap water and shower aerosols.<sup>114</sup> If only sterile

sources of fluids are used for oral care, suctioning, and feeding, there may be little opportunity for intubated patients to be exposed to *Legionella* pathogens.<sup>118,119</sup> Nevertheless, the true incidence of Legionnaires' disease as a cause of VAP remains unknown and warrants further prospective evaluation in geographically diverse areas, in addition to ongoing prevention efforts.<sup>120</sup>

### ***Legionella*-Like Amoebal Pathogens**

An unusual aspect of the microbiology and pathogenesis of Legionnaires' disease is the fact that *Legionella* species are facultative intracellular pathogens that preferentially replicate within human alveolar macrophages.<sup>121-123</sup> It turns out that *Legionellae* also parasitize free-living amoebae in environmental water sources.<sup>124,125</sup> In recent years a number of *Legionella* species and related *Parachlamydiaceae*, called legionella-like amoebal pathogens or amoeba-resisting pathogens, have been identified. These organisms share the ability to infect amoebae and potentially cause human lung infection.<sup>126-128</sup> In an effort to learn whether these pathogens might be involved in otherwise unexplained cases of VAP, La Scola and co-workers conducted a careful prospective study of both environmental water sources and rigorously defined episodes of VAP in their institution in Marseilles, France.<sup>129</sup> Although bronchoscopy was performed in all cases, a clinical and radiographic case definition of VAP was used so that patients with negative routine microbiology results could be included. They found 310 isolates of 10 different species of *Legionella*-like amoebal pathogens in the water faucets and ice machines in their ICUs. None were isolated from BAL samples from 30 concurrent VAP patients, but most patients were already receiving antibiotics that may have reduced the sensitivity of cultures to detect these fastidious organisms. Nevertheless, 12 (40%) VAP patients developed specific humoral responses against 6 of these organisms, and deoxyribonucleic acid from the serologically implicated organisms was found in BAL fluid from 2 cases. Although the specificity of these assays may be questioned, the authors support the potential importance of the findings by noting that seroconversions were much more common in patients without another explanation for VAP.<sup>129</sup> *Legionella*-like amoebal pathogens may turn out to be important causes of VAP. For now, firm conclusions about the role of these organisms in VAP must await confirmation of these intriguing initial results.

### ***Mycoplasma* and *Chlamydia* Species**

*Mycoplasma pneumoniae* is well-known as a cause of community-acquired pneumonia that is transmitted from person-to-person and usually causes mild disease. Casalta and co-workers have reported an interesting case series of

4 men who developed diffuse pneumonia within several days of mechanical ventilation following vascular surgical procedures.<sup>130</sup> *M. pneumoniae* was isolated from respiratory secretions in one patient, and the diagnosis was confirmed by enzyme-linked-immunoassay-based IgM serology testing in all four. Because there was no common epidemiologic link, and because all of the patients were asymptomatic at the time of admission for surgery, the authors speculate that these patients may have become ill as a result of reactivation of endogenous asymptomatic pharyngeal carriage.<sup>130,131</sup> *M. pneumoniae* may be a more common cause of VAP than is commonly believed, but this report is not definitive because of the small numbers and potential problems with the specificity of the serologic diagnosis.

*Chlamydia pneumoniae* is another pathogen typically associated with community-acquired respiratory infections and acquired by person-to-person transmission. Sporadic nosocomial cases have been reported after major surgery, severe trauma, and pneumonectomy for lung cancer resection.<sup>132</sup> Nosocomial transmission of *Chlamydia psittaci*, the human and avian pathogen and cause of psittacosis, has been reported after exposure to an ill pet-shop worker, but the secondary cases were all health-care workers rather than patients on mechanical ventilation.<sup>133,134</sup>

How often *Mycoplasma* or *Chlamydia* infections are acquired by patients on mechanical ventilation is unknown. Even non-ventilator-associated nosocomial cases appear unusual. A prospective surveillance study of nosocomial pneumonia in Winnipeg, Manitoba, found serologic evidence of *Mycoplasma* and *Chlamydia* infection in only one instance each, out of 135 consecutive nosocomial pneumonia cases.<sup>134</sup> Two other large series of nosocomial pneumonia cases did not investigate the presence of these organisms.<sup>108,109</sup>

### Role of Nonbacterial Pathogens in VAP

#### Viruses

**Influenza.** Influenza epidemics occur on an annual basis, usually in the winter months in temperate North America. Community-dwelling patients with influenza infection often are admitted to the hospital when they also have substantial cardiopulmonary comorbidities, complications such as superinfection, or particularly severe primary influenza disease. Once hospitalized, influenza patients can readily transmit the infection to others. Infected health-care workers serve as another, perhaps more important, source of nosocomial transmission. Influenza outbreaks have been reported in ventilated infants in neonatal units and in a variety of general adult acute care settings, but the acquisition of influenza by adult patients on mechanical

ventilation appears to be uncommon.<sup>135</sup> This may be another instance, like Legionnaires' disease, in which patients on mechanical ventilation are somehow protected from acquisition of infection. Vaccination of health-care workers and careful hand hygiene and infection control practices can prevent nosocomial influenza cases.<sup>120,136</sup>

**Herpes Simplex Virus.** Herpes simplex virus (HSV) infection is prevalent in adult populations and usually exists in a latent form that can reactivate during periods of stress or immunosuppression. HSV typically causes pneumonia only in immunocompromised patients after aspiration of infected oropharyngeal secretions.<sup>137</sup> However, HSV reactivation can occur in critically-ill patients,<sup>138,139</sup> and it is conceivable that HSV could cause or contribute to VAP. In fact, HSV can be isolated from airway secretions and lung tissue in up to 30% of patients with acute respiratory failure due to medical problems, post-operatively, or after burns.<sup>140-145</sup> The question is whether these isolates represent an unimportant marker of oral HSV reactivation, or whether they are contributing to cause pneumonia. Tuxen and co-workers reported that ARDS patients randomized to receive acyclovir were far less likely to develop HSV reactivation, but experienced no benefits in terms of the severity of ARDS, duration of mechanical ventilation, or mortality.<sup>142</sup> In another series of 4,141 episodes of bronchoscopically-evaluated persistent pneumonia (95% on mechanical ventilation), bronchoscopic specimens yielded HSV in 113 (2.7%) instances in 64 patients. Unfortunately, the features that prompted HSV testing and the denominator of patients tested were not reported.<sup>144</sup> Bruynseels and colleagues conducted an elegant prospective study of the appearance of HSV in the upper and lower airways of critically ill patients (81% on mechanical ventilation).<sup>145</sup> They found HSV in the upper and lower airways of 22% and 16% of patients, respectively. HSV isolation from the upper airways was associated with greater severity of illness, a greater prevalence of ARDS, longer length of stay in the ICU, and longer duration of mechanical ventilation, whereas the strongest predictor of HSV in the lower respiratory tract was HSV in the upper tract.<sup>145</sup> No confirmation of invasive infection was attempted, and whether these associations represent cause or effect is unknown. At present, the role of HSV in patients with VAP is unclear.

**Cytomegalovirus.** Cytomegalovirus is another prevalent herpes virus with a latent state and propensity for reactivation in critically ill patients. Although similar to HSV, cytomegalovirus is more likely to result in viremia and visceral organ involvement.<sup>146-149</sup> Cytomegalovirus pneumonia is a well-recognized complication experienced by immunosuppressed patients, but whether cytomegalovirus can cause VAP in nonimmunosuppressed critically

ill patients requiring mechanical ventilation has been unknown. Recently, Papazian and co-workers in Marseille, France, have clearly demonstrated that cytomegalovirus pneumonia can occur in this setting, and their work helps to form the clinical profile of patients with this diagnosis.<sup>150</sup> Of 2,785 patients admitted to their ICU over a 5-year period, open lung biopsies<sup>26</sup> or autopsies<sup>60</sup> were performed on 86 (3%) patients with acute respiratory failure and suspected but unexplained VAP. Excluding immunocompromised patients, cytomegalovirus pneumonia was histologically confirmed in 25 of these cases, and cytomegalovirus was the sole pathogen in 88%. Cytomegalovirus pneumonia occurred after a median ICU stay of 18 days and was associated with bilateral and interstitial radiographic infiltrates more often than were bacterial VAP cases. Otherwise, no clinical features distinguished the cytomegalovirus cases. Reactivation of latent infection appeared likely, in that 13 (72%) patients were cytomegalovirus seropositive at the time of admission. However, the majority of these patients also received unscreened blood products and some may have become infected or re-infected by that means. Although little information is provided about the denominator of tests performed and selection of patients for testing, the authors report that BAL performed within the week prior to diagnosis had a sensitivity of 53% and specificity of 92% for detecting cytomegalovirus pneumonia.<sup>150</sup> To summarize these findings, cytomegalovirus clearly can cause pneumonia in patients with suspected VAP. It appears to occur at a later stage of critical illness that may reflect a period of relative immunosuppression. Isolation of cytomegalovirus from BAL samples in this setting is strongly predictive of histologically-confirmed cytomegalovirus pneumonia. More information is needed about the prevalence of and predictors of cytomegalovirus pneumonia in a less highly selected population.

## Fungi

**Yeasts.** Infection caused by *Candida* species is an increasingly important complication experienced by immunosuppressed and critically ill patients.<sup>151</sup> However, whether *Candida* causes pneumonia in immunocompetent patients has been unclear. This uncertainty can place clinicians in an uneasy situation when a patient with suspected VAP grows *Candida* species from bronchoscopy specimens, particularly when the yeasts are present in quantities exceeding the threshold for diagnosing bacterial causes of VAP. Two studies have addressed the potential importance of these findings. El-Ebiary and co-workers evaluated the importance of isolation of yeasts from the airways of mechanically-ventilated patients by performing immediate post-mortem examinations on 25 patients who died while on mechanical ventilation. *Candida* species were

found in the lung tissues of 10 patients, but evidence of tissue invasion was seen in only 2 cases.<sup>152</sup>

Rello and colleagues addressed the same question using a somewhat more clinically relevant (premortem) but less definitive approach (composite clinical definition). They retrospectively evaluated all cases of suspected pneumonia over a 5-year period in which *Candida* species were isolated from bronchoscopic specimens.<sup>153</sup> Although they lacked histological confirmation of the diagnosis in most cases, they used a priori definitions to assign patients into categories of definite contamination, probable contamination, indeterminate status, and proven invasive disease. Of 37 non-neutropenic patients with pneumonia (23 on mechanical ventilation), 3 were felt to have definite contamination because of definitive negative histological evidence, and 30 were felt to have probable contamination because they received no antifungal therapy and either died from another cause or improved without specific therapy. Two patients were categorized as indeterminate because they received treatment (without definitive confirmation of the diagnosis) and recovered. There were no cases of proven invasive candida pneumonia. Interestingly, 33 of the 37 patients grew > 1,000 CFU/mL of *Candida* species from protected-specimen-brush samples, and 2 grew > 100,000 CFU/mL.<sup>153</sup> A major limitation of this study is that there was no confirmation that the large number of patients with probable contamination who died of other causes were free of candidal pneumonia. My interpretation of these data are that candidal pneumonia can occur rarely in critically ill, mechanically ventilated patients, but most isolates of *Candida* species from the airways are clinically unimportant, even when present in large quantities. Better approaches are needed to identify the small subset of patients with true invasive candidal pneumonia.

**Molds.** Pulmonary infection by *Aspergillus* species and other molds is a common problem and daunting clinical challenge in profoundly immunocompromised patients following chemotherapy and transplantation. Fortunately, these infections appear to be unusual in typical cases of VAP. Most reported series of VAP cases have excluded immunocompromised patients, but COPD patients on corticosteroid treatment are known to be at risk for invasive pulmonary aspergillosis.<sup>154,155</sup> Invasive aspergillosis occurred in 9 (7%) of 132 patients with VAP identified in a careful prospective cohort study of 880 mechanically ventilated patients in a large community hospital.<sup>156</sup> However, 8 of these patients were neutropenic and the other was receiving corticosteroid therapy.

In a large retrospective survey of invasive aspergillosis in a medical ICU setting, Meersseman and colleagues found 105 proven or probable cases out of 1,850 admissions during a 3-year period.<sup>157</sup> Of those, 103 patients received mechanical ventilation, but it is unclear if this was neces-

sary as a result of the fungal infection or if the fungal infection occurred during mechanical ventilation for other indications. In 84 cases (66%) there was reportedly no suspicion of aspergillosis at the time of ICU admission, suggesting that some of the cases were indeed “ventilator associated.” Risk factors for invasive aspergillosis in this population included (in order of decreasing frequency) hematologic malignancy, COPD, solid-organ transplant, immunosuppressive therapy for autoimmune disease, liver cirrhosis, and miscellaneous conditions. In another series of 37 cases of invasive aspergillosis culled from 8,988 medical ICU admissions, 20 cases occurred in patients with COPD, cirrhosis, or with ARDS due to burns, trauma, near-drowning, or bacterial pneumonia.<sup>158</sup> From this information, it appears that invasive aspergillosis is an unusual cause of pneumonia among patients requiring mechanical ventilation for other reasons. However, aspergillosis can occur in this setting, even in patients without classical risk factors for invasive mycoses.

**Other Fungi.** Other less common fungal infections, including *Pneumocystis carinii* pneumonia, also may occur in patients at risk because of immunosuppressive therapy, autoimmune disease, or severe malnutrition.<sup>159,160</sup>

#### Miscellaneous Other Causes of VAP

No concise review can exhaustively catalog all of the potential microbial causes of VAP. It is likely that some have yet even to be discovered. The bacterial and nonbacterial organisms discussed in the preceding sections account for the vast majority of VAP cases. Nevertheless, clinicians should remain alert for unusual and unexpected causes of VAP. For instance, latent tuberculosis or endemic fungal infections may reactivate in a chronically critically ill patient; strongyloidiasis with hyperinfection syndrome may erupt due to corticosteroid treatment for a COPD exacerbation; a hematogenous pneumonia may develop from an intravascular site of infection; or an extrapulmonary infection may invade the lung via direct extension.

#### The Microbiology of VAP in Particular Clinical Circumstances

##### Determining the Importance of Differences in Microbiology Patterns

A variety of clinical circumstances may influence the microbiology of VAP. In assessing whether there are unique microbiological features of VAP in a particular patient group or clinical circumstance, it is important to consider whether the differences are due to a unique and durable risk profile or whether they are due simply to differences

between groups in the duration of hospitalization and mechanical ventilation, in the use of prior antibiotic therapy, or due to differences between centers or across time periods. Patient groups that are especially worthy of individual mention include those with acute lung injury and ARDS, those managed with tracheotomy, those with VAP soon after intubation, those with serious injuries and burns, and those with substantial immunosuppression.

#### VAP in Patients With ARDS

VAP is a common complication in patients with acute lung injury and ARDS<sup>161</sup> and has serious potential consequences, including sepsis and death due to the multiple-organ-failure syndrome.<sup>162,163</sup> Sutherland and co-workers in Seattle, Washington, were among the first to systematically investigate lung infection in ARDS.<sup>164</sup> They performed 201 bronchoscopies with BAL or protected-specimen-brush sampling on 105 mechanically ventilated patients with ARDS. Small quantities of bacteria were commonly isolated, but the cultures met standard quantitative culture criteria for pneumonia in only 16 (15%) patients. These data suggest a low incidence of VAP in patients with ARDS, but several caveats must be considered. Specifically, this was a series of patients with ARDS (not always with suspected VAP) who underwent bronchoscopy at predetermined times as part of a study investigating the pathophysiology of ARDS (not when VAP was suspected). Also, most of the patients were receiving antibiotic therapy at the time of bronchoscopy. As a result, it is likely that the incidence of VAP was underestimated.

Subsequent studies that have directed diagnostic testing at ARDS patients with suspected VAP have found positive quantitative cultures confirming VAP in 37–60% of cases.<sup>165–168</sup> The series reported by Chastre and co-workers is particularly illustrative.<sup>166</sup> They followed 243 consecutive patients requiring mechanical ventilation for  $\geq 48$  hours, including 56 patients with ARDS. When VAP was suspected clinically, the diagnosis was confirmed bronchoscopically, using standard quantitative culture criteria. Overall, VAP occurred in 55% of patients with ARDS, as compared with 28% of patients without ARDS. This difference was due mainly to the more prolonged duration of mechanical ventilation (and greater period of risk) experienced by the ARDS patients. Also, prior antibiotic therapy had been given to 94% of ARDS patients with VAP, compared with 66% of non-ARDS patients with VAP, and VAP occurred within the first week of mechanical ventilation in only 10% of ARDS-associated VAP cases, versus 40% of non-ARDS VAP cases. Staphylococci and Gram-negative bacilli were the most common bacterial isolates. Methicillin-resistant *Staphylococcus aureus* was significantly more common in the patients with ARDS, but this difference disappeared when the ARDS patients were com-

## THE MICROBIOLOGY OF VENTILATOR-ASSOCIATED PNEUMONIA

Table 4. Microbiologic Causes of Ventilator-Associated Pneumonia in Patients With and Without ARDS

Pathogen	With ARDS 80 patients no. (%) <sup>*</sup>	Without ARDS 226 patients no. (%) <sup>*</sup>
Gram-negative		
<i>Pseudomonas aeruginosa</i>	36 (45)	86 (38)
<i>Acinetobacter baumannii</i>	15 (19)	20 (9)
<i>Stenotrophomonas maltophilia</i>	7 (9)	10 (4)
<i>Enterobacteriaceae</i>	24 (30)	64 (28)
<i>Haemophilus</i> species	3 (4)	22 (10)
Miscellaneous	7 (9)	4 (2)
Gram-Positive		
<i>Staphylococcus aureus</i> , methicillin-resistant	34 (43)	51 (23)
<i>Staphylococcus aureus</i> , methicillin-sensitive	7 (9)	45 (20)
<i>Streptococcus</i> species	16 (20)	30 (13)
<i>Streptococcus pneumoniae</i>	1 (1)	5 (2)
<i>Enterococcus</i> species	3 (4)	8 (4)
Coagulase-negative staphylococci	2 (3)	5 (2)
<i>Corynebacterium</i> species	1 (1)	2 (1)
Anaerobic bacteria	3 (4)	4 (2)
Fungi	6 (8)	1 (1)

ARDS = acute respiratory distress syndrome

<sup>\*</sup>Number of isolates. Sums of percentages exceed 100 due to multiple isolates in some episodes of ventilator-associated pneumonia (VAP) and multiple episodes of VAP in some patients.

Data from References 166 and 168.

pared with the subgroup of non-ARDS patients who, like the ARDS patients, had received prior antibiotic treatment and who had received mechanical ventilation for greater than one week.<sup>166</sup> Similarly, Markowicz and colleagues reported a higher incidence of nonfermenting Gram-negative bacilli in patients with ARDS (47% vs 34% of isolates) and also attributed this difference to the more frequent use of early empiric antibiotics and the greater duration of mechanical ventilation in the ARDS group.<sup>168</sup> The microbial causes of VAP in patients with and without ARDS from these 2 studies are compiled in Table 4.

VAP appears to be a common complication experienced by patients with ARDS. This is due, at least in part, to their prolonged duration of mechanical ventilation. The onset of VAP appears to be delayed in ARDS patients, probably because of the near-universal use of antibiotics for the treatment of other conditions early in the course of ARDS. When VAP does occur, the microbial causes appear no different than those among patients without ARDS who have required mechanical ventilation for similar periods of time and who have experienced similar levels of exposure to antibiotic therapy.

### VAP in Patients After Tracheotomy

Tracheotomy is typically performed in patients with acute respiratory failure who are expected to require prolonged mechanical ventilation, or who are unable to protect the airway because of facial injuries or altered level of con-

sciousness. Two large series of patients developing VAP after tracheotomy have been reported, one using operative tracheotomy<sup>169</sup> and the other percutaneous dilational tracheotomy.<sup>170</sup> Whether performed operatively or by the percutaneous dilational technique, tracheotomy is associated with an increased risk of VAP developing a median of 7–9 days into the post-tracheotomy period. Airway colonization prior to the procedure appears to be a major risk factor for VAP after tracheotomy, particular if fever is present and if continued sedation is necessary after the procedure.<sup>169,170</sup> Interestingly, no other clinical features predict the development of VAP. The causes of VAP in these series, in order of frequency, were *P. aeruginosa*, *S. aureus* (mostly methicillin-resistant), *A. baumannii*, and other Gram-negative bacilli. Tracheotomy is also an independent risk factor for VAP due to *S. maltophilia*.<sup>171</sup> This multidrug-resistant microbiologic spectrum reflects the prolonged hospital stay and duration of mechanical ventilation, and the frequency of prior antibiotic treatment experienced by these patients. Not surprisingly, when prophylactic amoxicillin-clavulanate was used routinely at the time of the procedure, isolates from pre-procedure endotracheal aspirates accounted for the cause of a subsequent pneumonia in only 61% of cases. This improved to 69% if only cases of VAP occurring within one week of tracheotomy were considered.<sup>170</sup> Thus, VAP following tracheotomy generally is caused by multidrug-resistant pathogens, and pre-tracheotomy tracheal aspirate cultures can-

not be relied upon entirely to predict the microbial cause of a subsequent episode of VAP.

### VAP Soon After Intubation

Most studies of VAP define VAP as occurring after  $\geq 48$  hours of mechanical ventilation, to help distinguish hospital-acquired VAP from community-acquired infections that were incubating or “brewing” at the time of intubation but that didn’t become clinically evident until 1–2 days later. However, some patients develop true nosocomial infections very soon after intubation. Rello and colleagues have described a series of cases with “very-early”-onset VAP, occurring within the first 48 hours of intubation.<sup>172</sup> In their experience, 32 of 250 (13%) patients developed VAP in this short time period after intubation. Independent risk factors for very early post-intubation VAP were the use of cardiopulmonary resuscitation and continuous sedation. Prior antibiotic use had a protective effect against the development of very early VAP. The microbial causes of VAP in this very-early-onset group largely mirror those seen in early-onset VAP, but *Pseudomonas aeruginosa* was isolated in 15% of instances. This may be explained by the fact that over half of the patients had been hospitalized for some period of time prior to intubation, and 14% were being reintubated because of failed weaning attempts or after self-extubation, implying substantial exposure to the critical care environment prior to the index intubation.<sup>172</sup> The microbial causes of very early VAP in patients intubated at the time of arrival to the hospital would be expected to be different, with fewer multiple-drug-resistant organisms.

### VAP in Patients With COPD

COPD is a recognized risk factor for the development of VAP,<sup>173,174</sup> probably because of the advanced age of the patients, the high prevalence of pre-existing colonization of the lower airways, inhibition of mucociliary function due to cigarette smoking, the inability to generate an effective cough because of airflow obstruction, and the suppressive effects of corticosteroids on lung host defenses. When patients with COPD do develop VAP, they are at increased risk for infection with *H. influenzae*, as well as *Pseudomonas* species, methicillin-resistant *S. aureus*, and *Aspergillus* species.<sup>36,53,155</sup>

### VAP in Patients With Traumatic Injuries

Many published series of VAP cases include injured patients, who are at increased risk for VAP relative to medical patients.<sup>4,175,176</sup> However, relatively few studies have compared the microbiology of VAP in injured patients versus some referent group. Rello and colleagues

found increased incidence of staphylococcal VAP in injured patients in coma (Glasgow coma scale  $< 9$ ), but a predominance of aerobic Gram-negative bacilli in injured patients not in coma.<sup>177</sup> The microbial implications of early- and late-onset VAP appear to be the same for injured patients as for other groups.<sup>78,93,178</sup> In one series, early VAP due to *H. influenzae* was significantly more common in trauma patients, compared with other surgical and post-operative populations,<sup>179</sup> perhaps because of less use of antibiotics for other indications in the trauma patients.

### VAP in Patients With Burns

Patients with serious burn injuries are at high risk for developing VAP,<sup>176,180,181</sup> especially if there is coexistent inhalation injury or if the patient is intoxicated at the time of admission.<sup>182</sup> There is little published data on the microbial causes of VAP in burn patients specifically.<sup>183,184</sup> For the most part, the causes appear to reflect those seen in the general mechanically ventilated population,<sup>185</sup> including the delayed appearance of multiple-drug-resistant pathogens.<sup>186</sup>

### VAP in Immunocompromised Patients

Immunocompromised patients frequently develop pulmonary infectious complications that may lead to respiratory failure and mechanical ventilation. However, in published series it is usually difficult to determine whether a nosocomial bacterial pulmonary infection led to respiratory failure or developed after the onset of respiratory failure and while on mechanical ventilation. Immunocompromised patients also are at risk for opportunistic infections. Occasional opportunistic pathogens are reported in most series of VAP cases, unless immunocompromised patients are excluded. The incidence and relative importance of these infections among patients receiving mechanical ventilation is unknown but may be similar to that of similar patients not receiving mechanical ventilation.<sup>160</sup> Certainly, immunocompromised patients are at risk for developing VAP due to the same common pathogens seen in other patients. These routine infections may be more common than opportunistic causes of VAP because of the myriad factors that lead to an increased risk of VAP in general and the high incidence of VAP caused by standard pathogens.

### Summary

The microbial causes of VAP are many and varied. Most cases are caused by routine bacterial pathogens that reach the lung after aspiration of oropharyngeal secretions or direct inoculation into the airways. The causes of VAP and the likelihood of infection by an antibiotic-resistant



strain can be predicted based on the patient characteristics, the duration of hospitalization, the duration of mechanical ventilation, prior exposure to antibiotic therapy, and prior colonization patterns. However, the relative prevalence of individual pathogens varies substantially between different geographic regions, different institutions, and even different units in the same hospital. Local microbiology and antibiotic susceptibility data are essential for making informed antibiotic treatment choices. Atypical bacterial, viral, and fungal pathogens appear to be unusual causes of VAP, but may be important in a subset of patients. Unusual diagnoses and more extensive testing should be considered in patients with specific risk factors or who respond poorly to initial therapy. VAP is particularly common in patients with ARDS, after tracheotomy, in patients with COPD, and in injured and burned patients. However, the prevalence of individual pathogens in these settings generally appears to depend mostly on the same predictive factors listed above.

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## Discussion

**Kollef:** With the acinetobacter data from Harborview it was striking how common it is now and how prevalent it is as a cause of VAP there. Do you know if they have done any typing of the organism to see if it's a single clone or a few clones that are being spread throughout the hospital? And also can you describe for us what you do from an infection-control perspective when you isolate one of these organisms in a patient?

**Park:** Yes. We have had a striking increase in the prevalence of acinetobacter infection. Now about a quarter of them are sporadic isolates that are of a variety of carbapenem-sensitive genotypes. We are in the midst of an outbreak of a multidrug-resistant strain that now accounts for over three quarters of our acinetobacter isolates. It was imported to Harborview by a returning serviceman from the Middle East theater, and I don't know the exact characterization of the strain, but it is a single strain that is accounting for all of the multidrug-resistant cases. I'll talk later tomorrow about how we've approached this in terms of treatment, but it's very challenging. Many of the isolates are susceptible

only to colistin, and that hasn't been terribly effective in our hands.

What we've focused on is infection control. Probably, like many of your institutions, we were lulled into a false sense of body-substance-isolation security, and we have not been doing a very good job of preventing transmission by health-care workers and environmental surfaces. With these multi-drug-resistant cases we've modified our infection-control policy to what we're calling "BSI-plus," involving gloving and gowning for any contact with the patient or equipment in the room. We're cohorting infected patients in similar ICUs or similar parts of an ICU, and we're performing surveillance cultures to detect colonized patients at the time of ICU admission. The impact of these changes appears to be measurable, but we haven't eliminated the outbreak by any means.

**Rello:** Why do you perform 2 diagnostic techniques, and how do you interpret discordant samples? For example, if you had a positive BAL culture for *Acinetobacter baumannii* with negative protected-specimen-brush sample or a count of colonies under the threshold, do you consider that microorganism responsible for a contamination or a true infection?

**Park:** We don't routinely perform both BAL and protected-specimen-brush sampling, but among our dozen or so faculty there are personal preferences toward one or the other. Personally, I prefer BAL, except in situations where distal purulent secretions are evident, and especially when BAL return is poor from dependent areas.

I would ask the group, what should we do if there are discordant results? I would personally ask the fellow what they thought, and hope they would say, "Let's treat the one that's positive." I share the view that was expressed earlier that we often treat this condition too gingerly and too late.

**Solomkin:** I too believe one should accept any one positive test as diagnostic of infection.

I want to discuss candida. Colonization patterns and their implications for infection have not been explored with many organisms. Candida is in many ways an unusual organism, and I think colonization of the upper respiratory tract is an index and indicator of intestinal colonization. I think those patients, particularly if they are critically ill, receiving broad spectrum antibiotics and having gastrointestinal disturbances, are at substantial risk of developing subsequent candidemia,

with an inapparent source. I would venture that those patients from whom you do culture candida from a BAL specimen really may be at a risk, not necessarily of invasive pulmonary candida infection, but rather of a later disseminated candidemia of gastrointestinal origin, and that alone may well warrant prophylactic therapy.

**Maki:** We do get *Candida* in BAL samples periodically. We don't get 4 logs of it, and I was impressed that it was a pathogen, because it was not from a protected-brush sample, and I think they're pushing the stuff down. I think there are patients who are really neutropenic, or who are on half a gram of methylprednisolone to treat rejection or something else and in whom candida can cause invasive disease, but in general I've not been impressed. It's a very uncommon pathogen, other than in those rare circumstances. We've seen it occasionally in bone-marrow-transplant patients, but that's about it.

**Solomkin:** I would say that there is a correlation between patients (and they are uncommon) with positive BAL cultures and who subsequently, over a 4-week interval, are at risk of developing candidemia.

**Park:** Most cases we see are on our trauma surgery service. The surgeons determine the management of these patients, and they're fairly aggressive about treating patients with open wounds, with visceral perforation, and with colonization of more than 1 site. They'll routinely treat these patients, so it's very unusual to follow the natural history of colonization with yeast in our institution. In the medical ICU I think we tend to adopt more of a watch-and-wait approach, but we see very few of these patients, compared with the trauma surgery service. At Harborview we don't have a big population of profoundly immunocompromised medical patients, because they are hospitalized at the University of

Washington Medical Center or at the Fred Hutchinson Cancer Research Center.

**Niederman:** When you were looking at the time lines for pneumonia, I think you talked about the chronically critically ill, and I agree that patients who are chronically ventilated and tracheostomized certainly do develop pneumonia, but I think it's important to note that their per-day risk is dramatically less, and there probably is something self-selecting about people who manage to live that long on a ventilator. Certainly long-term-tracheostomy patients, for example, who are out of the hospital may get tracheobronchitis from time to time, but rarely do they get VAP.

To follow up on the comment earlier that VAP is related to the ventilator and the tube, they alone are not enough. I mean, if patients have that ventilator and tube in place, and if they somehow reach a point of host-defense stability, they can coexist with these pathogens.

There are also a couple of other bacteriologic issues you didn't mention. One of Jordi Rello's studies<sup>1</sup> was about very-early-onset pneumonia (immediately following intubation), which may be a different disease than other early-onset pneumonias, presumably because patients are inoculated with a huge amount of bacteria during the intubation process. Usually it's emergency intubation in unconscious patients.

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**Park:** Right. A kind of intubation-associated pneumonia.

**Niederman:** Right. And I think that there are data to suggest that those patients don't get pneumonias as of-

ten if they are on antibiotics, and so with some but not a lot of data, we—among other places—believe that anybody who is emergency-intubated should get 24 hours of antibiotics, and if the radiograph is clear the next day, we stop the antibiotics. I think the high frequency of inoculation in an emergency-intubation process is a concern.

The other pathogens I want to mention are anaerobes. I think there's pretty convincing data that anaerobes are not important in VAP and that even in people who aspirate outside the hospital (at least older people in nursing homes), anaerobes are probably not important, compared to Gram-negative organisms.

The fungus that wasn't mentioned was aspergillus, but I think that is the fungus that we worry the most about, and although I am much more willing than Joe Solomkin to ignore candida in a lower-respiratory-tract culture, I am not that willing to ignore aspergillus, particularly if the patient is on corticosteroids and antibiotics. I think aspergillus is probably the fungus we have to be on top of.

**Park:** I agree. I think invasive aspergillosis is very uncommon as a cause of VAP, but when we isolate any form of mold we generally treat it if the patient has risk factors and a compatible illness. I'll talk more tomorrow about the impact of early antibiotic treatment on lessening the incidence of early ventilator-associated pneumonia, but this is a 2-edged sword, the other edge being a greater propensity for drug-resistant pathogens if pneumonia develops later on.

**Chastre:** You alluded to legionella as a cause of VAP. In my own experience it's very unusual in patients requiring mechanical ventilation. Did you observe one single case of *Legionella* infection?

**Park:** We don't routinely test for legionella in every case of VAP. It's not part of our protocol. It's a deci-

sion made by the individual care team. We do detect sporadic cases of Legionnaires' disease in ventilated patients in our ICU, but I can't tell you the precise incidence. It's clear that legionella has tremendous geographic variability. I think some institutions are largely free of it, but I think the experience also is that when you look systematically and aggressively to detect legionella you find cases that you weren't aware were occurring. Do you routinely test for legionella in cases of suspected VAP?

**Chastre:** With cultures of specialized media we never found one single case of legionella infection in patients under mechanical ventilation. Of course, you can get a lot of patients with nosocomial pneumonia in the hospital, but not in the ICU in a patient on mechanical ventilation.

**Park:** I think this may be an instance in which intubation is protective against infection. You have to brush your teeth or shower or drink the water to get Legionnaires' disease. Ventilated patients may be somewhat safer from it because they're prevented from getting to the sink or taking a shower.

**Maki:** But if you watch the nurse doing oral care, patients often want and get ice chips, and sometimes a washcloth to suck on, so they do get water, and we've seen ventilator-associated legionella pneumonia. I'll talk a little about it this afternoon. It's not very common, but there have been a number of outbreaks, and I've always been curious how they've gotten it. I surmise that it might be the wet washcloth or the ice chips. If you have legionella in your water and you have a lot of compromised patients, you're going to see legionella pneumonia. We had this problem more than 10 years, and we didn't realize that we had a nosocomial problem, but have now resolved it.

**Park:** I think there are institutions that have particularly good infection-control practices or that have a particularly pure water supply that just don't see Legionnaires' disease.

**Maki:** At least 70% of municipal water has legionella in it. Probably most of us showered in it today.

**Solomkin:** I want to raise one other issue that seems to disappear into his-

tory, and that is the role of anaerobes in VAP.

**Park:** A couple of studies have looked at that.<sup>1,2</sup> To summarize, my interpretation is that anaerobes may play a role, particularly in very-early VAP, just as they may in other forms of aspiration pneumonia. But it's been very difficult to isolate them from the airways of patients with VAP. I guess the other comment I would make is that many of the antibiotic treatment regimens that are recommended for empiric therapy have fairly good anaerobic coverage, particularly for the anaerobes that are present in the oropharynx. Whether anaerobes play any role, I don't know. I don't think they're very important in late VAP. If they are present, I think we're generally treating them anyway.

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