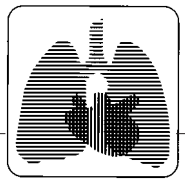

consensus conference

International Conference for the Development of Consensus on the Diagnosis and Treatment of Ventilator-Associated Pneumonia*

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Ventilator-associated pneumonia (VAP) is an important health problem that still generates great controversy. A consensus conference attended by 12 researchers from Europe and Latin America was held to discuss strategies for the diagnosis and treatment of VAP. Commonly asked questions concerning VAP management were selected for discussion by the participating researchers. Possible answers to the questions were presented to the researchers, who then recorded their preferences anonymously. This was followed by open discussion when the results were known. In general, peers thought that early microbiological examinations are warranted and contribute to improving the use of antibiotherapy. Nevertheless, no consensus was reached regarding choices of antimicrobial agents or the optimal duration of therapy. Piperacillin/tazobactam was the preferred choice for empiric therapy, followed by a cephalosporin with antipseudomonal activity and a carbapenem. All the peers agreed that the pathogens causing VAP and multiresistance patterns in their ICUs were substantially different from those reported in studies in the United States. Pathogens and multiresistance patterns also varied from researcher to researcher inside the group. Consensus was reached on the importance of local epidemiology surveillance programs and on the need for customized empiric antimicrobial choices to respond to local patterns of pathogens and susceptibilities.

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Key words: consensus; de-escalation; diagnosis; fungal infections; ICU; outcome; pneumonia; therapy; treatment; ventilator-associated pneumonia

Abbreviations: ATS = American Thoracic Society; BPSB = blinded protected-specimen brush; MRSA = methicillin-resistant *Staphylococcus aureus*; PSB = protected-specimen brush; VAP = ventilator-associated pneumonia

Ventilator-associated pneumonia (VAP) is the most common ICU-acquired infection. Its prevalence varies from 6 to 52 cases per 100 patients depending on the population studied, the type of ICU, and the diagnostic criteria used.[1] In intubated patients, rates of pneumonia may be between 6 and 21 times higher than in other patients; the risk rises

For editorial comment see page 702

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between 1% and 3% for each day the patient requires endotracheal intubation and mechanical ventilation.[2,3] Not only is incidence high, but mortality is high as well. The risk of mortality is between 2 and 10 times higher in VAP patients.[4–6]

Nosocomial pneumonia is a contributing factor in 60% of patients with infection-related mortality and is the most common nosocomial infection that contributes to death.[7,8] The mortality rate attributable to VAP is significantly lower than its crude mortality rate, ranging near 27%. Certain pathogens, such as *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, and methicillin-resistant *Staphylococcus aureus*, are particularly lethal.[6,9] VAP increases hospital costs mainly due to an increase in length of ICU stay.[6,9,10] VAP is a common and important problem in ICUs, and its risk factors, infection control measures, clinical diagnosis, microbiological diagnosis, and empiric therapy are still widely discussed by specialists.

In fact, there is no accepted "gold standard" for diagnosis, as no study to date (and to our knowledge) has shown the superiority of a specific diagnostic method. The methods proposed have different sensitivities and specificities.[11–13] The etiology of VAP varies according to the method of diagnosis, the patient population studied, and the local epidemiology. Therapy is usually started empirically, based on patients' clinical and radiologic findings, previous antibiotic use, day of onset after intubation, and the patients' specific risk factors for particular pathogens.[14] A few general guidelines have been published, but there is a vast range of approaches in different centers, reflecting differences in epidemiology, "case-mixes," access to diagnostic methods, prevalence of causative pathogens, pattern of resistances and susceptibilities, and antibiotic policies. A number of studies[15–18] have demonstrated clearly that the appropriateness of the initial antibiotic regimen is a vital factor in determining outcome. Therefore, the correct choice of the empiric regimen is crucial.

Materials and Methods

This conference was held on May 22, 2000, at the Hospital Joan XXIII, Tarragona, Spain. The consensus group consisted of 12 intensivists from Spain, Portugal, Argentina, and Uruguay. Jordi Rello, acting as conference coordinator and host, selected the peers, based on their interest and experience in the study and treatment of infectious diseases in the ICU, their previous participation in congresses, and their publications in the field.

The conference format followed roughly that of the International Conference for the Development of a Consensus on the Management and Prevention of Severe Candida Infections, which was chaired by John E. Edwards Jr.[19] The conference coordinator, Dr. Rello, and the conference secretary, Dr José Artur Paiva, drew up a list of 21 questions on diagnostic methods, the interpretation of microbiological results, and treatment strategies based on their implications in clinical practice, and commonly asked questions concerning management. During the meeting, questions were put simultaneously to all participants. Answers were given independently and anonymously by each one, without any discussion. Abstentions were permitted. Results were obtained and were reported to all participants. A period of discussion followed. The reasons for individual answers were stated and debated, and peers were allowed to change their vote. A first draft of the text was made by Dr. Paiva and Dr. Margarida Rios and was released again to all participants for comments and suggestions. The text then was reformulated and redistributed for a second round of comments. The final text then was written, and it was approved by all participants.

Terminology

A diagnosis of *pneumonia* was defined as the presence of new, persistent pulmonary infiltrates not otherwise explained, appearing on chest radiographs. Moreover, at least two of the following criteria also were required: (1) temperature of $> 38°C$; (2) leukocytosis $> 10{,}000$ cells/mm^3; and (3) purulent respiratory secretions. A pneumonia was considered to be ventilator-associated when it occurred after intubation and was judged not to have incubated before an artificial airway was put in place.

Refractory VAP is one that does not respond to > 3 days of adequate antibiotic therapy.

A *multiresistant microorganism* is a microorganism that is resistant to the antibiotic considered to be the "gold standard" for treatment of infections caused by that microorganism, or one that is only susceptible to antibiotics with more serious side effects than the standard ones.

Background Data and Questions

1. Do you think that microbiological examinations are useful for the initial choice and further modification of empiric antibiotherapy in VAP?

Background Data: Lower respiratory airways are uniformly colonized only a few hours after intubation[20,21]; therefore, the recovery of a pathogen is by no means sufficient for the diagnosis of infection. Not even the finding of a high concentration of colonies is diagnostic of pneumonia.[22,23] Blood cultures do not provide useful additional information.[15,24] However, there is now clear evidence that episodes caused by methicillin-resistant *S aureus* (MRSA), *P aeruginosa*, or *A baumannii* present excess mortality compared with predictions made on the basis of severity of illness on ICU admission.[6,25–28] This suggests that patients in whom VAP is suspected to be caused by these pathogens may benefit from the performance of microbiological examinations. Furthermore, the impact of microbio-

logical tests on outcome depends on the adequacy of the initial antibiotic choice. The fact is that the inappropriateness of therapy ranges between 21% and 68%.[15,16] Microbiological tests also have shown that the spectrum of the antibiotic regimen may be reduced in some patients.[15,29] This may help to reduce the number of infection episodes caused by multiresistant organisms that are associated with higher mortality.[30]

Responses: The 12 intensivists answered this question in the affirmative; this strong consensus was based on two facts:

1. The presence of intracellular bacteria and a positive Gram's stain or other direct tests may be of great help in selecting the initial antibiotic regimen[31–33] but not in making the diagnosis of pneumonia.
2. The quantitative microbiological findings can make it possible to change, adjust, or reduce the administration of antibiotics in some patients.

In summary, the peers stressed that the diagnosis of VAP on clinical grounds may be as sensitive as other methods. Microbiological findings are useful for the choice of the antibiotic regimen, and particular emphasis was placed on the quality of the respiratory sample, either invasive or noninvasive. All participants agreed that microbiological examination should not be used to decide whether a ventilated patient has pneumonia. However, they agreed that microbiological tests are recommended and are important in improving the use of antimicrobial agents.

2. *In the case of a negative Gram's stain of a respiratory sample of a patient with a suspicion of VAP, would you wait for cultures to start antibiotics?*

Background Data: The direct staining of respiratory samples is possible, and the information obtained should be used as part of the initial evaluation of all patients, as it provides essential data on the quality of the sample and may guide the choice of antibiotic regimen.[34] Gallego and Rello[35] reported a high negative predictive value for Gram's stain when comparing Gram's stain and culture. Nevertheless, sensitivity for the diagnosis of VAP is not 100%, and, therefore, the initial diagnosis depends on clinical criteria and the appearance of a new pulmonary opacity that does not clear in < 24 h or the progression of a previous one. Concomitant antibiotic and corticosteroids use[32,36] reduces the sensitivity of the technique, and false-negative results are possible. One study[32] showed that one third of episodes caused by *P aeruginosa* are associated with negative direct staining; this is a pathogen associated with a higher mortality.[25,26] A more recent study,[37] which was reported on after the conference was held, suggested that a combination of direct staining of tracheal aspirate and invasive samples helps in the management and interpretation of suspected VAP in patients.

Results: Ten of the 12 peers agreed that they would not wait for the results of the cultures to start antibiotherapy in the case of a negative result of a Gram's stain. Moreover, even a negative result of direct staining of a high-quality sample requires initial broad-spectrum coverage until the culture results are available. Two of the peers answered that it depends on the patient, but they agreed that if the clinical situation is clearly suggestive of pneumonia and if the patient is high risk or the patient's condition deteriorating, they would start therapy empirically.

3. *When would you perform a bronchoscopic sampling in VAP?*

Background Data: Many studies have sought to define the right method for collecting respiratory samples, but no conclusion has been reached. Some researchers who advocate bronchoscopic samples, either protected-specimen brush (PSB) or BAL, state that the visualization of the bronchial tree is useful for the diagnosis of pneumonia.[38] Studies comparing bronchoscopic samples with endotracheal aspirates found the former to be more specific.[39–43] Those investigators[44,45] who favor noninvasive samples argue that the selection of a bronchus is not necessary since bronchopneumonia affects all the lung and that results from bronchoscopic PSB or blinded PSB (BPSB) are clearly correlated. The sensitivity of blinded techniques is similar to that of fiberoptic bronchoscopy techniques, ranging from 74 to 97% for blinded bronchial sampling, 63 to 100% for mini-BAL, and 58 to 86% for BPSB. Their specificity is also similar to that of bronchoscopic techniques, ranging from 74 to 100% for blinded bronchial sampling, from 66 to 96% for mini-BAL, and from 71 to 100% for BPSB.[46] Furthermore, due to the possibility that the invasive techniques available will provide false-negative results, an algorithm of stopping antibiotic therapy in patients with negative results poses the risk of undertreating patients with pneumonia.[47] Furthermore, it has not been proven that the use of bronchoscopic sampling decreases mortality in patients with the suspicion of VAP.[48,49] In fact, a randomized multicenter study[50] comparing an invasive approach using bronchoscopic PSB and BAL and an approach using Gram's stain

and qualitative cultures of tracheal aspirates showed the invasive approach to be associated with fewer deaths at 14 days, less organ dysfunction, and less antibiotic use. However, Ruiz et al[51] randomized 76 patients using bronchoscopic-directed PSB and BAL, and quantitative culturing of tracheal aspirates and found no benefit of the invasive strategy, but they did find a trend of lower related mortality in the invasive group (56% vs 71%, respectively; p = 0.36).

The cost of the procedure and the fact that some hospitals lack a skilled bronchoscopist over a 24-h period also were discussed. Randomized studies[50] may be difficult to perform and interpret, as we have no adequate "gold standard." Despite the potential risks involved in performing bronchoscopies in ventilated patients, the strict adherence to formal contraindications and the adequate management of systemic problems and ventilator settings are associated with a very low incidence of adverse events.[52] The external diameter of the endotracheal tube should be at least 1.5 mm larger than the internal diameter of the bronchoscope. All intubated patients should be sedated and, probably, temporarily paralyzed with a short-acting agent. Severe thrombocytopenia should be corrected, and fluids must be at hand for the correction of episodic hypotension. The fraction of inspired oxygen should be set at 100%, the respiratory rate should be set at a minimum of 20 breaths/min, the peak inspiratory flow should be set at ≤ 60 L/min, and the peak pressure alarm should be increased to a level that allows adequate ventilation. If hypoxemia is severe, continuous positive airway pressure must be administered as previously.[18] Moreover, samples must be transported to the laboratory without delay and cultured within 1 h.

Results: Invasive diagnostic techniques in VAP were always performed by 10 of the peers. One expert used these techniques in both immunocompromised patients and in refractory episodes, and another expert used them in immunocompromised patients alone. The vast majority of the peers prefer to obtain an invasive sample as soon as the diagnosis of VAP is suspected, as this procedure seems to provide results with higher specificity and positive predictive value. Thus, it is more able to differentiate colonization or contamination from infection. The peers prefer to implement this procedure early on because the use of invasive diagnostic testing is associated with increased cost but may not deliver results early enough to influence survival if the procedure is performed 12 h after diagnosis. An appropriate initial regimen, or early modification, based on microbiological studies performed within 12 h of diagnosis allows a higher survival rate.[15,17] The peers also think that invasive sampling is to be preferred in VAP patients without good clinical resolution, although no evidence of improved survival has been documented. Several studies[29,18] have shown that microbiological results from bronchoscopic samples often lead to a change of antibiotic regimen.

All peers place special emphasis on the quality of the sample. The presence of $> 1\%$ of epithelial cells in invasive samples suggests oropharyngeal contamination,[53] and if the presence of neutrophils is $< 10\%$, the diagnosis of pneumonia is unlikely. Patterns of quality for endotracheal aspirate samples require < 10 epithelial cells per low-power field. Although VAP is unlikely if the result of testing a qualitative endotracheal aspirate is negative unless the patient has received antibiotic therapy,[54] the fact is that only 15% of endotracheal suction aspirate specimens satisfy the quality criteria.[55] Therefore, as it is difficult to obtain samples free of oropharyngeal contamination by nonbronchoscopic techniques, the majority of the peers prefer to collect invasive samples as early as possible in all patients without contraindications.

4. *Do you think that the American Thoracic Society guidelines are acceptable for the treatment of VAP?*
5. *For the treatment of VAP, do you follow guidelines customized to each institution (localized) or general guidelines?*

Background Data: The American Thoracic Society (ATS) published a set of guidelines for treating nosocomial pneumonia.[14] These guidelines are based on the severity of the infection, the presence of risk factors for specific organisms, and the timing of diagnosis in terms of days after hospital admission. On the basis of these three factors, patients are divided into three groups: (1) patients without risk factors with mild or moderate pneumonia starting at any time or with early-onset severe pneumonia; (2) patients with specific risk factors with mild or moderate pneumonia starting at any time; and (3) patients with early-onset severe pneumonia and specific risk factors or late-onset severe pneumonia. Severe pneumonia is defined as pneumonia associated with one of the following: the need for ICU admission; respiratory failure (*ie*, a need for mechanical ventilation or for a fraction of inspired oxygen of $> 35\%$ to keep oxygen saturation at $> 90\%$); swift radiologic progression or multilobar or cavitated pneumonia; or, finally, evidence of severe sepsis or septic shock.

Other authors[56] argue, however, that the number of previous days the patient has received mechanical

ventilation and the previous use of antibiotics are the only factors that are independently associated with the development of nosocomial pneumonia due to multiresistant organisms. This could allow the drawing of a simpler algorithm of treatment with the prescription of broad-spectrum antibiotics to fewer patients, reserving vancomycin for patients with late-onset pneumonia and patients who previously have received antibiotics. In fact, Ibrahim et al[57] showed that pathogens associated with early-onset and late-onset nosocomial pneumonia may be similar, due, at least in part, to prior hospitalization and the use of antibiotics in many patients developing early-onset pneumonia.

The etiology of VAP varies widely according to the hospital, the unit, and the kind of patients admitted.[30,58–65] For instance, in the series by Torres et al,[63] far more cases of pneumonias were caused by Acinetobacter spp and far fewer by *S aureus* than in the study by Fagon et al.[59]

Comparing multicenter studies from the United States (the National Nosocomial Infections Surveillance System)[66] and Europe (European Prevalence of Infection in Intensive Care),[67] Enterobacter was found to be more prevalent in the United States and Acinetobacter was found to be more prevalent in Europe.

Results: All 12 peers answered "no" to question 4, and they answered "local guidelines" to question 5. This consensus is due to the fact that all agreed that pathogens causing VAP and multiresistance patterns at their sites were substantially different from those in the United States and different from one another. The participants did not favor the risk stratification proposed by ATS as it ignores important variables such as the previous use of antibiotics. Knowledge of the local pathogens associated with VAP in each ICU and their local pattern of resistance aids the selection of the empiric regimen. Therefore, even if the suspected etiology of VAP were correct according to the ATS guidelines, it would be unwise to be dogmatic about the ATS recommendations because of the differences in antimicrobial resistances between hospitals. It is vital that each ICU should have a local epidemiologic surveillance program, as several studies indicate that pathogens are becoming progressively more resistant and more difficult to treat.

6. What is the maximum time that you would wait to start treatment for VAP? (1) 12 h; (2) 24 h; (3) 48 h

Background Data: As VAP is a potentially severe infection, the timely use of an appropriate antibiotic regimen is essential to reduce mortality. It may be that antibiotics show limited efficacy when used in patients who are too sick to profit from them, even if the causative microorganism is sensitive to the antibiotic(s) used.

Therefore, the timing of the initiation of antibiotherapy is critical to the overall effect on the natural history of the disease.[68] Luna et al[69] and Ibrahim et al[70] showed that there is a trend toward lower mortality if antibiotherapy is started early in the course of the pneumonia and that patients with severe VAP whose antibiotherapy was started > 48 h after the diagnosis were more likely to die than those who started receiving antibiotic therapy in the first 48 h after diagnosis.

In patients with community-acquired pneumonia, Meehan et al[71] showed that the sooner the disease is treated, the better the outcome. Despite the lack of a clear cutoff point, the difference reached statistical significance at 8 h, meaning that administering antibiotics within 8 h of hospital arrival was associated with improved survival.[71]

Results: Eleven peers answered that they would not wait for > 12 h to start an empiric antibiotic regimen in the case of suspected VAP. One chose not to answer, considering that there was no convincing study of this question and suggesting that a study of this type should be conducted in the near future.

7. A course of antibiotic therapy for the treatment of VAP should last: (1) 5 days; (2) 7 days; (3) 10 days; (4) 14 days; (5) > 14 days

Background Data: The duration of antibiotherapy for VAP has never been defined clearly. Most series[72,73] show a duration of around 10 days, although this figure is probably influenced by the inclusion of patients who die early in the course of the pneumonia, as most courses of antibiotics are planned for 14 days. Long courses may do the following: (1) select resistant microorganisms at an individual level and probably at a hospital level[74,75]; (2) increase the risk of adverse effects that are well-proven for aminoglycosides, quinolones, and even β-lactams; and (3) increase the cost substantially, as many of the antibiotics used, especially for late-onset pneumonia, are very expensive.

However, short courses of antibiotic therapy may lead to therapeutic failure or relapse, particularly in the case of patients with certain species such as *P aeruginosa*, which are difficult to eradicate.

The American Thoracic Society[14] recommends that the duration of antibiotherapy should be decided according to the severity of the pneumonia, the time to clinical response, and the causative

microorganism, but they stress this last factor above all, recommending a course of therapy of 7 to 14 days for *S aureus* or *Haemophilus influenzae* pneumonia and a course of 14 to 21 days for *P aeruginosa*, Acinetobacter spp pneumonia, Gram-negative necrotizing pneumonia, and cases of cavitation, multilobar involvement, or malnutrition.

Results: The answers are shown in Table 1, and they reflect clearly the lack of consensus. Nevertheless, the vast majority of peers would treat VAP for 7 to 14 days. During the discussion, it was agreed that the main factor for deciding the duration of therapy should be the time to clinical response and not the pathogen involved, and therefore, that all patients should be treated for at least 72 h after clinical response. Not even *P aeruginosa* would justify, by itself, a longer course of treatment, as most of the recurrent episodes reported[76] are markers of persistent colonization and are not true reinfection.

8. Is monotherapy enough for treating early-onset (< 7 days after intubation) VAP in a patient who has not previously received antibiotherapy?

Background Data: The microbiological etiology of VAP varies according to the day of onset of the infection. Early-onset pneumonia is associated with *Streptococcus pneumoniae*, *H influenzae*, enteric Gram-negative bacilli, and methicillin-susceptible *S aureus*.[14,30,77–79]

The prior use of antibiotics, especially broad-spectrum antibiotics, is linked to a higher incidence of infections by Acinetobacter spp, *P aeruginosa*, and multiresistant organisms.[14,30,56,59,60,80] Trouillet et al[56] found that among 125 patients with early-onset, ICU-acquired pneumonia none was caused by multiresistant microorganisms and that these two factors (*ie*, the number of days that ventilation had been required previously and the number of days that antibiotherapy had been received previously) were the only ones associated in the multivariate analysis with the development of pneumonia due to multiresistant organisms. Therefore, pathogens that are most likely to cause early-onset VAP in patients who have received antibiotherapy previously are adequately treated with monotherapy. Based on several studies[81–86] that suggest that the success rate of monotherapy is similar to that of combined therapy, several authors recommend one of these classes: β-lactam/β-lactamase inhibitor; non-antipseudomonal, third-generation cephalosporin, or even a second-generation cephalosporin (*eg*, cefuroxime); a new-generation fluoroquinolone; or a carbapenem.

Nevertheless, most of these studies include patients with pneumonia diagnosed on the basis of clinical criteria and endotracheal aspirate cultures. A comparison based on invasive samples would be helpful.[87] The data from the study by Ibrahim et al[57] suggested that *P aeruginosa* and MRSA may be significantly associated with early-onset VAP, probably due to patient hospitalization prior to ICU admission and the use of antibiotics in many patients who had received this diagnosis. However, these studies include a heterogeneous population of patients, and, therefore, some other authors prefer to use combination therapy in the first days until the results from cultures are available.

Results: Nine of the 12 peers answered in the affirmative, although they stated that the cutoff day for early-onset pneumonia vs late-onset pneumonia (that is, the day when the shift from a primary endogenous pattern to a secondary endogenous pattern was apparent) varies from ICU to ICU and must be established inside each ICU.

Three of the peers answered "no," emphasizing that if VAP occurred in a COPD patient or in patients with a prolonged use of corticotherapy or malnutrition, they would use combination therapy even in patients with early-onset pneumonia without previous antibiotic use.

There was general agreement that the number of previous days of hospitalization was a more important factor than the number of previous days of ventilation and that other factors concerning the individual patient must be considered before monotherapy is chosen, such as the absence of structural lung disease, the absence of corticotherapy, the absence of immunosuppression, and the absence of antibiotherapy in the last 3 months.

*9. Does late-onset VAP (*ie*, > 7 days after intubation) require combination therapy?*

Background Data: Generally, antibiotic monotherapy has shown success rates and rates of superinfections and colonization by multiresistant microorganisms that are similar to those for combination therapy.[81–87] But other studies have demonstrated that patients with severe infections by *P aeruginosa* and multiresistant Klebsiella spp or Acinetobacter

Table 1—*Duration of Antibiotic Therapy*

Days, No.	Patients, No.
5	0
7	3
10	6
14	2
> 14	1

spp are better treated with combination antibiotherapy, such as antipseudomonal β-lactam plus aminoglycoside.[88,89] The fact is that we still lack studies comparing monotherapy with polytherapy for VAP using both clinical and microbiological criteria, preferably PSB or BAL samples.

Results: Eleven peers answered "yes," and 1 answered "no." The vast majority agreed that monotherapy should be reserved for infections not caused by *P aeruginosa* or multiresistant bacteria, as Acinetobacter, Enterobacter, or Klebsiella often are. The onset of VAP after 1 week of intubation is more likely to be caused by these bacteria and is often polymicrobial. Furthermore, monotherapy for *P aeruginosa* is more likely to result in the development of resistance and higher mortality rates than combination therapy.[72,89] Therefore, an empiric antibiotic regimen should include two antibiotics, at least for the first few days until these bacteria can be excluded as causal agents.

Combination therapy consists of an aminoglycoside or fluoroquinolone with an antipseudomonal, extended-spectrum β-lactam or a carbapenem plus an aminoglycoside. Vancomycin should be considered only in selected patients (*ie*, in those with prior antibiotic use) in particular sites[57,70] who have endemic rates of MRSA.

10. Does P aeruginosa *pneumonia require combination therapy?*

Background Data: VAP caused by *P aeruginosa* is associated with high mortality. *P aeruginosa* as the causal agent contributes to excess mortality in multivariate analysis.[26,27] We also know that many species of *P aeruginosa* produce class I cephalosporinases, which make them resistant to piperacillin, aztreonam, and ceftazidime, and that resistance to carbapenems and fluoroquinolones is rising.

Data show that the use of monotherapy for *P aeruginosa* infection is more likely to result in the development of resistance and higher mortality rates than combination therapy.[72,89,90]

Results: All 12 peers considered that this kind of pneumonia requires combination therapy. The rates of resistance to different antibiotics vary from center to center but cause concern in all. Combination therapy consists of an antipseudomonal, extended-spectrum β-lactam with an aminoglycoside, for some patients, and with a fluoroquinolone, for others.

11. When you choose a combination regimen, do you prefer (1) carbapenem plus quinolone, (2) carbapenem plus aminoglycoside, (3) another β-lactam plus aminoglycoside, or (4) another β-lactam plus quinolone?

Background Data: Combination therapy consists of an aminoglycoside or fluoroquinolone combined with an extended-spectrum β-lactam or a carbapenem.[14] Aztreonam is not included in this list of empiric choices because its spectrum of coverage is too limited. The fear of diagnosis of *P aeruginosa*, Acinetobacter spp, or Enterobacter spp is the main reason for using one of these combination therapies.

Synergistic bactericidal activity against *P aeruginosa* can be demonstrated *in vitro* with the combination of an antipseudomonal β-lactam and an aminoglycoside, but there is still considerable doubt about the existence of a synergistic advantage *in vivo*.[89,91,92] Although aminoglycosides have bactericidal activity and a prolonged postantibiotic effect, the presence of a narrow therapeutic range, poor penetration in lung parenchyma, and decreased activity in the low pH of the infected airways may be responsible for the lack of evidence of *in vivo* advantages. However, a β-lactam combined with a fluoroquinolone does not demonstrate synergy *in vitro* but is probably at least as effective *in vivo*.[92] Fluoroquinolones reach high intracellular concentrations in most tissues, including lung, bronchial mucosa, and alveolar neutrophils and macrophages. In fact, the concentrations of quinolones in bronchial secretions are 0.8 to 2.0 higher than those in plasma, and concentrations of aminoglycosides are 0.2 to 0.6 higher.[93] Unfortunately, to our knowledge no clinical trials have compared these two types of combination therapies. A once-daily dose of aminoglycosides is highly recommended.

Results: Answers are shown in Table 2.

Only three of the peers preferred a carbapenem to the other β-lactam. Aminoglycoside and quinolone were chosen by an equal number of peers for combination therapy, reflecting the lack of undisputed scientific data regarding this question.

Table 2—*Preferred Combination Regimens*

Variable	β-lactam + Quinolone	β-lactam + Aminoglycoside	Carbapenem + Aminoglycoside	Carbapenem + Quinolone
Patients, No.	5	4	2	1

12. Should empiric coverage of A baumannii *only be considered in patients who have previously received antibiotherapy?*

Background Data: Antibiotherapy for VAP caused by Acinetobacter is challenging because of extensive resistance. In fact, Acinetobacter is uniformly resistant to β-lactams and cephalosporins, to aminoglycosides in ≥ 70% of cases, and to fluoroquinolones in ≥ 97% of cases. The best antibiotherapy is provided by carbapenems or sulbactam in patients with imipenem-resistant strains.[94–96] IV colistin is reserved for patients with multiresistant strains. Because of this pattern of resistance and also because of its high virulence, Acinetobacter pneumonia has a high attributable mortality,[59] significantly lengthens ICU stays, and seems to be associated with excess mortality.[97]

The reported incidence of *A baumannii* varies widely between hospitals and even between ICUs in the same hospital.[98] Fagon et al,[59] Rello et al,[60] and Torres et al[63] reported *A baumannii* as the cause of VAP in 9.5%, 3.5%, and 39.1%, respectively, of episodes. A comparison of the results of a retrospective multicenter study evaluating microorganisms documented by quantitative cultures from bronchoscopic samples in episodes of VAP from three different institutions in Barcelona, Montevideo, and Seville[98] with those of Trouillet et al[56] in Paris showed that the distribution of *A baumannii* VAP varied markedly from center to center. In Paris, ≥ 90% of episodes were confined to patients who had stayed in the ICU for at least 7 days and had been treated previously with antibiotics, but in the other centers > 50% of episodes were documented outside this epidemiologic setting, and 18% were documented in patients who had not been treated previously with antibiotics.

Although some studies[56,99,100] establish a clear association between the use of antimicrobial agents (that is, some cephalosporins) and *A baumannii* infection, others[101–103] report no association with prior antibiotic use. Corbella et al[100] found that *A baumannii* may rapidly colonize in patients admitted to the ICU when the infection is endemic, and Mulin et al[104] reported that conversion from open rooms to isolation rooms was highly effective in achieving successful control of the transmission of airway colonization in intubated patients.

Results: Eight of the peers stated that treatment covering *A baumannii* should not be reserved for patients who have received antibiotic therapy previously, and four peers said that they would only cover this microorganism if antibiotics had previously been used in treating the patient in question.

These results reflect the differences in distribution of this kind of VAP in the various centers represented at the conference. In the discussion, everybody agreed that risk factors for acquisition of, dissemination of, and infection by *A baumannii* vary from one institution to another and that, as a result, antimicrobial prescribing practices should be based on updated information customized to each institution rather than on general guidelines.

13. Should antibiotics for VAP cover anaerobes?

Background Data: Anaerobes are found in 35% of cases of nosocomial pneumonia,[76] but the number of anaerobes isolated in ventilated patients is low. Several series showed incidences that varied between 1.1%[105] and 3.5%.[59] The question is whether this means that anaerobes are seldom the cause of VAP or that our diagnostic techniques have low sensitivity for their diagnosis.[106] Indeed, the isolation of anaerobes requires the appropriate media for transport and culture in < 30 min after sampling. PSB sampling has been recommended as the method of choice for the isolation of anaerobes in patients receiving ventilation.[107] Several studies[59,88,108–111] using bronchoscopically directed PSB sampling and anaerobic culture media have isolated anaerobic bacteria in patients suspected of having VAP in 0 to 2% of cases. Only one study by Doré et al,[112] using bronchoscopically directed PSB sampling, anaerobic transport broth, and anaerobic culture media, showed a significant recovery rate of anaerobes (23%) in patients with suspected VAP.

Results: Eleven of the peers answered "no," stating that while anaerobes are quantitatively important oropharyngeal commensals, they may be unimportant pulmonary pathogens in patients with VAP. One of the peers stated that he would consider covering anaerobes in patients with proven or suspected bronchoaspiration because this is still controversial,[113] and, for instance, a recent study showed that patients with VAP receiving well-adapted empiric antibiotherapy against anaerobic bacteria had better outcomes at day 10.[114]

14. Does the isolation of Candida spp in respiratory samples in nonneutropenic patients require the use of an antifungal?

Background Data: Candida spp are often found in respiratory samples of critically ill patients, especially in those who have received antibiotic therapy.[115] Except in neutropenic patients, Candida spp hardly ever cause VAP. The detection of Candida in bronchoscopic samples in nonimmunosuppressed pa-

tients, even when the number of colonies is high, should be considered as contamination.[23,116]

Results: All peers stated that the finding of Candida spp in respiratory samples, even if bronchoscopic, would not lead them to prescribe an antifungal agent in a nonneutropenic patient.

15. Should the empiric antibiotic regimen for patients with VAP who have not received antibiotics previously include vancomycin?

Background Data: Most patients who die of pneumonia were infected with nonfermentative Gram-negative bacilli or MRSA. Episodes caused by these bacteria cause excess mortality compared with predictions made on the basis of severity of illness on ICU admission.[27,30,56] The study by Ibrahim et al[57] showed that early-onset pneumonia may be caused by MRSA, but they attributed most of these cases to prior antibiotherapy. VAP caused by MRSA occurs in patients with the following specific risk factors: mechanical ventilation for > 6 days; previous corticotherapy; COPD; age > 25 years; and previous antibiotherapy.[25] In this series reported by Rello et al,[25] all patients with MRSA pneumonia had received antibiotics previously. In the report by Trouillet et al,[56] 31 of 32 cases of VAP occurred in patients who had been treated previously with antibiotics. In a series of 41 episodes of VAP caused by MRSA, Pujol et al[117] found that all episodes were in patients who had received prior antibiotic therapy. Even late-onset VAP in patients who had not previously received antibiotics is caused only rarely by MRSA.[25,27,30]

Results: The 12 peers stated that patients who had not previously received antibiotics should not be treated with vancomycin empirically, as the incidence of MRSA is very low. They emphasized that comatose, neurosurgical, and head-trauma patients are at a particular risk of developing methicillin-susceptible *S aureus* pneumonia.[118–120] This kind of pneumonia is better treated with oxacillin or nafcillin than with a glycopeptide, as was elegantly proven in a series of 54 cases of bacteremic *Staphylococcus aureus* pneumonia reported by Gonzalez et al,[121] and has a low mortality rate when adequately treated.[25,122]

16. Do you think that continuous-infusion vancomycin is the best treatment for MRSA pneumonia?

Background Data: Glycopeptides show little concentration-dependent activity. When the concentration exceeds a critical value, killing proceeds at a zero order rate and increasing drug concentration does not change the microbial death rate.

In fact, glycopeptides, like β-lactams, show time-dependent or concentration-independent killing, meaning that the time that serum levels exceed the minimal inhibitory concentration or minimal bacterial concentration for the suspected or proven pathogens at the site of the infection is the best predictor of clinical outcome.[123–125] The time-kill kinetics observed in cultures are characterized by a progressive increase during the first few hours with a maximum activity around 24 h. By using constant infusion, the clinician can optimize the time the antibiotic level remains above its minimal inhibitory concentration by using the lowest daily dose and the least amount of nursing and pharmacy time with a reduced risk of reactions, a lower risk of technical errors, and easier monitoring.[126]

Results: Nine of the peers answered that continuous-infusion vancomycin is, for the time being, the best treatment for MRSA pneumonia. Only three peers did not answer, as they had doubts about the clinical evidence gathered to date. All nine peers used a loading dose followed by continuous infusion with the daily monitoring of serum levels until stabilization of the levels was reached, and then they used lower dosing. The peers also agreed that although teicoplanin has a similar spectrum to vancomycin, its effectiveness for MRSA pneumonia has not been clinically proven. Experience with linezolid was limited, and the clinical trials available show no benefit for it over vancomycin.

17. Which antibiotic would you choose for the treatment of VAP in trauma patients with (1) early-onset VAP or (2) late-onset VAP

18. And for VAP in postsurgical patients?

19. And for VAP in medical patients?

Background Data: VAP is a frequent problem in postsurgical and trauma patients, occurring in those patients even more often than in medical patients.[127] The incidence of pneumonia in trauma patients varies from 6 to 45%.[128] The repeated aspiration of oropharyngeal secretions that were previously colonized by potentially pathogenic microorganisms is accepted as the pathogenic mechanism.[129] The causative agents in this group of patients are different from those in other groups. Methicillin-sensitive *S aureus*, *H influenzae*, and *S pneumoniae* are responsible for almost half of the cases in the first days after the event, because they colonize the upper airway from the time of hospital admission onward (*ie*, they constitute a primary endogenous infection). Later,

Enterobacteriaceae, *P aeruginosa*, and *A baumannii* would be the main pathogens, after they had colonized the upper airway (*ie*, secondary pathogens) or had been acquired exogenously.[119,130,131] Patients in coma, patients with head trauma, and/or neurosurgical patients are specially prone to developing infections from *S aureus*.[118–120]

The development of VAP in surgical patients usually is related to secondary endogenous flora and does not differ from pneumonia in other groups of patients. These forms tend to occur later than in the trauma patient. Many series show that environmental Gram-negative bacilli are the most frequent causes, with *P aeruginosa* predominating.[132–135]

Results: Answers are shown in Figure 1. The peers thought that the trauma patient question should be divided in two to consider patients with head trauma and those without. For the head trauma patient with VAP, the most frequent answer was "another antibiotic," meaning that a drug with antipseudomonal coverage was not considered to be necessary by five of the peers and that the use of amoxicillin/clavulanate, or cefuroxime, or a third-generation cephalosporin was thought to be adequate as most of the infections occur soon after hospital admission and often in patients who have not been treated with antibiotics previously.

For non-head trauma patients, eight of the peers would use one of the four antipseudomonal drugs. Two of the peers stressed that coverage for methi-

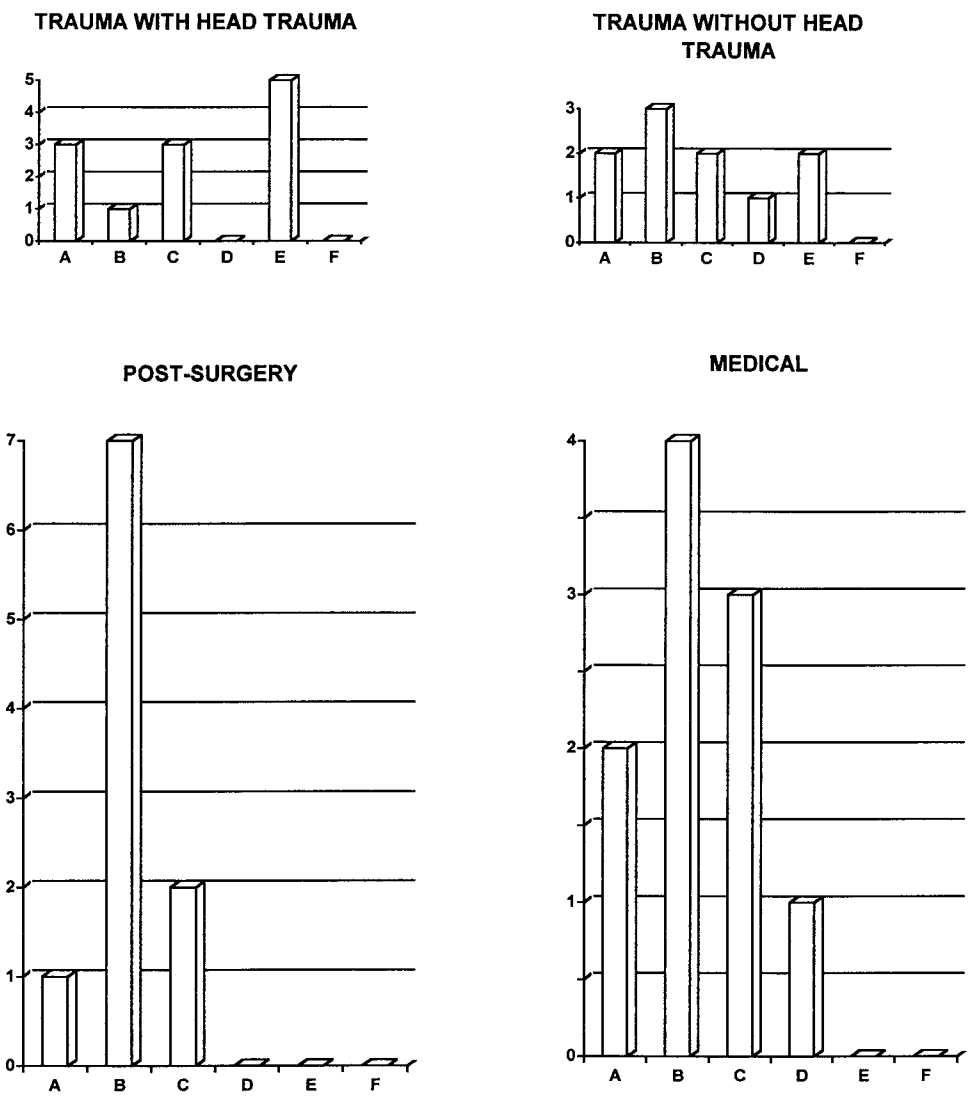

FIGURE 1. Recommended choices of antibiotics for specific populations. Note that two participants did not answer the postsurgery and medical patient questions. A = carbapenem; B = piperacillin/tazobactam; C = cefepime; D = fluoroquinolone; E = other; F = vancomycin.

cillin-sensitive *S aureus* with cloxacillin or nafcillin is necessary in all trauma patients in whom coverage is not obtained by use ofthe other antibiotic selected, at least until the causative organism is identified.

Since (1) the onset of VAP in postsurgical and medical patients tends to occur later than in trauma patients, (2) these patients tend to have been receiving antibiotics, and (3) some of the medical patients have COPD, first-line coverage for nonfermentative, Gram-negative bacilli was considered to be fundamental by the peers. Therefore, piperacillin/tazobactam and cefepime were the answers most often given to questions 16 and 17.

It is also interesting that none of the peers answered "vancomycin." Indeed, they stated that the empiric use of vancomycin for the treatment of patients with VAP at their centers was low, in particular due to its low efficacy for methicillin-sensitive *S aureus* pneumonia, as has been shown previously.[121] The main message that emerged from the discussion around these three questions is that the empiric antibiotic regimen should be, and in fact is, customized according to the flora and pattern of resistance of the centers. Several of the peers, like other investigators in the literature,[72] stated that they were concerned about the increasing incidence of carbapenem-resistant and quinolone-resistant *P aeruginosa*.

20. Do you think that the use of broad-spectrum antibiotics for not > 48 h leads to a high risk of development of multiresistances?

Background Data: It is true that no class of antibiotics is totally free of responsibility in the development of resistance. Nevertheless, there are convincing data showing that antibiotic resistance is not related per se to the use of any particular antibiotic but varies with each antibiotic class, and even with each antibiotic within the same class.[136] To minimize the development of resistance, it is important that appropriate antibiotics be administered in full therapeutic doses for the shortest period appropriate for each particular organism/infection.

The use of antibiotics associated with resistance will produce problems, and a long period of use will make a bad situation worse. So, it is not the spectrum of the antibiotic that makes it an inductor of resistance; one must avoid inappropriate and prolonged antibiotic therapies that may markedly favor resistance.[137,138]

Results: Only 2 of the peers thought that the use of large-spectrum antibiotics for not > 48 h would induce a significant risk of multiresistance, and 10 peers thought that it would not. But, they all agreed that the antibiotic chosen and the duration of its use are much more important factors for determining the reduction of multiresistance than the spectrum of the antibiotic.

21. Do you agree with the concept of de-escalation therapy?

Background Data: All intensivists taking care of critically ill patients with severe infections must achieve the following two goals, which may sometimes be difficult to combine: to treat the patient efficiently, quickly, and safely, on the one hand; and to avoid inappropriate and prolonged antibiotic therapies that could favor resistances, on the other.[137,138]

Almost all episodes of VAP are initially treated empirically as it is often difficult to ascribe them to a particular causative microorganism because the patient is usually critically ill and sometimes in hemodynamically unstable condition. Therefore, the use of broad-spectrum antibiotics and even combination therapy is often mandatory. Susceptible microorganisms exposed to subinhibitory concentrations of the antibiotic are the ones most likely to lead to the emergence of resistance from a large inoculum of surviving microorganisms owing to incomplete killing by the suboptimal antibiotic doses. Therefore, one should use appropriate antibiotics at full therapeutic doses for the shortest possible period of time that is consistent with the resolution of the infection.

It is vital that the initial strategy be reassessed after a few days when more clinical and microbiological data are available. At that time, in the light of the results of susceptibility tests, it is possible to stop the use of the antibiotic(s) that initially were prescribed or to change to another antibiotic with a narrower spectrum.

De-escalation therapy is based on the use of a large-spectrum, high-dose, empiric, first-hand therapy that is reassessed when microbiological data become available and reduction to a narrower spectrum therapy that is oriented by the results of microbiological and susceptibility tests.

Results: All peers agreed with the concept of de-escalation therapy. Their antibiotic policy is based on a quick and appropriate choice of the initial empiric antibiotics that cover all potential pathogens and a modification of the regimen as soon as staff have access to the results of microbiological and susceptibility tests. Even if it is sometimes difficult to change a treatment that seems to be working, it is useful and important to go back to antibiotics either with a sharper spectrum and limited influence on endogenous flora or with fewer toxic effects or even

less expensive compounds, when microbiological information is available.[139]

Summary

Although consensus was not reached on many of the questions, the conclusions of the conference can be summarized as follows.

The diagnosis of VAP on clinical grounds may provide adequate sensitivity when compared to other methods. Microbiological examinations are useful for the choice of the antibiotic regimen, and special emphasis was placed on the quality of the respiratory sample (*ie*, either invasive or noninvasive). Invasive diagnostic testing such as bronchoscopy may be required to improve test specificity, because it is difficult to obtain samples free of oropharyngeal contamination by noninvasive techniques. A potential problem with using invasive diagnostic techniques is that the increased cost and accuracy may not deliver results sufficiently early to influence survival if they are obtained $>$ 12 h after the development of fever.

VAP should be treated in accordance with guidelines that are customized to local epidemiology, microbiology, and patterns of resistance. Indeed, the antibiotics chosen by the peers differed markedly. The factor "previous days of hospitalization" was considered to be more important than "previous days of ventilation."

The appropriateness of the initial antibiotic regimen is a vital determinant of outcome. Therefore, therapy must be started empirically, preferably within the first 12 h of the suspicion of pneumonia. No consensus was reached concerning the best duration of therapy, but most peers prefer a 10-day period. The following three questions should be formulated: (1) is the patient at risk of *P aeruginosa*; (2) is the patient at risk of MRSA; and (3) is *A baumannii* a problem in the institution?

Although most participants would use monotherapy for treatment of patients with early-onset pneumonia, several of the following individual factors must be weighed and excluded before such a decision is made: presence of COPD; corticotherapy; and immunosuppression and antibiotherapy received in the last 3 months. However, patients with late-onset pneumonia should be treated with combination therapy because of the risk of *P aeruginosa* or multiresistant Acinetobacter, Enterobacter, or Klebsiella species. No consensus was reached concerning the best combination regimen.

All agreed that risk factors (and sensitivity) for Acinetobacter vary from one institution to another and, therefore, that antimicrobial prescription practices should be based on updated information customized to each institution rather than on general guidelines. Most peers thought that the coverage of anaerobes is not mandatory and the use of antifungal agents for Candida spp should be considered only in neutropenic patients. The initial antibiotic regimen should not include vancomycin in patients who have not received antibiotics previously, but the preferred treatment for MRSA pneumonia was continuous-infusion vancomycin. Piperacillin/tazobactam was the preferred choice for empiric therapy, excepting patients with head trauma in whom antipseudomonal activity was not considered necessary. Treatment with a cephalosporin with antipseudomonal activity was considered to be the second option, followed by treatment with carbapenems. The use of fluoroquinolones or vancomycin was marginal. Finally, all peers agreed with the concept of de-escalation therapy and used it in their clinical practices. The use of broad-spectrum antibiotics for not $>$ 48 h, until the results of microbiological tests become available, does not seem to lead to the development of multiresistance.

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