

# Clinical Approach to the Patient With Suspected Ventilator-Associated Pneumonia

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Summary

Management of ventilator-associated pneumonia needs to balance the avoidance of unnecessary antibiotic overuse with the provision of adequate initial empiric therapy. A clinical diagnosis based on new pulmonary opacity and purulent respiratory secretions plus other signs of inflammation is valuable in screening for patients with suspected ventilator-associated pneumonia. A rational strategy starts with immediate initiation of adequate antibiotics and collection of respiratory secretions to evaluate the causative organism. As a minimum, an endotracheal aspirate with direct staining and quantitative cultures should be obtained. Overall, the need to choose adequate antibiotics correctly and expeditiously calls for the use of broad-spectrum antibiotics, but the choice should be narrowed quickly in the light of microbiologic information. However, some patients (those who develop an infection within 5 days of hospitalization, those without recent antibiotic exposure, and those without hospitalization in the past 3 months) are at low risk of infection by resistant organisms. In that subset, adequate initial selection could be a nonpseudomonal third-generation cephalosporin, since antibiotics should target usual community-acquired organisms in addition to some *Enterobacteriaceae* and *Staphylococcus aureus*. Coverage of methicillin-resistant *S. aureus* should be limited only to intensive care units with concomitant index cases and to patients under antibiotic exposure. Patients at risk of *Pseudomonas aeruginosa* (eg, 1 week of prior hospitalization or chronic obstructive pulmonary disease) require initial use of a combination of piperacilin/tazobactam and ciprofloxacin, or amikacin plus imipenem, meropenem, or an antipseudomonal cephalosporin. If risk of *Acinetobacter baumannii* exists, one of these agents should be a carbapenem. After 48 hours of therapy, each patient should be re-evaluated based mainly on resolution of hypoxemia and fever plus the initial microbiologic information. Whereas broad-spectrum therapy is initially warranted in many patients, this treatment may be narrowed considerably as culture results identify the causative organism and its sensitivity. Recent data suggest that reducing overall treatment duration to a maximum of 1 week is safe, effective and is less likely to promote the growth of resistant organisms in patients who are clinically improving. Optimal management should be based on a strategy combining early high doses of an effective agent for a short period of time, which is then simplified in the light of microbiologic information. *Key words:* ventilator-associated pneumonia, clinical resolution, de-escalation, therapy. [Respir Care 2005;50(7):965–974. © 2005 Daedalus Enterprises]

## Introduction

Ventilator-associated pneumonia (VAP) is the leading nosocomial infection in the intensive care unit (ICU).<sup>1</sup> The true attributable mortality of VAP episodes in critically ill patients has been debated.<sup>2</sup> However, well designed matched cohort studies have demonstrated the association between late-onset VAP and higher mortality, particularly when caused by virulent bacteria, such as *Pseudomonas aeruginosa*, producing type III secretory proteins.<sup>3</sup> Virulence rather than resistance is a key feature.

However, associated mortality and morbidity in VAP is increased in patients with wrong or delayed initial antibiotic treatment, which is frequently associated with the presence of resistant strains.<sup>4,5</sup> Nonfermenting Gram-negative bacteria other than *P. aeruginosa* are usually resistant to multiple antibiotics, but they have a tendency to colonize rather than to cause invasive disease. For example, in a recent study, *Acinetobacter baumannii* was identified in 17 patients with airways colonization before tracheostomy,<sup>6</sup> but only one of them acquired pneumonia. Epidemiologic studies have confirmed<sup>7</sup> that most patients with VAP died with, rather than of, *A. baumannii*.

With the universal colonization of *P. aeruginosa* in patients intubated longer than 5 days<sup>8</sup> and the evidence that methicillin-resistant *Staphylococcus aureus* (MRSA) is currently the most common identified antibiotic-resistant pathogen in United States hospitals, the spotlight focuses mainly on these 2 pathogens. Mortalities as high as 50% have been consistently reported for MRSA pneumonia and *P. aeruginosa* pneumonia. The highest mortality rates are reported in immunocompromised patients or patients with renal failure.

When a VAP episode is suspected in the ICU, the attending physician needs to answer 3 questions. First, does this patient actually have a VAP? Second, are microbiologic studies indicated? Third, which antibiotic regimen is the best option? Once those questions have been answered,

the attending physician should follow the evolution of these patients in order to evaluate the response to therapy and optimize antibiotic treatment and thus limit the emergence of multi-resistant bacteria.

We have previously published 2 reviews on management of VAP,<sup>9-10</sup> and here we expand upon and update our recommendations, adding recent evidence reported in the literature, particularly on clinical resolution and duration of therapy.

## Does This Patient Currently Have VAP?

The suspicion of a new episode of VAP has to be established in all intubated patients with clinical signs of sepsis. Once a patient develops fever and leukocytosis, the physicians must promptly identify the source of infection in order to (1) start adequate antibiotic therapy for sepsis, and (2) control the source of infection if needed, as has been previously described.<sup>11</sup>

The pathophysiology of VAP includes the spread of infecting organisms to the lower respiratory tract, overwhelming the local respiratory defenses. A local inflammatory response develops in the respiratory tract, manifested as respiratory purulent secretions. In fact, the absence of purulent secretions in the respiratory tract makes the diagnosis of VAP unlikely,<sup>12</sup> but their presence may be due to other conditions, frequently due to tracheobronchitis. The differential diagnosis between tracheobronchitis and VAP should be based on radiographic tools, usually chest radiograph, despite its known limitations in the ICU. For definite diagnosis of VAP, radiological opacity with alveolar consolidation has to be present.

The pre-test probability of development of VAP has been measured by the clinical pulmonary infection score (CPIS),<sup>13</sup> which measures the degree of fever, volume and appearance/characteristics of tracheal secretions, chest radiograph, white blood cell count, oxygenation, and tracheal aspirate culture. The score establishes the likelihood that the patient has VAP. Serial versions have been used to establish clinical resolution of VAP.<sup>14</sup> Singh et al used a modification of the CPIS and reported that low-risk patients (CPIS < 6) with suspected VAP could be treated with 3 days of antibiotic and had better clinical outcomes and fewer antibiotic-resistant superinfections than those administered 10–21 days of therapy.<sup>15</sup> Unfortunately, some variables are subjective, and the value given to each element of the score is arbitrary. So clinical suspicion of VAP has to be established when otherwise unexplained pulmonary infiltrates (new or persistent) develop on chest radiograph in conjunction with purulent respiratory secretions and clinical signs of sepsis (fever and/or leukocytosis).

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### What Microbiologic Studies Are Indicated?

The decision to start antibiotic therapy depends on the microorganisms presumed to be involved in the etiology of VAP. The choice of empirical antibiotic treatment can be improved if the decision is based on direct staining of respiratory samples. Gram stains are available for protected-specimen-brush samples,<sup>16</sup> bronchoalveolar lavage,<sup>17</sup> or tracheal aspirates.<sup>18</sup> The quality of the lower-respiratory-tract samples is also crucial in the interpretation of the microorganisms involved in the etiology of VAP. The presence of > 1% of epithelial cells in bronchoscopic samples suggests heavy oropharyngeal contamination,<sup>19</sup> as does a proportion of > 10% of epithelial cells if tracheal aspirate has been performed.<sup>20</sup> The microbiologic information is of vital importance to ensure the appropriateness of antibiotic therapy and to optimize therapy from broad to narrow spectrum if the patient is responding to therapy. Direct staining of respiratory secretions is a simple procedure and can give valuable information (in less than an hour) to guide initial therapy. Moreover, Gram staining is useful for determining the quality of the respiratory sample. On this issue some important problems are detected: for example, the previous use of antibiotic therapy or steroids, or the presence of *P. aeruginosa*, has been associated with negative direct staining.<sup>21</sup> In an international consensus conference<sup>22</sup> on the diagnosis and treatment of VAP, several experts agreed that microbiologic findings are useful and that the presence of intracellular bacteria and a positive Gram-stain (or other direct tests) may be of great help in selecting the initial antibiotic regimen, but not in making the diagnosis of pneumonia. In a recent report,<sup>23</sup> the diagnostic technique used (bronchoscopic or tracheal aspirate with quantitative cultures) did not influence either the rate of de-escalation or mortality.

Indeed, it is often forgotten that early modification of antibiotic therapy based on early-diagnosis bronchoscopic techniques performed in the hours immediately after pneumonia onset has been associated with resolution of 63% of episodes.<sup>4</sup> Performing e-test sensitivity analysis in respiratory or blood samples before microorganism identification provides important information the day following pneumonia onset, with a substantial reduction in the period of inadequate therapy (Emilio Bouza MD, Hospital General Universitario Gregorio Marañón, Madrid, Spain, conference presentation, 2005). Indeed, the rapid initiation of antibiotic therapy, avoiding delay in microbiologic sampling, has more impact on outcome than the type of semi-quantitative or quantitative technique used.<sup>23-25</sup> In summary, when VAP is clinically suspected, the antibiotic therapy should be started immediately after the collection of a microbiological sample, which should be, at the very minimum, a quantitative tracheal aspirate.

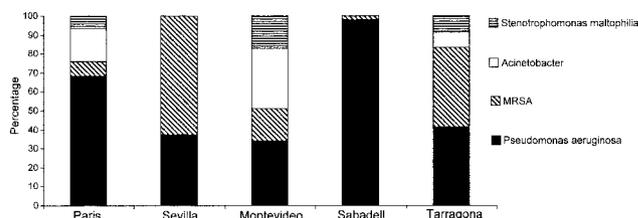


Fig. 1. Distribution of pathogens for late-onset ventilator-associated pneumonia and antibiotic exposure subset across 5 institutions in 5 cities. MRSA = methicillin-resistant *Staphylococcus aureus*. (Adapted from Reference 29.)

### What Is the Best Initial Management of VAP?

Cardiovascular support and supportive measures to improve hemodynamics and oxygenation are critical to overcoming a severe infection. The most important lesson that we have learned in the last decade is probably that delay in administration of effective therapy for intubated patients with VAP is associated with increases in mortality rate,<sup>26</sup> length of stay, and cost.<sup>27</sup>

Early, expeditious implementation of adequate antibiotics, as soon as there is clinical suspicion of VAP, should increase the likelihood of early reduction of bacterial burden of the pathogens responsible, thus minimizing the risks and the potential consequences of delayed therapy.<sup>25</sup> In addition, information regarding risk factors/comorbidities, previous antibiotic exposure, and length of hospitalization can provide useful assistance in selecting the initial antibiotic agent. The use of broad-spectrum antibiotics should be quickly narrowed, based on microbiologic information whenever possible. In this way, initial use of narrow-spectrum antibiotics may increase the probability of death due to inadequate therapy if resistant pathogens are involved.

Second, quantitative microbiological findings can enable physicians to change, adjust, or reduce the administration of antibiotics in certain patients. The majority of experts agreed that the use of broad-spectrum antibiotics for less than 48 hours would not induce substantial risk of multiresistance.<sup>22</sup>

Classifying patients according to prior duration of mechanical ventilation or prior exposure to antibiotics provides a basis for anticipating the pathogens.<sup>28</sup> Considerable information is available on the influence of certain comorbidities or risk factors such as steroids, head trauma, lung structural disease, and immunocompromise on the spectrum of the pathogens responsible for an infectious event.<sup>29</sup> However, the causes of VAP vary across different ICUs,<sup>30,31</sup> as indicated in Figure 1. These differences can be explained by differences in patients' demographics, strategies for prophylaxis, methods of diagnosis, and local patterns of resistant organisms.<sup>31</sup> Table 1 summarizes the points that determine the management of VAP in our in-

Table 1. Tarragona Strategy for Therapy of Ventilator-Associated Pneumonia

1. Antibiotic therapy should be started immediately.
2. Antibiotic choice can be targeted, in some cases, based on direct staining.
3. The prescription should be modified in the light of microbiologic findings.
4. Prolonging antibiotic treatment does not prevent recurrences.
5. Patients with chronic obstructive pulmonary disease or 1 week of intubation should receive combination therapy, because of the risk of ventilator-associated pneumonia caused by *Pseudomonas aeruginosa*.
6. Methicillin-resistant *Staphylococcus aureus* is not expected in the absence of antibiotic exposure, whereas methicillin-sensitive *S. aureus* should be strongly suspected in comatose patients.
7. Therapy against yeast is not required, even in presence of *Candida* species colonization.
8. Vancomycin administration for Gram-positive pneumonia is associated with a very poor outcome.
9. The specific choice of agent should avoid any regimen to which a patient has been exposed previously.
10. Guidelines should be regularly updated and customized to local patterns.

(Adapted from Reference 9.)

stitution. Knowledge of the local microbial epidemiology and susceptibility patterns is crucial for initial choice of antibiotics.<sup>9</sup>

Overall, some patients (those who develop infection within 5 d of hospitalization, those without recent antibiotic exposure, and those who have not had hospitalization in the past 3 months) are at low risk of infection by resistant organisms. In this subset, adequate initial selection would be a nonpseudomonal third-generation cephalosporin, because the antibiotics should target common community-acquired organisms in addition to some *Enterobacteriaceae* and methicillin-sensitive *S. aureus* (MSSA). The presence of MSSA should be strongly suspected in comatose patients. Several reports have demonstrated a higher incidence of MSSA in patients with altered level of consciousness.<sup>32</sup> Drugs effective against *S. aureus* should be included in the empirical regimen for treating nosocomial pneumonia in patients in coma.

MRSA pneumonias are common in patients with prolonged intubation periods and prior use of antibiotics. MRSA is the second most frequently isolated pathogen from patients who die of pneumonia. The treatment options for this pathogen are limited. A high mortality rate (around 50%) among patients treated with vancomycin for pneumonia caused by MRSA or MSSA has been consistently reported.<sup>33</sup> This may be because of the poor lung penetration of vancomycin, which results from prescribing label doses (1 g/12 h).<sup>34</sup> In addition, underdosing of glycopeptides is frequent in ventilated septic patients with

renal failure who have an increase in the volume of distribution. Achieving adequate steady-state levels usually takes 4 days with teicoplanin.<sup>35</sup> This evidence suggests that current glycopeptides are suboptimal for MRSA pneumonia.<sup>33,36</sup> Alternative treatment choices are restricted in 2005 to daptomycin, quinupristin/dalfopristin, or linezolid therapy. Daptomycin is ineffective in the treatment of pneumonia (Cubist Pharmaceuticals, Lexington, Massachusetts, data on file). It has limited penetration into pulmonary epithelial fluid, and its activity is inhibited by pulmonary surfactant. In a randomized trial, patients with nosocomial MRSA pneumonia<sup>37</sup> who received quinupristin/dalfopristin had a clinical response rate of 19.4%, compared with 40% in vancomycin recipients. The potential superiority of linezolid therapy over vancomycin therapy in treating nosocomial pneumonia (and VAP) due to MRSA has been noted.<sup>38,39</sup>

*P. aeruginosa* is frequent in patients with severe chronic obstructive pulmonary disease, 1 week of prior hospitalization, prolonged intubation (> 8 d), and prior exposure to antibiotics. Pneumonia caused by *P. aeruginosa* are associated with increased mortality rate and prolonged ICU stay.<sup>40</sup> Empirical treatment in patients meeting these criteria should include combination therapy with drugs with antipseudomonal activity, until a microbiological diagnosis is established; for example, those patients require initial use of combination of piperacilin/tazobactam and ciprofloxacin, or amikacin plus imipenem, meropenem, or an antipseudomonal cephalosporine. On the other hand, carbapenems are the drug of choice for patients with suspected *P. aeruginosa* infection who are receiving beta-lactamase agents. If the patient is receiving a carbapenem, an antipseudomonal fluoroquinolone is a reasonable option. Finally, if a patient with VAP is receiving a quinolone, combination therapy based on piperacillin-tazobactam should be considered.<sup>41</sup>

*A. baumannii* has specific risk factors that differ from *P. aeruginosa* or other nonfermenters. Baraiibar et al<sup>42</sup> identified the following risk factors for VAP caused by *A. baumannii*: neurosurgery, acute respiratory distress syndrome (ARDS), head trauma, and large-volume pulmonary aspiration. Resistance is increasing, and carbapenems, sulbactam, and colistin are the most sensitive agents. Sulbactam is bacteriostatic and it is suitable for mild infections, at 8 g/d. Colistin, like aminoglycosides or vancomycin, has extremely poor lung penetration. Tygeciline may be a reliable alternative in the future. *A. baumannii* tends to cause polymicrobial infections colonizing the respiratory tract of patients with artificial airways, rather than to cause invasive disease. If risk of *A. baumannii* exists, experimental models confirm that antimicrobial therapy should include a carbapenem, alone or associated to rifampin or tobramycin.<sup>43</sup>

**How to Evaluate the Clinical Resolution of VAP**

Once a patient has been diagnosed with VAP and empiric broad-spectrum antibiotic has been started, the evaluation of resolution of different clinical variables of VAP is a useful tool to tailor the response to treatment. According to standard clinical practice, the clinical response to therapy is evaluated on the third day of VAP onset, but at present there is no definition of treatment failure. No absolute consensus has been achieved regarding the gold standard to monitor response to treatment in VAP. The most widely used variables to evaluate the response to treatment in VAP have been the resolution of local or systemic inflammatory variables involved. Resolution of hypoxemia or improvement of the ratio of arterial partial pressure of oxygen to fraction of inspired oxygen ( $P_{aO_2}/F_{IO_2}$ ), resolution of radiological infiltrates, and clearance of purulent secretions as local inflammatory markers, evolution of core temperature and white blood cell count as systemic inflammatory markers, or microbiologic follow-up cultures have been used in different studies evaluating clinical resolution or failure to improve in VAP.<sup>38,39,42</sup>

Denessen et al<sup>44</sup> prospectively studied a cohort of patients with clinical diagnosis of VAP and evaluated the response to treatment based on 3 clinical variables (highest daily body temperature, highest daily leukocyte count, and  $P_{aO_2}/F_{IO_2}$  daily) and microbiologic variables measured as semi-quantitative cultures of endotracheal secretions. They defined clinical resolution of pneumonia as when fever was  $< 38^\circ\text{C}$ , leukocyte count was  $\leq 10,000$  cells/ $\mu\text{L}$ ,  $P_{aO_2}/F_{IO_2}$  was  $\geq 187$  mm Hg, and 0 or +1 growth on endotracheal cultures. The time up to resolution of VAP for clinical variables was 6 days and was delayed to 9 days when a microbiologic variable was added, even though all patients had appropriate antibiotic treatment. The earliest resolution variable was the improvement of hypoxemia. The failure of clearance of some microorganisms, mainly *P. aeruginosa* and *Enterobacteriaceae* in serial microbiologic cultures was also documented, but this variable was not a reliable variable to assess the clinical response to therapy.<sup>45</sup> The CPIS has also been evaluated to tailor the response to treatment.<sup>14,46</sup> This score has been used to evaluate response to treatment in patients with VAP,<sup>46,47</sup> with a fall in this score to  $< 6$  achieved after the fifth day of treatment interpreted as complete resolution of VAP. Similarly, a reduced version of CPIS score, analyzing the evolution of clinical variables in a cohort of patients with VAP, found that the improvement of  $P_{aO_2}/F_{IO_2}$  ratio was the only predictor of clinical response to therapy. In the same study, fever, leukocytosis, radiographic infiltrates, and clearance of purulent secretions were poor predictors of clinical response to treatment. Unfortunately, these stud-

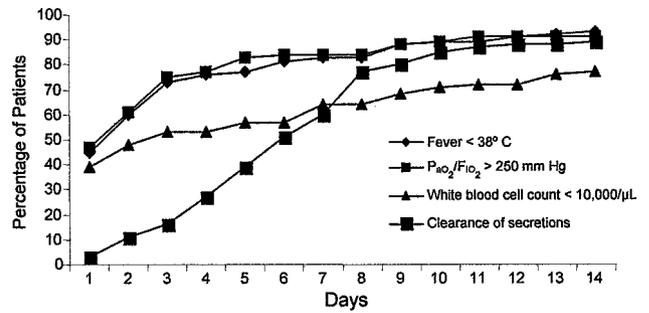


Fig. 2. Probability of clinical resolution in patients without acute respiratory distress syndrome.  $P_{aO_2}/F_{IO_2}$  = ratio of arterial partial pressure of oxygen to fraction of inspired oxygen.

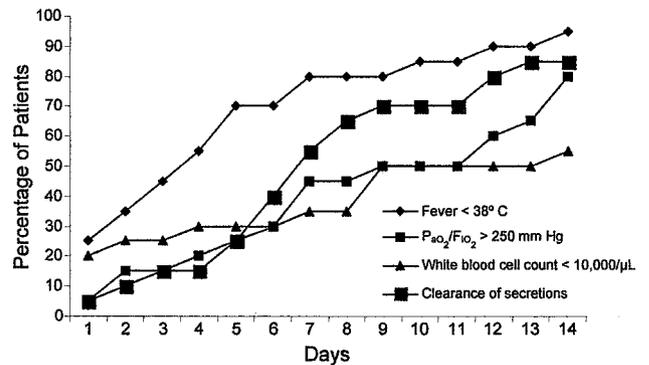


Fig. 3. Probability of clinical resolution in patients with acute respiratory distress syndrome.  $P_{aO_2}/F_{IO_2}$  = ratio of arterial partial pressure of oxygen to fraction of inspired oxygen.

ies did not evaluate the influence of ARDS in the clinical response to treatment in VAP.

Our group<sup>48</sup> has evaluated patterns of clinical resolution in patients with clinical suspicion of VAP, with or without ARDS. We prospectively evaluated 95 episodes of VAP with appropriate initial antibiotic treatment: 20 of them with ARDS and 75 without. The clinical variables for evaluating response to treatment were measured daily, starting at the time of VAP onset and followed for 15 days or until discharge from ICU or death. The 5 main variables analyzed were the evolution of core temperature, oxygenation, white blood cell count, clearance of purulent secretions, and chest radiograph infiltrates. The evolution of these variables in patients with VAP is described in Figures 2 through 4. In the group of patients without ARDS we found that  $> 70\%$  of the patients resolved fever and  $P_{aO_2}/F_{IO_2}$  within the first 48 hours of antibiotic treatment, in contrast with white blood cell count, clearance of purulent respiratory secretions, and chest radiograph infiltrates, which resolved later. The presence of ARDS delayed significantly the clinical response to treatment in critically ill patients with VAP, although temperature remained the earliest resolution variable in this group of patients. Radiological resolution was an extremely poor

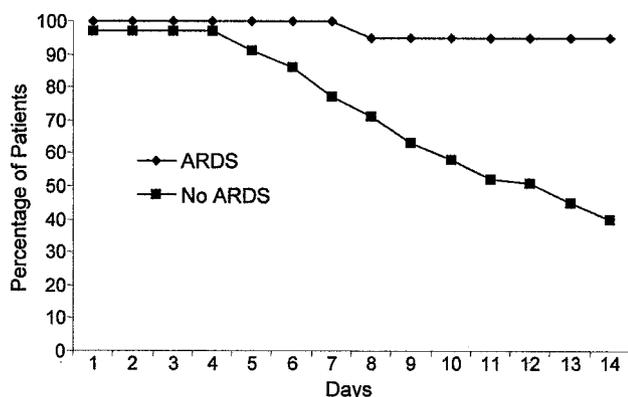


Fig. 4. Probability of clearance of radiographic infiltrates in 95 episodes of ventilator-associated pneumonia in the presence and absence of acute respiratory distress syndrome (ARDS).

indicator, being present in only 10% of ARDS patients after 15 days of follow-up. Indeed, quick radiologic resolution excludes the diagnosis of pneumonia (see Fig. 4) Failure to improve was defined as lack of resolution of at least 2 out of these 5 signs after 48 hours of therapy, and was documented in 65% of ARDS patients and 14.7% of controls ( $p < 0.05$ ). In conclusion in evaluating response to therapy in patients with VAP, the presence of ARDS should be considered in any interpretation of the variables of resolution. In patients with ARDS, monitoring fever is the most useful indicator, but median resolution takes 6 days. In contrast, 3 out of 4 patients without ARDS presented clinical resolution of fever and hypoxemia within 48 hours of therapy. In summary, to evaluate clinical response to antibiotic therapy, fever and hypoxemia are 2 clinical variables that can be easily monitored at the bedside simply by physical examination.

#### Evaluation of Patients With Delayed Resolution

In critically ill patients with clinical suspicion of pneumonia and absence of ARDS who present persistence of fever or hypoxemia after the first 3 days of therapy, physicians should look for potential causes of treatment failure, such as inappropriate initial antibiotic therapy, concomitant infection, non-infectious conditions, and causes related to the host response.<sup>49</sup> First, it is imperative to confirm that the antibiotic prescribed is appropriate to treat the microorganism responsible for VAP and optimize antibiotic therapy early. Other potential, although infrequent, causes of treatment failure are complications related to VAP, such as lung abscesses or empyema. A computed tomogram to exclude these complications should be considered. Once adequate therapy is administered for the initial microorganism, and complications related to VAP have been excluded, the presence of an early superinfection by a microorganism resistant to the antibiotic prescribed should be considered. Another possibility is a bronchoscopy with pro-

tected-specimen-brush or bronchoalveolar lavage to obtain a microbiologic sample able to diagnose superinfection and justify a concomitant change in antibiotic therapy. In addition, some *Enterobacteriaceae* may have a chromosomal ampC beta-lactamase, which is inducible, and it may be associated with poor clinical resolution despite an initial report of sensitivity. Recent reports suggest that monitoring certain inflammatory markers, such as procalcitonin or C reactive protein, may be of help in the evaluation of response to therapy.<sup>50</sup> Concomitant nonpulmonary infections, which can slow down clinical resolution of VAP, should be taken into account when evaluating a patient who fails to respond to antibiotic treatment. In the presence of treatment failure, some noninfectious conditions, such as pulmonary bleeding or bronchiolitis obliterans with organizing pneumonia, should be considered. In a subset of 71 patients with VAP,<sup>39</sup> the main causes of nonresponse to antibiotic treatment were inappropriate treatment, superinfection, concomitant infection, and noninfectious causes.

#### How Can Antibiotic Therapy Be Optimized?

The main goal of treatment of VAP in critically ill patients is the start of appropriate initial antibiotic therapy as early as possible in order to diminish mortality related to this nosocomial infection.<sup>5,51,52</sup> The initial antibiotic therapy has to cover all the responsible pathogens involved, as described in reports on management of VAP. However, the overuse of antibiotics is associated with the emergence of resistant bacteria.<sup>53</sup>

#### De-escalation of Antibiotic Therapy

An approach to the treatment of VAP based on de-escalation of antimicrobial therapy, once the microorganism responsible for VAP is isolated, diminishes the overuse of antibiotics and the emergence of resistant bacteria.

Our group<sup>23</sup> recently reported the evaluation of the practice of de-escalation in a cohort of critically ill patients with clinical suspicion of VAP. De-escalation requires the implementation of initial broad-spectrum empirical antibiotic therapy and aims to avoid the overuse of antibiotics. The first stage involves administering broad-spectrum antibiotics, and the second stage focuses on simplifying the antibiotic therapy. This approach to the management of VAP involves: (1) changing the focus from multiple agents to a single agent if *P. aeruginosa* is not present, (2) shortening the therapy to  $< 5$  days if the culture is negative and there have been  $> 48$  hours of defervescence, and (3) changing from a broad to a narrow agent in the light of culture data. In that study, patients receiving carbapenems were de-escalated to piperacillin-tazobactam, and patients receiving piperacillin-tazobactam were de-escalated to an antipseudomonal cephalosporin in the presence of *P.*

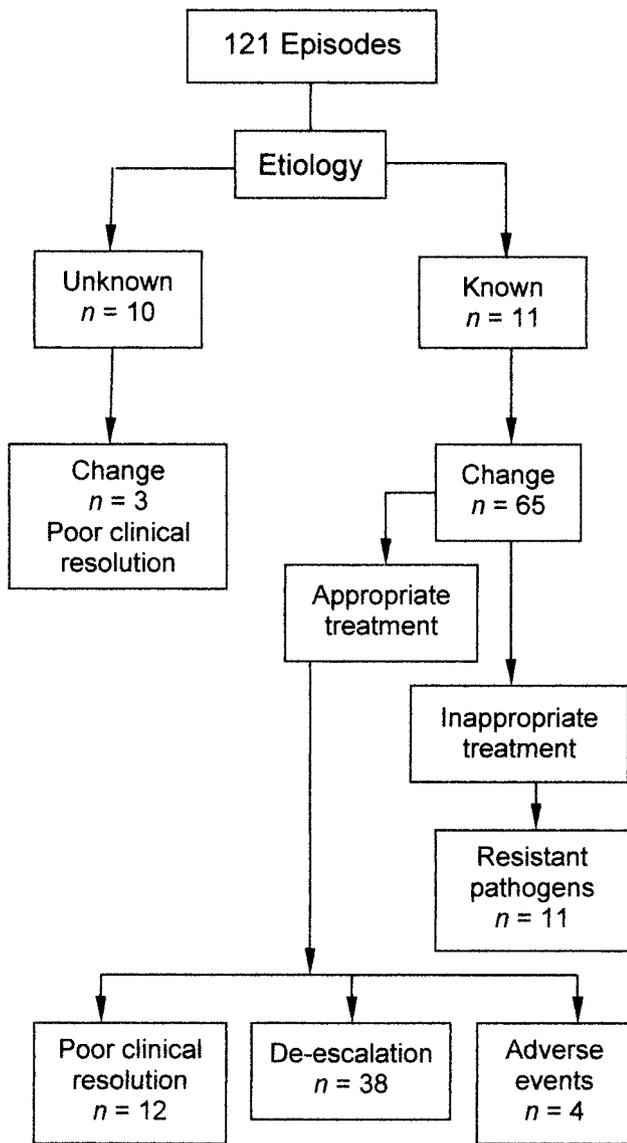


Fig. 5. Algorithm detailing changes in antibiotic therapy based on microbiological results. (Adapted from Reference 23, with permission.)

*aeruginosa*, if possible. In the absence of *P. aeruginosa*, patients with combination therapy were switched to monotherapy after discontinuation of ciprofloxacin or amikacin. Similarly, the second agent was changed to a nonantipseudomonal beta-lactam, in accordance with susceptibilities.

The changes in antibiotic therapy in the 121 episodes of VAP evaluated prospectively are detailed in Figure 5. The etiology was known in 111 episodes, and initial inadequate antibiotic therapy was reported in 9%. The microbiological results allowed a narrowing of the antibacterial spectrum in about one third of the patients. In 46 patients the empiric antibiotic therapy was not changed (Fig. 6). Interestingly, the mortality of patients with de-escalation was

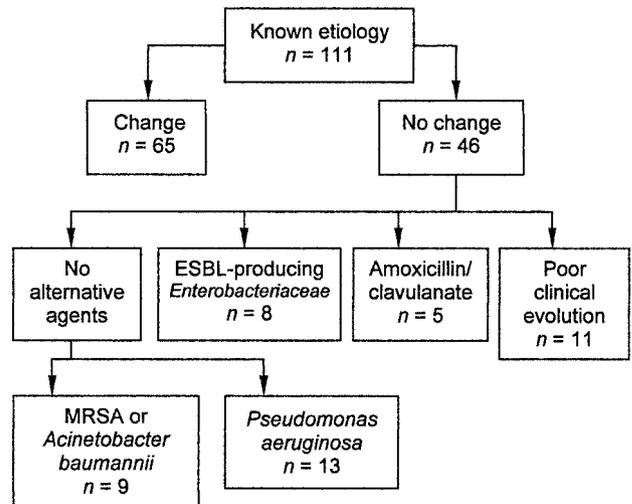


Fig. 6. Causes of no change in antibiotic therapy in ventilator-associated pneumonia episodes with known etiology. MRSA = methicillin-resistant *Staphylococcus aureus*. ESBL = extended-spectrum beta-lactamase.

lower than that observed in the group with unchanged initial antibiotic therapy (18% vs 43%,  $p < 0.05$ ).

The rate of de-escalation was significantly lower in episodes caused by potentially resistant Gram-negative bacilli. In a previous study, a rate of de-escalation of 6.1% was reported<sup>4</sup> in a cohort of patients in which almost half of the episodes were due to *P. aeruginosa*. These data suggest that the effectiveness of this approach varies according to local patterns.

In conclusion, de-escalation avoids the overuse of antibiotics, in the attempt to reduce the emergence of resistant bacteria. It is based on the change from broad-spectrum to narrow-spectrum therapy in the light of the results obtained from cultures of the lower respiratory tract. It allows the introduction of early, appropriate initial antibiotic therapy, which can increase survival in patients with VAP.

### Shorten Antibiotic Therapy

The duration of antibiotic therapy is still a controversial issue. In recent years a course of 14–21 days of antibiotic treatment has been advocated to treat VAP,<sup>54</sup> but the length of antibiotic treatment is crucial to avoid the overuse of antibiotic treatment and the emergence of multiresistant bacteria. Longer courses of antibiotics can increase costs, adverse effects, and resistant phenotypes, and do not necessarily prevent recurrences.<sup>55</sup> Shorter antibiotic regimens have been used to reduce antimicrobial costs, adverse events, and the emergence of antibiotic-resistant pathogens.<sup>15</sup> Recently, a shorter course of antibiotics has been proposed. In a prospective randomized clinical trial, Chastre et al<sup>56</sup> demonstrated that an 8-day antibiotic regimen is

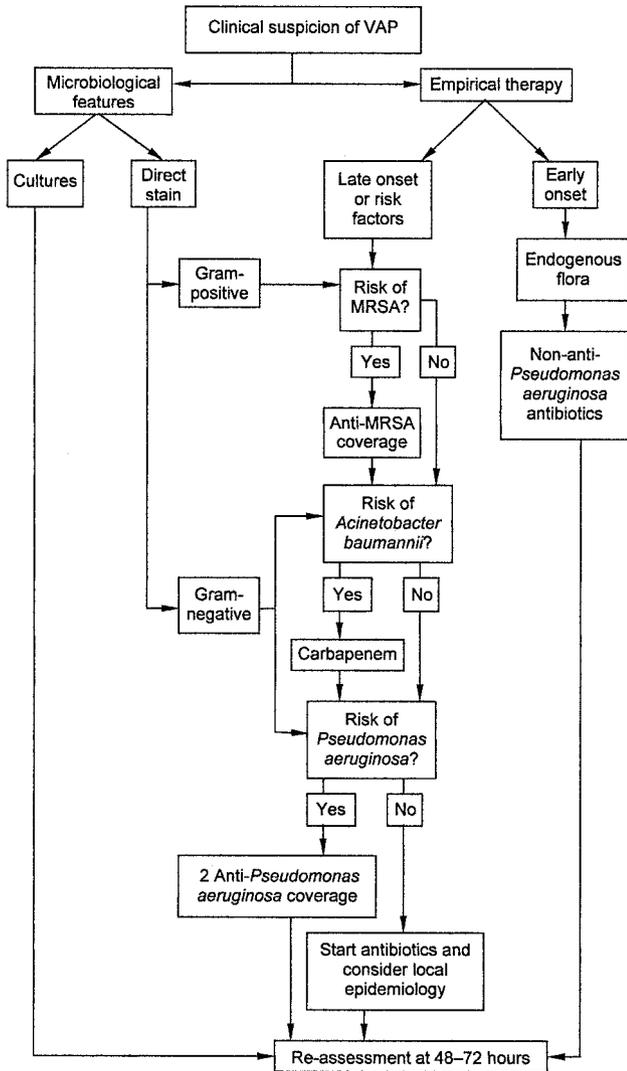


Fig. 7. Flow diagram for guidance in initial management decisions for the patient with suspected ventilator-associated pneumonia (VAP). MRSA = methicillin-resistant *Staphylococcus aureus*.

comparable to a 15-day regimen, in terms of mortality, superinfections, and relapses of VAP.

As reported elsewhere,<sup>9</sup> we recommend a patient-based approach. The duration of antibiotic therapy has to be individualized, based on clinical resolution of VAP and the response to treatment. Resolution patterns can help to optimize the duration of antibiotic therapy. After 48 hours of defervescence and resolution of hypoxemia the antibiotic therapy can be withdrawn. In the subset of patients with ARDS, fever is the main clinical variable useful for evaluating response to therapy.

**Summary**

An algorithm for the initial clinical approach to a patient with suspected VAP is summarized in Figure 7. Once a

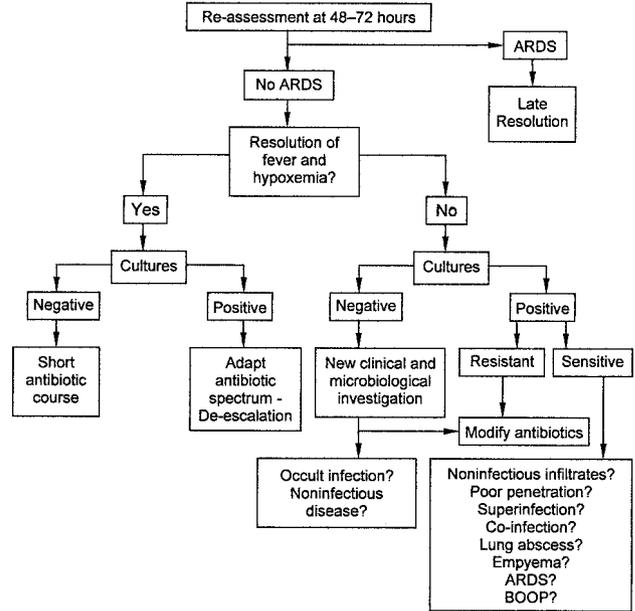


Fig. 8. Clinical approach to the patient with ventilator-associated pneumonia (VAP) at 48–72 hours of VAP onset. ARDS = acute respiratory distress syndrome. BOOP = bronchiolitis obliterans organizing pneumonia.

clinical suspicion of VAP is present (based on purulent respiratory secretions accompanied by new pulmonary opacities), lower respiratory samples with quantitative cultures, and direct staining if possible, should be obtained immediately, followed by prompt start of empirical antibiotic therapy. The choice of initial antibiotic therapy should be patient-based, taking into account the risks factors associated with VAP caused by *P. aeruginosa*, as well as the presence of index cases and risk factors for MRSA or *A. baumannii*. In the subset of patients without risk factors for these 3 organisms, a nonantipseudomonal antibiotic therapy can be prescribed. Overall, the need for expeditious choice of initial appropriate antibiotics requires the use of broad-spectrum antibiotics, followed by de-escalation, involving a switch from broad-spectrum to narrow-spectrum therapy once the microbiologic results are available.

In addition, after 48–72 hours of therapy, each patient should be re-evaluated (Fig. 8) for resolution, based mainly on evolution of hypoxemia and core temperature, in order to ensure adequate interpretation of microbiologic information. Whereas broad-spectrum therapy is warranted in many patients initially, this treatment may be narrowed considerably as culture results identify the causative organism and its sensitivity. Recent data suggest that reducing overall treatment duration to a maximum of one week is safe, effective, and less likely to promote the growth of resistant organisms in patients who are clinically improving. Optimal management should be based on a strategy

combining early high doses of an effective agent with good lung penetration for a short period of time, which can then be simplified in many patients in the light of microbiologic information and clinical resolution.

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## Discussion

**Niederman:** That was an excellent summary. If I understood your algorithm, the difference between your algorithm and the one that was published in the guideline was that if they had a clinical failure and a positive culture, they modified antibiotics but didn't do the rest of the workup for other processes. I think that at that point you need to do the rest of the workup as well, in addition to changing antibiotics.

My other comment is that it's not clear when you stop the antibiotics in that protocol. In your ARDS population, even though the clinical resolution

looked different from the nonresolution, were there differences in the duration of therapy between the 2 groups? In other words, did you use the differences in clinical resolution to lead to different durations of therapy?

**Rello:** Our protocol is recommending to stop therapy, except in the presence of severe immunocompromise or in patients with necrotizing pneumonia, 3 days after defervescence. That means that if most people had the resolution of fever in 3 days, it is expected that therapy will not be prolonged longer than one week. But the decision is left in the hands of the attending physician.

We have a protocol with a general recommendation, but the attending physician has the last word. What we realize is that patients with ARDS had only one and a half days longer antibiotic therapy. I think that this is due to the scarce information that existed in the literature until recently to use short-duration therapies. Probably attendants were reluctant to remove them and delayed the end of the antibiotic regimen. Probably with the information that it is currently available, and some newer that will be available very soon, people will be more confident with the possibility to stop antibiotics earlier.