CHEST

Official publication of the American College of Chest Physicians

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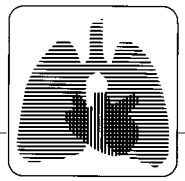
Chest 2002;122;2183-2196
DOI 10.1378/chest.122.6.2183

ISSN:0012-3692



critical care review

Nosocomial Pneumonia*

The Importance of a De-escalating Strategy for Antibiotic Treatment of Pneumonia in the ICU

Gert Höffken, MD; and Michael S. Niederman, MD, FCCP

Nosocomial pneumonia is the second most frequent nosocomial infection and represents the leading cause of death from infections that are acquired in the hospital. In the last decade, a large body of data has accumulated that points to the substantial impact of inadequate antibiotic treatment as a major risk factor for infection-attributed mortality in ventilator-associated pneumonia (VAP) patients. In most instances, high-risk pathogens (*eg*, highly resistant Gram-negative bacilli, such as *Pseudomonas aeruginosa* and Acinetobacter spp, as well as methicillin-resistant staphylococci) are the predominant microorganisms causing excess mortality. Among various risk factors for mortality from VAP, which include the severity of the underlying disease and the degree of functional physiologic impairment caused by the pulmonary infectious process, only inappropriate antibiotic therapy is directly amenable to modification by clinicians. Secondary modifications of an initially failing antibiotic regimen do not substantially improve the outcome for these critically ill patients. Therefore, the best approach for reducing infection-related mortality seems to be the initial institution of an adequate and broad-spectrum antibiotic regimen in severely ill patients, which should be modified in a de-escalating strategy when the results from microbiologic testing become available. To circumvent the inherent danger of the emergence of resistance in ICU patients, additional measures have to be implemented and tested in clinical trials to reduce antibiotic consumption, shorten the duration of antibiotic treatment, and reduce the selection pressure on the ICU flora. This latter goal could be met by new antibiotic strategies including scheduled changes of recommended empiric antibiotic regimens at fixed intervals on a rotating basis. ***(CHEST 2002; 122:2183–2196)***

Key words: de-escalating antibiotic strategy; ICU; nosocomial pneumonia; ventilator-associated pneumonia

Abbreviations: APACHE = acute physiology and chronic health examination; ATS = American Thoracic Society; CI = confidence interval; CPIS = clinical pulmonary infection score; NP = nosocomial pneumonia; OR = odds ratio; VAP = ventilator-associated pneumonia

Nosocomial pneumonia (NP) or hospital-acquired pneumonia is defined as pneumonia occurring ≥ 48 h after hospital admission and excluding any infection that is incubating at the time of hospital admission.[1] NP is currently the second most common hospital-acquired infection.[2–4] Depending on the underlying illnesses, comorbid diseases, and therapeutic interventions, the incidence ranges from 5 to 10 cases per 1,000 hospital admissions in patients without major risk factors, but may increase 6-fold to 20-fold in ICU patients who are receiving mechanical ventilation.[1,5] The duration of stay in the ICU and the duration of mechanical ventilation are the major predisposing factors for acquiring NP. Depending on the type of ICU that was studied, the patient population that was included, and the diagnostic techniques that were applied, the incidence of acquiring NP varies from 7.8 to 68% (in mechanically ventilated patients), as reported by several authors.[5–7]

The NP rate increases with the length of the ICU stay (rate at 7 days, 15.8%; rate at 14 days, 23.4%),

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Manuscript received December 11, 2001; revision accepted July 12, 2002.

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the use of mechanical ventilation (12.5 cases per 1,000 patient-days compared to 20.5 cases per 1,000 ventilator-days), as well as with the duration of mechanical ventilation.[6–11] In the study by Langer et al,[9] the risk of VAP increased from 5% in patients who received ventilation for 5 days to > 68.8% for patients who received ventilation for 30 days. The actuarial risk of VAP equaled 6.5% at day 10 of ventilation and increased to 28% at day 28.[10] However, in the prospective cohort study of the Canadian Critical Care Trials Group,[12] a decreasing daily hazard of VAP during mechanical ventilation (3% per day during the first week vs 1% per day during the third week and beyond) was reported, indicating that long-term survivors in the ICU exhibited a lower intrinsic risk per day for ventilator-associated pneumonia (VAP) than did short-term ventilated patients. Some of the other risk factors for VAP showed a similar time dependency, with the risk ratio of VAP associated with antibiotics being 0.30 (95% confidence interval [CI], 0.17 to 0.52) at day 5 and increasing to 0.89 (95% CI, 0.25 to 3.31) at day 20, indicating that the magnitude of the protective effect of antibiotic exposure decreased over time.

These incidence rates might not represent the real frequency of NP because in most studies cited, the diagnosis *pneumonia* was established only by clinical criteria. This imposes a substantial bias because of the intermediate sensitivity and specificity of this approach.[13] In an older study, Fagon et al[14] used a protected specimen brush as the reference method in 147 ventilated patients, and found that the appearance of pulmonary infiltrates and purulent tracheal secretions did not correlate with microbiological criteria for pneumonia in the majority (70%) of the their patients. Even with the knowledge of all clinical, radiologic, and laboratory data, the same group could demonstrate that the clinical diagnosis of pneumonia, for patients in whom pneumonia was subsequently diagnosed by bronchoscopic methods, was accurate in only 62% of patients.[13] Using histologic criteria combined with positive lung culture results as a reference standard for diagnosing pneumonia, Fabregas et al[15] found a sensitivity of only 69% and a specificity of 75% for clinical criteria. Even worse, combining noninvasive as well as invasive sampling techniques to improve the diagnostic yield in the patients who had infiltrates seen on a chest radiograph and two of three clinical criteria, there were still 15% of patients in whom the diagnosis of pneumonia could not be established. Thus, in some settings, the potential of underdiagnosis means that the precise incidence of NP might be higher than that reported, and this failure or delay in diagnosis might impair the outcomes for these patients who went without a diagnosis. On the other hand, in other settings, the overdiagnosis of pneumonia might enhance antibiotic consumption, increase the emergence of resistance, or increase the likelihood of fungal colonization in the respiratory tract.

Attributable Mortality

There are numerous studies[16–20] that have described increased mortality in ICU patients who have developed nosocomial infections, but some of these patients may have died regardless of the presence of infection, and thus not all deaths are attributable to infection. However, with an attributable mortality rate from nosocomial bacteremia ranging from 14 to 38% (average, 27%), it was estimated that up to 62,000 deaths are the direct consequence of this infection each year in the United States.[19] Since the cause of death in patients with nosocomial infections is multifactorial, the crude and attributable mortality rates may differ considerably. For example, Freeman and McGowan[21] reported a crude prevalence odds ratio (OR) for mortality of 4.0 for nosocomial infection but, after controlling for the severity of the underlying illnesses, could not demonstrate excess mortality. Nevertheless, since the risk factors for nosocomial infection and the risk factors for death are directly related, the severity of the underlying disease can influence both events, especially confounding the effect in patients with increasing severity of illness. When measuring the severity of the underlying illness according to various prognostic scoring systems (*eg*, APACHE [acute physiology and chronic health examination] II score and therapeutic intervention scoring system score), the greatest impact of nosocomial infection on mortality has been found in patients with moderately severe illness, rather than in those patients with mild or extremely severe illness.[16,17,22] Thus, patients with a relatively good *a priori* prognosis stand to benefit the most from vigorous and accurate antiinfective strategies. However, those patients with very mild illnesses may recover independently of the presence of infection, while those with very severe illnesses may die regardless of the accuracy of the antibiotic therapy.

In the case of patients with NP, the crude mortality rate is as high as 70%,[23,24] but the American Thoracic Society (ATS) has defined the term *attributable mortality* as the percentage of deaths that would not have occurred in the absence of this infection.[1] This definition implies the presence of two components for mortality. First is the impact of timely and appropriate antibiotic therapy, which can help some patients survive their infection. In these instances, the term *attributable mortality* refers to

the possibility that, with adequate and fully effective therapy, NP would not be associated with excess mortality, particularly in those patients with moderately severe illness. However, patients with certain infecting microorganisms (*eg*, *Pseudomonas aeruginosa*) may not be able to be treated adequately, and in addition, these organisms also can promote inflammation and pathophysiologic alterations in the lung parenchyma. Thus, in these instances, attributable mortality refers to both the pneumonia process and its consequences, as well to the efficacy of therapy.[25–27]

While early studies[8,14,28–35] reported excess mortality and the prolongation of hospital stays in patients with NP, more recent have studies employed methodologies that could appropriately define the component of attributable mortality. More recent studies[14,30–35] have compared the mortality rates of those patients with NP to patients with similar degrees of illness but without pneumonia using matched-cohort and case-control designs that were adjusted for confounding factors. In all of these studies,[14,30–34] NP increased the length of stay in the ICU, but the impact on mortality was less clear. Some authors could not demonstrate an excess death rate that was attributable to NP, whereas others found that one third to one half of all deaths in patients with NP were the direct result of pulmonary infection.[5,14,30–35] Thus, Fagon et al[14] showed that in ventilated patients with a total mortality rate of 54%, half of the deaths could be attributed to the infection itself (Fig 1). Differences in study design and case mix can account for some of these varied results, but it is also possible that different investigators achieved different results as a consequence of using different approaches to diagnosis and treatment. In general, attributable mortality has been reduced in centers that use prompt and adequate antibiotic therapy, and very little attributable mortality has been observed in surgical patients compared to that in medical patients.[30,31] Attributable mortality may be especially high in patients infected with certain high-risk organisms, such as *P aeruginosa* or Acinetobacter spp, infections that can have an attributable mortality rate as high as 42.8%.[27,30,36–38]

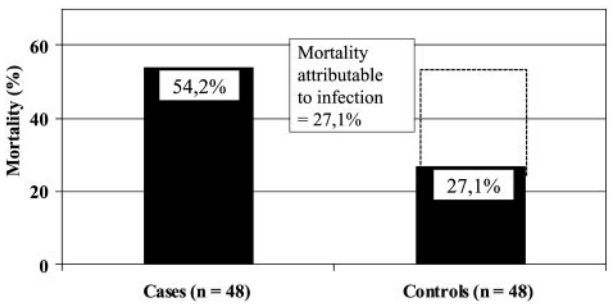

FIGURE 1. Mortality attributable to infection in mechanically ventilated patients with NP. Adapted from Fagon et al.[13]

Risk factors in patients with NP can be separated into those for developing infection, those for crude mortality, and those for attributable mortality (Table 1). Risk factors influencing crude mortality are type of ICU (*ie*, medical vs surgical), age, type and severity of underlying disease, time of onset of pneumonia, radiographic pattern, severity of pneumonia, presence of high-risk respiratory pathogens, respiratory failure, shock, or inappropriate antibacterial treatment.[3,8,23,28,36,37] The risk factors for attributable mortality include severity of illness, virulence of the etiologic pathogen, and the use of inappropriate antibiotic therapy.[3,13] Each of these factors is examined in detail below.

Influence of Severity of Illness

While Bueno-Cavanillas et al[22] found that patients at the extremes of disease severity did not have excess mortality from nosocomial infection, others[8,37,39,40] have found that, in general, severity of illness is an independent risk factor for excess mortality in patients with NP, with a worse prognosis for those with more severe illness. However, severity must be assessed serially throughout the hospital stay, since the APACHE II score on admission to the ICU is a poor predictor of outcome in patients who subsequently develop VAP.[41] On the other hand, there is a closer correlation between APACHE II score or simplified acute physiologic score II, measured after the development of VAP, and the outcome in patients with VAP.[42] In cardiac surgery

Table 1—*Independent Risk Factors of VAP for Incidence and Mortality in Patients With NP

Variables	Relative OR
Incidence	
Gastric aspiration	5.1
Reintubation more than once	5.0
COPD	1.9
PEEP	1.7
MV duration > 3 days	1.2
Mortality	
Worsening ARF	11.9
Underlying condition (UF/RF)	8.8
Inappropriate antibiotic treatment	5.8
ICU—noncardiac surgery	3.4
Shock	2.8

*Adapted from Torres et al.[8] PEEP = positive end-expiratory pressure; MV = mechanical ventilation; ARF = acute renal failure; UF = ultimately fatal; RF = rapidly fatal.

patients, acquiring an organ system failure index score of ≥ 3 during the ICU stay that correlated with the APACHE II score was the most important determinant of mortality.[43] Similarly, in a study by Rello et al,[37] the severity of illness when NP was diagnosed (and not at ICU admission or 24 h after ICU admission) was the most important predictor of survival. These findings indicate that the development of pneumonia itself has an impact on outcome that cannot be predicted at the time of ICU admission, before the onset of VAP, since the development of pneumonia itself increases the severity of illness and the APACHE II score.[37] These observations also suggest that the degree to which the observed mortality exceeds the mortality predicted by ICU admission APACHE II score is another measure of the impact, or attributable mortality, of infection on outcome in critically ill patients.

Influence of Specific Etiologic Agents

Some pathogens impair prognosis to a greater degree than others. Infections caused by pathogens of primary endogenous origin (*ie*, organisms colonizing patients on ICU admission), such as oral flora, do not generally cause significant excess mortality if appropriate therapy is started early.[40,41,44] In contrast, episodes caused by Gram-negative bacilli of secondary endogenous origin (*ie*, microorganisms acquired during the ICU stay) colonizing the digestive tract and upper respiratory tract cause significant excess mortality, even if appropriate therapy is initiated early.[27,37,40,44] Pathogens acquired exogenously (*eg*, from ventilator circuits) seem to have a similar impact on mortality. In a study of late-onset VAP by Rello et al,[38] nonfermenting Gram-negative bacilli accounted for < 25% of the pathogens isolated by protected specimen brush, yet they caused up to 80% of pneumonia-related deaths. Similarly, in patients with late-onset VAP, Kollef et al[36] found that NP due to certain high-risk microorganisms (*ie*, nonfermenting Gram-negative bacilli) was an independent risk factor for hospital mortality.

When pneumonia is caused by *P aeruginosa* or Acinetobacter spp, the attributable mortality rate exceeds 40% and the relative risk of death is 2.50.[13] In a study of ICU patients with VAP due to *P aeruginosa*, all of whom received early and appropriate antimicrobial chemotherapy, the mortality rate attributed to the pulmonary infection was 13.5%.[27] In this investigation, by excluding patients who did not receive adequate antimicrobial treatment, the true impact of *P aeruginosa* VAP, despite the use of accurately targeted therapy, could be assessed. In another investigation, Rello et al[45] observed that patients with infections caused by methicillin-resistant *Staphylococcus aureus* had a mortality rate that was up to 20 times greater than that of patients with infections caused by methicillin-sensitive strains.

There are multiple risk factors for VAP with high-risk pathogens. Kollef et al[36] found that the recovery of high-risk microorganisms from patients with late-onset VAP was related to the duration of mechanical ventilation and the length of hospital stay prior to ICU admission. Rello and colleagues[38,46] found that previous antibiotic therapy, particularly third-generation cephalosporin agents, increased the likelihood of VAP due to oxacillin-resistant staphylococci and highly resistant Gram-negative bacilli. Similar associations were recorded in other clinical trials.[47–51] In the study by Trouillet et al,[52] the following three variables remained significant, by logistic regression, as risk factors for the presence of potentially drug-resistant bacteria (such as methicillin-resistant *S aureus* or *P aeruginosa*) in patients with VAP: duration of mechanical ventilation ≥ 7 days (OR, 6.9); prior antibiotic use (OR, 13.5); and prior use of broad-spectrum antimicrobial agents (OR, 4.1). The rate for the presence of multiresistant microorganisms in 135 episodes of VAP increased from 0%, in the low-risk group of patients who had received mechanical ventilation for < 7 days and had no prior antibiotic use, to 58.6%, in the group with both risk factors present. Additional risk factors for high-risk pathogens (*eg*, *P aeruginosa*) included structural lung disease and the prior administration of corticosteroids.[1,49]

Influence of Inappropriate Antibiotic Therapy

In the last 10 years, evidence has accumulated showing that initial inappropriate antibiotic treatment is an important independent risk factor for excess mortality in patients with NP. The term *inadequate antibiotic therapy* is not standardized, thus making conclusions from these studies difficult and only partially comparable. In some investigations, the *adequacy of antibiotic treatment* refers to the administration of antibiotics according to the recommendations and guidelines of scientific societies in conjunction with pharmacologic and microbiologic considerations.[8] Other authors[44,53] have restricted the definition of adequate antibiotic therapy to sensitivity patterns from *in vitro* tests that result in the antibiogram of the etiologic pathogen instead of relating it to the clinical response to therapy, thus focusing only on microbiologically documented infections. In 1988, Celis et al[23] described inappropri-

ate antibiotic treatment as an independent risk factor for mortality in nonneutropenic patients with NP, however, outcome was not adequately controlled for confounding factors (*eg*, severity of underlying disease). In 1990, Torres et al[8] found that inappropriate antibiotic therapy was associated with a relative OR for death of 6.81.

Four studies have confirmed these findings. In a prospective observational study, Luna et al[54] investigated the impact of inadequate antibiotic treatment at three different time points during the course of VAP on the mortality of patients with VAP. At the time of the clinical diagnosis, or at the first suspicion of the development of VAP, 25% of patients received adequate antibiotic therapy and 52% received inadequate treatment, as judged retrospectively by the therapy given, compared to the *in vitro* sensitivity of organisms recovered in BAL fluid. The remainder of the patients received no initial antibiotic therapy. Most of the patients receiving antibiotic therapy at the time of VAP onset were treated for other reasons. In only a few patients was antibiotic treatment initiated because of evolving VAP. At this early time point, Luna et al[54] observed a mortality rate of 38% if antibiotic treatment was appropriate and a mortality rate of 91% if this treatment was inadequate. This difference was statistically significant. However, at later time points, there was no reduction in mortality for adequate therapy, compared to inadequate therapy, emphasizing the need to provide the right therapy in a timely fashion. (Fig 2)

Rello et al[47] made similar observations, showing a doubling of attributable mortality for patients with VAP who had inadequate initial treatment compared to adequate antibiotic therapy (37.0% vs 15.4%, respectively). In their prospective 1-year study of NP that was acquired in medical and surgical ICUs, Alvarez-Lerma[55] also found a significant influence of inappropriate antibiotic treatment on mortality (24.7% of patients [36 of 146 patients] who received inadequate therapy died vs 16.2% of patients [46 of 284] receiving appropriate therapy; p = 0.03). Inadequate antimicrobial treatment also was associated with an increase in the number of complications per patients (2.25 vs 1.73, respectively), a higher incidence of shock (28.8% vs 17.1%, respectively), and a higher incidence of GI bleeding (21.2% vs 10.7%, respectively). More corroborating data were provided by Kollef and Ward[56] using mini-BAL fluid cultures in 130 patients with suspected VAP. They found a higher OR for mortality in patients receiving inadequate antibiotic therapy than in those receiving adequate therapy (Table 2).

In a large prospective cohort study of 2,000 critically ill patients, Kollef and coworkers[39] investigated the influence of inadequate antimicrobial treatment of community-acquired and nosocomial infections as a risk factor for hospital mortality. Inappropriate antibiotic treatment, which was defined as the initial use of antibiotics to which the identified pathogens were resistant, was identified as the most important risk factor for hospital mortality for the entire cohort. Of all infected patients who were admitted to ICU, almost half (43.7%) developed a nosocomial infection, and 8.5% of all patients initially received inadequate antibiotic treatment of the infection. Inadequate treatment was most common among patients with nosocomial infections that developed after the treatment of a community-acquired infection (45.2%) and among those with nosocomial infections alone (34.3%). These populations had a high incidence of inadequate therapy, because they were very likely to acquire infection with antibiotic-resistant Gram-negative organisms (41.1% and 43.2%, respectively) and antibiotic-resistant Gram-positive organisms (30.1% and 15.0%, respectively.). Those who received adequate therapy had a statistically significant greater crude mortality rate than those who

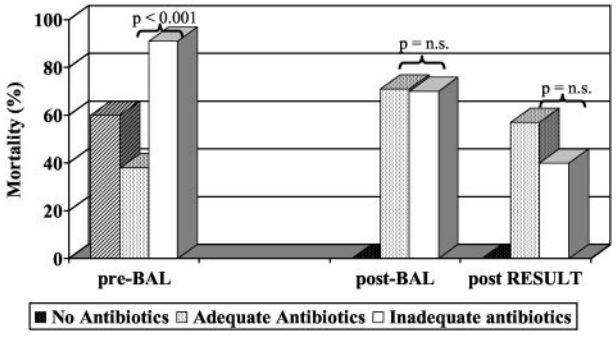

FIGURE 2. Mortality rates plotted in relation to the adequacy of antibiotic therapy at three different time points (*ie*, pre-BAL, post-BAL, and postresult) Adapted from Luna et al.[54]

Table 2—*Risk Factors for Mortality in Patients With VAP

Clinical Feature	Adjusted OR	95% CI
Inadequate antibiotic therapy†	3.28	2.12–5.06
Cancer	2.56	1.51–4.36
Immunocompromised status	2.45	1.56–3.85
Start or change of antibiotic therapy‡	1.27	0.96–1.69
Premorbid lifestyle score§	1.18	0.91–1.54
Age‖	1.01	1.00–1.03

*Adapted from Kollef and Ward.[56]
†Defined as patients who had microorganisms isolated from mini-BAL cultures that were resistant to the prescribed antibiotic regimen.
‡After performing mini-BAL.
§One-point increments.
‖One-year increments.

received inadequate therapy (52.1% vs 23.5%, respectively), and there were also differences in infection-related mortality rates (42.0% vs 17.7%, respectively) [Fig 3]. In this study, as well as others, the main reason for inadequate antibiotic treatment was the presence of either antibiotic-resistant Gram-positive bacteria or antibiotic-resistant Gram-negative bacteria (Table 3). This association also may explain why inadequate therapy also was associated with prior administration of antibiotics, the presence of bloodstream infection, and increasing severity of illness, which are common associations of antibiotic resistance.

Impact on Outcome of Modifying Empiric Therapy According to the Results of Diagnostic Testing

With strong data showing that initial appropriate antibiotic therapy is crucial for improving the prognosis of patients with NP, some investigators have evaluated whether microbiologic data, obtained by noninvasive or invasive bronchoscopic procedures, can be used to modify antibiotic therapy. When the value of this strategy (*ie*, changing from inadequate to adequate antibiotic therapy) on outcome has been evaluated, most studies have found no improvement in mortality.[47,54,56,57] For example, in a study by Rello et al,[47] inadequate antibiotic therapy was identified microbiologically by using the results of bronchoscopy and modified in 23.9% of patients with VAP with very little beneficial effect. Sanchez-Nieto et al[57] compared the impact of invasive diagnostic techniques (via fiberoptic bronchoscopy) and noninvasive diagnostic techniques (via quantitative endotracheal aspirates) on the outcomes of patients with VAP. They found that bronchoscopy led to more frequent changes in antibiotic therapy than noninvasive techniques, but did not favorably influence mortality.

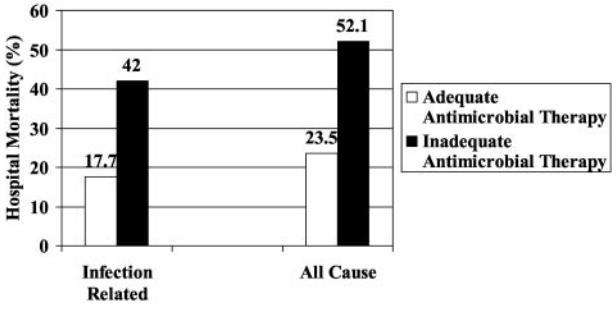

Figure 3. Hospital mortality and infection-related mortality rates for infected patients from all causes in patients receiving either initially inadequate antimicrobial treatment or initially adequate antimicrobial treatment. Adapted from Kollef et al.[39]

Kollef and Ward[56] obtained a positive culture by mini-BAL in 60 of their 130 patients with VAP (46.2%), but 73.3% of these patients had received inadequate antibiotic therapy. Based on the mini-BAL fluid culture results, antibiotic therapy was started or changed in 51 patients, remained unchanged in 51 patients, and was stopped in 28 patients. The hospital mortality rate of the subgroup with started/changed antibiotic treatment was significantly greater than in the other two subgroups (60.8% vs 33.3% and 14.3%, respectively). Thus, changing or modifying initially inadequate antibiotic treatment did not improve outcome, probably because the change occurred too late in the course of illness to have a beneficial effect. In the investigation by Luna et al,[54] modification of the antibiotic treatment according to the BAL data resulted in 88% adequate treatment in the patients still alive when results became available. However, this adjustment did not improve the outcome significantly (*ie*, mortality was no better in patients receiving adequate treatment after the BAL results were known than in patients who continued to receive inadequate therapy) [Fig 2].

All these studies show that modifying an initial inadequate therapy (including no initial antibiotic therapy), according to microbiological results, in severely ill patients with VAP does not translate into a better outcome. This is probably because the time window is too short to change an inappropriate antibiotic therapy regimen soon enough to reduce mortality in patients with VAP. This relates to the controversies in diagnosing VAP, since invasive diagnostic methods are unlikely to impact mortality in VAP patients unless they increase the likelihood of adequate initial therapy, and no study has claimed that these methods are capable of creating such a result. For example, Fagon et al[58] found that patients who had received a diagnosis of VAP and were treated for VAP based on bronchoscopic data, rather than on clinical data, had a reduced mortality, but that the different outcomes in the groups could be ascribed to differences in the adequacy of the initial empiric therapy, which seemed to vary randomly, and not as the direct result of a specific diagnostic strategy. In addition, the number of resistant organisms was fewer in the bronchoscopically managed group, which may explain some of the differences in the adequacy of initial therapy. All of these data argue for the wisdom of initial therapy being broad-spectrum and accurate, but once the microbiological data become available and the patient's response to therapy is evaluated, it is also necessary to de-escalate therapy in order to avoid prolonged use of a broader spectrum of antibiotic therapy than is justified by the available information. While a de-esca-

Table 3—*Pathogens Present in Patients Receiving Inadequate Initial Empiric Therapy of VAP

Variables	Alvarez-Lerma[55]	Kollef and Ward[56]	Luna et al[54]	Rello et al[47]
Culture-positive patients	430	60	65	100
Patients receiving initial inadequate therapy	146 (34)	44 (73)	34 (52)	27 (27)
Organisms associated with inadequate therapy				
P aeruginosa	64	19	7	20
S aureus†	30	12	25	3
Acinetobacter spp	28	3	27	0
K pneumoniae	2	1	13	0
S pneumoniae	3	0	0	0
H influenzae	1	0	0	1
E coli	4	0	0	2
Enterobacter spp	8	4	0	0
Proteus mirabilis	4	0	1	0
S marcescens	5	3	0	0
S maltophilia	0	5	0	0

*Values given as No. (%). Adapted from Kollef.[69]
†Commonly methicillin-resistant.

lating approach to antibiotic therapy (*ie*, culture-guided treatment) may not help individual patients, it could benefit the ICU as a whole by reducing the selection pressure for resistance. The use of microbiological data also may reveal important information for future patients. Cultures of respiratory specimens from clinical infection sites can serve as a form of database for defining local patterns of antibiotic resistance, which then can guide therapy recommendations.[1] In addition, in patients with "nonresolving" NP, either bronchoscopy or tracheal aspirates might identify a bacteriologic reason for nonresponse even in presence of antibiotics.[59,60]

The clinical impact of a de-escalating strategy was evaluated by Singh et al[61] in ICU patients with pulmonary infiltrates. These authors used the clinical pulmonary infection score (CPIS), which is based on clinical, laboratory, microbiological, and radiologic measurements as the operational measures used in the decision making about antibiotic treatment. In patients with clinically diagnosed pneumonia and a CPIS score of ≤ 6 at the time of the initiation of antibiotic treatment (implying a low likelihood of pneumonia or an early form of infection), patients were randomized to a standard duration of therapy or a strategy for shortening the duration of therapy using a high-dose quinolone therapy regimen (intervention group). If the CPIS was ≤ 6 at day 3, the intervention group was allowed to discontinue therapy, but if the score was > 6, they continued to receive therapy. When comparing patients in the intervention group to patients who received the standard therapy, there were no differences in mortality, but there were reductions in cost, antibiotic usage, and antibiotic resistance. In fact, antimicrobial resistance, superinfections, or both developed in 15% of patients (5 of 37 patients) in the intervention group vs 35% of patients (14 of 37 patients) in the standard therapy group.

The ability to use clinical methods to de-escalate antibiotic therapy was well-demonstrated in the study by Singh et al, but similar results can also be accomplished using invasive microbiologic investigations.[58,62] Not only did Fagon et al[58] show that invasive management (protected specimen brush or BAL) of suspected VAP could reduce the 14-day mortality rate compared to a noninvasive approach, but they also demonstrated that the invasive approach allowed the withholding or stopping of therapy in many patients, which in turn led to significantly more antibiotic-free days and less of an emergence of Candida spp. In contrast, Ruiz et al[62] conducted a multicenter prospective study of suspected VAP using the following two diagnostic approaches: a noninvasive strategy (*ie*, endotracheal aspirates only); and an invasive strategy (*ie*, bronchoscopy-retrieved respiratory specimens). The crude 30-day mortality rate, the adjusted mortality rate, and the mortality rate in patients with microbiologically confirmed pneumonia were equal in both groups. One possible explanation for their findings was the high rate of using adequate therapy in both groups, and thus no impact on mortality was likely. However, the study was not set up to show the feasibility of using either approach to de-escalate therapy. In looking at both of these studies, the importance of appropriate initial antibiotic therapy as a major predictor of outcome is once again clear. However, the need for initial therapy that is accurate must be combined with a commitment to the de-escalation of therapy, and even the shortening of the duration of therapy, once microbiological and clini-

cal data become available. Although this approach has been suggested, there are few studies that have applied the combination of aggressive empiric therapy and de-escalation, so this approach requires validation. However, one recent study[63] utilized a broad-spectrum empiric therapy regimen with a plan to focus therapy on culture data after 24 to 48 h and to shorten the duration of therapy to 7 days if possible, with the end result being more accurate therapy of a shorter duration, with no negative effect on mortality.

Etiologic Spectrum and Therapeutic Implications

In patients with early onset of severe NP (*ie*, a stay of < 5 days in the hospital), a group of core organisms are most likely responsible for infection, and these include *Streptococcus pneumoniae*, methicillin-sensitive *S aureus*, *Haemophilus influenzae*, as well as nonresistant enteric Gram-negative bacilli like *Escherichia coli*, Klebsiella spp, Proteus spp, Enterobacter spp, and *Serratia marcescens*.[1] In addition, up to half of the episodes of VAP are polymicrobial in origin.[64–66]

In patients who develop severe NP later (*ie*, a stay of ≥ 5 days in the hospital), the spectrum includes the above-mentioned core organisms plus highly resistant Gram-negative bacteria, such as *P aeruginosa* and Acinetobacter spp as well as methicillin-resistant *S aureus*.[67–73] For example, Luna et al[54] most frequently isolated *S aureus*, Acinetobacter spp, *Klebsiella pneumoniae*, and *P aeruginosa*, with each being involved in 20 to 50% of the cases. Twenty of the 32 isolated organisms of *S aureus* were methicillin-resistant. Acinetobacter spp and/or *S aureus* (at least one of them) were involved in 74% of the episodes of pneumonia. Thus, many of the late-onset pneumonias involve resistant organisms, and this may add to the high frequencies of inadequate therapy that have been reported in some series. In fact, *P aeruginosa*, multiresistant *S aureus*, Acinetobacter spp, *K pneumoniae,* Enterobacter spp, and *Stenotrophomonas maltophilia* have been the most common pathogens associated with inadequate antimicrobial therapy in patients with culture-proven VAP (Table 3).[47,54–56,69] The clinical impact of these highly resistant pathogens is not well-understood, but some investigations point to an increased fatality rate attributed to these microorganisms, compared to bacteria lacking major resistance patterns.[36,72]

In patients who have received previous antibiotic treatment, the spectrum of etiologic microorganisms is especially diverse, including high-risk pathogens such as Acinetobacter spp, *P aeruginosa*, and Gram-negative bacilli.[10,36,38,46] In the study of Trouillet et al,[52] among 135 patients with VAP, a duration of mechanical ventilation of ≥ 7 days, prior antibiotic use (OR, 13.5), and prior use of broad-spectrum drugs were the most important risk factors associated with antibiotic-resistant bacteria. Likewise, Rello et al[27] established the presence of chronic obstructive lung disease, prolonged duration of mechanical ventilation, and prior use of antibiotics as being major determinants for infections by *P aeruginosa* in patients with VAP. Methicillin-resistant *S aureus* was shown to be associated with prior steroid treatment, prolonged mechanical ventilation, age of ≥ 25 years, preceding COPD, and prior antibiotic therapy.[48]

Thus, the chance of multidrug-resistant pathogens being present in patients with VAP is greatest in those with long hospital and ICU stays, prior antibiotic therapy, multiple comorbidities, and prolonged mechanical ventilation.[1,36] In these circumstances, initial narrow-spectrum antibiotic regimens should not be used since they will most likely not cover the most common microorganisms and will necessitate the modification of the initial regimen due to poor clinical response or primary resistance.[54,67] In addition, several studies have documented the need to know local microbiologic patterns of resistance in order to predict the likely etiologic pathogens and their sensitivity to antibiotics, and thus assure that the initial empiric therapy is adequate. In a retrospective multicenter trial, a statistically significant difference in the incidence of specific multiresistant pathogens was observed at four different centers that collected quantitative cultures of bronchoscopic samples in patients with late-onset VAP.[68] In the subgroup of patients with the highest probability of having potentially drug-resistant bacteria (*ie*, those with a duration of mechanical ventilation of ≥ 7 days with prior antibiotic use), a high rate of VAP by multiresistant bacteria was noted (at least 58%), but the centers differed in the frequency of specific species (*eg*, *P aeruginosa*, *Acinetobacter baumannii*, or *S maltophilia*).

Multiresistant bacteria add to the number of adverse outcomes for VAP patients in a number of ways but can commonly predispose the patient to initially inadequate therapy. In the study of Alvarez-Lerma,[55] antibiotics were administered empirically at the time of 490 of 565 NP episodes in 530 ICU patients. The initial empiric treatment had to be changed in 214 episodes (43.7%), and the failure to cover an infecting pathogen (62% of episodes) was the most common reason for switching antibiotics. In this study, *P aeruginosa*, *S aureus*, and Acinetobacter spp were associated most often with ICU-acquired pneumonia, and initial therapy failed to cover 50% of *Acinetobacter* and Enterobacter spp, and 36.8% of

Table 4—*Pathogens Not Covered by Initial Antimicrobial Therapy for ICU-Acquired Pneumonia

Microorganisms Isolated	Total No.	Appropriate Antibiotic, No.	Inappropriate Antibiotic, No.	Not Covered by Antibiotic, %
P aeruginosa	174	110	64	36.8
S aureus	102	72	30	29.4
Acinetobacter spp	56	28	28	50.0
Klebsiella spp	21	19	2	9.5
S pneumoniae	21	18	3	14.3
H influenzae	21	20	1	4.8
E coli and other enteric Gram-negative bacilli†	61	40	21	34.4

*Adapted from Alvarez-Lerma.[55]
†Enterobacter spp, *P mirabilis*, and *S marcescens*.

P aeruginosa isolates. Other pathogens most likely to be treated insufficiently were *S marcescens* and *S aureus* (Table 4). Administration of combination therapy with β-lactam antibiotics and aminoglycosides (in > 75% of the cases these regimens were given) was significantly associated with the need for modification and, consequently, increased mortality, indicating the limited efficacy of aminoglycosides in the treatment of pneumonia in the ICU in this study.[55]

In the study by Kollef and Ward,[56] the most common reason for inadequate coverage was isolation of Gram-negative bacteria that were resistant to the prescribed third-generation cephalosporin (ceftazidime, 19 patients; ceftriaxone, 4 patients). Other reasons for treatment alteration were the need to add therapy with vancomycin for the treatment of methicillin-resistant *S aureus*, the identification of Gram-negative bacteria resistant to an aminoglycoside, ciprofloxacin, or imipenem, and the need to add antifungal or antiviral therapy.

VAP is widely believed to result from the microaspiration of oropharyngeal material despite the presence of an inflated endotracheal tube cuff. Anaerobic bacteria are frequently encountered in the oropharyngeal flora, but the role of anaerobes as a cause of VAP is not clear and has been widely debated.[69–71] In most studies, the importance of anaerobes was not evaluated with rigorous isolation and identification techniques for anaerobes, although some studies[47,54–56,70,71] have used accurate diagnostic procedures and standardized specimen processing. In the study of Marik and Careau,[70] the respiratory specimens obtained by protected specimen brush were processed by the microbiological laboratory within 20 min and were cultured on specific plates for anaerobic enrichment. Nevertheless, in no case of VAP could anaerobes be detected as the causative microorganism. In contrast, using the protected specimen brush as in the study of Marik and Careau,[70] Doré et al[71] isolated anaerobes in 30 of 130 patients (23%). However, in only four patients (3%) were anaerobes the only strains isolated in the cultures. In the remaining patients, polymicrobial infections were recorded. Thus, the occurrence of pure anaerobic VAP seems to be a rare event, and routine therapy for infections caused by these organisms may not be needed, especially since it can add to further resistance problems with such organisms as vancomycin-resistant enterococcus.[74]

Guidelines for Rational Empiric Therapy

The need to use initial empiric therapy that is of a broad spectrum, as recommended by the ATS guidelines,[1] is justified by an awareness that antibiotic-resistant organisms are common in critically ill patients, and that their presence adds to an enhanced likelihood that certain narrow-spectrum therapies will be inadequate and thereby will add to the risk of death from nosocomial infection. Initial adequate therapy must be given promptly, since modifying an initially inadequate regimen is unlikely to improve outcome. In order to choose an appropriate initial antibiotic treatment, local as well as national resistance data, can be used to guide the decision. For the treatment of infection by Gram-negative bacteria, imipenem, ciprofloxacin, and gentamicin display good *in vitro* activity in contrast to that of broad-spectrum penicillins and cephalosporins (Table 5).[73] According to the ATS recommendations,[1] the antibiotics used for the treatment of patients with early-onset severe NP should be second-generation or third-generation cephalosporins, β-lactam/β-lactamase inhibitor combinations, a fluoroquinolone, or clindamycin plus aztreonam. In patients with late-onset severe NP, the recommended treatment includes an aminoglycoside or ciprofloxacin plus one of the following: imipenem; an antipseudomonal, broad-spectrum penicillin; antipseudomonal, third-generation cephalosporins; or aztreonam. Meropenem, piperacillin/tazobactam, or cefepime might also be administered as antipseudomonal antibiotics.

Table 5—*Antimicrobial Resistance in Gram-Negative Enteric Bacteria in 49 Hospitals in the United States

Drugs	*E coli*	*K pneumoniae*	*Enterobacter cloacae*	*P aeruginosa*	*S marcescens*
Ampicillin	655 (41)	524 (98)	329 (96)	169 (92)	142 (97)
Pipericillin	417 (41)	368 (36)	247 (41)	367 (9)	108 (16)
Ampicillin/sulbactam	382 (38)	355 (40)	182 (84)	131 (92)	97 (89)
Cefotaxime	304 (2)	288 (12)	171 (37)	198 (78)	82 (7)
Ceftriaxone	376 (1)	331 (9)	246 (39)	244 (73)	110 (9)
Aztreonam	301 (3)	245 (9)	187 (46)	286 (26)	68 (4)
Imipenem	397 (1)	369 (1)	295 (1)	407 (10)	98 (4)
Gentamicin	657 (3)	541 (13)	387 (12)	481 (19)	157 (8)
Ciprofloxacin	520 (1)	424 (8)	261 (7)	437 (15)	123 (7)
Trimethoprim-sulfamethoxazole	627 (14)	500 (17)	350 (15)	252 (87)	152 (4)

*Values given as No. of isolates tested (% resistant). Original data[73] included other antibiotics. Adapted from Edmond et al.[73]

Glycopeptides should be added if infection with methicillin-resistant *S aureus* is strongly suspected, but for now linezolid or quinupristin/dalfopristin might serve as alternatives for glycopeptides.[1]

In Favor of De-escalating Initially Broad-Spectrum Therapy

Considering the importance of adequate initial antibiotic therapy in critically ill patients with NP, a de-escalating strategy (*ie*, starting with broad-spectrum antibiotic therapy followed by narrow-spectrum specific therapy, according to microbiological results) seems to be the preferred approach rather than starting narrow-spectrum therapy and then broadening the spectrum once culture data are available. Initial broad-spectrum antibiotic therapy provides maximum benefit for the individual, severely infected patient, whereas switching to a specific antibiotic therapy according to microbiological data may help to minimize the risk of emerging resistance.[52,75–79] According to the data of Trouillet et al,[52] only broad-spectrum combination antibiotic regimens will cover all relevant potentially drug-resistant bacteria in patients with VAP. They observed that the combination of imipenem plus amikacin and vancomycin provided the broadest *in vitro* coverage against the spectrum of methicillin-resistant *S aureus, P aeruginosa,* Acinetobacter spp, and *S maltophilia* that were found in their ICU. Each ICU should have a profile of its own organisms and sensitivity patterns in order to design a similar ICU-specific antibiotic regimen that is likely to be effective when used empirically.

According to the guidelines of the ATS,[1] the initial antibiotic therapy should be based on specific risk factors that influence the spectrum of causative microorganisms in patients with NP. In patients with a high probability of infection due to multiresistant bacteria, such as late-onset pneumonia, in those who have received prior antibiotic treatment, or in those who have had prolonged stays in the ICU before developing pneumonia, combination antimicrobial therapy is recommended with drugs that are active against *P aeruginosa,* Acinetobacter spp, and possibly methicillin-resistant *S aureus*. Some patients may be de-escalated to a monotherapy regimen, based on the clinical response and the results of pertinent cultures that are available at day 2 to 3. In general, for nonbacteremic infections, monotherapy is as effective as combination therapy, although the emergence of resistance of *P aeruginosa* is a major threat that might require the use of combination therapy.[80–86] The rationale for initial combination therapy is to prevent this emergence of resistance during therapy and to take advantage of the observation that some studies[81] have shown improved outcomes in patients with *P aeruginosa* infections that were treated in this way. On the other hand, a large body of evidence has shown the efficacy and cost-effectiveness of certain monotherapy regimens if highly resistant organisms are not present. Effective monotherapy agents for patients with severe NP that is not due to highly resistant organisms include imipenem, ciprofloxacin, meropenem, piperacillin/tazobactam, and cefepime.[82–85]

One great concern about the widespread use of broad-spectrum empiric therapy in the ICU is the fear of the emergence of multidrug-resistant pathogens. The factors predisposing the patient to resistance are numerous, including prior antibiotic use especially at suboptimal levels, suboptimal treatment duration, or prolonged duration of stay in the hospital or ICU.[10,38,72,77] However, if empiric therapy is administered in a timely manner, using highly effective agents that lead to rapid bacterial killing, the emergence of resistance could theoretically be minimized.[85] The Centers for Disease Control and Prevention have suggested[79] that the optimization of antibiotic use can be enhanced by education about appropriate antibiotic use and by providing data to

physicians about the types of resistant organisms seen in their own ICU as part of an ongoing surveillance program that could minimize the risk of antibiotic resistance.

Additionally, strategies such as scheduled changes of antibiotic regimens or routine microbiological surveillance-guided changes of antibiotic policy also may reduce the risk of emerging resistant strains. Kollef et al[78] have shown that a planned proactive approach of change by routinely varying the antibiotic policy (*eg*, from using ceftazidime to using ciprofloxacin) in an ICU setting may be useful in preventing the emergence of resistance by reducing the selection pressure for bacteria. Instead of using a certain standard antibiotic regimen for a period of time and then changing to another regimen for the next period, an alternative might be treating consecutive patients with different antibiotic regimens within the same time period to reduce selection pressure for highly resistant nosocomial pathogens within the ward.

The first trials on antibiotic cycling have yielded conflicting results. Dominguez et al[86] observed a reduced rate of Gram-negative resistance in their hematology-oncology unit when comparing four different time periods with different antibiotic regimens, but also observed an increase in Gram-positive resistance, which was due mainly to a marked increase in enterococcal infection. In the study of Kollef et al,[78] two 6-month periods in a cardiac surgical ICU were compared, one period in which ceftazidime was used and the other period in which ciprofloxacin was used. The incidence of VAP was significantly decreased in the second period, mainly because of a reduction of antibiotic-resistant, Gram-negative bacteria that were associated with VAP, but there was no change in the incidence of pneumonia caused by Gram-positive bacteria. In another study by Gruson et al,[87] the antibiotic policy in a medical ICU was changed from the nonrestrictive prescription of mainly ceftazidime and ciprofloxacin (in the 2-year period before change) to the restriction of the prescription of these two drugs to empiric and therapeutic use, combined with the rotation of antibiotic regimens for VAP, without favoring any one drug in the 2-year period after the change. Interestingly, a significant reduction of clinically suspected and microbiologically documented VAP in the period after the change was found, accompanied by an increase of susceptibilities of potentially antibiotic-resistant bacteria, especially *P aeruginosa* and *Burkholderia cepacia*, and a decrease in methicillin-resistant *S aureus* that were responsible for VAP. No impact on mortality was noted in either of these studies. To date, the impact of antibiotic rotation strategies on Gram-negative resistance seems to be favorable, but studies of Gram-positive rotation are needed now that we have therapeutic alternatives to vancomycin.

Conclusion

Substantial resources have been directed to and efforts have been made to improve and promote rational antibiotic use in ICUs. To date, no antibiotic or antibiotic regimen could be linked to a sustained better outcome in severely ill patients with VAP in terms of morbidity, mortality, and related costs. However, we have learned that there is a reduction in mortality with any regimen that is given promptly and is adequate for the identified etiologic pathogens. One approach to solving these problems might be to establish a local antibiotic policy that focuses on one of the main factors predicting mortality in patients with VAP, which is the use of initial inadequate empiric antibiotic therapy in critically ill patients with NP. Besides vigorous efforts to improve the diagnostic procedures for establishing the presence of NP, only a strategy of initiating an immediate broad-spectrum antibiotic treatment covering all potential high-risk pathogens in severely ill patients with VAP might lower the unacceptably high fatality rate of this common disease in the ICU. An approach of initially using narrow-spectrum therapy, correcting for initially inadequate therapy once culture data are available, is unlikely to be successful. On the other hand, if initial therapy must be broad-spectrum in order to be adequate, it is also necessary to de-escalate the therapy once microbiological and clinical response data become available. For many patients, the culture data will not show the presence of highly resistant pathogens, and in these individuals therapy can be narrowed, or even reduced, to a single agent. In some patients, the clinical response will allow for a shortening of the duration of therapy.

To circumvent the inherent danger of augmenting the selection pressure on microorganisms following from the use of broad-spectrum antibiotic therapy, additional measures have to be implemented and tested in prospective clinical trials, focusing on the following questions. (1) Can invasive procedures with quantitative cultures of respiratory specimens distinguish between high-risk and low-risk patients with VAP, using specific concentrations of colony-forming units as a threshold? (2) Do broad-spectrum antibiotic regimens with a single drug produce the same clinical outcome, with less selection pressure on the microbial flora, as does combination therapy? (3) Can high-dose, broad-spectrum antibiotic coverage enhance the clearance of infecting pathogens

from the respiratory tract with the chance of shortening the treatment duration, thus reducing the potential for the emergence of resistance? (4) What is the impact of alternating antibiotic regimens, using a scheduled change of antibiotic treatment in the ICU, on clinical outcomes, costs, and the emergence of resistance? (5) What is the optimal duration of antibacterial therapy in patients with VAP? (6) How can we best de-escalate therapy while achieving good outcomes and controlling resistance?

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Chest 2002;122; 2183-2196
DOI 10.1378/chest.122.6.2183