

# Conference Summary: Ventilator-Associated Pneumonia

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## Summary

Ventilator-associated pneumonia (VAP), which is usually defined as an infection occurring greater than 48 hours after hospital admission in a patient requiring mechanical ventilation, is an entity that should be viewed as a subcategory of health-care-associated pneumonia, which includes any patient who was hospitalized in an acute care hospital for 2 or more days within 90 days of the infection; resided in a nursing home or long-term care facility; received recent antibiotic therapy, chemotherapy, or wound care within the past 30 days of the current infection; or attended a hospital or hemodialysis clinic. VAP is the most frequent intensive-care-unit (ICU)-acquired infection among patients receiving mechanical ventilation. In contrast to infections of other frequently involved organs (eg, urinary tract and skin), for which mortality is low, the mortality rate for VAP ranges from 20% to 50% and can reach 70% in some specific settings or when lung infection is caused by high-risk pathogens and/or when initial antibiotic therapy is inappropriate. Although the attributable mortality rate for VAP is still debated, it has been shown that these infections prolong both the duration of ventilation and the duration of ICU stay. These prolonged hospitalizations underscore the considerable financial burden imposed by the development of VAP. The causes of VAP are many and may vary by hospital, patient population, and type of ICU, emphasizing the need for timely, local surveillance data. In many cases infection is caused by multiple-drug-resistant pathogens. Risk factors for such resistant microorganisms are the duration of mechanical ventilation, prior antibiotic treatment, and contact with the health care system. Preventive measures should be guided with regard to a full understanding of pathogenesis and epidemiology. Because respiratory-tract colonization of ICU patients is generally very complex, corresponding to a mix of self-colonization and cross-transmission, only a multifaceted and multidisciplinary program can be effective. Antimicrobial therapy of patients with VAP should follow a 2-stage process. The first stage involves administering broad-spectrum antibiotics to avoid inappropriate treatment in patients with true bacterial pneumonia. The second stage focuses on trying to achieve this objective without overusing and abusing antibiotics, combining a number of different steps, such as stopping therapy in patients with a low probability of the disease, streamlining treatment once the etiologic agent is known, switching to monotherapy after days 3–5, and shortening duration of therapy to 7–8 days, as dictated by the patient's clinical response to therapy and information about the bacteriology of the infection. *Key words: ventilator-associated pneumonia, health care-associated pneumonia, epidemiology, multiple-drug-resistant microorganisms, prevention, fiberoptic bronchoscopy, bronchoalveolar lavage, quantitative culture techniques, antimicrobial therapy.* [Respir Care 2005;50(7):975–983. © 2005 Daedalus Enterprises]

## Introduction

A few months ago, when I was invited to serve as the summarizer for the RESPIRATORY CARE Journal Conference on ventilator-associated pneumonia (VAP), my gut feeling was to refuse, due to the overwhelming complexity of the task. Probably it would have been a very wise and prudent decision, yet the topic has been near and dear to my heart for more than 20 years, since my fellowship in Bichat hospital in Paris. Furthermore, this is such an honor that it was impossible to refuse.

Despite an enormous amount of research and many official statements, the definition, diagnosis, treatment, and prevention of VAP remain controversial. In this summary I will not only present what I took to be the key messages of the conference but also indicate some of the ways we could do a better job for our patients, translating new understandings into improved patient care, based on a synthesis of the proceedings, along with personal observations and editorial remarks.

## Definition and Epidemiology of VAP

Four presentations, by Drs Kollef, Maki, Park, and MacIntyre, were devoted to the definition and epidemiology of the disease. First of all, Marin Kollef pointed out that VAP, which is usually defined as an infection occurring > 48 hours after hospital admission in a patient requiring mechanical ventilation, is in fact an entity that should be viewed as a subcategory of health care-associated pneumonia (HCAP). This point may have very important therapeutic implications, since early-onset VAP, as defined by a prior duration of mechanical ventilation of less than 5 days, can occur in patients with previous contact with the health care system, and thus may need therapy for multiple-drug-resistant bacterial pathogens. HCAP includes any patient who was hospitalized in an acute care hospital for 2 or more days within 90 days of the infection; resided in a nursing home or long-term care facility; received recent antibiotic therapy, chemotherapy, or wound care within the past 30 days of the current infection; or attended a hospital or hemodialysis clinic.<sup>1,2</sup> As underlined by Kollef, the microorganisms responsible for infection in such settings are exactly the same as those observed in

late-onset lung infection, and that type of information should be taken into account for selecting initial antimicrobial treatment.

## Why VAP Is Important

Ventilator-associated pneumonia is the most frequent intensive care unit (ICU)-acquired infection among patients receiving mechanical ventilation.<sup>2,3</sup> In contrast to infections of other frequently involved organs (eg, urinary tract and skin), for which mortality is low, ranging from 1% to 4%, the mortality rate for VAP, defined as pneumonia occurring > 48 hours after endotracheal intubation and mechanical ventilation initiation, ranges from 20% to 50% and can reach 70% in some specific settings or when lung infection is caused by high-risk pathogens.<sup>2-4</sup> Although the attributable mortality rate for VAP is still debated, it has been shown that these infections prolong both the duration of ventilation and the duration of ICU stay.<sup>2,3,5</sup> These prolonged hospitalizations underscore the considerable financial burden imposed by the development of VAP. However, a precise and universal evaluation of such overcosts is very difficult, as underlined by Joseph Solomkin at the end of the conference. Cost analysis is, indeed, dependent on a wide variety of factors, which differ from one country to another, including health care system, organization of the hospital and the ICU, the possibility of patients being treated by private practitioners, cost of antibiotics, and confounding factors such as the responsible pathogen or the severity of the underlying disease. Recently, the extra hospital charges attributed to nosocomial pneumonia occurring in a large data set of United States ICU patients were evaluated to be > \$40,000 United States dollars.<sup>5</sup> Interestingly, approximately 50% of all antibiotics prescribed in an ICU are administered for respiratory-tract infections.<sup>6</sup> Because several studies have shown that appropriate antimicrobial treatment of patients with VAP significantly improves outcome, more rapid identification of infected patients and accurate selection of antimicrobial agents represent important clinical goals.<sup>2,3</sup> All these data were discussed in depth by Drs Kollef, Maki, and Rello and underscore why VAP can so terribly impact patients in the ICU and why its diagnosis, prevention, and treatment are so important.

## Pathogenesis and Prevention

Dennis Maki then talked about the pathogenesis and prevention of VAP in the ICU. Very importantly, he reminded us that preventive measures should be guided with regard to a full understanding of pathogenesis and epidemiology. Thus, we need to be able to precisely define the route of respiratory-tract colonization by Gram-negative bacilli (GNB) in that setting, distinguishing between pa-

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tients in whom colonization originates from endogenous sources, such as the intestinal tract, and those in whom colonization originates from exogenous sources, such as contaminated equipment or other patients colonized with multi-resistant bugs. The intestines are considered the most important endogenous source of microorganisms reaching the respiratory tract via the gastropulmonary route, via colonization of the skin, or via transiently colonized hands of health care workers during tending.<sup>7</sup> The potential importance of exogenous sources of GNB (eg, contaminated equipment) has been repeatedly demonstrated during outbreaks of infections with those organisms.<sup>8</sup> In addition, colonized patients serve as continuous exogenous sources of microorganisms from which other patients can be colonized via cross-acquisition.<sup>9,10</sup> Knowledge about the relative importance of exogenous and endogenous routes of colonization is essential in order to design targeted strategies for infection prevention. Obviously, preventive strategies will be different when either of the 2 routes is dominant. Unfortunately, the relative importance of both routes of colonization in endemic settings has seldom been determined.

For *Pseudomonas aeruginosa* the epidemiology of colonization is generally characterized by polyclonality, with most patients being colonized with unique genotypes of *P. aeruginosa*.<sup>7,11</sup> Respiratory-tract colonization is frequently present on admission, and, when it is acquired in the ICU, the intestinal tract seems to be more important as a source than are cross-acquisition and acquisition from the gastric reservoir. Therefore, increasing compliance with infection-control measures, as well as attempts to interrupt intestinal or gastric colonization, are unlikely to decrease the endemic level of *P. aeruginosa* colonization. Antibiotics providing *P. aeruginosa* with a selective growth advantage are the most important risk factors for acquisition of respiratory-tract colonization. In such circumstances, a regimen that prevents colonization of the upper respiratory tract would be much more effective in preventing VAP. Such an approach has been tested twice, and in both studies oropharyngeal decontamination with nonabsorbable antibiotics significantly reduced the incidence of VAP.<sup>12,13</sup>

The epidemiology of nosocomial respiratory-tract colonization and/or infection with other GNB and even *P. aeruginosa* is, however, often much more complex because of the coexistence of epidemic cases with unrelated sporadic cases caused by different strains, underlining the necessity to use molecular typing to improve the detection of microepidemics amenable to early control.<sup>14–18</sup> For example, in a study of 20 patients with nosocomially acquired *Acinetobacter baumannii* infection, ribotyping of the responsible isolates showed that an epidemic of 11 cases was coexisting with 17 sporadic cases characterized by the diversity of their banding patterns.<sup>14</sup> Using case-control analyses, the only independent risk factor for ep-

idemic *Acinetobacter* infection was to have undergone a surgical procedure in the emergency operating room before being admitted to the ICU, and the only risk factor for sporadic *Acinetobacter* infection was a prior receipt of fluoroquinolone. Without the use of sophisticated molecular techniques to clearly identify which exact microorganism was responsible for each infection, the epidemiology of this outbreak would have been impossible to determine and, therefore, efficacious control measures difficult to implement.

Neil MacIntyre then reviewed the relationship between ventilator-induced lung injury and VAP; that is, can lung-protective management strategy increase the rate of VAP or not? The recent National Institutes of Health ARDS [acute respiratory distress syndrome] Network randomized trial demonstrated that, in patients with acute lung injury or ARDS, ventilation with a tidal volume of 6 mL/kg of predicted body weight reduced mortality to 31%, compared with a mortality rate of 40% in patients treated with a tidal volume of 12 mL/kg.<sup>19</sup> Organ-failure-free days also were significantly improved. Although there are several potential reasons for some clinicians not adopting the 6 mL/kg ventilation strategy, one possibility is that some physicians are concerned that use of the protocol will necessitate an increase in the need for supportive therapies, including sedation and neuromuscular blockade, and/or will increase the total amount of fixed atelectasis. These potential effects are of particular concern, since prolonged sedation can complicate assessment of neurologic dysfunction, can increase utilization of unnecessary diagnostic studies, and may lead to delayed extubation and worse clinical outcomes. Similarly, an increased use of neuromuscular blocking agents could be complicated by prolonged paralysis or diffuse atrophic myopathy, particularly in the setting of administration of corticosteroids, thus increasing the risk for VAP. In fact, as demonstrated in a subgroup analysis of the ARDS Network trial, when compared with a tidal volume of 12 mL/kg predicted body weight, ventilation with a protocol of 6 mL/kg was not associated with adverse effects on hemodynamics or an increased need for sedation and neuromuscular blockade.<sup>20</sup> Therefore, concerns regarding adverse effects of treatment with the 6 mL/kg predicted body weight tidal volume protocol on supportive care requirements should not preclude its use in patients with acute lung injury or ARDS.

### Microbiology of VAP

David Park then talked about the microbiology of VAP, discussing 3 major points:

1. The causes of VAP are many and may vary by hospital, patient population, and type of ICU, emphasizing the need for timely, local surveillance data.

2. Infection is caused by multiple-drug-resistant pathogens in many cases.

3. Resistant microorganisms can usually be predicted by the duration of mechanical ventilation, the length of stay before the onset of VAP, and other risk factors such as prior antibiotic treatment and contact with the health care system.

*Legionella* species, anaerobes, fungi, and even viruses should be mentioned as potential causative agents, but are not considered to be common in the context of pneumonia acquired during mechanical ventilation. However, several of these causative agents may be more common, and potentially underreported because of difficulties involved with the diagnostic techniques used to identify them, including anaerobic bacteria and viruses.<sup>21,22</sup> By examining currently available data, the clinical importance of anaerobes in the pathogenesis and outcome of VAP remains unclear, except as etiologic agents in patients with necrotizing pneumonia, lung abscess, or pleuropulmonary infections.<sup>23</sup> Isolation of fungi, most frequently *Candida* species, at substantial concentrations poses interpretative problems. Invasive disease has been reported in VAP, but more frequently yeasts are isolated from respiratory-tract specimens in the apparent absence of disease. One prospective study examined the relevance of isolating *Candida* species from 25 non-neutropenic patients who had been mechanically ventilated for at least 72 hours.<sup>24</sup> Just after death, multiple culture and biopsy specimens were obtained with bronchoscopic techniques. Although 10 patients had at least one biopsy specimen positive for *Candida* species, only 2 had evidence of invasive pneumonia as demonstrated by histologic examination. Many of the endotracheal aspirates, protected-specimen-brush specimens, and bronchoalveolar lavage specimens also yielded positive cultures for *Candida* species, sometimes in high concentrations, but they did not contribute to diagnosing invasive disease. Based on these data and other studies,<sup>25</sup> the use of the commonly available respiratory sampling methods (bronchoscopic or nonbronchoscopic) in mechanically ventilated patients appears insufficient for the diagnosis of *Candida* pneumonia. At present, the only sure method to establish that *Candida* is the primary lung pathogen is to demonstrate yeast or pseudohyphae in a lung biopsy. Probably, a lot of drugs active against *Candida* are prescribed in the ICU without any benefit for patients, physicians misinterpreting the presence of *Candida* in respiratory secretions as being the etiological agent of pneumonia.

The incidence of VAP caused by viruses is also low in immunocompetent hosts. Outbreaks of VAP and HCAP due to viruses such as influenza A and B, parainfluenza, adenovirus, measles, and respiratory syncytial virus have, however, been reported and are usually seasonal. Influenza is transmitted directly from person to person when infected persons sneeze, cough, or talk, and is highly con-

tagious. The use of influenza vaccine, along with prophylaxis and early anti-viral therapy of at-risk health care workers dramatically reduces spread of influenza within the hospital and health care facilities and should be proposed to all health care workers working in the ICU, since influenza infection could have dramatic consequences in patients requiring mechanical ventilation. Herpes simplex virus is occasionally detected in the lower respiratory tract of ICU patients, but its clinical importance in such situations remains unclear.<sup>22</sup> In most patients the herpes virus is probably only a bystander, but in some cases, for example in patients with ARDS, it could be responsible for tracheo-bronchitis and/or bronchopneumonia and leads to clinical deterioration.

### Recommendations for VAP Prevention: A Personal Recipe

Certainly, no conference on how to do the best for patients in the ICU could be held without a serious and in-depth discussion on how to prevent VAP. I was very impressed by the work done by Richard Branson, Dennis Maki, Dean Hess, Jordi Rello, and Richard Kallet; they reviewed all the literature concerning modifiable risk factors and respiratory care for the prevention of VAP and presented a very detailed and comprehensive discussion of each potential prophylactic measure. I would like to encourage everybody interested in this issue to carefully read their articles.

Because respiratory-tract colonization of ICU patients is generally very complex, corresponding to a mix of self-colonization and cross-transmission, only a multifaceted and multidisciplinary program can be effective. The efficiency of such a program, based on a bundle of 14 preventive measures that should be taken simultaneously, was nicely demonstrated by Zack et al in a pre-intervention and post-intervention observational study conducted in 5 ICUs in Barnes-Jewish Hospital.<sup>26</sup> Following implementation of the education module, the rate of VAP decreased from 12.6 per 1,000 ventilator days in the 12 months before the intervention, to 5.7 per 1,000 ventilator days—a decrease of 58% ( $p < 0.001$ ). The estimated cost savings secondary to the decreased rate of VAP for the 12 months following the intervention were between \$425,606 and \$4.05 million.

My personal recipe is summarized in Table 1 and includes 12 specific measures. I would like to emphasize some of them. First of all, a large number of studies show that overcrowding, understaffing, or a misbalance between work load and resources are important determinants of nosocomial infections and cross-transmission of microorganisms in the hospital.<sup>27–29</sup> Importantly, not only the number of staff but also the level of their training affect outcomes. The causal pathway between understaffing and infection is complex, and factors might include lack of

Table 1. ICU Policy for the Prevention of Ventilator-Associated Pneumonia: A Personal Recipe

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1. Assure adequate intensive care unit staffing levels.<sup>27-29</sup>
2. Immunize health care workers for influenza.<sup>1</sup>
3. Implement hand hygiene with alcohol rubs.<sup>1,30,31</sup>
4. Adopt an antibiotic policy restricting the prescription of broad-spectrum agents and useless antibiotics by implementing strict guidelines, avoiding treating patients without bacterial infection, using narrow-spectrum antibiotics whenever possible, and reducing the duration of treatment.<sup>32-34</sup>
5. Follow a restrictive transfusion trigger policy.<sup>35</sup>
6. Reduce as much as possible the duration of mechanical ventilation (a major risk factor for ventilator-associated pneumonia), using:
  - Improved methods of sedation and avoidance of paralytic agents<sup>36</sup>
  - Protocols to facilitate and accelerate weaning<sup>37,38</sup>
  - Intensive insulin therapy, with tight control of blood glucose level<sup>39</sup>
  - Noninvasive mechanical ventilation whenever possible<sup>40</sup>
7. Avoid nasal insertion of endotracheal and gastric tubes to minimize the risk of nosocomial sinusitis.<sup>41</sup>
8. Maintain endotracheal tube cuff pressure above 20 cm H<sub>2</sub>O, to prevent leakage of bacteria around the cuff into the lower respiratory tract.<sup>42</sup>
9. Reintubate promptly patients who would inexorably fail extubation.<sup>43</sup>
10. Keep patients in the semirecumbent position, especially in case of enteral nutrition.<sup>44</sup>
11. Provide adequate oral hygiene with an antiseptic such as chlorhexidine.<sup>45</sup>
12. Use a heat-and-moisture exchanger or heated-wire circuit instead of a conventional active humidifier to prevent formation of contaminated tubing condensates and their inadvertent flushing into the lower airways.<sup>46</sup>

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time to comply with infection control recommendations, job dissatisfaction, job-related burnout, absenteeism, and a high staff turnover. The evidence that cost-driven downsizing and changes in staffing patterns cause harm to patients cannot be ignored and should not be considered as an inevitable outcome. We need to put the pressure on the hospital administration. It is not always our fault if we observe a lot of infection in the ICU: we need more people in the ICU and more educated people.

Second, while hand disinfection remains uncontested as the most important infection-control practice, physicians and nurse compliance with this procedure remains low in most hospitals. Because hand-rubbing with an alcohol-based solution is substantially more efficient in reducing hand contamination than is hand-washing with antiseptic soap, and considerably reduces time needed for hand disinfection, this method should be highly promoted in the ICU.<sup>1,30,31</sup>

Specific strategies aimed at reducing the duration of mechanical ventilation (a major risk factor for VAP), such as improved methods of sedation,<sup>36</sup> use of protocols to facilitate and accelerate weaning,<sup>37,38</sup> and intensive insulin therapy with tight control of blood glucose level,<sup>39</sup> should be considered integral parts of any infection-control program. All are based on the application of strict protocols. In the study by van den Berghe et al, when compared to the control group, patients treated with intensive insulin therapy had a 46% reduction of bloodstream infections; decreased frequency of acute renal failure requiring dialysis by 41%; fewer antibiotic treatment days; and significantly shorter length of mechanical ventilation, ICU stay, and mortality.<sup>39</sup> Similarly, noninvasive positive-pressure ventilation using a face mask should be employed whenever possible.<sup>40</sup>

Adoption of an antibiotic policy restricting the prescription of broad-spectrum agents and useless antibiotics is of major importance. Several studies clearly demonstrated that the use of antibiotics in the hospital setting was associated with an increased risk of nosocomial pneumonia and selection of resistant pathogens.<sup>47-50</sup> Better utilization of antibiotics in the ICU can be achieved by implementing strict guidelines, avoiding treating patients without bacterial infection, using narrow-spectrum antibiotics whenever possible, and reducing the duration of treatment.<sup>32,33</sup> On the same line, transfusion of red blood cells and other allogenic blood products should follow a strict restricted transfusion trigger policy, since multiple studies have identified exposure to allogenic blood products as a risk factor for postoperative infection and pneumonia.<sup>35,51</sup>

Finally, some very simple, safe, inexpensive, and logical measures, including avoiding nasal insertion of endotracheal and gastric tubes;<sup>41</sup> maintaining the endotracheal tube cuff pressure above 20 cm H<sub>2</sub>O to prevent leakage of bacteria around the cuff into the lower respiratory tract;<sup>42</sup> prompt reintubation of patients who would inexorably fail extubation;<sup>43</sup> keeping patients in the semirecumbent position, especially in case of enteral nutrition;<sup>44</sup> removal of tubing condensate;<sup>46</sup> and providing adequate oral hygiene with an antiseptic, such as chlorhexidine,<sup>45</sup> may have tremendous impact on the frequency of VAP in mechanically ventilated patients.<sup>1,2</sup>

### Diagnosis and Treatment

Drs Niederman, Park, Rello, Solomkin, and I then talked about the diagnosis and management of VAP—2 very controversial topics. We all, however, agree that the major

goals of any management strategy of patients with true VAP are early, appropriate antibiotics in adequate doses, while avoiding excessive antibiotics and the emergence of multiple-drug-resistant strains.<sup>2,3</sup> The only way to do that is to follow 3 steps:

1. To obtain a lower-respiratory-tract sample for culture (quantitative or semiquantitative) and microscopy before introduction of new antibiotics.

2. To immediately start empiric antimicrobial treatment, unless there are both a negative microscopy and no signs of severe sepsis.

3. To re-evaluate treatment on day 2 or 3, based on microbiologic cultures results and clinical outcome.

Very importantly also, ICU physicians should understand the differences between an *appropriate* treatment and an *adequate* treatment. Appropriate is matching antibiotic susceptibilities to the antibiotic used. To achieve adequate therapy it is necessary to use not only the correct antibiotic, but also the optimal dose and the correct route of administration (oral, intravenous, or aerosol) to assure that the antibiotic penetrates to the site of infection, and that combination therapy is used if necessary. Many antibiotics in the ICU are incorrectly used, being administered at too low doses, promoting the emergence of resistant strains and decreasing their potential efficacy.

Based on this background, antimicrobial treatment of patients with VAP could be outlined in 6 steps, as summarized in Table 2. The first one is starting treatment using broad-spectrum antibiotics. Because of the emergence of multiresistant GNB, such as *Pseudomonas aeruginosa* and/or extended-spectrum beta-lactamase-producing *Klebsiella pneumoniae* in many institutions, and the increasing role played by Gram-positive bacteria such as methicillin-resistant *Staphylococcus aureus* (MRSA), empirical treatment with broad-spectrum antibiotics is justified in most patients with a clinical suspicion of HCAP.<sup>3,4</sup> The choice of agents should be based on local patterns of antimicrobial susceptibility, and anticipated adverse effects, and should also take into account which therapies patients have recently received (within the past 2 weeks), striving not to repeat the same antimicrobial class, if possible.<sup>59</sup> Having a current and frequently-updated knowledge of local bacteriologic patterns can increase the likelihood that appropriate initial antibiotic treatment will be prescribed.<sup>60</sup> Only patients with early-onset infection and no specific risk factors, such as prolonged duration of hospitalization, admission from a health care-related facility, and recent prolonged antibiotic therapy, can be treated with a narrow-spectrum drug, such as a nonpseudomonal third-generation cephalosporin.<sup>2</sup>

Because clinical signs of infection are nonspecific and can be caused by any condition associated with an inflammatory response, many more patients than necessary are initially treated with antibiotics. Thus, it is important to

use serial clinical evaluations and microbiologic data to re-evaluate therapy after 48–72 hours, in order to be able to stop therapy if infection becomes unlikely. To reach this objective, all diagnostic strategies that are designed for managing patients with a clinical VAP suspicion should make explicit the decision tree they utilize to identify patients with a low probability of infection and thus to stop therapy when infection appears improbable.

For many patients with VAP, including those with late-onset infection, therapy can be narrowed once the results of respiratory tract and blood cultures become available, because an anticipated organism (such as *P. aeruginosa*, *Acinetobacter* species, or MRSA) was not recovered or because the organism isolated is sensitive to a less-broad-spectrum antibiotic than used in the initial regimen. For example, vancomycin and linezolid should be stopped if no MRSA is identified, unless the patient is allergic to beta-lactams and has developed an infection caused by a Gram-positive microorganism. Very-broad-spectrum agents, such as carbapenems, piperacillin-tazobactam, and/or cefepime should also be restricted to patients with infection caused by pathogens only susceptible to these agents.

The commonly cited reason to use combination therapy is to achieve synergy in the therapy of *P. aeruginosa* or other difficult-to-treat GNB. However, synergy has been clearly documented to be valuable only in vitro and in patients with neutropenia<sup>61</sup> or bacteremic infection,<sup>62,63</sup> which is uncommon in VAP.<sup>3</sup> A recent meta-analysis has evaluated all prospective randomized trials of beta-lactam monotherapy compared to beta-lactam-aminoglycoside combination regimens in patients with sepsis, of which at least 1,200 of the reported 7,586 patients had either HCAP or VAP.<sup>56</sup> In this evaluation, clinical failure rate was similar with combination therapy, and there was no advantage in the therapy of *P. aeruginosa* infections, compared to monotherapy. In addition, combination therapy did not prevent the emergence of resistance during therapy, but did lead to a significantly higher rate of nephrotoxicity. Based on these data, therapy could be switched to monotherapy in most patients after 3 or 5 days, provided that initial therapy was appropriate, clinical course appears favorable, and that microbiological data do not point to a very difficult-to-treat microorganism, with a very high in vitro minimal inhibitory concentration, as can be observed with some nonfermenting GNB.

Efforts to reduce the duration of therapy for VAP are justified by studies of the natural history of the response to therapy. Dennesen et al demonstrated that when VAP was adequately treated, significant improvements were observed for all clinical variables, generally within the first 6 days after the start of antibiotics.<sup>64</sup> The consequence of prolonged therapy to 14 days or more was newly acquired colonization, especially with *P. aeruginosa* and *Enterobac-*

## CONFERENCE SUMMARY: VENTILATOR-ASSOCIATED PNEUMONIA

Table 2. Proposed Strategy for Conducting Antimicrobial Therapy in Patients With VAP

Proposed Strategy	Rationale
Step 1: Start therapy using broad-spectrum antibiotics	Because of the emergence of multiresistant Gram-negative bacteria, such as <i>Pseudomonas aeruginosa</i> and extended-spectrum beta-lactamase-producing Gram-negative bacteria in many institutions, and the increasing role played by methicillin-resistant <i>Staphylococcus aureus</i> , empirical treatment with broad-spectrum antibiotics is justified in most patients with a clinical suspicion of VAP. <sup>2,49</sup>
Step 2: Stop therapy if the diagnosis of infection becomes unlikely	Because clinical signs of infection are nonspecific and can be caused by any condition associated with an inflammatory response, many more patients than necessary are initially treated with antibiotics. <sup>52</sup>
Step 3: Use narrower-spectrum drugs once the agent of infection is identified	For many patients with VAP, including those with late-onset infection, therapy can be narrowed once the results of respiratory tract and blood cultures become available, because an anticipated organism (such as <i>Pseudomonas aeruginosa</i> , <i>Acinetobacter</i> species, or methicillin-resistant <i>Staphylococcus aureus</i> ) was not recovered or because the organism isolated is sensitive to a less-broad-spectrum antibiotic than used in the initial regimen. <sup>52,53</sup>
Step 4: Use pharmacokinetic-pharmacodynamic data to optimize treatment	Clinical and bacteriologic outcomes can be improved by optimizing the therapeutic regimen according to pharmacokinetic-pharmacodynamic properties of the agent(s) selected for treatment. <sup>54,55</sup>
Step 5: Switch to monotherapy on days 3–5	There are no clinical benefits to using a regimen combining 2 antibiotics after days 3–5, provided that initial therapy was appropriate, clinical course appears favorable, and that microbiological data do not point to a very-difficult-to-treat microorganism. <sup>56,57</sup>
Step 6: Shorten the duration of therapy	Reducing duration of therapy in patients with VAP has led to good outcomes with less antibiotic use. Prolonged therapy simply leads to colonization with antibiotic-resistant bacteria, which may precede a recurrent episode of VAP. <sup>34,58</sup>

VAP = ventilator-associated pneumonia

*teriaceae*, generally during the second week of therapy. These data support the premise that most patients with VAP who receive appropriate antimicrobial therapy have a good clinical response within the first 6 days.<sup>64–66</sup> Prolonged therapy simply leads to colonization with antibiotic-resistant bacteria, which may precede a recurrent episode of VAP. A recent multicenter, randomized controlled trial in a large series of 413 patients with microbiologically-proven VAP demonstrated that patients who received appropriate, initial empiric therapy for 8 days had similar outcomes to patients who received therapy for 15 days.<sup>34</sup> A trend to greater rates of relapse for short-duration therapy was seen if the etiologic agent was *P. aeruginosa* or *Acinetobacter* species, but clinical outcomes were exactly the same. These results were recently confirmed by 2 other studies, including a prospective, randomized trial of 290 patients evaluating an antibiotic discontinuation policy.<sup>58,67</sup>

### Summary

This conference brought together a diverse and stimulating group of investigators and clinicians with broad expertise and a dedication to improve the care of ICU patients who require mechanical ventilation and are exposed to the risk of developing VAP. I believe it succeeded in its goals and that the documents developed from it, as well as

the recently published guidelines endorsed by the American Thoracic Society and the Infectious Diseases Society of America,<sup>2</sup> will prove valuable to clinicians who deal with VAP and to their patients who suffer from this disease. Persistently high mortality rates for pneumonia in the ICU argue, however, for the continued reassessment of our current therapeutic modalities and design of better protocols. More active and less toxic antibacterial agents are still needed, especially for some problematic pathogens, such as multiresistant nonfermenting GNB and MRSA.

The conference co-chairs and the American Respiratory Care Foundation have done a superb job in facilitating the process of this conference, and it has been an honor and a privilege for me—as well as a challenge—to bring it to a conclusion.

### REFERENCES

1. Tablan OC, Anderson LJ, Besser R, Bridges C, Hajjeh R; CDC; Healthcare Infection Control Practices Advisory Committee. Guidelines for preventing health-care-associated pneumonia, 2003. Recommendations of CDC and the Healthcare Infection Control Practices Advisory Committee. *MMWR Recomm Rep* 2004;53(RR-3): 1–36.
2. American Thoracic Society; Infectious Diseases Society of America. Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. *Am J Respir Crit Care Med* 2005;171(4):388–416.

3. Chastre J, Fagon JY. Ventilator-associated pneumonia. *Am J Respir Crit Care Med* 2002;165(7):867-903.
4. National Nosocomial Infections Surveillance (NNIS) System report, data summary from January 1990-May 1999, issued June 1999. *Am J Infect Control* 1999;27(6):520-532.
5. Rello J, Ollendorf DA, Oster G, Vera-Llonch M, Bellm L, Redman R, et al. Epidemiology and outcomes of ventilator-associated pneumonia in a large US database. *Chest* 2002;122(6):2115-2121.
6. Bergmans DC, Bonten MJ, Gaillard CA, van Tiel FH, van der Geest S, de Leeuw PW, Stobberingh EE. Indications for antibiotic use in ICU patients: a one-year prospective surveillance. *J Antimicrob Chemother* 1997;39(4):527-535.
7. Bonten MJ, Bergmans DC, Speijer H, Stobberingh EE. Characteristics of polyclonal endemicity of *Pseudomonas aeruginosa* colonization in intensive care units: implications for infection control. *Am J Respir Crit Care Med* 1999;160(4):1212-1219.
8. Craven DE, Lichtenberg DA, Goularte TA, Make BJ, McCabe WR. Contaminated medication nebulizers in mechanical ventilator circuits: source of bacterial aerosols. *Am J Med* 1984;77(5):834-838.
9. Maki DG. Control of colonization and transmission of pathogenic bacteria in the hospital. *Ann Intern Med* 1978;89(5 Pt 2 Suppl):777-780.
10. Thuong M, Arvaniti K, Ruimy R, de la Salmoniere P, Scanvic-Hameg A, Lucet JC, Regnier B. Epidemiology of *Pseudomonas aeruginosa* and risk factors for carriage acquisition in an intensive care unit. *J Hosp Infect* 2003;53(4):274-282.
11. Pirnay JP, De Vos D, Cochez C, Bilocq F, Pirson J, Struelens M, et al. Molecular epidemiology of *Pseudomonas aeruginosa* colonization in a burn unit: persistence of a multidrug-resistant clone and a silver sulfadiazine-resistant clone. *J Clin Microbiol* 2003;41(3):1192-1202.
12. Pugin J, Auckenthaler R, Lew DP, Suter PM. Oropharyngeal decontamination decreases incidence of ventilator-associated pneumonia: a randomized, placebo-controlled, double-blind clinical trial. *JAMA* 1991;265(20):2704-2710.
13. Bonten MJ, Gaillard CA, Johanson WG Jr, van Tiel FH, Smeets HG, van der Geest S, Stobberingh EE. Colonization in patients receiving and not receiving topical antimicrobial prophylaxis. *Am J Respir Crit Care Med* 1994;150(5 Pt 1):1332-1340.
14. Villers D, Espaze E, Coste-Burel M, Giauffret F, Ninin E, Nicolas F, Richet H. Nosocomial *Acinetobacter baumannii* infections: microbiological and clinical epidemiology. *Ann Intern Med* 1998;129(3):182-189.
15. Hartstein AI, Morthland VH, Rourke JW Jr, Freeman J, Garber S, Sykes R, Rashad AL. Plasmid DNA fingerprinting of *Acinetobacter calcoaceticus* subspecies *anitratus* from intubated and mechanically ventilated patients. *Infect Control Hosp Epidemiol* 1990;11(10):531-538.
16. Biendo M, Laurans G, Lefebvre JF, Daoudi F, Eb F. Epidemiological study of an *Acinetobacter baumannii* outbreak by using a combination of antibiotyping and ribotyping. *J Clin Microbiol* 1999;37(7):2170-2175.
17. Wisplinghoff H, Perbix W, Seifert H. Risk factors for nosocomial bloodstream infections due to *Acinetobacter baumannii*: a case-control study of adult burn patients. *Clin Infect Dis* 1999;28(1):59-66.
18. Bergmans DC, Bonten MJ, van Tiel FH, Gaillard CA, van der Geest S, Wilting RM, et al. Cross-colonisation with *Pseudomonas aeruginosa* of patients in an intensive care unit. *Thorax* 1998;53(12):1053-1058.
19. The Acute Respiratory Distress Syndrome Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *N Engl J Med* 2000;342(18):1301-1308.
20. Cheng IW, Eisner MD, Thompson BT, Ware LB, Matthay MA; Acute Respiratory Distress Syndrome Network. Acute effects of tidal volume strategy on hemodynamics, fluid balance, and sedation in acute lung injury. *Crit Care Med* 2005;33(1):63-70; discussion 239-240.
21. Dore P, Robert R, Grollier G, Rouffineau J, Lanquetot H, Charriere JM, Fauchere JL. Incidence of anaerobes in ventilator-associated pneumonia with use of a protected specimen brush. *Am J Respir Crit Care Med* 1996;153(4 Pt 1):1292-1298.
22. Bruynseels P, Jorens PG, Demey HE, Goossens H, Pattyn SR, Elseviers MM, et al. Herpes simplex virus in the respiratory tract of critical care patients: a prospective study. *Lancet* 2003;362(9395):1536-1541.
23. Marik PE, Careau P. The role of anaerobes in patients with ventilator-associated pneumonia and aspiration pneumonia: a prospective study. *Chest* 1999;115(1):178-183.
24. el-Ebiary M, Torres A, Fabregas N, de la Bellacasa JP, Gonzalez J, Ramirez J, et al. Significance of the isolation of *Candida* species from respiratory samples in critically ill, non-neutropenic patients: an immediate postmortem histologic study. *Am J Respir Crit Care Med* 1997;156(2 Pt 1):583-590.
25. Rello J, Esandi ME, Diaz E, Mariscal D, Gallego M, Valles J. The role of *Candida* sp isolated from bronchoscopic samples in nonneutropenic patients. *Chest* 1998;114(1):146-149.
26. Zack JE, Garrison T, Trovillion E, Clinkscale D, Coopersmith CM, Fraser VJ, Kollef MH. Effect of an education program aimed at reducing the occurrence of ventilator-associated pneumonia. *Crit Care Med* 2002;30(11):2407-2412.
27. Harbarth S, Sudre P, Dharan S, Cadenas M, Pittet D. Outbreak of *Enterobacter cloacae* related to understaffing, overcrowding, and poor hygiene practices. *Infect Control Hosp Epidemiol* 1999;20(9):598-603.
28. Hugonnet S, Harbarth S, Sax H, Duncan RA, Pittet D. Nursing resources: a major determinant of nosocomial infection? *Curr Opin Infect Dis* 2004;17(4):329-333.
29. Needleman J, Buerhaus P, Mattke S, Stewart M, Zelevinsky K. Nurse-staffing levels and the quality of care in hospitals. *N Engl J Med* 2002;346(22):1715-1722.
30. Pittet D, Mourouga P, Perneger TV. Compliance with handwashing in a teaching hospital. *Infection Control Program. Ann Intern Med* 1999;130(2):126-130.
31. Girou E, Loyeau S, Legrand P, Oppein F, Brun-Buisson C. Efficacy of handrubbing with alcohol based solution versus standard handwashing with antiseptic soap: randomised clinical trial. *BMJ* 2002;325(7360):362.
32. Kollef MH. Optimizing antibiotic therapy in the intensive care unit setting. *Crit Care* 2001;5(4):189-195.
33. Struelens MJ, Byl B, Vincent JL. Antibiotic policy: a tool for controlling resistance of hospital pathogens. *Clin Microbiol Infect* 1999;5 Suppl 1:S19-S24.
34. Chastre J, Wolff M, Fagon JY, Chevret S, Thomas F, Wermert D, et al. Comparison of 8 vs 15 days of antibiotic therapy for ventilator-associated pneumonia in adults: a randomized trial. *JAMA* 2003;290(19):2588-2598.
35. Shorr AF, Duh MS, Kelly KM, Kollef MH; CRIT Study Group. Red blood cell transfusion and ventilator-associated pneumonia: a potential link? *Crit Care Med* 2004;32(3):666-674.
36. Kress JP, Pohlman AS, O'Connor MF, Hall JB. Daily interruption of sedative infusions in critically ill patients undergoing mechanical ventilation. *N Engl J Med* 2000;342(20):1471-1477.
37. Ely EW, Baker AM, Dunagan DP, Burke HL, Smith AC, Kelly PT, et al. Effect on the duration of mechanical ventilation of identifying patients capable of breathing spontaneously. *N Engl J Med* 1996;335(25):1864-1869.

38. Kollef MH, Shapiro SD, Silver P, St John RE, Prentice D, Sauer S, et al. A randomized, controlled trial of protocol-directed versus physician-directed weaning from mechanical ventilation. *Crit Care Med* 1997;25(4):567-474.
39. van den Berghe G, Wouters P, Weekers F, Verwaest C, Bruyninckx F, Schetz M, et al. Intensive insulin therapy in the critically ill patients. *N Engl J Med* 2001;345(19):1359-1367.
40. Girou E, Schortgen F, Delclaux C, Brun-Buisson C, Blot F, Lefort Y, et al. Association of noninvasive ventilation with nosocomial infections and survival in critically ill patients. *JAMA* 2000;284(18):2361-2367.
41. Rouby JJ, Laurent P, Gosnach M, Cambau E, Lamas G, Zouaoui A, et al. Risk factors and clinical relevance of nosocomial maxillary sinusitis in the critically ill. *Am J Respir Crit Care Med* 1994;150(3):776-783.
42. Rello J, Sonora R, Jubert P, Artigas A, Rue M, Valles J. Pneumonia in intubated patients: role of respiratory airway care. *Am J Respir Crit Care Med* 1996;154(1):111-115.
43. Torres A, Gatell JM, Aznar E, el-Ebiary M, Puig de la Bellacasa J, Gonzalez J, et al. Re-intubation increases the risk of nosocomial pneumonia in patients needing mechanical ventilation. *Am J Respir Crit Care Med* 1995;152(1):137-141.
44. Drakulovic MB, Torres A, Bauer TT, Nicolas JM, Nogue S, Ferrer M. Supine body position as a risk factor for nosocomial pneumonia in mechanically ventilated patients: a randomised trial. *Lancet* 1999;354(9193):1851-1858.
45. DeRiso AJ 2nd, Ladowski JS, Dillon TA, Justice JW, Peterson AC. Chlorhexidine gluconate 0.12% oral rinse reduces the incidence of total nosocomial respiratory infection and nonprophylactic systemic antibiotic use in patients undergoing heart surgery. *Chest* 1996;109(6):1556-1561.
46. Craven DE, Goularte TA, Make BJ. Contaminated condensate in mechanical ventilator circuits: a risk factor for nosocomial pneumonia? *Am Rev Respir Dis* 1984;129(4):625-628.
47. Rello J, Ausina V, Ricart M, Castella J, Prats G. Impact of previous antimicrobial therapy on the etiology and outcome of ventilator-associated pneumonia. *Chest* 1993;104(4):1230-1235.
48. Kollef MH. Ventilator-associated pneumonia: a multivariate analysis. *JAMA* 1993;270(16):1965-1970.
49. Trouillet JL, Chastre J, Vuagnat A, Joly-Guillou ML, Combaux D, Dombret MC, Gibert C. Ventilator-associated pneumonia caused by potentially drug-resistant bacteria. *Am J Respir Crit Care Med* 1998;157(2):531-539.
50. Gruson D, Hilbert G, Vargas F, Valentino R, Bebear C, Allery A, et al. Rotation and restricted use of antibiotics in a medical intensive care unit: impact on the incidence of ventilator-associated pneumonia caused by antibiotic-resistant Gram-negative bacteria. *Am J Respir Crit Care Med* 2000;162(3 Pt 1):837-843.
51. Leal-Noval SR, Marquez-Vacaro JA, Garcia-Curiel A, Camacho-Larana P, Rincon-Ferrari MD, Ordonez-Fernandez A, et al. Nosocomial pneumonia in patients undergoing heart surgery. *Crit Care Med* 2000;28(4):935-940.
52. Chastre J, Fagon JY. Pneumonia in the ventilator-dependent patient. In: Tobin MJ, editor. *Principles and practice of mechanical ventilation*. New York: McGraw-Hill; 1994:857-890.
53. Rello J, Vidaur L, Sandiumenge A, Rodriguez A, Gualis B, Boque C, Diaz E. De-escalation therapy in ventilator-associated pneumonia. *Crit Care Med* 2004;32(11):2183-2190.
54. Schentag JJ. Antimicrobial action and pharmacokinetics/pharmacodynamics: the use of AUC to improve efficacy and avoid resistance. *J Chemother* 1999;11(6):426-439.
55. Kashuba AD, Nafziger AN, Drusano GL, Bertino JS Jr. Optimizing aminoglycoside therapy for nosocomial pneumonia caused by Gram-negative bacteria. *Antimicrob Agents Chemother* 1999;43(3):623-629.
56. Paul M, Benuri-Silbiger I, Soares-Weiser K, Leibovici L. Beta lactam monotherapy versus beta lactam-aminoglycoside combination therapy for fever with neutropenia: systematic review and meta-analysis. *BMJ* 2004;328(7441):668. Erratum in: *BMJ* 2004 10; 328(7444):884.
57. Chamot E, Boffi El Amari E, Rohner P, Van Delden C. Effectiveness of combination antimicrobial therapy for *Pseudomonas aeruginosa* bacteremia. *Antimicrob Agents Chemother* 2003;47(9):2756-2764.
58. Micek ST, Ward S, Fraser VJ, Kollef MH. A randomized controlled trial of an antibiotic discontinuation policy for clinically suspected ventilator-associated pneumonia. *Chest* 2004;125(5):1791-1799.
59. Trouillet JL, Vuagnat A, Combes A, Kassis N, Chastre J, Gibert C. *Pseudomonas aeruginosa* ventilator-associated pneumonia: comparison of episodes due to piperacillin-resistant versus piperacillin-susceptible organisms. *Clin Infect Dis* 2002;34(8):1047-1054.
60. Rello J, Sa-Borges M, Correa H, Leal SR, Baraibar J. Variations in etiology of ventilator-associated pneumonia across four treatment sites: implications for antimicrobial prescribing practices. *Am J Respir Crit Care Med* 1999;160(7):608-613.
61. The EORTC International Antimicrobial Therapy Cooperative Group. Ceftazidime combined with a short or long course of amikacin for empirical therapy of Gram-negative bacteremia in cancer patients with granulocytopenia. *N Engl J Med* 1987;317(27):1692-1698.
62. Hilf M, Yu VL, Sharp J, Zuravleff JJ, Korvick JA, Muder RR. Antibiotic therapy for *Pseudomonas aeruginosa* bacteremia: outcome correlations in a prospective study of 200 patients. *Am J Med* 1989;87(5):540-546.
63. Korvick JA, Bryan CS, Farber B, Beam TR, Schenfeld L, Muder RR, et al. Prospective observational study of *Klebsiella* bacteremia in 230 patients: outcome for antibiotic combinations versus monotherapy. *Antimicrob Agents Chemother* 1992;36(12):2639-2644.
64. Dennesen PJ, van der Ven AJ, Kessels AG, Ramsay G, Bonten MJ. Resolution of infectious parameters after antimicrobial therapy in patients with ventilator-associated pneumonia. *Am J Respir Crit Care Med* 2001;163(6):1371-1375.
65. Luna CM, Blanzaco D, Niederman MS, Matarucco W, Baredes NC, Desmery P, et al. Resolution of ventilator-associated pneumonia: prospective evaluation of the clinical pulmonary infection score as an early clinical predictor of outcome. *Crit Care Med* 2003;31(3):676-682.
66. Combes A, Figliolini C, Trouillet JL, Kassis N, Dombret MC, Wolff M, et al. Factors predicting ventilator-associated pneumonia recurrence. *Crit Care Med* 2003;31(4):1102-1107.
67. Ibrahim EH, Ward S, Sherman G, Schaiff R, Fraser VJ, Kollef MH. Experience with a clinical guideline for the treatment of ventilator-associated pneumonia. *Crit Care Med* 2001;29(6):1109-1115.