What Is Ventilator-Associated Pneumonia and Why Is It Important?

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Hospital-associated pneumonia (HAP) is one of the most common infections acquired among hospitalized patients. HAP is associated with excess mortality and increased medical care costs. The rise in HAP due to antibiotic-resistant bacteria has resulted in more common administration of inappropriate antimicrobial treatment, with an associated increased risk of hospital mortality. Ventilator-associated pneumonia (VAP) refers to HAP occurring in patients requiring mechanical ventilation. VAP is the most common nosocomial infection among patients with acute respiratory failure. Physicians treating patients with HAP and VAP should be aware of the predominant local pathogens associated with these infections and their antimicrobial susceptibility patterns. This will allow more appropriate initial antibiotic selection in order to optimize treatment regimens and clinical outcomes. Additionally, clinical strategies aimed at the prevention of HAP and VAP should be employed in all hospital settings caring for patients at risk for these infections. *Key words: pneumonia, hospital, nosocomial, ventilator, outcomes.* [Respir Care 2005;50(6):714–721. © 2005 Daedalus Enterprises]

What Is Ventilator-Associated Pneumonia?

Hospital-associated pneumonia (HAP) is an infection of the lungs, usually due to bacterial, viral, or fungal pathogens, that is defined to occur greater than 48 hours after hospital admission (Table 1). HAP is the second most common hospital-acquired infection but leads to the greatest number of nosocomial-related deaths.[1,2] In addition to increased morbidity and mortality, HAP also results in extended hospital stays and is often treated with prolonged antibiotic administration, resulting in further financial burdens and antibiotic-resistance pressures on hospitals. Treat-

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Table 1. Pneumonia Classification According to Location of Occurrence

Community-Associated Pneumonia: Infection occurring outside of the hospital in a patient lacking risk factors for health-care-associated pneumonia.
Health-Care-Associated Pneumonia: Infection present at the time of hospitalization in a patient not requiring mechanical ventilation. The patient has one of the following risk factors:
Receiving chronic dialysis
Home infusion therapy
Home wound therapy
Residence in a nursing home or chronic care facility
Recent hospitalization (more than 3 days during the preceding 90 days)
Hospital-Associated Pneumonia: Infection occurring > 48 hours after hospital admission in a patient not requiring mechanical ventilation.*
Ventilator-Associated Pneumonia: Infection occurring > 48 hours after hospital admission in a patient requiring mechanical ventilation.*

* Patients developing pneumonia within 48 hours of hospital admission are difficult to classify. Some of these patients may have begun to develop lung infection prior to hospital admission. Mechanical ventilation refers to ventilatory support administered via an endotracheal tube.

ment of HAP has become more difficult because of escalating emergence of antibiotic-resistant bacteria.[3,4] Successful outcomes depend on the prevention of HAP when possible and the administration of appropriate antibiotics in a timely manner when infection occurs.[5] The latter can be difficult to achieve when the etiology of HAP is initially unknown.

Ventilator-associated pneumonia (VAP), one form of HAP, specifically refers to pneumonia developing in a mechanically ventilated patient more than 48 hours after tracheal intubation.[5,6] Although not included in this definition, some patients may require intubation after developing severe HAP and should be managed similar to patients with VAP. Pneumonia occurring within 48 hours of hospital admission can be difficult to differentiate from community-associated pneumonia (CAP) (see Table 1). These early-onset infections may have begun to develop prior to hospital admission or possibly as a result of aspiration occurring with tracheal intubation at the time of hospital admission.

Health-care-associated pneumonia (HCAP) has recently been described as pneumonia developing in patients admitted to the hospital from high-risk environments. These high-risk environments include nursing homes and extended care facilities or patients' homes if they are receiving long-term dialysis, home infusion therapy, home wound therapy, or have had a recent hospitalization.[7] These risk factors increase the likelihood of infection with multiple-drug-resistant bacteria that are more commonly seen in HAP and VAP, as compared with CAP.[8–10] Although the following discussion focuses on VAP, it also applies to HCAP and HAP, which often occur in patients not requiring mechanical ventilation. However, patients with HCAP and HAP may go on to develop respiratory failure, further blurring the differences between these various classifications of pneumonia.

Time of onset of pneumonia is an important epidemiologic variable and risk factor for specific pathogens and outcomes in patients with HAP and VAP. Early-onset HAP and VAP (occurring within the first 4 d of hospitalization) usually carry a better prognosis and are more likely to be caused by antibiotic-sensitive bacteria.[11] Late-onset HAP and VAP (occurring greater than 4 days after hospital admission) are more likely to be caused by multiple-drug-resistant pathogens associated with increased hospital mortality and morbidity.[12–14] However, patients with early-onset HAP who have received prior antibiotics or who have been hospitalized within the previous 90 days are also at greater risk for colonization and infection with multiple-drug-resistant pathogens and should be treated similar to patients with HCAP, late-onset HAP, or VAP, in order to avoid the administration of inappropriate antimicrobial treatment.[7,15]

Why Is VAP Important?

VAP Is a Common Hospital-Associated Infection Linked With Excess Morbidity and Mortality

There are approximately 300,000 cases of HAP and VAP annually in the United States, representing roughly 5–10 cases per 1,000 hospital admissions.[1] Based on data from over 14,000 intensive care unit (ICU) patients in the United States National Nosocomial Infection Surveillance System, HAP and VAP represent the second most common nosocomial infection, affecting approximately 27% of all critically ill patients.[2] HAP accounts for up to 25% of all ICU infections and more than 50% of the antibiotics prescribed.[2] VAP occurs in 9–27% of all intubated patients.[5,16] Among ICU patients, nearly 90% of episodes of HAP occur during mechanical ventilation.

In mechanically ventilated patients the incidence of VAP increases with duration of ventilation. The risk of VAP is highest early in the course of hospital stay and is estimated to be 3% per day during the first 5 days of ventilation, 2% per day during days 5–10 of ventilation, and 1% per day after this.[17] Since most mechanical ventilation is short-term, approximately half of all episodes of VAP occur within the first 4 days of mechanical ventilation.[18] The intubation process itself contributes to the risk of pneumonia,[19] and when patients with acute respiratory failure are managed with noninvasive ventilation, nosocomial pneumonia is less common.[20–22] These studies support the importance of tracheal intubation as a risk factor promoting the occurrence of VAP.

When it occurs, VAP is the leading cause of nosocomial mortality for patients with respiratory failure. Approximately 60% of all deaths in patients with nosocomial infections are associated with HAP,[23] and the mortality rate is higher in critically ill patients and those patients developing VAP. In these populations, mortality by all causes increases 2–2.5-fold, compared to patients without VAP,[24,25] and reported crude mortality rates have ranged from 20% to 70%.[26] Mortality rates are also higher in older patients, patients with a depressed level of consciousness, and patients who have received prior antibiotic therapy.[24,27,28] Although patients with VAP are generally sicker than those without the infection, it is not simply a marker for other fatal illnesses in these patients. "Attributable mortality" in patients with VAP can account for up to 50% of all mortality.[29–35]

VAP Is Associated with Excess Hospital Costs

In addition to being the leading cause of mortality among nosocomial infections, VAP is the leading cause of nosocomial morbidity. Rates of secondary bacteremia have been reported to range from 4% to 38%, and VAP patients are hospitalized on average for an additional 4–13 days (median 7.6 d).[26]

In 1992, the Centers for Disease Control and Prevention estimated that each case of HAP was associated with 5.9 additional days in the hospital, corresponding to $5,683 in extra hospital charges.[36] Recent studies have suggested that incremental medical care charges for these patients are far higher than they were in the prior decade, with current estimates ranging from $20,000 to $40,000 per case of HAP or VAP in the ICU.[16,37] By definition, HAP and VAP start after the patient is admitted to the hospital, so less than 5% of the additional cost may be recovered under prospective reimbursement systems, providing a financial incentive to accompany the clinical rationale for preventing these infections more effectively.[38]

The Pathogenesis of VAP Suggests Many Cases Are Preventable

The pathogenesis of VAP, as well as HCAP and HAP, is linked to 2 separate but related processes: colonization of the aerodigestive tract with pathogenic bacteria, and aspiration of contaminated secretions. The most common sources of VAP pathogens are from microaspiration of oropharyngeal secretions, aspiration of esophageal/gastric contents, inhalation of infected aerosols, embolization of contaminated biofilm from the endotracheal tube surface, hematogenous spread from distant infection, exogenous penetration from the pleural space, or direct inoculation (eg, resulting from tracheal intubation).[5]

Bacterial colonization of the oropharynx is universal with *Streptococcus pneumoniae*, various anaerobes, and, occasionally, *Haemophilus influenzae* being found in normal subjects. However, colonization with Gram-negative bacilli, notably virulent organisms such as *Pseudomonas aeruginosa* and *Acinetobacter* species, is rare in healthy individuals.[39] It is known that oropharyngeal and tracheal colonization with *P. aeruginosa* and enteric Gram-negative bacilli increases with length of hospital stay and with severity of illness.[4,40] One older study noted that 35% of moderately ill patients and 73% of critically ill patients were colonized with Gram-negative bacilli.[41] The same investigators found that pneumonia occurred in 23% of colonized patients but in only 3.3% of uncolonized patients.[41,42]

Aspiration of oropharyngeal secretions is not uncommon, even in health. Approximately 45% of healthy subjects were shown in one study to aspirate during sleep,[43] and the rate of aspiration is higher than this in patients with impaired levels of consciousness and inability to protect their airways from aspiration events.[39,44] Factors promoting aspiration include an overall reduced level of consciousness, a blunted gag reflex, abnormal swallowing for any reason, delayed gastric emptying, or decreased gastrointestinal motility. Reflux and aspiration of nonsterile gastric contents is also a possible mechanism of pathogen entry into the lungs,[44–46] although its role is generally less important than that of oropharyngeal colonization.[47] The stomach has been particularly implicated in late-onset VAP as a potential reservoir for antibiotic-resistant bacteria.[48]

The understanding of the dual pathogenesis of VAP (colonization of the aerodigestive tract with pathogenic bacteria and their subsequent aspiration) has allowed for the development of intervention strategies aimed at the prevention of this infection. These education-based programs have shown that the occurrence of VAP can be reduced by 50% or more, using multiple interventions aimed at preventing colonization and aspiration.[49,50] The interventions applied in these strategies are aimed at preventing or reversing specific risk factors associated with promoting VAP, identified from multivariate analyses.[51,52]

Antibiotic-Resistant Bacteria Are Common Causes of VAP

Infectious organisms that commonly result in VAP, as well as HCAP and HAP, are generally different from those that are most commonly associated with CAP. Gram-negative aerobes compose the majority of HAP infections; however, *Staphylococcus aureus*, especially methicillin-resistant strains, are increasing in importance as a cause of VAP.[2,53] The individual organisms that are most commonly associated with VAP are *S. aureus* (18.1%), *P. aeruginosa* (17.0%), and *Enterobacter* species (11.2%).[54]

Table 2. Clinical Diagnostic Criteria for Hospital-Associated Pneumonia*

New and persistent infiltrate (radiographically present for greater than 48 hours) PLUS one of the following:
Positive pleural or blood culture for the same organism as that recovered in respiratory secretions
Radiographic evidence of cavitation or necrosis
Histopathologic evidence of pneumonia
Two of the following:
Core temperature > 38.3°C
Blood leukocytes > 10,000 cells/mL
Purulent tracheal secretions

(Adapted from References 5, 6, and 63.)

Recently, more virulent toxin-producing strains of methicillin-resistant *S. aureus*, identified in community settings, have been described as a cause of CAP and HAP.[55,56]

VAP in which Gram-negative bacilli are the causative pathogens is frequently associated with substantial mortality. Mortality increases by a factor of 2.6–6.4 in critically ill patients with *P. aeruginosa* infection,[57] and mortality may exceed 70% in ventilated patients with *P. aeruginosa* or *Acinetobacter* infections.[24,29,58] Intubated or mechanically-ventilated patients are more likely to have *P. aeruginosa* or *Acinetobacter* infections, but they are less likely to have *Escherichia coli* infections, and as many as 50% of all cases of VAP are due to polymicrobial infection.[59,60] The high mortality attributed to *P. aeruginosa* infections in mechanically-ventilated patients is due, in part, to frequent failure of standard antibiotic treatments.[58,60] Increasing antibiotic resistance and the administration of inappropriate antimicrobial therapy contribute to excess mortality among patients with VAP.[61]

The Diagnosis of VAP May Be Difficult to Establish

VAP is usually suspected when a patient develops a new or progressive pulmonary infiltrate with fever, leukocytosis, and purulent tracheobronchial secretions.[62] However, a number of noninfectious causes of fever and pulmonary infiltrates can also occur in these patients, making the above clinical criteria nonspecific for the diagnosis of VAP. Noninfectious causes of fever and pulmonary infiltrates that can mimic HAP include chemical aspiration without infection, atelectasis, pulmonary embolism, acute respiratory distress syndrome, pulmonary hemorrhage, lung contusion, infiltrative tumor, radiation pneumonitis, and drug or hypersensitivity reactions. Table 2 provides clinical criteria for the diagnosis of VAP, derived from a consensus panel.[63]

A number of studies have demonstrated the limitations of using clinical variables alone for establishing the diagnosis of VAP. Autopsy results in a series of patients with acute lung injury demonstrated that clinical criteria alone led to an incorrect diagnosis of VAP in 29% of clinically suspected cases.[64] Another study of 147 mechanically ventilated patients, using quantitative lower-airway cultures to establish the diagnosis of VAP, also found that clinical variables could not be used accurately to distinguish between patients with and without VAP.[65] In a third report, the accuracy of clinical judgment in formulating treatment plans for patients with suspected VAP was compared with quantitative lower-airway cultures obtained by bronchoscopy.[66] Clinical judgments about the presence of VAP were correct only 62% of the time, when compared to culture specimens, and only 33% of the treatment plans based on clinical judgment alone were deemed to be effective. Most clinical errors resulted in the unnecessary prescription of antibiotics, failure to diagnose VAP accurately, failure to treat all organisms causing polymicrobial VAP, and failure to treat VAP due to antibiotic-resistant pathogens.

The conclusion that the clinical diagnosis of VAP is markedly inferior to other methods has not been universal. As an example, one study of 25 deceased mechanically ventilated patients found that the presence of radiographic infiltrates and 2 of 3 clinical criteria (fever, leukocytosis, purulent secretions) had a sensitivity of 69% and a specificity of 75%, when compared with the combination of histologic evidence of pneumonia and positive post-mortem cultures as the accepted standard.[67] The performance of invasive diagnostic tests did not differ markedly from these clinical estimates, nor did their use in conjunction with clinical assessments dramatically improve diagnostic accuracy.

Radiographic criteria also are nonspecific for the diagnosis of VAP.[64,68,69] One report, for example, evaluated the chest radiographs of 69 patients who died in respiratory failure and upon whom autopsies had been performed.[69] Of the 30 patients fulfilling radiographic and clinical criteria for VAP, only 13 were found to have VAP at autopsy (57% false-positive rate). Stepwise logistic-regression analysis suggested that the finding of air bronchograms was the only radiographic sign that might predict the presence of VAP. The use of lower-airway quantitative cultures has been demonstrated to improve antibiotic decision making in clinically and radiographically suspected VAP. This has been achieved by allowing treatment with more specific antimicrobial regimens resulting from narrowing or de-escalation of initially prescribed broad-spectrum antibiotics.[70–75]

Inappropriate Antimicrobial Therapy Is Common in VAP

There are 2 overriding principles that make up the strategy of antibiotic treatment of VAP. The first is to provide

an appropriate initial antimicrobial regimen that is likely to be active against the pathogen(s) causing infection. The second principle is to limit the unnecessary use of antibiotics. The strategy of antimicrobial de-escalation attempts to unify these 2 principles into a single strategy that will optimize patient outcomes while minimizing the emergence of antibiotic resistance. In addition to these principles, clinicians must ensure that antibiotic administration follows certain minimal requirements, such as proper dosing, interval administration, optimal duration of treatment, monitoring of drug levels when appropriate, and avoidance of unwanted drug interactions.[76] Lack of adherence to these minimal requirements can result in inadvertently low or excessive tissue concentrations of the antibiotic, which increases the likelihood for antibiotic resistance, patient toxicity, and lack of effectiveness despite a qualitatively correct regimen.

The first principle of antibiotic "de-escalation" requires the administration of an appropriate empiric regimen to patients with suspected VAP. Decisions regarding antibiotic selection often occur in the absence of identified pathogens. It is imperative that clinicians be aware of the microorganisms likely to be associated with VAP in their patient population. The most common pathogens associated with the administration of inappropriate antimicrobial treatment in patients with VAP include potentially antibiotic-resistant Gram-negative bacteria (*P. aeruginosa*, *Acinetobacter* species, *Klebsiella pneumoniae*, and *Enterobacter* species) and *S. aureus*, especially the strains with methicillin resistance.[61] However, it is important to recognize that the predominant pathogens associated with VAP, as well as with other hospital-associated infections, can vary between hospitals as well as between specialized units within individual hospitals.[50,77,78] Therefore, clinicians should be aware of the prevailing bacterial pathogens in their hospitals and their associated antimicrobial susceptibilities. This should help in the selection of empiric antibiotic regimens that are more likely to provide appropriate treatment.

Clinicians should also be aware that health-care-associated infections are similar to hospital-associated infections in terms of the pathogens responsible for infection.[7] This is an important issue, as more than 25% of bloodstream infections due to *S. aureus* and *P. aeruginosa* may be health-care-associated.[79] Similarly, HCAPs have pathogen distributions that are similar to those seen among patients with HAP and VAP.[9,10] Therefore, physicians should be aware of factors that identify patients as being at risk for health-care-associated infections, in order to avoid the prescription of inappropriate antibiotic treatment (see Table 1).

Prolonged Antibiotic Treatment of VAP Can Promote Antimicrobial Resistance

The second goal of antibiotic de-escalation is to avoid the unnecessary administration of antibiotics, in order to prevent the emergence of resistance. Physicians practicing in the hospital setting are frequently faced with the dilemma of caring for acutely ill patients with suspected nosocomial infection because of the presence of nonspecific clinical findings (fever, leukocytosis, hemodynamic instability). Failure to provide treatment with an appropriate initial antimicrobial regimen may result in greater morbidity, while unnecessarily prolonged antibiotic treatment can lead to colonization or infection with antibiotic-resistant pathogens.[80] Therefore, several approaches have been developed to shorten the duration of antibiotic treatment for VAP.

Croce et al obtained quantitative bronchoalveolar lavage samples in trauma patients with suspected VAP to distinguish those with microbiologically confirmed infection from those with a probably trauma-induced systemic inflammatory response syndrome.[81] All patients received initial antibiotic treatment, and those with bronchoalveolar lavage cultures revealing $< 10^5$ colony-forming units/mL had their antibiotics discontinued without any statistically significant differences in mortality, compared to the patients who continued on their antimicrobial treatment. Similarly, Singh et al evaluate a group of patients at low likelihood of having VAP, based on a clinical pulmonary infection score ≤ 6, and randomized them to receive physician-directed antibiotic treatment (usually 10–21 d of antibiotic treatment) or discontinuation of antibiotics if the clinical pulmonary infection score remained ≤ 6 on day 3 of antimicrobial treatment.[82] No significant difference in mortality was observed; however, intensive care length of stay, duration of antibiotic use, and antibiotic costs were statistically less in the group having their antibiotics discontinued based on the clinical pulmonary infection score.

Ibrahim et al developed a clinical guideline for the treatment of VAP employing the goals of antimicrobial de-escalation.[83] They employed an ICU-specific antibiogram to select a 3-drug antibiotic regimen for the treatment of VAP that covered more than 90% of previously recognized pathogens. This guideline also recommended that antibiotic therapy be discontinued after a 7-day course unless prespecified criteria were met (eg, continued evidence of infection with leukocytosis and fever). These investigators found that the initial administration of appropriate antimicrobial treatment increased and the overall duration of antibiotic therapy for VAP was reduced by approximately one week, resulting in fewer secondary infections due to antibiotic-resistant organisms.[83] This approach has been validated in a randomized trial demonstrating that specific criteria for antibiotic discontinuation in VAP could reduce antibiotic days when applied by pharmacists rounding in the ICU setting.[84]

Recently, a large randomized trial comparing 8 days to 15 days of appropriate antibiotic therapy for VAP was reported.[80] Despite similar efficacy, the longer course of

antibiotic therapy was associated with statistically greater emergence of multiply-resistant bacteria. This study supported the de-escalation strategy of antimicrobial treatment for VAP. Initial antibiotics were selected based on patients' risk for infection with antibiotic-resistant pathogens. The antibiotic regimen was subsequently narrowed according to the bacteria isolated from respiratory cultures and their antimicrobial susceptibility. Although this study stopped antibiotic therapy in patients with VAP after 8 days, other studies have used clinical criteria for terminating antibiotics based on patients' clinical response to antibiotic treatment.[75,83,84]

Summary

VAP is a common hospital-associated infection occurring in mechanically ventilated patients. Increasingly, VAP is associated with antibiotic-resistant pathogens, resulting in excess morbidity, mortality, and medical care costs. Clinicians caring for mechanically ventilated patients should be aware of strategies aimed at preventing VAP and appropriately treating this infection when it occurs, in order to improve outcomes and minimize the emergence of antimicrobial resistance.

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Discussion

Kollef: We've always thought about MRSA [methicillin-resistant *Staphylococcus aureus*] pneumonia as something patients acquired in the hospital, and really did not expect that patients with CAP would have MRSA coming in. We're seeing them *routinely* now, and it's a scary thing for us in the St Louis area. Dennis, have you seen any of these patients?

Maki: We have not seen a lot, but we have seen several.

Kollef [to group]: Have you seen anybody with this type of picture coming in with a very progressive community-acquired MRSA pneumonia?

Maki: We've seen more necrotizing soft tissue infections.

Truscott:* I think we may be getting into biofilms a little more later, but how are you seeing them as beginning? External-to-internal with respect to the endotracheal tube, or when they are inserted? In other words, coming from the outside, the exterior portion?

Kollef: How does the biofilm have an impact on infections?

Truscott: Where do you see the colonization beginning: the initial inoculation, coming from the exterior of the tube, or the interior of the tube?

Kollef: Well, when you talk about the endotracheal tube and biofilms, there aren't a lot of systematic electron microscopy studies, for example, looking at where the biofilm initially forms. But studies have been done where they've taken endotracheal tubes out of patients and serially transected the tubes. Curt Sessler's group did a study like this in the nursing literature about 3–4 years ago.[1] We did a study[2] using acoustic reflectometry, making the point that it's really the internal lumen of the endotracheal tube that's impacted by—not just the biofilm, but the secretions that adhere to its surface. So, biofilm forms on all parts of the tube, but I think it's the internal portion of it, the internal surface, that's probably most important, because if you have narrowing of that surface, it results in increased airway resistance. I think that's the area where you can have more embolization of material into the lower respiratory tract.

But, that's not to say that the external part of the tube isn't important. We know about the fact that secre-

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tions can pool above the cuff, that they can make their way down into the lower respiratory tract as well. But, it's only recently that we've started paying attention to the endotracheal tube. And I think that there's a lot that can be done with that device, and similar devices, in terms of improving them.

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MacIntyre: Marin, I'm going to ask more simple questions. Is the incidence of VAP going up or going down? Are we doing any better at preventing this, or is it becoming a bigger problem?

Kollef: I can't answer that question from a national perspective. I think the only group that can do that is the Centers for Disease Control and Prevention. There have been some changes in some of the ways in which the Nationwide In-Patient Sample hospitals report their data, so you have to be careful, because sometimes they vary in terms of who is reporting and how many of them are reporting. But I haven't seen any systematic evidence suggesting that the rates of VAP are going down. The only times I have seen that are in specific institutions that have adopted programs for preventing the infection. Certainly, in those kinds of programs you can find a number of good examples in the literature where VAP rates came down.[1,2] They never get down to zero, but they generally show a 20–50% reduction in the rate of infection.

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MacIntyre: It's a broader problem. People like you teach us very important ways to try to reduce VAP. You show that it can work, and then of course the huge problem is getting the rest of the world to adopt those practices.

Kollef: I agree with that 100%, and part of the problem—in the United States at least—is that there are the cost concerns, and for many institutions, when they have to put an upfront cost into something in terms of purchasing a device or paying for infection-control practitioners—that's a hard-dollar cost for them. And then when you talk about preventing an infection and potentially reducing lengths of stay and reducing hospitalization costs, that's a little more nebulous. But it becomes powerful when you can demonstrate that.

In our own system, Barnes-Jewish Christian, which has about 11 hospitals in the corporate chain of command, we have a vice president whose job it is to oversee the medical-error and infection-control groups, and they have a very large budget. And they have a very large number of personnel working for them, because they understand and they've got good hard numbers in terms of the financial impact of this, that you can increase throughput by minimizing some of these problems. But that's a large system, and in the average hospital I think that becomes a much more difficult thing to get across. When I give talks I can't tell you how often I see a situation where there's a single infection-control practitioner in a 200- or 300-bed hospital who is supposed to be dealing with *all* of these issues. That's a tough thing to do.

Fishman:* Marin, in answer to your question about being mindful of the pathogens in your local institution, by what means is that generally communicated to the clinicians who are managing patients? What sort of "playing cards" of the bad bugs out there is given, generally?

Kollef: Another important question. How do you know what the local bugs are where you practice? For many clinicians in private practice they may be working in 2 or 3 different hospitals. I think that most of us rely on the hospital antibiogram, and certainly for a smaller hospital, maybe with one ICU, that may be an accurate way of approaching it. But when you get into more complicated areas, particularly when you are dealing with larger institutions, I think it's very clear that you can have variability from unit to unit and from building to building within the hospital setting. Having accurate information is also very powerful, and it should be incorporated into the treatment decisions.

When you have a situation where your best Gram-negative drug has 82% activity against an organism like pseudomonas, you still see people who are comfortable just using a single drug to cover a bug like pseudomonas when someone presents with severe hospital-acquired or ventilator-associated pneumonia. I don't think that's the right way to go. Unfortunately, sometimes this information isn't used in a practical sense at the bedside.

It's the same argument for the diagnostic approaches. I don't advocate to everyone that you do bronchoalveolar lavage with semi-quantitative cultures, or do a cytospin to look at the cell count and the Gram stain, because in many cases they won't utilize that information to modify the antibiotic therapy, so I think that there are a number of issues here related to

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that in terms of getting information, getting *good* information, and using it at the bedside. Sometimes I think there is a disconnect between the data and how it impacts on therapies.

Niederman: I would just like to say that one practical solution to getting the local microbiologic data, which I don't know that everybody takes advantage of, is that microbiology labs in every hospital can give you monthly printouts of what's growing in the ICU, and you can use that data. We get that every month in the ICU now. We've seen tremendous variability month-to-month. There are a lot of issues as to how you collect that data, so not only do you need it to be ICU-specific and institution-specific, but you also need it over the course of time.

Maki: We've had many debates in our hospital about ICU-specific susceptibility profiles, or transplant vs non-transplant, and if you look at them carefully there is enough overlap that I am not convinced that ICU-specific information is all that helpful, for the simple reason that there is plenty of MRSA everywhere; there's lots of resistant Gram-negative rods everywhere. Even though you might have 20% more in the ICU, you are not going to take a chance because there's a little bit less on a transplant unit, such that you wouldn't use coverage for resistant organisms when the patient's critically ill. But your point is well made, and I think it is particularly important, because if there's anything that I'm impressed by, and I think Marin has really published elegant studies that have proven this, it is that we are missing the boat on initial therapy of life-threatening infections on a major scale in this country, and it's having huge impacts.

Niederman: Let me just clarify 2 things, because I think it's important. I think you're right; I don't think you can ignore drug-resistant pathogens in other sites in the hospital, but I think where these data have been helpful for us is we know that we're going to get bad bugs in our ICU; we don't always know which drugs are going to work against them, and that's where that data can be useful. The only caveat that I think that people who do this need to understand is that it's *unfiltered* data, and one of the problems with unfiltered microbiologic data is that nobody is correcting for multiple isolates from the same patient.

Maki: Your lab should be doing that. Labs are supposed to be doing that.

Niederman: No, they would do that when they are reporting, but what I'm getting is just a printout of all the cultures in sum, and they're not filtering it for me. If you are getting unfiltered data, you need to understand that the absolute percentage of susceptibility may be irrelevant; it's a rank order of your drugs that's probably important. So even if you have your lab with that type of data reporting an 80% susceptibility of pseudomonas to a specific antibiotic, it might really be much higher. But what you really want to look at is taking *all* of your antibiotics for, say, pseudomonas, and evaluate where they rank, and that may help you make better choices.

Kollef: I can tell you that the information is helpful to us, and in fact I meet with our infection-control practitioner and our local infectious-disease infection-control person, who is one of the infectious-disease attendings there, on a quarterly basis now. We do have the filtered data. The filtered data gets reported to us quarterly, and it's unit-specific.

But the other thing they report to us—and we sit down and we go over it—it's like a report card, basically, is what's the occurrence of our 4 major nosocomial infections that we track in our unit, and that would be VAP, diarrheal infection, catheter-associated bacteremia, and urinary tract infections. Because we have interventions in place for each of those, if our rates are going in the wrong direction, we need then to do something to be proactive about that. I think that kind of information can be helpful, not only from a therapeutic standpoint but from a prevention standpoint as well.

Park: I wonder if you would comment on what you see in the future as far as either detecting or targeting therapeutically in some way the virulence factors of these organisms.

Kollef: In terms of virulence factors, Jordi Rello may want to speak to pseudomonas; I know he's done some work looking at some of them. Or Jean Chastre could also talk about the pseudomonas aspect.

In terms of MRSA, I think that certainly a very important virulence factor is PVL [Panton-Valentine leukocidin]. I think that right now our chief of microbiology runs the gels for us, and it takes a lot of effort to do this, and hopefully in the future we'll have better ways of doing it.

I think it might be helpful to have knowledge about a toxin-producing organism, because then we might want to add a drug like clindamycin, if it's susceptible, or another drug, and we do have—when you look at protein synthesis for the MRSA strains—quinipristin/dalfopristin, we have linezolid, and tigecycline is going to be coming. They all have an impact on protein synthesis. Maybe it's important to use combination therapy against those organisms, but we have no data. I'm worried that those studies will not be done because no one will support those studies.

Solomkin: Going through, for example, Jordi Rello's data from the large Cardinal database, and a lot of data that you presented, it appears we really need to focus on subsets, and on the fact that there are probably about 20% of these patients who are really at risk from resistant organisms, and, conversely, that they are the ones who

are at risk of death and are going to need early, perhaps even prophylactic, therapy.

We're probably doing pretty well in a fairly cost-effective manner with maybe 60% of these patients. It would be interesting to hear your thoughts on identifying that subset that is probably the group that would benefit, for example, from surveillance culturing and then provision of these very complicated multi-drug regimens if there is a suspicion of infection.

Kollef: The whole issue, to me, is still a little confusing in terms of doing surveillance cultures in the ICU, and I just don't know the utility of doing surveillance cultures in these patients. We do them from the perspective of doing nasal swabs and rectal cultures. There is some evidence suggesting that if you do routine surveillance cultures in high-risk patients and know what they are colonized with, if they then begin to look infected, one can then preemptively strike with the appropriate antibiotic therapy. If we can identify who those patients are, I think that might be useful, to target our surveillance cultures.

But the other issue is that in the future we may have very rapid diagnostic methods. We may have the ability not only to identify the bug but also to identify its susceptibility from a respiratory specimen in a matter of 4–6 hours, and that certainly will also be helpful when we get to that point.

Niederman: I think this is a dangerous thing that we are about to do, but I'm willing to go on record to say that I don't think we're ever going to have a rapid diagnostic test for ventilator-associated pneumonia—simply because the distinction between colonization, early infection, and full-blown infection is so much on a continuum that if you develop a sensitive-enough tool, it will be too sensitive, and a specific-enough tool may be too late. I'm just a little bit concerned that this is not a diagnosis for which we're going to be able to have a test like troponin that tells us positive or negative. Pneumonia can be a very slowly progressive phenomenon, and I think the blurring between colonization, early infection, and full-blown infection is enough that I don't know how you would design a tool that would tell you when to treat.

Kollef: The tool that I was alluding to would not tell you when to treat, but would very quickly tell you what bug is there. So you still need to make your own decision as to whether or not you'll treat, but at least if you make that decision, you may have a very rapid answer in terms of what you need to use.

Niederman: I agree. There are a variety of new technologies to tell you what bugs are there, but I think the decision about whether to treat is going to be a very difficult one to rely on a diagnostic test.

Maki: I can't be quite so pessimistic. If you said 40 years ago, are we going to be able to precisely diagnose subendocardial myocardial infarction, people would have laughed. I think that it may well be possible to measure inflammatory mediator profiles in combination with rapid techniques for detecting either bacterial products or up-regulated inflammatory cells. I think it's not quite so impossible. I think it may well be plausible.

Niederman: OK, that's why I said it was a dangerous thing.

Rello: I would like to add some comments regarding the usefulness of surveillance. I think that a key factor is virulence. Virulence is very difficult to determine, but it is very, very important—probably more important than the emphasis on resistance patterns. For example, Vallés et al[1] reported a 3-year prospective study of 1,607 isolates of *Pseudomonas aeruginosa* colonizing intubated patients, using pulse-field electrophoresis, with implications for prevention of VAP. It was very exciting to learn that early colonization was often due to exogenous strains that never developed into infection, but when he was colonized by a virulent strain, the patient developed pneumonia within the first 24 hours post-colonization.

I have some additional data that will not be reported in my upcoming presentation regarding tracheostomy. A very challenging hypothesis was the possibility to anticipate the pathogen responsible for pneumonia after tracheostomy by tracheal aspirate at the moment of performing the procedure or the day before. Unfortunately, we found that a positive tracheal culture result obtained before tracheostomy was associated with a risk of developing pneumonia of 19.7%, whereas the study of tracheostomy culture was associated with a risk of 14.3% ($p > 0.20$). Moreover, *Acinetobacter baumannii* was identified colonizing 17 patients, but only one of them acquired pneumonia. Therefore, I think that surveillance is not helpful. I don't know if research with micro-arrays would report something new, but probably we should work more on virulence factors.

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