Advances in lower respiratory tract infections in critically ill patients

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The present article is an update of the literature on lower respiratory tract infections in critical patients.
A multidisciplinary group of Spanish physicians with expertise in the field selected what they considered to be the most important papers published during 2004 and 2005. Each article was analyzed and discussed by one of the members of the panel.
A critical review of all these contributions constitutes the body of this paper.
After a review of the state of the art, papers selected in the field of new guidelines, risk factors, new diagnostic methods, antimicrobial therapy, and prevention are discussed.

Key words: **Pneumonia. Ventilator-associated pneumonia. Community-acquired pneumonia. Guidelines. Quantitative diagnostic methods. CPIS. Therapy.**

Avances en las infecciones del tracto respiratorio inferior en los pacientes en situación clínica crítica

El artículo presente recoge una actualización de la bibliografía médica relativa a las infecciones del tracto respiratorio inferior en los pacientes en situación clínica crítica. Un grupo multidisciplinario de clínicos españoles con experiencia en este área seleccionó los que consideró los artículos más importantes sobre este campo publicados en 2004 y 2005. Cada artículo fue analizado y discutido por uno de los miembros del grupo.
El artículo presente recoge una revisión crítica de todas estas contribuciones. Tras una revisión de la situación actual, se comentaron los artículos seleccionados relativos a las nuevas directrices, los factores de riesgo, los nuevos métodos diagnósticos, el tratamiento antimicrobiano y la prevención.

Palabras clave: **Neumonía. Neumonía asociada a respirador. Neumonía extrahospitalaria. Directrices. Métodos diagnósticos cuantitativos. CPIS. Tratamiento.**

Introduction (Dr. Muñoz, Dr. Torres)

In this review of the state of the art, we summarize the most relevant studies in the area of respiratory infection in critically ill patients. The period 2004-5 has been rich in manuscripts dealing with this type of infection. As regards hospital-acquired pneumonia (HAP) and specifically ventilator-associated pneumonia (VAP), the American Thoracic Society (ATS) and the Infectious Diseases Society of America (IDSA) have published guidelines for the management of HAP, VAP and health care-associated pneumonia (HCAP)[1]. The basic aims of these guidelines are to avoid having untreated or inadequately treated patients, recognize the variability of bacteriology between hospitals and units, avoid the overuse of antibiotics by focusing on accurate diagnosis, tailoring therapy to the results of lower respiratory tract cultures, shortening therapy to the minimal effective period and, applying prevention strategies aimed at modifiable risk factors. Notably, these guidelines are also addressed to patients with health-care-associated pneumonia who were considered as community-acquired pneumonia (CAP) patients in the past.

Diagnosis of VAP is still a controversial issue. Luyt et al[2] retrospectively assessed the diagnostic value of the clinical pulmonary infection score (CPIS). In our opinion, the calculation of the CPIS on day 1 does not add significantly to the use of clinical parameters for the suspicion of VAP. In addition, the many different ways to calculate it confuse the issue even more. This score is probably more useful as a prognostic tool and to detect non-responding patients.

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Sampling methods for VAP have been a matter for discussion for the last decade. Another study[3] comparing different sampling methods of respiratory secretions in suspected VAP confirmed that blind protected methods are as accurate as bronchoscopic methods. Specifically, blind protected specimen brush (PSB) resulted in a similar diagnostic yield to PSB and bronchoalveolar lavage (BAL) via fiberoptic bronchoscopy. This type of sampling is very useful for those units that do not have bronchoscopy available 24 hours a day.

Prevention of VAP and identification of potentially modifiable risk factors are important goals, and methods with level-I evidence should be considered performance indicators. Shorr et al[4] have explored the potential link between red blood cell tranfusion and VAP, and have found a significant correlation between the number of units transfused and the risk of VAP. One of the explanations for this finding is the increased inflammatory response triggered by leukocytes in the transfused blood. Regulatory authorities in some countries have implemented the policy of depleting leukocytes from red blood cell transfusion.

Aspiration of secretions through the endotracheal tube or tracheostomy is a cause for concern due to the potential risk of exogenous transmission of infection. For that reason, closed systems have been developed. A randomized trial[5] comparing closed and open systems demonstrated no advantage of the closed systems in preventing VAP, thus indicating that there is no reason for giving up conventional procedures to aspirate respiratory secretions.

As mentioned above, one of the main focuses of the HAP Guidelines1 is to avoid the overuse of antibiotics. A study published this year[6] confirms the safety of withdrawing antibiotics in the case of negative cultures from BAL samples in patients with suspected VAP. To follow this policy, it is imperative to obtain respiratory secretions for culture before administering antibiotics.

Lack of response to empiric antibiotic treatment is a frequent clinical problem in HAP and in VAP. In one study, Ioanas et al[7] found a 62% incidence of lack of response. Methicillin-resistant *Staphylococcus aureus* (MRSA) was one of the main causes of non-response, and this was associated with higher TNF alpha levels on day 1. Overall non-response and mortality were associated with higher levels of inflammatory response (IL6 in blood), indicating that non-response can be detected at an early stage of infection by inflammatory markers.

Although the attributable mortality of VAP has recently been questioned in a multicenter study[8], VAP caused by MRSA has a high morbidity and high crude mortality. One of the main reasons for this may be the lack of good antibiotics against this infection. The new HAP guidelines recommend vancomycin or linezolid to treat MRSA infection. Linezolid is specifically recommended for renal failure. Several recently published studies, all of them from post-hoc analyses, found linezolid to be superior to vancomycin against MRSA. Kollef et al confirm[9] this finding in a new study. Multivariate analysis revealed that clinical cure (odds ratio [OR] 20) and mortality (OR 4.6) were significantly better with linezolid than with vancomycin. This evidence sheds doubt on whether we should continue to treat MRSA pneumonia with vancomycin instead of linezolid.

Implementation of and adherence to guidelines is followed by better outcomes both in HAP and in CAP. In 2005, three studies confirmed the beneficial effects of guidelines. In one study on HAP, Soo-Hoo et al[10] found an important decrease in two-week mortality after the implementation of the 2001 ATS guidelines. In CAP, Bodi et al[11] reported increased survival in ICU cases when applying the current IDSA guidelines (OR 1.66). One of the main issues concerning lack of adherence was the absence of coverage of community-acquired *Pseudomonas* infections. Finally, Menendez et al[12] also found increased mortality and lack of response when CAP guidelines were not followed. These studies and others provide a body of evidence in favor of the development and implementation of guidelines for HAP, VAP, and CAP.

The hypothesis that the administration of steroids in severe respiratory infections is beneficial is not new. In fact, they have proven to be effective in *P. jirovecii* pneumonia and in varicella and SARS pneumonia. The rationale of administering steroids in pneumonia is to reduce increased lung and systemic inflammatory response due to pneumonia or secondary to the administration of bactericidal antibiotics (Beta-lactams). Confalonieri et al[13] provide evidence of this in a randomized trial comparing hydrocortisone plus antibiotics vs. antibiotics alone. The zero mortality in the study group and the imbalances between groups mean that more evidence should be obtained before indicating steroids for adjunctive therapy in severe CAP.

Papers selected and discussed

The following articles were selected and discussed by members of the group.

American Thoracic Society Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. Am J Respir Crit Care Med. 2005;171:388-416.

This document, prepared by a joint committee of the ATS and IDSA, focuses on the epidemiology, pathogenesis, etiology, diagnosis, and treatment of bacterial HAP, including HCAP and VAP. Some of the key recommendations and principles in this new, evidence-based guideline are as follows:

– HCAP is included in the spectrum of HAP and VAP, and patients with HCAP need therapy for multi-drug resistant (MDR) pathogens.

– A lower respiratory tract culture needs to be collected from all patients before antibiotic therapy, but collection of cultures should not delay the initiation of therapy in critically ill patients.

– Either "semiquantitative" or "quantitative" microbiological culture data can be used for the management of patients with HAP.

– Lower respiratory tract cultures can be obtained bronchoscopically or non-bronchoscopically, and can be cultured quantitatively or semiquantitatively.

– Quantitative cultures increase the specificity of the diagnosis of HAP with no deleterious consequences, and the specific quantitative technique should be chosen on the basis of local expertise and experience.

– Negative lower respiratory tract cultures can be used to stop antibiotic therapy in a patient whose cultures were obtained in the absence of a change in antibiotic during the past 72 hours.

– Early, appropriate, broad-spectrum, antibiotic therapy should be prescribed with adequate doses to optimize antimicrobial efficacy.

– An empiric therapy regimen should include agents that are from a different antibiotic class than those the patient has recently received.

– Combination therapy for a specific pathogen should be used judiciously in the therapy of HAP, and short-term (5 days) aminoglycoside therapy should be considered when used in combination with a beta-lactam to treat *P. aeruginosa* pneumonia.

– Linezolid is an alternative to vancomycin, and unconfirmed, preliminary data suggest it may have an advantage for proven VAP due to MRSA.

– Colistin should be considered as therapy for patients with VAP due to a carbapenem-resistant *Acinetobacter* species.

– Aerosolized antibiotics may have value as adjunctive therapy in patients with VAP due to some MDR pathogens.

– Tapering of antibiotics should be considered once data are available on the results of lower respiratory tract cultures and the patient's clinical response.

– A shorter duration of antibiotic therapy (7 to 8 days) is recommended for patients with uncomplicated HAP, VAP, or HCAP who have initially received appropriate therapy and have had a good clinical response, with no evidence of infection with non-fermenting gram-negative bacilli.

These new HAP guidelines mean that this information can now reach medical staff (administrators for quality and safety, physicians, and nurses). It will provide epidemiologic data on the prevalence and types of MDR pathogens in ICU patients, to help select appropriate initial antibiotic therapy. Specific parts of the guidelines are useful for the medical and surgical services, including the ICU. It will be necessary to monitor adherence to the guidelines for patient outcome in HAP. The guidelines should also be used to identify modifiable risk factors for HAP, and develop programs to reduce the risk of pneumonia by changing these risk factors.

Unfortunately these guidelines have some limitations. Firstly, they do not provide information for immunosuppressed patients with HAP, VAP, or HCAP (HIV infection, hematologic malignancy, chemotherapy-induced neutropenia, organ transplantation, etc). However, they do provide information on adult patients with bacterial HAP, VAP, or HCAP, although other causes of pneumonia (fungal, viral) were excluded. The committee extrapolated data on risk factors and bacteriology to all patients with HAP, although there were few data available on HAP in non-intubated patients and on HCAP. Finally, nearly all of the evidence-based data on risk factors for bacterial HAP have been collected from observational studies, and there were only a few prospective and randomized therapy trials. Despite these limitations, the new ATS/IDSA guidelines provide very useful information for the initial management of patients in whom HAP, VAP, or HCAP is suspected.

Luyt CE, Chastre J, Fagon JY. Value of the clinical pulmonary infection score for the identification and management of ventilator-associated pneumonia. Intensive Care Med. 2004;30:844-52.

The objective of the study by Luyt et al was to evaluate the potential ability of an algorithm based on the CPIS to identify and treat patients with suspected bacterial VAP compared with a strategy based on quantitative cultures of bronchoscopic specimens[2].

This was a case-control study using data previously recorded from a multicenter randomized trial considering microbiological diagnosis as the gold standard. The study included 201 patients clinically suspected of having VAP who had been included in the "invasive strategy" group of the French multicenter randomized trial. In all cases, quantitative cultures from bronchoscopically obtained specimens were available. CPIS was determined retrospectively using data collected for the initial multicenter study.

Interestingly, the CPIS was similar in both groups on day one (when the pneumonia was first suspected), although when the same score was analyzed on day 3, the results were statistically significant.

The CPIS showed an acceptable sensitivity (89%) but a rather poor specificity (47%). Thus, the negative predictive value of the CPIS is acceptable, although the frequency of VAP used in its calculation is 44%, which is probably greater than in most ICU. There is low concordance with the microbiological results.

The authors propose that it could be more appropriate to give different weights to some of the variables used to calculate the CPIS. However, the study was not designed to analyze this. The analysis of the receiver operating characteristic (ROC) curve of the CPIS is also interesting, since it suggest that a breakpoint of 7, instead of the currently used 6, would be more appropriate (positive likelihood ratio from 1.6 to 2.21).

The CPIS score is useful when the clinician suspects VAP but it lacks specificity, probably due to the lack of specificity of some of the variables used for its calculation. Besides, some variables are observer-dependent, which represents an additional difficulty.

Mentec H, May-Michelangelo L, Rabbat A, Varon E, Le Turdu F, Bleichner G. Blind and bronchoscopic sampling methods in suspected ventilator-associated pneumonia. A multicentre prospective study. Intensive Care Med. 2004;30:1319-26.

Microbiological evaluation of VAP is important when confirming diagnosis and ensuring adequate use of antimicrobials. The relative efficacy of invasive and non-in-

vasive tracheobronchial sampling methods for microbiologial diagnosis remains unclear. This study evaluated different diagnostic techniques for VAP.

Mentec et al performed a prospective multicenter study to compare blind tracheal aspirate (TA), blind protected telescopic catheter (PTC), bronchoscopic PTC, and BAL for confirmation of VAP[3]. Patients receiving mechanical ventilation for more than 48 hours with clinically suspected VAP and no recent (< 72 hours) modification of antibiotic treatment were included. All four specimens were forwarded to the microbiology laboratory for direct examination and quantitative culture within 15 minutes of sampling. Five ICUs in France participated in the study. Sixty-three patients were enrolled and after microbiological testing were classified as definite pneumonia[1], probable pneumonia (33), uncertain pneumonia (11) (were excluded from analysis), probable absence of pneumonia (13), and definitive absence of pneumonia (5).

In summary, 34 patients constituted the VAP group and 18 patients the non-pneumonia group. Direct examination of PTC (either blind or bronchoscopic) did not differ from direct examination of bronchoscopic BAL in predicting VAP and in guiding initial antibiotic treatment. Qualitative concordance of cultures of the sampling methods was low. Compared with that of bronchoscopic BAL (0.977), the area under the ROC curve was smaller for blind TA (0.783, p = 0.002), blind PTC (0.829, p = 0.009), and bronchoscopic PTC (0.848, p = 0.01). When samples with visible secretions expelled from the catheter were considered, blind and bronchoscopic PTC had areas under the ROC curve close to those of bronchoscopic BAL (0.902, p = 0.22 and 0.913, p = 0.27, respectively), and showed better operating characteristics.

In our opinion, two clear conclusions may be drawn from this study. First, qualitative agreement between the Gram stain on direct sample and organisms that were eventually considered clinically significant was low (42-63%). Second, the highest negative predictive values were provided by the absence of bacteria on direct examination of bronchoscopic BAL (100%) and, to a lesser extent, on blind TA (82%). These data, along with the limited contribution of routine microbiological specimens in guiding the initial choice of an antimicrobial for VAP and the high prevalence of inappropriate initial antibiotic therapy when it was based on colonization and direct examination, favor the initial prescription of a broad-spectrum antibiotic according to general and local guidelines. The diagnostic yield of a sampling technique depends on the quality of each step of the procedure. As far as we know, few studies have emphasized the need for quality assessment when interpreting distal bronchial samples in cases of suspected VAP. The observation that some routine PTC showed no polymorphonuclear cells or bacteria on direct examination and no growth in culture is a matter for concern, since resampling was of less value when antibiotics had been started. In the present study, when visible secretions were expelled from the catheter, the diagnostic yield pf PTC, both blind and bronchoscopic, was considerably improved.

In summary, if the present results are confirmed, blind TA and blind PTC sampling would be an inexpensive, safe, and readily available alternative to bronchoscopic BAL for microbiological confirmation of suspected VAP. The clinical efficiency of this strategy should be prospectively studied.

Shorr AF, Duh MS, Kelly KM, Kollef MH, the CRIT Study Group. Red blood cell transfusion and ventilator-associated pneumonia: A potential link? Crit Care Med. 2004;32:666-74.

Shorr et al[4] analyzed the possible relationship between packet red blood cell (pRBC) transfusion and the development of VAP. To address this issue, they performed a secondary analysis of a large, multicenter, prospective observational study (CRIT trial) that tracked ICU transfusion practice in the United States[14]. The original study was performed between August 2000 and April 2001 in 284 ICUs of varying types, and included 4892 patients, of whom 1563 (32.2%) received mechanical ventilation (MV) for ≥ 48 hours. The primary endpoint of the secondary analysis by Shorr et al[4] was the development of VAP. Pneumonia was prospectively defined based on a modification of the American College of Chest Physicians clinical criteria[15]. Specifically, pneumonia required the presence of fever, leukocytosis, and purulent secretions. Additionally, patients had to have new or progressive infiltrates on a chest radiograph. The subset of late-onset VAP (VAP arising after ≥ 5 days of MV) was an additional endpoint.

The investigators used different factors to compare 311 (20.5%) patients who developed VAP with 1207 ventilated subjectswho did not. Multivariate analysis revealed that transfusion independently increased the risk for VAP (odds ratio [OR] 1.89; 95% CI, 1.33-2.68). Other factors increasing the risk for VAP included male sex (OR 1.54; 95% CI, 1.15-2.07), admission after trauma (OR 1.68; 95% CI, 1.15-2.47), use of continuous sedation (OR 1.43; 95% CI, 1.07-1.92), and type of nutritional support (e.g., early enteral nutrition: OR 2.65; 95% CI, 1.93-3.63; total parenteral nutrition: OR 3.27; 95% CI, 2.24-4.75). The effect of transfusion on late-onset VAP was more pronounced (OR 2.16; 95% CI, 1.27-3.66) and demonstrated a positive dose-response relationship (p = 0.0223 for trend test).

Although the correlation between transfusion and nosocomial infection has been reported elsewhere[16-18], the study by Shorr et al. is the first to identify transfusion as an independent risk factor for VAP. They found that both small transfusion volumes (1-2 units of pRBC) and large volumes (> 2 units of pRBC) are associated with VAP. It has been speculated that transfusion promotes the release of cytokines, which, in turn, enhances several cytokine cascades. Additionally, the donor's white blood cells in a unit of pRBC may serve as a foreign antigen and induce an immunomodulatory effect by altering T-cell function. Nevertheless, the reasons why transfusion might promote VAP are not clear. A major shortcoming of this study[4] is that microbiologic cultures from patients with VAP were not collected. In this regard, it can be argued that some patients included in the study could not really have pneumonia and that transfusion could have been the true cause of fever and pulmonary infiltrates. Therefore, further studies to confirm these results are warranted.

In summary, Short et al found that pRBC transfusions should be regarded as a risk factor for developing VAP.

Therefore, avoiding the unnecessary use of pRBC transfusions may decrease the occurrence of VAP.

Lorente L, Lecuona M, Martín MM, García C, Mora ML, Sierra A. Ventilator-associated pneumonia using a closed versus an open tracheal suction system. Crit Care Med. 2005;33:115-9.

The closed-tracheal suctioning system (CTSS) is claimed to cause lower respiratory and hemodynamic impairment during respiratory secretion suctioning than the open tracheal suctioning system (OTSS), since with the latter technique patients need to be disconnected from the respiratory circuit. However, there is no clear evidence of a relationship with VAP.

Lorente et al studied 433 medical/surgical patients who had undergone more than 24 hours of MV in a prospective and randomized study[5]. The endpoints were overall incidence of VAP, VAP incidence-density (number of cases of VAP/1000 days of MV), and VAP incidence in relation to different durations of MV (1-2, 3-4, 5-9, 10-14, 15-19, 20-24, and 25 days). VAP was classified as endogenous or exogenous according to the microorganisms colonizing the throat before pneumonia. The cost of tracheal suction per day was compared, but unfortunately, hemodynamic or respiratory complications during suctions were not analyzed.

The study included 443 patients (210 with CTSS and 233 with OTSS). The incidence of VAP (20.47% vs 18.02%) and the number of VAP cases per 1000 MV-days (17.59 vs 15.84) was similar in both groups. There were no differences in the incidence of VAP according to duration of MV. The proportion of exogenous pneumonia was also comparable: 4.35% with CTSS vs 4.25% with OTSS. There were no differences in the microorganisms responsible for pneumonia: *Pseudomonas aeruginosa* (12 cases in the CTSS group vs 12 cases in the OTSS group); *Stenotrophomonas maltophilia* (2 vs 7 cases); *Acinetobacter* species (1 vs 2 cases); *Escherichia coli* (3 vs 2 cases); *Klebsiella* species (4 vs 2 cases); *Enterobacter* species (3 vs 3 cases); *Serratia marcescens* (5 vs 1 case); *Morganella morganii* (0 vs 1 case); *Proteus mirabilis* (0 vs 2 cases); *Haemophilus influenzae* (1 vs 2 cases); methicillin-sensitive *Staphylococcus aureus* (2 vs 6 cases); MRSA (8 vs 5 cases); *Streptococcus pneumoniae* (2 vs 1 case); *Enterococcus faecalis* (0 vs 2 cases); *Streptococcus agalactiae* (0 vs 1 case); *Candida albicans* (2 vs 0 cases) and *Candida parapsilosis* (0 vs 1 case). Suction was more expensive with the closed system: \$11.11 ± 2.25 per day vs \$2.25 ± 1.12 per day.

In conclusion, according to the results of this study, CTSS did not reduce the incidence of VAP, even for exogenous pneumonia, and it is more expensive.

Kollef MH, Kollef KE. Antibiotic utilization and outcomes for patients with clinically suspected ventilator-associated pneumonia and negative quantitative BAL culture results. Chest. 2005;128:2706-13.

Kollef et al evaluated antibiotic utilization and clinical outcome of patients with clinically suspected VAP and culture-negative BAL (CNBAL)[6]. This was a prospective observational cohort study including 101 patients with clinical suspicion of VAP and CNBAL.

Patients were prospectively followed-up. Antibiotics were discontinued according to clinical guidelines and not because of the results of BAL cultures. The average age of the patients was 60 years and the mean APACHE II and CPIS scores were 23 and 6, respectively. Empiric antibiotic therapy for VAP was begun in 65 patients (64%) following BAL. The median duration of empiric antibiotic treatment following BAL was 2 days (range, 1 to 3 days). Six patients (6%) were treated with antibiotics for a secondary episode of VAP or nosocomial pneumonia developing at least 72 hours after CNBAL and empiric antimicrobial therapy was discontinued for the initially suspected episode of VAP.

Overall, 35 patients (35%) died during hospitalization. Two deaths occurred in patients with a secondary episode of VAP following CNBAL and discontinuation of empiric antimicrobial therapy. Neither of these two deaths was attributed to VAP. The authors conclude that, although the decision to discontinue antibiotic treatment was based on clinical criteria and not on BAL culture results, patients with a clinical suspicion of VAP and CNBAL can have antimicrobial therapy safely discontinued within 72 hours or, in some cases, withheld altogether.

Increasingly, patients in the ICU setting have risk factors for infection caused by antibiotic-resistant bacteria. Therefore, this patient population requires initial empiric treatment with broad-spectrum antibiotics. Nevertheless, competing with the need to administer appropriate initial antibiotic therapy is the necessity to prevent further antibiotic resistance. This study suggests that mechanically ventilated patients with a clinical suspicion of VAP and CNBAL can have antimicrobial therapy safely discontinued within 72 hours. Nevertheless, as the authors remark, there are several drawbacks that threaten the validity and generalizability of this study. It was performed in a single medical ICU. The relatively low CPIS values observed in this cohort suggest that they represent a group of patients at a very low risk for VAP. Furthermore, the authors were not able to compare CNBAL patients with those with positive or indeterminate BAL culture results. Large scale prospective, randomized studies are needed to determine the efficacy and safety of CNBAL as the primary criterion for the discontinuation of empiric antibiotic treatment for VAP.

Ioanas M, Ferrer M, Cavalcanti M, Ferrer R, Ewig S, Filella X et al. Causes and predictors of nonresponse to treatment of intensive care unit-acquired pneumonia. Crit Care Med. 2004;32:938-45.

Ioanas et al analyzed 71 patients with ICU-acquired pneumonia in a prospective study to evaluate the predictive factors for non-response to empiric antibiotic treatment and mortality[7]. Patients were enrolled in a one-year prospective cohort with suspicion of ICU-acquired pneumonia in five medical and surgical ICUs of the Hospital Clinic in Barcelona. The definition of non-response included at least one of the following: failure to improve the PaO_2/FiO_2 ratio or need for intubation because of pneumonia, persistence of fever or hypothermia and purulent

respiratory secretions, worsening of pulmonary infiltrates, occurrence of septic shock, or multiple organ dysfunctions not present at the onset of pneumonia. Clinical assessment included severity scores, blood and quantitative cultures of respiratory secretions, and cytokine measurements in serum and bronchoalveolar lavage at the onset of pneumonia and 72 hours after antimicrobial treatment.

A total of 44 patients (62%) fulfilled the criteria for non-response, and at least one cause of non-response could be determined in 28 cases (64%): inappropriate treatment in 10 (23%), superinfection in 6 (14%), concomitant foci of infections in 12 (27%), and non-infectious causes in 7 cases (16%). The remaining 16 patients with no definite case of non-response presented with septic shock, multiple organ dysfunction, or acute respiratory distress syndrome.

Increased levels of interleukin-6 at the onset of pneumonia (OR 9.7; p = 0.014) was an independent predictor of non-response to treatment. Similarly, an increased level of interleukin-6 at follow-up (OR 27; p = 0.001) was the only independent predictor for hospital mortality. The authors concluded that increased systemic inflammatory response was the main predictor of non-response to treatment and mortality.

Zahar JR, Clec'h C, Tafflet M et al. Is methicillin resistance associated with a worse prognosis in *Staphylococcus aureus* ventilator-associated pneumonia? Clin Infect Dis. 2005;41:1224-31.

The mortality caused by MRSA VAP has increased, although it is not completely clear whether the reason is methicillin resistance itself, or if some confounding variables may influence mortality. Furthermore, MRSA strains have not been proven to be more virulent than MSSA strains, as some experimental models have found that their pathogenicity was similar. In this study, Zahar et al evaluated whether the excess mortality due to MRSA in VAP was related to methicillin resistance or if it was related to other variables, such as treatment adequacy and length of stay in the ICU[8].

In a prospective observational study in the multiple health center Outcomerea database from 12 French ICUs, 134 episodes of *S. aureus* VAP were collected: 65 with MSSA VAP and 69 with MRSA VAP. The statistical analysis was stratified for duration of stay in ICU at the time of VAP diagnosis, and adjusted for confounders: severity on admission, characteristics at VAP diagnosis, and treatment adequacy.

The authors found that MRSA VAP was associated with a lower prevalence of coma on admission to the ICU, and a greater use of central venous lines and fluoroquinolones during the first 48 hours of ICU stay. However, the rates of shock, recurrence, and superinfection were similar in both groups. In line with previous studies, they found that treatment was adequate for 86% of the 65 MSSA-infected patients compared with 77% of the 69 MRSA-infected patients, although this difference did not reach statistical significance (p = 0.2). The crude mortality rate was higher for MRSA VAP than for MSSA VAP (59.4% vs 40%, p = 0.024).

In the multivariate analysis after controlling for time in the ICU before VAP and other parameters, this difference disappeared (OR 1.23 95% CI, 0.5-3.1, p = 0.7). After further adjustments for initial treatment adequacy and polymicrobial VAP, it was proven that there was no difference in mortality between MRSA VAP and MSSA VAP.

The study by Zahar et al confirms that there are differences in the clinical characteristics of MRSA VAP and MSSA VAP: time of ICU stay at VAP diagnosis was significantly longer (12 vs 6 days) and appropriate initial treatment was lower (76.8% vs 86.1%) in MRSA VAP. Patients with neurological failure on admission to the ICU had more MSSA VAP, and patients with MRSA colonization within the first 48 hours or a central venous line were more prone to MRSA VAP. Curiously, the previous use of fluoroquinolone therapy was four times more frequent in the MRSA group. This association has been previously reported by Weber et al in a case control study which included several variables analyzed as confounders[19]. A possible explanation would be that fluorquinolones might decrease the rate of MSSA VAP. Rello et al also found that patients with MRSA showed a 20 times higher crude mortality, although the patients were older, had more chronic respiratory diseases, more corticosteroid treatments, and a longer duration of MV[20].

In summary, the excess mortality of MRSA VAP may be explained by the differences in patient characteristics, inappropriate initial treatment, and longer length of stay in the ICU, but not by methicillin resistance itself.

Kollef MH, Rello J, Cammarata SK, Croos-Dabrera RV, Winderink RG. Clinical cure and survival in gram-positive ventilator-associated pneumonia: Retrospective analysis of two double-blind studies comparing linezolid with vancomycin. Intens Care Med. 2004;30:388-94.

Different studies have demonstrated that appropriate empiric antimicrobial therapy improves the survival rate of VAP. The options for treating MRSA VAP are scarce: vancomycin and teicoplanin. Both antibiotics have problems of tissue penetration and low drug levels in the lung. More recently, linezolid seems to have solved some of these problems. Kollef et al assess the effect of baseline variables, including treatment, clinical cure, and survival rates on patients with Gram-positive VAP[9].

The authors performed a retrospective analysis of two randomized, double-blind, prospective and multinational studies at 134 sites to compare linezolid with vancomycin as treatment of VAP. The study patients had clinical and radiographic findings which were compatible with the suspected diagnosis of VAP. Patients with resistant organisms were excluded. Participants were randomly assigned to receive either 600 mg of linezolid or 1 g of vancomycin intravenously every 12 hours for 7-21 consecutive days, and all patients received aztreonam 1-2 g every 8 hours to cover possible Gram-negative pathogens.

A total of 1030 patients were enrolled and randomized in the studies and 544 had VAP, including 264 with Gram-positive VAP (134 received linezolid and 130 vancomycin). The intention-to-treat analysis (ITT) of *S. aureus* VAP identified 110 patients in the linezolid arm and 111 the vancomycin group. Finally, a total of 91 patients with MRSA VAP were studied (44 with linezolid and 47 with

TABLE 1. **Clinical cure rates of patients treated with linezolid or vancomycin**

	Linezolid (%)	Vancomycin (%)	p
VAP	45.4	36.7	0.07
Gram-positive VAP	53.7	37.7	0.02
S. aureus VAP (All)	48.9	35.2	0.06
S. aureus VAP (INV)	49	34	0.10
MRSA VAP	62.2	21.2	0.001

All: all cases with *S. aureus* isolated using invasive or non-invasive diagnostic procedures INV: positive invasive diagnostic procedures or blood cultures.

TABLE 2. **Survival rates of patients treated with linezolid or vancomycin**

	Linezolid (%)	Vancomycin (%)	p
VAP	79.1	73.7	0.15
Gram-positive VAP	80.6	70.8	0.07
S. aureus VAP (All)	78.2	70.3	0.19
S. aureus VAP (INV)	77	68	0.26
MRSA VAP	84.1	61.7	0.02

All: all cases with *S. aureus* isolated using invasive or non-invasive diagnostic procedures INV: positive invasive diagnostic procedures or blood cultures.

vancomycin). Other Gram-positive pathogens included were *S. pneumoniae* (32 patients, including 9 with penicillin-resistant *S. pneumoniae*), *E. faecalis* (18 patients), *S. agalactiae* (10 patients), *E. faecium* (8 patients), and *S. pyogenes* (3 patients). No *S. aureus* had an MIC > 2 µg/ml for vancomycin. Clinical cure rates are shown in table 1.

Logistic regression analysis identified two independent predictors of clinical cure: APACHE II score (< 20) and use of linezolid. The results of the logistic regression for linezolid in each group were as follows: all VAP (n = 434) OR 1.8 (1.2-2.7; p = 0.008); ITT Gram-positive VAP (n = 214) OR 2.4 (1.3-4.3; p = 0.005); *S. aureus* VAP (n = 179) OR 2.1 (1.1-4.0; p = 0.031); and MRSA VAP (n = 70) OR 20.0 (4.3-92.0; p < 0.001).

Bacterial eradication rates were significantly better with linezolid than with vancomycin only in patients with MRSA VAP (60.5% vs 22.9%. p = 0.001), but not in patients with ITT Gram-positive VAP (49.2% vs 37.6%. p = 0.067) or ITT *S. aureus* (45.6% vs 33.3%. p = 0.091). Survival results are shown in table 2.

Linezolid therapy was an independent predictor of survival for all patients with VAP (OR 1.6; 95% CI, 1.0-2.4; p = 0.04), for patients with Gram-positive VAP (OR 2.6; 95% CI, 1.3-5.1; p = 0.006), and patients with MRSA VAP (OR 4.6; 95% CI, 1.5-14.8; p = 0.01). The authors conclude that initial therapy with linezolid instead of vancomycin was associated with significantly improved clinical cure rates, improved bacterial eradication, and improved survival in patients with MRSA VAP.

The clinical cure and survival benefits of linezolid in MRSA VAP compared with vancomycin therapy are similar to those of other studies of nosocomial MRSA pneumonia[21,22]. One possible reason is the poor tissue penetration in the lung and low concentrations of vancomycin in critical patients. For many experts, the main difference in clinical cure and survival between patients with MSSA and MRSA VAP is not the virulence of the microorganisms, but the low response to vancomycin.

This study has some limitations: it is a retrospective analysis; many patients have not been diagnosed with VAP by invasive procedures or blood culture (50% of MRSA VAP); there is no statistical difference in mortality in the subgroup of VAP patients with microbiological confirmation by invasive methods or blood or pleural fluid culture, or in the subgroup of patients with *S. aureus* VAP; and, it is not possible to determine whether some cases of VAP were mere colonizations. It is surprising that clinical cure, bacterial eradication, and survival rate were better for MRSA, but not for the overall *S. aureus* group. In fact, other studies that compared vancomycin with other antibiotics (for example, cloxacillin) in *S. aureus* pneumonia showed significantly better results with the second therapy.

Soo Hoo GW, Wen YE, Nguyen TV, Goetz MB. Impact of clinical guidelines in the management of severe hospital-acquired pneumonia. Chest. 2005;128: 2778-87.

Dr Soo Hoo et al[10] report their experience with the application of a clinical guideline for the management of severe VAP. In this observational cohort study, the authors compared the management of 48 patients with VAP and no antibiotic protocol with 58 VAP patients who were managed according to a specific protocol. Protocol-directed therapy was based on prior information about local antimicrobial resistance patterns and the recommendations of the 1996 ATS guidelines and required an initial broad-spectrum regimen (dual therapy with imipenem and amikacin/fluorquinolone). Empiric therapy for methicillin-resistant *Staphylococcus aureus* was recommended only in the presence of risk factors. The guideline also included the collection of invasively obtained microbiological specimens and required antibiotic treatment to be modified after 3 days based on the results of cultures.

Use of the guideline was associated with a statistically significant increase in the administration of appropriate antimicrobial treatment (81% with protocol vs 46% without; p < 0.01). The main reason for inadequate coverage in the guideline group was therapy for MRSA. Imipenem was considered to have been used appropriately in 74% of the cases (either because therapy was required based on microbiological results or because it was adjusted appropriately within 5 days based on these results). Tapering of imipenem was possible in 29.5% of the episodes. Despite the initial use of a broader combination of antibiotics in the guideline period, the percentage of imipenem-resistant isolates of *Pseudomonas* or other Gram-negative microorganisms remained unchanged throughout the study and was similar to the pre-guideline period, when the use of imipenem was more restricted.

Mortality within 2 weeks of VAP diagnosis was significantly lower in the guideline group (8% vs 23%, p = 0.03), and remained lower after 30 days and at the end of hospitalization However, this reduction in mortality did not achieve statistical significance.

Several published reports have demonstrated that VAP mortality is reduced when patients receive prompt and ad-

equate empiric therapy. The choice of antibiotics in VAP is particularly difficult because the infection is likely to result from highly resistant organisms, especially in patients who have previously received antibiotics or who have needed MV for more than 5 to 7 days. Moreover, the proportional distribution of multiresistant bacteria, and their antibiotic susceptibility may vary considerably between ICUs, even in the same institution.

The study by Soo Hoo et al. confirms the results of previous studies[23], by emphasizing the importance of local antimicrobial management guidelines for more effective antimicrobial use. The limited use of broad-spectrum antibiotics is a useful strategy for assuring timely and adequate antibiotic therapy, while at the same time avoiding overuse. Although the protocol did not reduce hospital mortality or length of stay, improving the effectiveness of prescribed antibiotic regimens and reducing the administration of unnecessary broad-spectrum antibiotics seem to be worthwhile outcomes. The reduction in mortality at two weeks, but not at the end of hospitalization, probably reflects the underlying condition of the study patients and suggests that a reduction in treatment failure, more than in crude mortality, could probably be a more realistic endpoint.

The implementation of guidelines is not an easy task. It requires the continuous collection of epidemiologic data, the use of reliable bacteriologic diagnostic techniques, and cooperation from attending physicians, nursing staff, pharmacists, and infectious disease consultants. In the Soo Hoo study, the protocol was followed carefully and adherence to guidelines was about 75%, which was crucial for the success of the program. However, the long-term impact of this practice is unknown and more studies of this type are needed.

The study does have some limitations. First, it was performed within a single center and variation between hospitals in such important variables as the affected patient population, diagnostic strategies used, causative organisms, and therapeutic approaches may not allow conclusions to be applied in other facilities. Second, the study design and relatively small sample size limited the ability to detect all possible differences in outcome between the study groups. Finally, the combination of broad-spectrum antibiotics used in this investigation may not be applicable to other institutions with different bacteriologic etiologies for VAP.

Bodi M, Rodríguez A, Sole-Violan J et al. Antibiotic prescription for community-acquired pneumonia in the intensive care unit: impact of adherence to Infectious Diseases Society of America guidelines on survival. Clin Infect Dis. 2005;41:1709-16.

In this prospective multicenter study carried out in Spain, Bodi et al analyze the prognostic factors associated with mortality in adult patients with severe CAP[11]. Pneumonia was considered community-acquired whether it had been acquired outside the hospital, in a long-term care facility, or in a nursing home. It was considered severe if the patient had to be admitted to the ICU to be ventilated or because of an unstable condition.

The authors analyzed the following variables: demographic characteristics, severity of the pneumonia (APACHE score), co-morbid factors, initial prescribed antibiotic regimen, microbiological findings, etiologic diagnosis, and chest radiograph findings on admission to the ICU. They also evaluated adherence to IDSA guidelines for the management of CAP.

The study reaches some remarkable conclusions that could help improve the management of adult patients with severe CAP. First, overall adherence to IDSA guidelines was low (52%) and, what is more important, non-adherence was associated with increased mortality (OR 1.66, 95% CI, 1.07-2.57). However, the actual adherence to IDSA guidelines might have been overestimated, as factors that could have biased the results are not explained in the study. For example, if attending physicians knew that their patients were being included in a prospective study and data on management were being collected, they would probably have had a better adherence to IDSA guidelines. Then, the actual adherence to guidelines in medical practice would be even lower than 54%. This highlights the importance of implementing measures to promote the use of guidelines recommended by scientific societies, most of which follow the principles of evidence-based medicine.

Another important conclusion of the study is that, in 15 (75%) patients with *Pseudomonas aeruginosa* infection, antibiotic treatment was inadequate, even in 8 patients for whom IDSA recommendations were followed. In fact, *P. aeruginosa* was the most frequent agent responsible for inadequate treatment. This stresses the importance of identifying risk factors for *P. aeruginosa* pneumonia. Logistic regression analysis showed the following variables associated with *P. aeruginosa* infection: chronic obstructive pulmonary disease (OR 17.9, 95% CI, 4.4-73.1), malignancy (OR 11.0, 95% CI, 2.2-54.3), previous antibiotic treatment (OR 6.2, 95% CI, 1.9-19.3), and rapid radiographic spread (OR 3.9, 95% CI, 1.1-13.6). All these factors should be borne in mind when making decisions about antibiotic treatment in an adult patient with pneumonia.

Menéndez R, Torres A, Rodríguez de Castro F et al. Reaching stability in community-acquired pneumonia: Effect of severity, treatment and characteristics of patients. Clin Infect Dis. 2004;39:1783-90.

Menéndez et al evaluate the level of adherence to the Spanish Guidelines (Spanish Chemotheraphy Society and Spanish Pneumology and Thoracic Surgery Society) for the empiric antibiotic treatment of CAP[12]. They also analyze factors related to poor adherence and the impact on therapeutic failure and mortality rates.

A prospective, observational and multicenter study was performed from October 2000 to April 2001 in the pneumology departments of 13 Spanish National Health hospitals. Eligible subjects were hospitalized non-immunocompromised adults with CAP. The clinician was classified as a pneumologist, other internal medicine-related specialist, pneumology resident, or other specialty resident. Empiric initial antibiotic treatment was considered guideline-concordant as follows: 1) Non-ICU patient: a) Cefotaxime, cef-

TABLE 3. **Predictors of adherence to guidelines: multivariate analysis**

Independent variables	OR	(95% CI)
Admission to ICU	0.43	0.24-0.78
Pneumologist vs others	5.24	2.74-10.21
Pneumology resident vs others	3.72	2.04-6.87
Non-pneumology resident vs others	1.41	0.86-2.28
Fine classification: II-V vs I	2.35	1.37-3.97

Definition of abbreviations: CI: confidence interval; ICU: intensive care unit; OR: odds ratio.

triaxone or amoxicillin/clavulanate, with/without a macrolide; b) 3rd or 4th generation quinolone monotherapy; 2) ICU patient: cefotaxime, ceftriaxone or cefepime with a macrolide or levofloxacin. Other variables collected included patients clinical and demographic data and initial severity of the disease (pneumonia severity index).

Adherence to guidelines was high (79.7%), with significant differences between hospitals (range, 47%-97%) and physicians (pneumologists, 81%; pneumology residents, 84%; non-pneumology residents, 82%; other specialists, 67%). A lower adherence level was observed in unemployed patients (OR 0.3; 95% CI, 0.2-0.7), confused patients (OR 0.6; 95% CI, 0.4-0.8), and hypotense patients (OR 0.3; 95% CI, 0.1-0.5). In patients with associated comorbidity, adherence was low when the treatment was prescribed by a non-pneumologist. Independent factors associated with higher adherence are detailed in table 3. Interestingly, ICU-admission was related to lower guideline adherence (67.4% vs 80%; $p < 0.05$). Seventy-four patients died (6.1%), and therapeutic failure was observed in 175 cases (14.2%). The independent factors associated with worse outcome (therapeutic failure and/or mortality) are included in table 4. The authors conclude that adherence to guidelines depends mainly on the hospital and the specialty/training status of prescribing physicians. Non-adherence was higher in non-pneumologists, and is an independent risk factor for treatment failure and mortality.

At the end of 1991 the first CAP-treatment guidelines were published[24]. Since then, many other societies have focused on the problem[25-29] by addressing empiric antibiotic treatment selection, diagnostic evaluation and, even, hospital/ICU admission criteria. Several authors have examined the effect of guidelines on patient management[11,30-39]. The design of these studies and the results obtained have not been uniform, so the real value of guideline application is not definitively clarified. Some studies demonstrated a reduction in hospital stay[30,36], others found a decrease in the mortality rates[11,30,31,34,37,38], whereas others showed no benefit[33,35,39].

Menendez's study showed that adherence to guidelines is an independent protective factor for therapeutic failure and mortality. Interestingly, factors influencing adherence are identified. Despite inter-hospital variability, adherence to guidelines was higher among pneumologists. The clinical value of this fact is uncertain, because in most cases, the initial treatment is prescribed by general/emergency physicians. This probably confirms the fact, also identified by other authors[40], that physicians who treat a wide specific-disease patient volume obtain better results. Therefore, the most important conclusion would be to promote knowledge and application of the guidelines. In this sense, future studies must look for other modifiable factors that impede or facilitate appropriate clinical practice (role of opinion leaders, local guidelines, promotion of activities aimed at continuous improvement of quality).

The authors also observed that the presence of comorbidity factors (e.g., diabetes, renal or CNS illness), confusion, and hypotension were accompanied by a lower level of adherence among non-pneumologists. Although these factors cannot be modified, they will help to identify a higher-risk subset of patients in which it would be convenient to optimize antibiotic treatment and global management[41,42].

Only 7% (86/1228) of the patients were admitted to the ICU. However, admission to this type of unit was an independent predictor associated with lower adherence, but not with therapeutic failure or mortality. In this study, the benefit of adherence to guidelines was demonstrated only in low-risk patients, although Bodi et al[11] demonstrated in a study with 529 ICU patients that non-adherence was an independent factor for mortality.

In summary, the authors observed that adherence to CAP guidelines can improve the outcome of these patients. Nevertheless, their effect probably does not only depend on an adequate antibiotic selection but on as yet undefined circumstances that warrant further study.

Confalonieri M, Urbino R, Potena A, Piatella M, Parigi P, Puccio G, Della Porta R, Giorgio C, Blasi F, Umberger R, Meduri GU. Hydrocortisone infusion for severe community-acquired pneumonia. A preliminary randomized study. Am J Respir Crit Care Med. 2005;171:242-8.

Severe cases of CAP admitted to the ICU have a high mortality due to respiratory failure and complications such as septic shock, adult respiratory distress syndrome (ARDS), and extrapulmonary organ dysfunction. Different studies have shown increased pulmonary and circulating inflammatory cytokine levels in patients with severe CAP,

TABLE 4. **Predictors of treatment failure and mortality (logistic regression analysis)**

Independent variables	Treatment failure		Mortality	
	OR (95% CI)	p	OR (95% CI)	p
Adherence	0.65 (0.5-0.9)	< 0.05	0.55 (0.3-0.9)	< 0.03
Residents and pneumologists vs others	0.6 (0.4-0.9)	< 0.05		
Fine IV-V vs I-III			10.8 (5.3-21.8)	< 0.001

Definition of abbreviations: CI: confidence interval; OR: odds ratio.
Area under receiver operating characteristic curve for treatment failure and death: 0.6 and 0.77, respectively.

suggesting that the degree and duration of systemic inflammation is related to outcome. On the basis of studies on prolonged glucocorticoid treatment for catecholamine-dependent septic shock, severe Pneumocystis pneumonia, or ARDS, in which glucocorticoids induced a significant reduction in circulating inflammatory cytokines over time, the authors establish the hypothesis that early administration of hydrocortisone in patients with severe CAP should attenuate systemic and pulmonary inflammation and lead to earlier resolution of pneumonia and a reduction in sepsis-related complications and mortality.

To contrast the hypothesis, Confalonieri et al evaluated the efficacy and safety of prolonged hydrocortisone administration in a prospective, randomized, double blind, placebo-controlled trial[13]. The study involved 46 patients with severe CAP who were admitted to the ICU, according to the 1993 ATS criteria modified by Ewig et al[43,44]. Patients with nosocomial pneumonia, severe immunosuppression, or a life expectancy of less than 3 months (for any reason) were excluded from the study. Patients received hydrocortisone infusion (a 200 mg bolus followed by 10 mg/h) or placebo for 7 days. The primary endpoints were an improvement in the PaO_2/FiO_2 ratio and the multiple organ dysfunction syndrome (MODS) score at day 8, or the development of delayed septic shock. The secondary endpoints were duration of MV or ICU stay and survival at discharge and at 60 days. There was no uniform protocol for the treatment of septic shock or refractory ARDS.

There were significant differences between the hydrocortisone and placebo groups for the primary and secondary endpoints. At day 8, the PaO_2/FiO_2 ratio (332 vs 237), the MODS score (0.3 vs 1), and delayed septic shock (0% vs 43%) were significantly better in the hydrocortisone group than in the placebo group. Similarly, the duration of MV (4 days vs 10 days), ICU stay (10 days vs 18 days), survival at discharge (100% vs 70%), and survival at 60 days (100% vs 62%) were also significantly better in the patients receiving hydrocortisone than in those on placebo. Interestingly, on enrolment, patients randomized to placebo had a higher PaO_2/FiO_2 ratio than those randomized to hydrocortisone ($p = 0.03$). The serum C-reactive protein was higher in the hydrocortisone than in the placebo group at randomization (median mg/dl: 55 vs 29, $p = 0.04$), although at day 8, it was lower in the hydrocortisone group than in the placebo group (18 vs 34, $p = 0.01$). There were no differences between the groups in terms of the number of nosocomial infections, ventilator-associated pneumonia, or upper gastrointestinal bleeding.

The results of this study suggest that the use of hydrocortisone at low doses is efficacious in reducing mortality in patients with severe CAP. It is important to underline that the administration of steroids was early and prolonged. One caveat of the study, in addition to other limitations discussed by the authors, is the low number of patients included. However, these results warrant a further trial, with a larger sample and determination of cytokine levels to confirm the impressive reduction in mortality with hydrocortisone observed in this study, in a clinical condition with mortality as high as that of severe CAP. The new trial must also analyze the characteristics of the high number of patients excluded from the study (60% of those initially evaluated) to know the impact of these results on clinical practice.

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