State of the Art

Ventilator-associated Pneumonia

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CONTENTS

Ventilator-associated pneumonia (VAP) continues to complicate the course of 8 to 28% of patients receiving mechanical ventilation (MV). In contrast to infections of more frequently involved organs (e.g., urinary tract and skin), for which mortality is low, ranging from 1 to 4%, the mortality rate for VAP ranges from 24 to 50% and can reach 76% in some specific settings or when lung infection is caused by high-risk pathogens. The predominant organisms responsible for infection are *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and Enterobacteriaceae, but etiologic agents widely differ according to the population of patients in an intensive care unit, duration of hospital stay, and prior antimicrobial therapy. Because appropriate antimicrobial treatment of patients with VAP significantly improves outcome, more rapid identification of infected patients and accurate selection of antimicrobial agents represent important clinical goals. Our personal bias is that using bronchoscopic techniques to obtain protected brush and bronchoalveolar lavage specimens from the affected area in the lung permits physicians to devise a therapeutic strategy that is superior to one based only on clinical evaluation. When fiberoptic bronchoscopy is not available to physicians treating patients clinically suspected of having VAP, we recommend using either a simplified nonbronchoscopic diagnostic procedure or following a strategy in which decisions regarding antibiotic therapy are based on a clinical score constructed from seven variables. Selection of the initial antimicrobial therapy should be based on predominant flora responsible for VAP at each institution, clinical setting, information provided by direct examination of pulmonary secretions, and intrinsic antibacterial activities of antimicrobial agents and their pharmacokinetic characteristics. Further trials will be needed to clarify the optimal duration of treatment and the circumstances in which monotherapy can be safely used.

Despite major advances in techniques for the management of ventilator-dependent patients and the routine use of effective procedures to disinfect respiratory equipment, ventilator-associated pneumonia (VAP) continues to complicate the course of 8 to 28% of the patients receiving mechanical ventilation (MV) (1–5). Rates of pneumonia are considerably higher among patients hospitalized in intensive care units (ICUs) compared with those in hospital wards, and the risk of pneumonia is increased 3- to 10-fold for the intubated patient receiving MV (1, 3, 6–13). In contrast to infections of more frequently involved organs (e.g., urinary tract and skin), for which mortality is low, ranging from 1 to 4%, the mortality rate for VAP, defined as pneumonia occurring more than 48 hours after endotracheal intubation and initiation of MV, ranges from 24 to 50% and can reach 76% in some specific settings or when lung infection is caused by high-risk pathogens (2, 11–20). Because several studies have shown that appropriate antimicrobial treatment of patients with VAP significantly improves outcome, more rapid identification of infected patients and accurate selection of antimicrobial agents represent important clinical goals (14, 21, 22). However, consensus on appropriate diagnostic, therapeutic, and preventive strategies for VAP has yet to be reached.

The present review is based on an evaluation of the literature, selected using a computerized MEDLINE search from 1980 through March 2001. Review articles, consensus statements, and the references cited therein were also considered in this endeavor to update our current knowledge on the epidemiology, diagnosis, and treatment of VAP. Because the Hospital Infection Control Practice Advisory Committee of the Centers for Disease Control and Prevention (CDC, Atlanta, GA) published extensive and up-to-date recommendations for the prevention of nosocomial pneumonia in 1997 (23), and other comprehensive reviews are also available (24–26), this topic is not covered herein.

EPIDEMIOLOGY

Accurate data on the epidemiology of VAP are limited by the lack of standardized criteria for its diagnosis. Conceptually, VAP is defined as an inflammation of the lung parenchyma caused by infectious agents not present or incubating at the time MV was started (27). Despite the clarity of this conception, the past three decades have witnessed the appearance of numerous operational definitions, none of which is universally accepted. Even definitions based on histopathologic findings at autopsy may fail to find consensus or provide certainty. Pneumonia in focal areas of a lobe may be missed, microbiologic studies may be negative despite the presence of inflammation in the lung, and pathologists may disagree about the findings (28–31). The absence of a "gold standard" continues to fuel controversy about the adequacy and relevance of many studies in this field.

Prolonged (more than 48 hours) MV is the most important factor associated with nosocomial pneumonia. However, VAP may occur within the first 48 hours after intubation. Since the princeps study by Langer and coworkers (32), it is usual to distinguish early-onset VAP, which occurs during the first 4 days of MV, from late-onset VAP, which develops five or more days after initiation of MV. Not only are the causative pathogens commonly different but the disease is usually less severe and the prognosis better in early-onset than late-onset VAP (27, 33).

Incidence of Ventilator-associated Pneumonia

A large-scale 1-day point prevalence study of pneumonia arising in the ICU was conducted on April 29, 1992, in 1,417 ICUs (6). A total of 10,038 patients was evaluated: 2,064 (21%) had ICU-acquired infections, including pneumonia in 967 (47%) patients, for an overall nosocomial pneumonia prevalence of 10%. In that study, logistic regression analysis identified MV as one of the seven risk factors for ICU-acquired infections. Another large-scale study, conducted in 107 European ICUs, demonstrated a crude pneumonia rate of 9% (7). In that study, MV was associated with a 3-fold higher risk of developing VAP than that observed for nonventilated patients. On the basis of their analyses of overall rates of nosocomial pneumo-

nia, Cross and Roup reported 10-fold higher frequencies for ventilated patients than for those without respiratory assistance (8). Similarly, in a nationwide American study, the pneumonia rate was 21-fold higher for patients receiving continuous ventilatory support than for those not requiring MV (34), in agreement with a multivariate analysis of 120 consecutive VAP episodes and 120 control subjects that had shown intubation to independently increase the risk of nosocomial pneumonia $\sim$ 7-fold (11). A large prospective cohort study was conducted in 16 Canadian ICUs: of the 1,014 mechanically ventilated patients included, 177 (18%) developed VAP, as assessed by bronchoscopic sampling with bronchoalveolar lavage (BAL) or protected specimen brush (PSB) in 131 (35). These data confirmed the considerably higher risk of VAP observed in the subset of ICU patients treated with MV.

In the majority of reports, VAP frequencies varied between 8 and 28% (9, 11, 12, 14, 15, 32, 35–51) (Table 1). A prospective investigation of VAP in 23 Italian ICUs that included 724 critically ill patients who had received prolonged (more than 24 hours) ventilatory assistance after admission found a mean rate of 23%; the frequency rose from 5% for patients receiving MV for 1 day to 69% for those receiving MV for more than 30 days (9, 32). Concerning a subset of 124 trauma patients, 67% of whom were ventilated, early-onset pneumonia, defined as pneumonia occurring within the first 96 hours after admission, represented 63% of the 41 pulmonary infections complicating the course of these patients (44). In another study of 244 medical, surgical, or trauma patients treated with MV, Prod'hom and coworkers defined early-onset pneumonia as occurring during the first 4 days of MV; overall, 53 (22%) VAP episodes were observed, with early-onset pneumonia representing 45% of all pneumonia episodes (52). When quantitative cultures of specimens obtained with a PSB during fiberoptic bronchoscopy (FOB) were used to define pneumonia in 567 ventilated patients, the VAP rate was 9% (12). According to an actuarial method, the cumulative risk of pneumonia in that context was estimated to be 7% at 10 days and 19% at 20 days after the onset of MV. Furthermore, in that study, the incremental risk of pneumonia was virtually constant throughout the entire ventilation period, with a mean rate of $\sim$ 1% per day. In contrast, Cook and coworkers demonstrated

TABLE 1. INCIDENCE AND CRUDE MORTALITY RATES OF VENTILATOR-ASSOCIATED PNEUMONIA

First Author	Ref.	Year of Publication	No. of Patients	Incidence (%)	Diagnostic Criteria	Mortality Rate (%)
Patients in ICU						
Salata	41	1987	51	41	Clinical–autopsy	76
Craven	15	1986	233	21	Clinical	55
Langer	9	1989	724	23	Clinical	44
Fagon	12	1989	567	9	PSB	71
Kerver	43	1987	39	67	Clinical	30
Driks	40	1987	130	18	Clinical	56
Torres	14	1990	322	24	Clinical–PSB	33
Baker	44	1996	514	5	PSB/BAL	24
Kollef	45	1993	277	16	Clinical	37
Fagon	51	1996	1,118	28	PSB/BAL	53
Timsit	46	1996	387	15	PSB/BAL	57
Cook	35	1998	1,014	18	Clinical–PSB/BAL	24
Tejada Artigas	47	2001	103	22	PSB	44
Patients with ARDS						
Sutherland	49	1995	105	15	PSB/BAL	38
Delclaux	17	1997	30	60	PTC/BAL	63
Chastre	16	1998	56	55	PSB/BAL	78
Meduri	50	1998	94	43	PSB/BAL	52
Markowicz	18	2000	134	37	PSB/BAL	57

Definition of abbreviations: ARDS = acute respiratory distress syndrome; BAL = bronchoalveolar lavage; ICU = intensive care unit; PSB = protected specimen brush; PTC = plugged telescoping catheter.

in a large series of 1,014 mechanically ventilated patients that, although the cumulative risk for developing VAP increased over time, the daily hazard rate decreased after Day 5 (35). The risk per day was evaluated at 3% on Day 5, 2% on Day 10, and 1% on Day 15. Independent predictors of VAP retained by multivariable analysis were a primary admitting diagnosis of burns (risk ratio [RR], 5.1; 95% confidence interval [CI], 1.5 to 17.0), trauma (RR, 5.0; 95% CI, 1.9 to 13.1), central nervous system disease (RR, 3.4; 95% CI, 1.3 to 8.8), respiratory disease (RR, 2.8; 95% CI, 1.1 to 7.5), cardiac disease (RR, 2.7; 95% CI, 1.1 to 7.0), MV during the previous 24 hours (RR, 2.3; 95% CI, 1.1 to 4.7), witnessed aspiration (RR, 3.2; 95% CI, 1.6 to 6.5), and paralytic agents (RR, 1.6; 95% CI, 1.1 to 2.4). Exposure to antibiotics conferred protection (RR, 0.4; 95% CI, 0.3 to 0.5), but this effect was attenuated over time. Thus, the daily risk for developing VAP is highly dependent on the population being studied and also on many other factors, particularly the number of patients in the given population who received antibiotics immediately after their admission to the ICU.

VAP is thought to be a common complication of the acute respiratory distress syndrome (ARDS) (Table 1). Most clinical studies have found that pulmonary infection affects between 34 and more than 70% of patients with ARDS, often leading to the development of sepsis, multiple organ failure, and death. When the lungs of patients who died of ARDS were examined histologically at autopsy, pneumonia could be demonstrated in as many as 73% (13, 53). The diagnosis of pulmonary infection in patients with ARDS, however, is often difficult. Several studies have clearly demonstrated the inability of physicians to accurately diagnose nosocomial pneumonia in this setting on the basis of clinical criteria alone (53). Using PSB and/or BAL techniques at predetermined times from Day 3 to 21 after the onset of the syndrome in a series of 105 patients with ARDS, Sutherland and coworkers concluded that VAP may indeed occur far less frequently than expected in this group of patients (49). Only 16 (15.2%) of their 105 patients met the quantitative criteria for pneumonia (PSB > 10^3 cfu/ml or BAL > 10^4 cfu/ml), and no correlations were found between total colony counts in BAL fluid or PSB cultures and severity of ARDS, as judged by $Pa_{O_2}/F_{I_{O_2}}$ (fraction of inspired oxygen) ratios, days receiving MV, static lung compliance, and/or survival. Unfortunately, these results are probably not of general value, because most patients included in the study were lavaged while receiving antibiotics and at predetermined times during the course of ARDS, rather than at the time of clinically suspected infection. According to four other studies, the VAP rate was higher in patients with ARDS than in other mechanically ventilated patients (16–18, 50). In one study of 56 patients with ARDS, PSB and BAL were used to define pneumonia and the VAP rate was 55% (16), whereas it was only 28% for 187 non-ARDS patients diagnosed according to the same criteria during the same period. It was specified that early-onset VAP (occurring before Day 7) was relatively rare in patients with ARDS: only 10% of the first VAP episodes, as opposed to 40% among non-ARDS patients. Those observations were confirmed in 30 patients with ARDS for whom repeated quantitative culture results of specimens obtained with a plugged catheter were available and in 94 ARDS patients with suspected VAP who underwent 172 bronchoscopies, with VAP rates of 60% (incidence density, 4.2/100 ventilator days) and 43%, respectively (17, 50). In another prospective multicenter study, VAP was bacteriologically confirmed in 49 (37%) of 134 patients with ARDS, versus 23% of ventilated non-ARDS patients (p < 0.002) (18).

The finding of a higher incidence of microbiologically provable VAP in patients with ARDS than in other populations of mechanically ventilated patients was not unexpected. Several studies have clearly shown that alveolar macrophages and neutrophils retrieved from the lungs of patients with ARDS have impaired phagocytic function and/or lower maximal activity after *ex vivo* stimulation by bacterial products than do corresponding cells from normal subjects, which could explain why these patients are at high risk of developing pulmonary infection (54, 55). However, the actuarial risk of pneumonia after 30 days of MV does not differ significantly between patients with and without ARDS (16). Therefore, the higher incidence of VAP observed in patients with ARDS is probably essentially the result of their need for a much longer duration of MV than that of other patients, thereby increasing the time during which they are at risk for developing VAP.

These findings emphasize (*1*) the major influence of underlying medical conditions on the epidemiologic characteristics of VAP, and (*2*) the critical role of the diagnostic techniques used to identify patients with VAP and to provide accurate epidemiologic data. As the data presented in Table 2 suggest, for the same patients, VAP was clinically diagnosed almost twice as often as it could be bacteriologically confirmed (12, 47, 56–63). Understanding this difference is crucial for the implementation of a rational and pertinent surveillance program in the ICU, with possible intra- and interunit comparisons, to evaluate new therapeutic strategies, particularly prophylactic measures, and to improve antibiotic use in this setting with accurate identification of infected patients and appropriate selection of antimicrobial agent(s). This distinction between clinically suspected versus bacteriologically confirmed VAP has now been integrated into the most recent CDC guidelines (23).

Mortality

Crude ICU mortality rates of 24 to 76% have been reported for VAP at a variety of institutions (*see* Table 1) (9, 12, 14, 15, 35, 40, 41, 43–47, 51, 57). ICU ventilated patients with VAP appear to have a 2- to 10-fold higher risk of death compared with patients without pneumonia. In 1974, fatality rates of 50% for ICU patients with pneumonia versus 4% for patients without pneumonia were reported (64). The results of several studies conducted between 1986 and 2001 have confirmed that observation: Despite variations among studies that partly reflect the populations considered, overall mortality rates for patients with or without VAP were, respectively: 55 versus 25% (15), 71 versus 28% (12), 33 versus 19% (14), 37 versus 9% (45), and 44 versus 19% (47). These rates correspond to increased risk ratios of mortality of VAP patients of 2.2, 2.5, 1.7, 4.4, and 2.3, respectively.

TABLE 2. BACTERIOLOGICAL CONFIRMATION OF CLINICALLY SUSPECTED VENTILATOR-ASSOCIATED PNEUMONIA

First Author	Ref.	Clinically Suspected VAP (*n*)	Bacteriological Confirmation	
			n	%
Fagon	12	84	27	32
Croce	56	136	46	34
Rodriguez de Castro	57	110	45	41
Luna	58	132	65	49
Bonten	59	138	72	52
Kollef	60	130	60	46
Sanchez-Nieto	61	51	36	71
Ruiz	62	76	42	55
Fagon	63	204	90	44
Tejada Artigas	47	103	23	22

Definition of abbreviation: VAP = ventilator-associated pneumonia.

Although these statistics indicate that VAP is a severe disease, previous studies have not clearly demonstrated that pneumonia is indeed responsible for the higher mortality rate of these patients. Two independent factors make it difficult to assign responsibility unambiguously. The first is, once again, the difficulty in establishing a firm diagnosis, that is, to clearly identify patients with VAP; thus, the widely diverging VAP mortality rates reported might reflect not only differences in the populations studied but also differences in the diagnostic criteria used. Second, numerous studies have demonstrated that severe underlying illness predisposes patients in the ICU to the development of pneumonia, and their mortality rates are, consequently, high (6, 7, 11, 36, 37, 42, 45). Therefore, it is difficult to determine whether such patients would have survived if VAP had not occurred. However, nosocomial pneumonia has been recognized in several studies as an important prognostic factor for different groups of critically ill patients, including cardiac surgery patients (48, 65) or those with acute lung injury (66), and immunocompromised patients, for example those with acute leukemia (67), lung transplantation (68), or bone-marrow transplantation (69). In contrast, in patients with extremely severe medical conditions, such as those surviving cardiac arrest (70), or young patients with no underlying disease, such as those admitted after trauma (44, 71, 72), nosocomial pneumonia does not seem to significantly affect prognosis. Similarly, VAP does not appear to markedly influence overall survival of patients with ARDS, as documented by several studies (13, 16–18, 50). However, studies evaluating excess mortality attributed to VAP in patients with ARDS are difficult to interpret, because most VAP in this subset of patients occurs late in the course of the disease, whereas patients with ARDS who do not develop VAP, but who nevertheless die, do so earlier than other patients with ARDS, thus having little opportunity to develop nosocomial infection (16).

Despite these difficulties and limitations, several arguments support the notion that the presence of VAP is an important determinant of the poor prognosis of patients treated with MV. Risk factors for death of ventilated patients who developed pneumonia have been systematically investigated only by two groups (11, 14). Using multiple logistic regression analysis, Torres and coworkers demonstrated that the worsening of respiratory failure, the presence of an ultimately or rapidly fatal underlying condition, the presence of shock, inappropriate antibiotic therapy, and/or type of ICU were factors that negatively affected the prognosis of VAP. Thus, those authors emphasized the complex relationships among the severity of underlying disease leading to ICU admission and treatment with MV, the severity of pneumonia itself, and the adequacy of initial antibiotic treatment. The important prognostic role played by the adequacy of the initial empiric antimicrobial therapy was also analyzed by several other investigators and is summarized in Table 3 (19, 58, 61, 62, 73–76).

The prognosis for aerobic, gram-negative bacilli (GNB) VAP is considerably worse than that for infection with gram-positive pathogens, when these organisms are fully susceptible to antibiotics. Death rates associated with *Pseudomonas* pneumonia are particularly high, ranging from 70 to more than 80% in several studies (12, 64, 77–81). According to one study, mortality associated with *Pseudomonas* or *Acinetobacter* pneumonia was 87% compared with 55% for pneumonias due to other organisms (12). Similarly, Kollef and coworkers demonstrated that patients with VAP due to high-risk pathogens (*Pseudomonas aeruginosa*, *Acinetobacter* spp., and *Stenotrophomonas maltophilia*) had a significantly higher hospital mortality rate (65%) than patients with late-onset VAP due to other microbes (31%) or patients without late-onset pneumonia (37%) (65). Concerning gram-positive pathogens, in a study comparing VAP due to methicillin-resistant *Staphylococcus aureus* (MRSA) or methicillin-sensitive *S. aureus* (MSSA), mortality was found to be directly attributable to pneumonia for 86% of the former cases versus 12% of the latter, with a relative risk of death equal to 20.7 for MRSA pneumonia (82).

Multivariate analyses conducted to evaluate the independent role played by VAP in inducing death failed to identify VAP as a variable independently associated with mortality in two studies (15, 45). In contrast, the EPIC (European Prevalence of Infection in Intensive Care) Study's stepwise logistic regression analyses demonstrated that ICU-acquired pneumonia increased the risk of death with an odds ratio of 1.91 (95% CI, 1.6 to 2.3), independently of clinical sepsis and bloodstream infection (6). Another study based on 1,978 patients in the ICU, including 1,118 patients receiving MV, demonstrated that, in addition to the severity of illness, the presence of dysfunctional organ(s); stratification according to the McCabe and Jackson criteria of underlying disease as fatal, ultimately fatal, or not fatal; and nosocomial bacteremia and nosocomial pneumonia independently contributed to the deaths of ventilated patients (51). Using the Cox model in a series of 387 patients, it was demonstrated that patients with clinically suspected pneumonia had an increased risk of mortality; however, confirmation of the diagnosis by invasive techniques added no prognostic information (respective relative risk of 2.1 and 1.7) (46).

Case–control studies have been used to assess mortality attributable to nosocomial pneumonia, that is, the difference between the mortality rates observed for case patients (patients with pneumonia) and control subjects (patients without pneumonia). The results of matched cohort studies evaluating mortality and relative risk attributable to nosocomial pneumonia are given in Table 4 (44, 81, 83–87). Of these seven studies, five concluded that VAP was associated with a significant attributable mortality. For example, it was reported that the mortality rate attributable to VAP exceeded 25%, corresponding to a relative risk of death of 2.0 (with respective values of 40% and 2.5 for cases of pneumonia caused by *Pseudomonas* or *Acinetobacter* spp.) (81). These results were supported by those of other authors who reported that the risk of mortality was almost three

TABLE 3. MORTALITY RATES ACCORDING TO INITIAL EMPIRIC ANTIBIOTIC THERAPY

First Author	Ref.	Crude Mortality Rates of Patients Receiving		p Value
		Inadequate Antibiotic Therapy	Adequate Antibiotic Therapy	
Luna	58	92.2% (n = 34)	37.5% (n = 15)	< 0.001
Alvarez-Lerma	74	34.9% (n = 146)	32.5% (n = 284)	NS
Rello	21	63.0% (n = 27)	41.5% (n = 58)	0.06
Kollef	60	60.8% (n = 51)	26.6% (n = 79)	0.001
Sanchez-Nieto	61	42.9% (n = 14)	25.0% (n = 24)	NS
Ruiz	62	50.0% (n = 18)	39.3% (n = 28)	NS
Dupont	76	60.7% (n = 56)	47.3% (n = 55)	NS

Definition of abbreviation: NS = not significant.

TABLE 4. MORTALITY RATES AND RISK RATIOS FOR DEATH ATTRIBUTABLE TO NOSOCOMIAL PNEUMONIA IN MATCHED CASE–CONTROL STUDIES

First Author	Ref.	Diagnostic Criteria	Type of Patient	No. of Cases	Crude Mortality		Attributable Mortality (%)	Risk Ratio	p Value
					Cases (%)	Controls (%)			
Craig	83	Clinical	ICU	54	20.4	5.6	14.8	3.6	< 0.01
Fagon	81	PSB + BAL	Ventilated	48	54.2	27.1	27.1	2.0	< 0.01
Cunnion	84	Clinical	Surgical	20	55.0	5.0	50.0	23.2*	< 0.002
			ICU	20	55.0	7.5	47.5	15.1*	< 0.002
Baker	44	PSB/BAL	Medical	62	24.0	24.0	0	1	NS
Papazian	85	PSB	ICU	85	40.0	38.8	1.2	1.3	NS
Heyland	86	PSB/BAL	Trauma	177	23.7	17.9	5.8	1.3	NS
Bercault	87	PSB	Ventilated	135	41.0	14.0	27.0	2.7*	0.03

Definition of abbreviations: BAL = bronchoalveolar lavage; ICU = intensive care unit; NS = not significant; PSB = protected specimen brush.
* Odds ratio.

times higher in patients with pneumonia (RR, 2.95; 95% CI, 1.73 to 5.03) than in those without, with a major impact being observed for patients with intermediate-grade severity (88).

Finally, only a few reports have been published on mortality as a result of nosocomial pneumonia for which autopsy material from patients who died during their hospital stay was analyzed. On the basis of the analysis of 200 consecutive hospital deaths, it was concluded that nosocomial pneumonia contributed to 60% of the fatal infections and was the leading cause of death from hospital-acquired infections (89). By matching control subjects with half of these patients who died in the hospital, the same authors found that nosocomial lower respiratory tract infection occurred in 18% of the patients but in only 4% of the control subjects. Among patients who did not have a terminal condition on admission, nosocomial infections were three times more frequent among those who died (46%) than among survivors (11%) (89). A clinical investigation to determine whether VAP is an independent risk factor for death matched 108 nonsurvivors with 108 survivors for their underlying diseases, age, admission date, severity of illness, and duration of MV (90); 39 patients in each group developed VAP. This finding contrasts with those of other investigations, which identified the occurrence of VAP as an independent determinant of hospital mortality. Other factors beyond the simple development of VAP, such as the severity of the disease or the responsible pathogens, may be more important determinants of outcome for patients in whom VAP as well as other nosocomial infections develop. Indeed, it may well be that VAP increases mortality only in the subset of patients with intermediate severity (88) and/or in patients with VAP caused by high-risk pathogens, as indicated above (12, 65, 82). It is probable that several case–control studies were confounded by the fact that patients with low-severity and early-onset pneumonia due to organisms such as *Haemophilus influenzae* or *Streptococcus pneumoniae* have excellent prognoses with or without VAP, whereas very ill patients with late-onset VAP occurring while they are in a quasi-terminal state would die anyway.

Thus, considering many different kinds of evidence, VAP seems indeed associated with a 20 to 30% higher risk of death than that due to the underlying disease alone, at least in several subgroups of patients requiring MV, which pleads for new approaches to improve the management of ventilator-dependent patients, including more effective prophylactic measures, and earlier diagnosis and treatment.

Morbidity and Cost

It is impossible to evaluate precisely the morbidity and excess costs associated with VAP. However, with respect to morbidity measures, the prolonged hospital stay as a direct conse-

quence of VAP has been estimated in several studies (46, 51, 81, 83, 84, 91). In one study, VAP prolonged the duration of MV from 10 to 32 days (42). In another, the median length of stay in the ICU for the patients who developed VAP was 21 days versus a median of 15 days for paired control subjects (81). Furthermore, a mean prolongation of ICU stay of 20 days was noted for patients with VAP when surviving pairs were compared. Reported mean durations of MV, ICU stay, and hospital stay were, respectively, 12.0, 20.5, and 43.0 days for trauma patients with pneumonia compared with 8.0, 15.0, and 34.0 days for their matched control subjects (44). Analyzing the same variables, others found, respectively, 27.3, 32.9, and 52.5 days for case patients versus 19.7, 24.5, and 43.2 days for patients without VAP (85). Similarly, it was demonstrated that the mean hospital stay after ICU admission was longer for surgical ICU patients (30.0 versus 22.3 days for control subjects) and medical and respiratory ICU patients who developed nosocomial pneumonia (40.9 versus 23.1 days for control subjects) (84). Heyland and coworkers compared 177 VAP patients with matched patients who did not develop VAP, and showed that VAP patients stayed in the ICU 4.3 days longer than did control subjects; the attributable ICU length of stay was longer for medical than surgical patients (6.5 versus 0.7 days), and for patients infected with "high-risk" as opposed to "low-risk" organisms (9.1 versus 2.9 days) (86). In patients with ARDS, all studies clearly identified prolonged duration of MV and lengthened ICU and hospital stays for patients with VAP compared with those without (16–18, 50). Thus, summarizing available data, VAP likely extended the ICU stay by at least 4 days.

These prolonged hospitalizations underscore the considerable financial burden imposed by the development of VAP. However, a precise and universal evaluation of such overcosts is difficult. Cost analysis is, indeed, dependent on a wide variety of factors that differ from one country to another, including health care system, organization of the hospital and the ICU, the possibility of patients being treated by private practitioners, cost of antibiotics, and so on. Only a few, and frequently discrepant, data are available: The average excess cost of nosocomial pneumonia was estimated to be US$1,255 in 1982 (92). In a similar study in 1985, the average extra cost was US$2,863 (93). More recently, the extra hospital charges attributed to nosocomial pneumonia occurring in trauma patients were evaluated to be US$40,000 (44).

Etiologic Agents

Microorganisms responsible for VAP may differ according to the population of patients in the ICU, the durations of hospital and ICU stays, and the specific diagnostic method(s) used.

The high rate of respiratory infections due to GNB in this setting has been repeatedly documented (12, 14, 19, 34, 94–97). Several studies have reported that more than 60% of VAP is caused by aerobic GNB. More recently, however, some investigators have reported that gram-positive bacteria have become increasingly more common in this setting, with *S. aureus* being the predominant gram-positive isolate. For example, *S. aureus* was responsible for most episodes of nosocomial pneumonia in the EPIC Study, accounting for 31% of the 836 cases with identified responsible pathogens (97). The data from 24 investigations conducted with ventilated patients, for whom bacteriologic studies were restricted to uncontaminated specimens, confirmed those results: GNB represented 58% of recovered organisms (12, 14, 16, 18–21, 44, 46, 48, 50, 62, 63, 70, 98–107) (Table 5). The predominant GNB were *P. aeruginosa* and *Acinetobacter* spp., followed by *Proteus* spp., *Escherichia coli*, *Klebsiella* spp., and *H. influenzae*. A relatively high rate of gram-positive pneumonias was also reported in those studies, with *S. aureus* involved in 20% of the cases (Table 5).

The high rate of polymicrobial infection in VAP has been emphasized repeatedly. In a study of 172 episodes of bacteremic nosocomial pneumonia, 13% of lung infections were caused by multiple pathogens (77). Similarly, when the PSB technique was used to identify the causative agents in 52 consecutive cases of VAP, a 40% polymicrobial infection rate was found (12), a value similar to that observed in another study conducted at the same time on a comparable population of ventilated patients (96). Findings were also similar for patients with ARDS: 58% of the 106 VAP episodes were polymicrobial, of which 55 and 60%, respectively, occurred in patients with and without ARDS (16).

Underlying diseases may predispose patients to infection with specific organisms. Patients with chronic obstructive pulmonary disease (COPD) are, for example, at increased risk for *H. influenzae*, *Moraxella catarrhalis* or *S. pneumoniae* infections; cystic fibrosis increases the risk of *P. aeruginosa* and/or *S. aureus* infections, whereas trauma and neurologic patients are at increased risk for *S. aureus* infection (33, 44, 72, 82). Furthermore, the causative agent for pneumonia differs among ICU surgical populations (108), with 18% of the nosocomial pneumonias being due to *Haemophilus* or pneumococci, particularly in trauma patients, but not in patients with malignancy, transplantation, or abdominal or cardiovascular surgery.

Several studies tried to identify specific risk factors for infection by a given pathogen; for example, logistic regression analysis identified neurosurgery, head trauma, and large-volume aspiration as risk factors for VAP due to *Acinetobacter baumannii* (109). In studies of patients with ARDS compared with non-ARDS patients, there were no major differences in the distributions of pathogens responsible for VAP, with, however, a predominance of nonfermenting GNB and MRSA among the latter (16–18). Rather, the differences observed seemed primarily to reflect the duration of MV before VAP onset (16).

Despite somewhat different definitions of early-onset pneumonia, varying from < 3 to < 7 days (33, 107), high rates of *H. influenzae*, *S. pneumoniae*, MSSA, or susceptible Enterobacteriaceae were constantly found in early-onset VAP, whereas *P. aeruginosa*, *Acinetobacter* spp., MRSA, and multiresistant GNB were significantly more frequent in late-onset VAP (33, 106, 107). This different distribution pattern of etiologic agents between early- and late-onset VAP is also linked to the frequent administration of prior antimicrobial therapy in many patients with late-onset VAP. In a prospective study that included 129 episodes of nosocomial pneumonia documented by PSB specimens, the distributions of responsible pathogens were compared according to whether the patients had received antimicrobial therapy before pneumonia onset (19). The most striking finding was that the rate of pneumonia caused by gram-positive cocci or *H. influenzae* was significantly lower (p < 0.05) in patients who had received antibiotics, whereas the rate of pneumonia caused by *P. aeruginosa* was significantly higher (p < 0.01). A stepwise logistic regression analysis retained only prior antibiotic use (odds ratio [OR] = 9.2, p < 0.0001) as significantly influencing the risk of death from pneumonia (19). Similar results were obtained when multivariate analysis was used to determine risk factors for VAP caused by potentially drug-resistant bacteria such as MRSA, *P. aeruginosa*, *A. baumannii*, and/or *S. maltophilia* in 135 consecutive episodes of VAP (107). Only three variables remained significant: duration of MV before VAP onset $\geqslant 7$ days (OR = 6.0), prior antibiotic use (OR = 13.5), and prior use of broad-spectrum drugs (third-generation cephalosporin, fluoroquinolone, and/or imipenem) (OR = 4.1) (107). Not all studies, however, have confirmed this distribution pattern. For example, one study found that the most common pathogens associated with early-onset VAP were *P. aeruginosa* (25%), MRSA (18%), and *Enterobacter* spp. (10%), with similar pathogens being associated with late-onset VAP (110). Their finding may, in part, be due to the prior hospitalization and use of antibiotics in many patients developing early-onset VAP before their transfer to the ICU.

The incidence of multiresistant pathogens is also closely linked to local factors and varies widely from one institution to another. Consequently, each ICU must continuously collect meticulous epidemiologic data. With these aims, variations of VAP etiology among three Spanish ICUs were analyzed (106) and compared with data collected in Paris (107). The authors concluded that VAP pathogens varied widely among these four treatment centers, with marked differences in all of the microorganisms isolated from VAP episodes in Spanish centers as compared with the French site. Clinicians must clearly be aware of the common microorganisms associated with both early-onset and late-onset VAP in their own hospitals to avoid the administration of initial inadequate antimicrobial therapy.

Legionella species (111, 112), anaerobes (100), fungi (113), viruses (114), and even *Pneumocystis carinii* should be mentioned as potential causative agents but are not considered to

TABLE 5. ETIOLOGY OF VENTILATOR-ASSOCIATED PNEUMONIA AS DOCUMENTED BY BRONCHOSCOPIC TECHNIQUES IN 24 STUDIES FOR A TOTAL OF 1,689 EPISODES AND 2,490 PATHOGENS

Pathogen	Frequency (%)
Pseudomonas aeruginosa	24.4
Acinetobacter spp.	7.9
Stenotrophomonas maltophilia	1.7
Enterobacteriaceae*	14.1
Haemophilus spp.	9.8
Staphylococcus aureus†	20.4
Streptococcus spp.	8.0
Streptococcus pneumoniae	4.1
Coagulase-negative staphylococci	1.4
Neisseria spp.	2.6
Anaerobes	0.9
Fungi	0.9
Others (< 1% each)‡	3.8

* Distribution when specified: *Klebsiella* spp., 15.6%; *Escherichia coli*, 24.1%; *Proteus* spp., 22.3%; *Enterobacter* spp., 18.8%; *Serratia* spp., 12.1%; *Citrobacter* spp., 5.0%; *Hafnia alvei*, 2.1%.
† Distribution when specified: methicillin-resistant *S. aureus*, 55.7%; methicillin-sensitive *S. aureus*, 44.3%.
‡ Including *Corynebacterium* spp., *Moraxella* spp., and *Enterococcus* spp.

be common in the context of pneumonia acquired during MV. However, several of these causative agents may be more common and potentially underreported because of difficulties involved with the diagnostic techniques used to identify them, including anaerobic bacteria and viruses (100, 114). In a study conducted to determine the frequency of anaerobes in 130 patients with a first episode of bacteriologically documented VAP, with special precautions taken to preserve anaerobic conditions during PSB transport and microbiologic procedures (100), anaerobes were involved in 23% of the total number of episodes and the main strains isolated were as follows: *Prevotella melaninogenica* (36%), *Fusobacterium nucleatum* (17%), and *Veillonella parvula* (12%). The probability of recovering anaerobic bacteria was particularly high in orotracheally intubated patients and patients in whom pneumonia occurred during the 5 days after ICU admission. However, in a study conducted among 143 patients who developed 185 episodes of suspected VAP and 25 patients with aspiration pneumonia, only 1 anaerobic organism (*V. parvula*) was isolated from 1 patient with aspiration pneumonia, and none from patients with VAP (99).

Thus, examining currently available data, the clinical significance of anaerobes in the pathogenesis and outcome of VAP remains unclear, except as etiologic agents in patients with necrotizing pneumonitis, lung abscess, or pleuropulmonary infections. Anaerobic infection and coverage with antibiotics, such as clindamycin or metronidazole, should probably also be considered for patients with gram-positive respiratory secretions documenting numerous extra- and intracellular microorganisms in the absence of positive cultures for aerobic pathogens.

Isolation of fungi, most frequently *Candida* species, at significant concentrations poses interpretative problems. Invasive disease has been reported in VAP but, more frequently, yeasts are isolated from respiratory tract specimens in the apparent absence of disease. One prospective study examined the relevance of isolating *Candida* spp. from 25 non-neutropenic patients who had been mechanically ventilated for at least 72 hours (113). Just after death, multiple culture and biopsy specimens were obtained by bronchoscopic techniques. Although 10 patients had at least one biopsy specimen positive for *Candida* spp., only two had evidence of invasive pneumonia as demonstrated by histologic examination. Many of the endotracheal aspirates, PSB specimens, and BAL specimens also yielded positive cultures for *Candida* spp., sometimes in high concentrations, but they did not contribute to diagnosing invasive disease. On the basis of these data, the use of the commonly available respiratory sampling methods (bronchoscopic or nonbronchoscopic) in mechanically ventilated patients appears insufficient for the diagnosis of *Candida* pneumonia. At present, the only sure method to establish that *Candida* is the primary lung pathogen is to demonstrate yeast or pseudohyphae in a lung biopsy. However, the significance of *Candida* isolation from the respiratory samples of mechanically ventilated patients merits being investigated in greater depth (115).

In another study conducted over a 5-year period, cytomegalovirus (CMV) was identified as a possible cause of VAP in 25 of 86 patients on the basis of histologic examination of lung tissues obtained at autopsy or open-lung biopsy (114). The authors concluded that CMV should not be excluded as a pathogen potentially responsible for VAP in patients in the ICU, even those without acquired immunodeficiency syndrome, hematologic malignancy, or immunosuppressive therapy.

Pathogenesis

Pneumonia results from microbial invasion of the normally sterile lower respiratory tract and lung parenchyma caused by either a defect in host defenses, challenge by a particularly virulent microorganism, or an overwhelming inoculum. The normal human respiratory tract possesses a variety of defense mechanisms that protect the lung from infection, for example: anatomic barriers, such as the glottis and larynx; cough reflexes; tracheobronchial secretions; mucociliary lining; cell-mediated and humoral immunity; and a dual phagocytic system that involves both alveolar macrophages and neutrophils (27). When these coordinated components function properly, invading microbes are eliminated and clinical disease is avoided, but when these defenses are impaired or if they are overcome by virtue of a high inoculum of organisms or organisms of unusual virulence, pneumonitis results.

As suggested by the infrequent association of VAP with bacteremia, the majority of these infections appear to result from aspiration of potential pathogens that have colonized the mucosal surfaces of the oropharyngeal airways. Intubation of the patient not only compromises the natural barrier between the oropharynx and trachea, but may also facilitate the entry of bacteria into the lung by pooling and leakage of contaminated secretions around the endotracheal tube cuff (10, 33). This phenomenon occurs in most intubated patients, whose supine position may facilitate its occurrence. In previously healthy, newly hospitalized patients, normal mouth flora or pathogens associated with community-acquired pneumonia may predominate. In sicker patients who have been hospitalized more than 5 days, GNB and *S. aureus* frequently colonize the upper airway (33).

Uncommonly, VAP may arise in other ways (116). Observed "macroaspirations" of gastric material initiate the process in some patients. Allowing condensates in ventilator tubing to drain into the patient's airway may have the same effect (25). FOB, tracheal suctioning, or manual ventilation with contaminated equipment may also bring pathogens to the lower respiratory tract. More recently, concerns have focused on the potential role of contaminated in-line medication nebulizers, but these devices are infrequently associated with VAP (116).

Although tracheal colonization by potentially pathogenic microorganisms occurs before lung infection in a majority of ventilated patients, its relationship with VAP development remains controversial. In 1972, Johanson and coworkers established that upper airway colonization is a frequent occurrence in ventilated patients and that it can act as a harbinger of nosocomial pneumonia in this setting (117). Those authors demonstrated that 45% of 213 patients admitted to a medical ICU became colonized with aerobic GNB by the end of 1 week in the hospital. Among the 95 colonized patients, 22 (23%) subsequently developed nosocomial pneumonia. By comparison, only four of the 118 (3.4%) noncolonized patients developed pneumonia. As determined in that study and several others, the tracheobronchial tree as well as the oropharynx of mechanically ventilated patients are frequently colonized by enteric GNB (118–121). In a study of 130 intubated patients, GNB were found in the trachea of 58% of those who had received antacids and/or H_2 blockers to prevent bleeding and in 30% of those receiving sucralfate for this purpose (40). Risk factors for tracheobronchial colonization with GNB appear to be the same as those that favor pneumonia and include more severe illness, longer hospitalization, prior or concomitant use of antibiotics, malnutrition, intubation, azotemia, and underlying pulmonary disease (119). Experimental investigations have linked some of these risk factors to changes in adherence of GNB to respiratory epithelial cells. Although formerly attributed to losses of cell surface fibronectin, these changes in adherence more likely reflect alterations of cell surface carbohydrates (27). Bacterial adhesins and prior antimicrobial ther-

apy appear to facilitate the process. Interestingly, Enterobacteriaceae usually appear in the oropharynx first, whereas *P. aeruginosa* more often appears first in the trachea (122, 123).

Other sources of pathogens causing VAP include the paranasal sinuses, dental plaque, and the subglottic area between the true vocal cords and the endotracheal tube cuff. The role of the gastrointestinal tract as a source of oropharyngeal and tracheal colonization by GNB is more controversial (118–120). A sequence of events leading to colonization from the stomach to the trachea, with increasing frequency in direct correlation to the gastric pH, was reported by several investigators, with 27 to 45% of patients having primary colonization of the gastric juice and subsequent colonization of the tracheobronchial tree $\sim$ 2 days later (124–127). In addition to those microbiologic studies, other studies have clearly proven, by means of radiolabeled gastric juice or other techniques, that the gastric juice of intubated patients is aspirated into the tracheobronchial tract within a few hours (128–131). Those investigations convincingly corroborate the microbiologic studies demonstrating that tracheobronchial colonization originates in the stomach in at least 25 to 40% of patients and, therefore, lend support to the role of the gastric barrier in the pathogenesis of nosocomial pneumonia. Whether bacteria ascend from the intestines or descend from the oropharynx, the stomach may act as a reservoir in which pathogens can multiply and attain high concentrations. Alkalinization of the normally acid gastric environment seems to be a prerequisite for this mechanism to be operational.

However, not all authors agree that the gastropulmonary route of infection is truly operative in ICU patients (120, 132). Colonization from the stomach to the upper respiratory tract, eventually leading to 14 VAP episodes, could not be clearly demonstrated in one study (132). The same group, in another study conducted with 141 patients (117), reported that intragastric acidity influenced gastric colonization but not colonization of the upper respiratory tract or the incidence of VAP, suggesting therefore that it is unlikely that the gastropulmonary route contributes importantly to VAP development. Similarly, de Latorre and coworkers demonstrated that only 19 of 72 patients developed tracheal colonization after pharyngeal or gastric colonization by the same organisms; moreover, among the 12 patients who developed VAP, the microorganism(s) responsible had already colonized the trachea in 10 of them, but only 10 of the 21 responsible microorganisms isolated from VAP had previously colonized the pharynx or stomach (133). Last, efforts to eliminate the gastric reservoir by antimicrobial

therapy without decontaminating the oropharyngeal cavity have generally failed to prevent VAP (134, 135). In fact, there is more than one potential pathway for colonization of the oropharynx and trachea in such a setting, including fecal–oral cross-infection on the hands of health care personnel, and contaminated respiratory therapy equipment. Patient care activities, such as bathing, oral care, tracheal suctioning, enteral feeding, and tube manipulations, provide ample opportunities for transmission of pathogens when infection control practices are substandard (136).

In summary, the relationship between VAP and tracheal, pharyngeal, and/or gastric colonizations remains to be elucidated for patients with an endotracheal tube. To date, these findings lead to the following conclusions: (*1*) tracheal colonization precedes VAP in most, but not all, patients; (*2*) only a minority of patients with tracheal colonization develop VAP; (*3*) the stomach can be a reservoir for pneumonia pathogens, although this is not the case in many ICU patients requiring MV.

Risk Factors

Risk factors provide information about the probability of lung infection developing in individuals and populations. Thus, they may contribute to the elaboration of effective preventive strategies by indicating which patients might be most likely to benefit from prophylaxis against pneumonia. Independent factors for VAP that were identified by multivariate analyses in selected studies are summarized in Table 6 (7, 11, 14, 15, 19, 35, 36, 45, 72, 84, 137).

Surgery. Postsurgical patients are at high risk for VAP, which accounts for nearly one-third of the pulmonary infiltrates in these ICU patients (11, 45, 108, 138). In a 1981 report, the pneumonia rate during the postoperative period was 17% (37). Those authors stated that the development of pneumonia was closely associated with preoperative markers of severity of the underlying disease, such as low serum albumin concentration and high American Society of Anesthesiologists preanesthesia physical status classification score (37). A history of smoking, longer preoperative stays, longer surgical procedures, and thoracic or upper abdominal surgery were also significant risk factors for postsurgical pneumonia. Another study comparing adult ICU populations demonstrated that postoperative patients had consistently higher rates of nosocomial pneumonia than did medical ICU patients, with a RR of 2.2 (84). Multiple regression analysis was performed to identify independent predictors of nosocomial pneumonia in the two groups; for surgical ICU patients, MV ($>$ 2 days) and

TABLE 6. INDEPENDENT FACTORS FOR VENTILATOR-ASSOCIATED PNEUMONIA IDENTIFIED BY MULTIVARIATE ANALYSIS IN SELECTED STUDIES*

Host Factors	Intervention Factors	Other Factors
Serum albumin, $<$ 2.2 g/dl	H_2 blockers $\pm$ antacids	Season: fall, winter
Age, $\geqslant$ 60 yr	Paralytic agents, continuous intravenous sedation	
ARDS	$>$ 4 units of blood products	
COPD, pulmonary disease	Intracranial pressure monitoring	
Coma or impaired consciousness	MV $>$ 2 d	
Burns, trauma	Positive end-expiratory pressure	
Organ failure	Frequent ventilator circuit changes	
Severity of illness	Reintubation	
Large-volume gastric aspiration	Nasogastric tube	
Gastric colonization and pH	Supine head position	
Upper respiratory tract colonization	Transport out of the ICU	
Sinusitis	Prior antibiotic or no antibiotic therapy[†]	

Definition of abbreviations: ARDS = acute respiratory distress syndrome; COPD = chronic obstructive pulmonary disease; ICU = intensive care unit; MV = mechanical ventilation.
* *See* references 7, 11, 14, 15, 19, 35, 36, 45, 72, 84, and 137.
[†] *See* text.

acute physiology and chronic health evaluation score were retained by the model; for the medical ICU population, only MV (> 2 days) remained significant. It has been suggested that different surgical ICU patient populations may have different risks for nosocomial pneumonia: cardiothoracic surgery (139) and trauma (particularly the head) patients were more likely to develop VAP than medical or other types of surgical patients (35).

Antimicrobial agents. The use of antibiotics in the hospital setting has been associated with an increased risk of nosocomial pneumonia and selection of resistant pathogens (19, 45, 72, 80, 97, 107, 117, 140, 141). In a cohort study of 320 patients, prior antibiotic administration was identified by logistic regression analysis to be one of the four variables independently associated with VAP along with organ failure, age > 60 years, and the patient's head positioning (i.e., flat on his back or supine versus head and thorax raised 30 to 40° or semirecumbent) (45). However, other investigators found that antibiotic administration during the first 8 days was associated with a lower risk of early-onset VAP (142, 143). For example, Sirvent and coworkers showed that a single dose of a first-generation cephalosporin given prophylactically was associated with a lower rate of early-onset VAP in patients with structural coma (144). Moreover, multiple logistic regression analysis of risk factors for VAP in 358 medical ICU patients identified the absence of antimicrobial therapy as one of the factors independently associated with VAP onset (105). The same result was obtained for a particular subset of 250 patients with very early-onset VAP, occurring within 48 hours of intubation, that was investigated to identify potential risk factors for developing VAP (145). Multivariate analysis selected cardiopulmonary resuscitation (OR = 5.13) and continuous sedation (OR = 4.40) as significant risk factors for pneumonia, whereas antibiotic use (OR = 0.29) had a protective effect. Finally, the results of the multicentric Canadian study on the incidence of and risk factors for VAP indicated that antibiotic treatment conferred protection against VAP (35). This apparent protective effect of antibiotics disappears after 2 to 3 weeks, suggesting that a higher risk of VAP cannot be excluded beyond this point. Thus, risk factors for VAP change over time, thereby explaining why they differ from one series to another.

In contrast, prolonged antibiotic administration to ICU patients for primary infection is thought to favor selection and subsequent colonization with resistant pathogens responsible for superinfections (12, 107, 140, 146–148). According to our data on 567 ventilated patients, those who had received antimicrobial therapy within the 15 days preceding lung infection were not at higher risk for development of VAP (12), but 65% of the lung infections that occurred in patients who had received broad-spectrum antimicrobial drugs versus only 19% of those developing in patients who had not received antibiotics were caused by *Pseudomonas* or *Acinetobacter* spp. In a 1988 investigation of mechanically ventilated baboons treated with a variety of regimens of intravenous and topical antibiotics or no antibiotics at all (146), polymicrobial pneumonia occurred in almost all untreated animals. However, baboons that had received prophylactic topical polymycin had only a slightly lower incidence of pneumonia and the prevalence of drug-resistant microorganisms in the tracheal secretions was high: 60 and 78% after 4 and 8 days of MV, respectively. Therefore, strong arguments suggest that the prophylactic use of antibiotics in the ICU increases the risk of superinfection with multi-resistant pathogens, while only delaying the occurrence of nosocomial infection.

Stress ulcer prophylaxis. In theory, patients receiving stress ulcer prophylaxis that does not change gastric acidity should have lower rates of gastric bacterial colonization and, consequently, a lower risk for nosocomial pneumonia. A direct relationship between alkaline gastric pH and gastric bacterial colonization has been demonstrated in several studies (124–127). For example, 86% of 28 postoperative patients had sterile gastric juice at ICU admission; 2 days later, the gastric secretions were colonized in 61% of the patients and the pH was more than 4 in 43% of them (125). These findings were fully confirmed by an analysis of 153 ICU patients receiving antacid or cimetidine: Total gastric colonization, particularly with GNB, was highly significantly increased ($p < 0.001$) (127). When the pH was less than 2, the gastric juice was sterile in 65% of the cases, but when it rose above 4, gastric juice GNB colonization was documented in at least 60% of the patients.

The results of several studies have indicated lower rates of pneumonia for patients given a gastroprotective agent (sucralfate) rather than agents that neutralize gastric secretions (antacids) or block gastric acid secretion (H_2 blockers) (40, 52, 137, 149, 150). In a well-designed, randomized study of 244 mechanically ventilated patients that compared stress ulcer prophylaxis with antacids, ranitidine, or sucralfate, the potential benefit of using sucralfate was confirmed (52). Although no differences in the incidence of macroscopic gastric bleeding and early-onset (within 4 days of ICU entry) VAP were found among the three groups, late-onset VAP was observed in only 5% of the patients who had received sucralfate compared with 16 and 21% of the patients who had received antacids or ranitidine, respectively ($p < 0.02$). Sucralfate-treated patients also had a lower median gastric pH and less frequent gastric colonization compared with the other groups. Molecular typing showed that 84% of the patients with late-onset GNB pneumonia had gastric colonization with the same strain before pneumonia developed.

According to meta-analyses of the efficacy of stress ulcer prophylaxis in ICU patients, respiratory tract infections were significantly less frequent in patients treated with sucralfate than in those receiving antacids or H_2 blockers (150–159). However, this conclusion was not fully confirmed in a large, multicenter, randomized, blinded, placebo-controlled trial that compared sucralfate suspension (1 g every 6 hours) with the H_2 receptor antagonist ranitidine (50 mg every 8 hours) for the prevention of upper gastrointestinal bleeding in 1,200 patients who required MV (160). Clinically relevant gastrointestinal bleeding developed in 10 of the 596 (1.7%) patients receiving ranitidine, as compared with 23 of the 604 (3.8%) receiving sucralfate (RR, 0.44; 95% CI, 0.21 to 0.92; $p = 0.02$). In the ranitidine group, 114 of 596 (19.1%) patients had VAP, as diagnosed by an adjudication committee using a modified version of the CDC criteria, versus 98 of 604 (16.2%) in the sucralfate group (RR, 1.18; 95% CI, 0.92 to 1.51; $p = 0.19$). Thus, although pneumonia rates were similar for the two groups, the relative risks suggest a trend toward a lower pneumonia rate for patients receiving sucralfate. Furthermore, VAP occurred significantly less frequently in patients receiving sucralfate when the diagnosis of pneumonia was based on Memphis VAP Consensus Conference criteria (if there was radiographic evidence of abscess and a positive needle aspirate, or histologic proof of pneumonia at biopsy or autopsy) ($p = 0.03$) (160).

Sucralfate appears to have a small protective effect against VAP because stress ulcer prophylactic medications that raise the gastric pH might themselves increase the incidence of pneumonia. This contention is supported by direct comparisons of trials of H_2 receptor antagonists versus no prophylaxis, which showed a trend toward higher pneumonia rates among the patients receiving H_2 receptor antagonists (OR, 1.25; 95% CI, 0.78 to 2.00) (158). Furthermore, the comparative effects of

sucralfate and no prophylaxis are unclear. Among 226 patients enrolled in two randomized trials, those receiving sucralfate tended to develop pneumonia more frequently than those given no prophylaxis (OR, 2.11; 95% CI, 0.82 to 5.44) (161, 162).

Endotracheal tube, reintubation, and tracheotomy. The presence of an endotracheal tube by itself circumvents host defenses, causes local trauma and inflammation, and increases the probability of aspiration of nosocomial pathogens from the oropharynx around the cuff. Scanning electron microscopy of 25 endotracheal tubes revealed that 96% had partial bacterial colonization and 84% were completely coated with bacteria in a biofilm or glycocalyx (163). The authors hypothesized that bacterial aggregates in biofilm dislodged during suctioning might not be killed by antibiotics or effectively cleared by host immune defenses (163, 164). Clearly, the type of endotracheal tube may also influence the likelihood of aspiration. Use of low-volume, high-pressure endotracheal cuffs reduced the rate to 56% and the advent of high-volume, low-pressure cuffs further lowered it to 20% (131). Leakage around the cuff allows secretions pooled above the cuff to enter the trachea; this mechanism, recently confirmed, underlines the importance of maintaining adequate intracuff pressure for preventing VAP (145). The relationship between tracheal colonization and VAP occurrence was confirmed in a study of 100 patients with head trauma and Glasgow Coma Scale scores less than 12 (165): within 24 hours of intubation, 68% of the patients who required intubation and MV for coma had tracheal *S. aureus*, *H. influenzae*, or *S. pneumoniae* colonization, which was identified as an independent risk factor for developing early-onset (less than 5 days) VAP.

Continuous or intermittent suction of oropharyngeal secretions has been proposed to avoid chronic aspiration of secretions through the tracheal cuff of intubated patients (Table 7) (166–169). Among 145 ventilated patients, pneumonia occurred less frequently (13%) in those whose endotracheal tube had a separate dorsal lumen for hourly suctioning of stagnant secretions above the cuff than the others (29%; p < 0.05) and VAP developed later (16.2 versus 8.3 days for the control group) (166). Similarly, in a 3-year prospective, randomized, controlled study, a lower VAP rate was documented when continuous subglottic suction was applied (18 versus 33% of the control subjects, NS; corresponding to an incidence density of 19.9 versus 39.6 episodes per 1,000 ventilator days, p < 0.03) (168). However, this difference was fully explained by the VAP occurring during the first week (3 of 76 versus 21 of 77, p < 0.009), whereas late-onset pneumonias were more frequent in the continuous subglottic-suctioning group (11 of 76 versus only 4 of 77) than the control group. Furthermore, detailed microbiologic analysis demonstrated that this reduction concerned only pneumonia due to *H. influenzae* or gram-positive cocci. The incidence of VAP due to *P. aeruginosa* or Enterobacteriaceae and mortality rates did not differ between the two groups (168). On the basis of 343 patients who had undergone cardiac surgery, continuous subglottic suction significantly delayed VAP occurrence but did not modify the overall VAP frequency (5 versus 8%; p = 0.24) (169).

In addition to the presence of endotracheal tubes, reintubation is, per se, a risk factor for VAP (170). This finding probably reflects an increased risk of aspiration of colonized oropharyngeal secretions into the lower airways by patients with subglottic dysfunction or impaired consciousness after several days of intubation. Another explanation is direct aspiration of gastric contents into the lower airways, particularly when a nasogastric tube is kept in place after extubation. According to a case–control study, the pneumonia rate was 47% for reintubated patients compared with 4% for control subjects matched for the duration of prior MV. In another study evaluating the risk of VAP after intrahospital patient transport, reintubation was identified as one of the independent risk factors for VAP (OR, 3.05; p < 0.001) (171). A recent case–control study of 135 patients following heart surgery also found reintubation to be a major risk factor, since VAP occurred in 92% of the reintubated patients versus 12% of the control subjects (48). Multivariate analysis associated reintubation with a greater risk for the development of pneumonia.

The role of early tracheotomy in VAP prevention remains controversial, with only a few studies that examined this issue (122, 172–177). Whereas some studies found a reduction in the rate of VAP in patients with early tracheotomy (173–175), others could not demonstrate any benefit (122, 172, 177). For example, in a randomized, prospective, multicenter trial including 112 patients who were thought to need prolonged MV, there were no differences, at least until Day 14, between ICU length of stay, pneumonia rate, or mortality between the 53 patients who underwent early (Day 3 to 5) tracheotomy and the 59 who were managed by translaryngeal intubation (177). The major problem that doomed that study was the overwhelming physician bias, which led to limited patient entry

TABLE 7. RESULTS OF RANDOMIZED TRIALS EVALUATING THE IMPACT OF DIFFERENT RESPIRATORY EQUIPMENT ON INCIDENCE OF VENTILATOR-ASSOCIATED PNEUMONIA

First Author	Ref.	No. of Patients	Incidence of VAP (%)		p Value
			Intervention	Control	
Continuous or intermittent aspiration of oropharyngeal secretions versus standard care					
Mahul	166	145	13	29	< 0.05
Valles	168	153	18	33	NS
Kollef	169	343	5	8	NS
Open versus closed endotracheal suction					
Deppe	194	84	26	29	NS
Johnson	195	35	50	53	NS
Combes	196	104	17	8	NS
Heat and moisture exchangers versus heated humidifiers					
Martin	200	73	6	19	NS
Roustan	201	112	10	15	NS
Dreyfuss	202	131	10	11	NS
Hurni	203	115	8	13	NS
Kirton	204	280	6	16	< 0.05

Definition of abbreviations: NS = not significant; VAP = ventilator-associated pneumonia.

and premature arrest of the study. In the absence of any meaningful data, practice patterns are influenced and guided by strong assumptions and quasi-religious dogma. Until a properly constructed randomized trial is performed to define the timing and utility of tracheotomy in the ICU, its true impact on decreasing VAP will remain merely speculative (178).

Nasogastric tube, enteral feeding, and position of the patient. Almost all patients receiving MV have a nasogastric tube inserted to evacuate gastric and enteral secretions, prevent gastric distention, and/or provide nutritional support. The nasogastric tube is not generally considered to be a potential risk factor for VAP, but it may increase oropharyngeal colonization, cause stagnation of oropharyngeal secretions, and increase reflux and the risk of aspiration. A multivariate analysis retained the presence of a nasogastric tube as one of the three independent risk factors for nosocomial pneumonia based on a series of 203 patients admitted to the ICU for 72 hours or more (36). The case–control study cited above also identified a nasogastric tube as one of the four independent risk factors for VAP in postcardiac surgery patients (48).

Early initiation of enteral feeding is generally regarded as beneficial in critically ill patients, but it may increase the risk of gastric colonization, gastroesophageal reflux, aspiration, and pneumonia (179, 180). Cultures of simultaneously sampled daily gastric, tracheal, and oropharyngeal specimens from 18 MV-dependent patients not receiving antacids or H_2 antagonists (181) showed that, after enteral feeding was started, the number of gram-negative isolates increased significantly, and 5 (28%) patients had gram-negative rods that were first recovered in the stomach and subsequently isolated from the trachea. The mechanism of transfer of gastric organisms into the trachea appears to have been aspiration. Among enterally fed, critically ill patients with small-bore nasogastric tubes, aspiration was reported in 38%, even though the bolus technique was used to feed all patients (130). Other observations suggested that aspiration is infrequent when small-bore feeding tubes and continuous infusion are used (182–186), but the real benefit of using small-bore tube is still unclear. To determine whether gastroesophageal reflux and microaspiration in intubated patients can be reduced by the use of a small-bore nasogastric tube, 17 patients intubated for more than 72 hours were assigned, after instillation of radioactive technetium colloid in each patient's stomach, to receive in randomized order one of two different types of nasogastric tubes (one with a 6.0-mm external bore and the other with a 2.85-mm external bore) (187). No differences were found between tube types when the time course and cumulative counts of pharyngeal and tracheal samples were compared, suggesting that small-bore nasogastric tubes do not reduce gastroesophageal reflux or microaspiration in intubated patients.

The aspiration rate generally varies as a function of differences in the patient population, neurologic function, type of feeding tube, location of the feeding port, and method of evaluating aspiration (182, 188). Clinical impressions and preliminary data suggest that postpyloric or jejunal feeding entails less risk of aspiration and may therefore be associated with fewer infectious complications than gastric feeding, although this point remains controversial (129, 189). Nonetheless, aspiration can easily occur should the feeding tube be inadvertently dislodged. A retrospective study of noncritically ill adult patients showed a 40% rate of accidental feeding-tube dislodgment, but all the patients whose tube was dislodged were confused, disoriented, or had altered awareness, as is frequently observed in patients in ICUs (190).

Maintaining mechanically ventilated patients with a nasogastric tube in place in a supine position is also a risk factor for aspiration of gastric contents into the lower airways. When ra-dioactive material was injected through a nasogastric tube directly into the stomach of 19 mechanically ventilated patients, the mean radioactive counts in endobronchial secretions were higher in a time-dependent fashion in samples obtained from patients in a supine position than in those obtained from patients in a semirecumbent position (128). The same microorganisms were isolated from the stomach, pharynx, and endobronchial samples of 32% of the specimens taken while patients were lying supine. However, the results of a subsequent study published by the same group from Barcelona were disappointing, as they demonstrated that gastroesophageal reflux in mechanically ventilated patients with a nasogastric tube occurs irrespective of body position (191). The same investigators then conducted a randomized trial comparing semirecumbent and supine positions (192). The trial, which included 86 intubated and mechanically ventilated patients, was stopped after the planned interim analysis because the frequency and the risk of VAP were significantly lower for the semirecumbent group. These findings were indirectly confirmed by the demonstration that the head position of the supine patient during the first 24 hours of MV was an independent risk factor for acquiring VAP (45).

Respiratory equipment. Respiratory equipment itself may be a source of bacteria responsible for VAP. In the 1980s, the major risk of infection was associated with contaminated reservoir nebulizers, designed to deliver small-sized particles suspended in the effluent gas (15). Those observations led to the current practices in respiratory therapy, for example, the use of cascade humidifiers, which do not generate microaerosols. Nevertheless, respiratory equipment continues to be a source of bacterial contamination. For example, medication nebulizers inserted into the inspiratory-phase tube of the mechanical ventilator circuit may inadvertently be responsible for bacterial aerosols after a single use (193).

To avoid hypoxia, hypotension, and contamination of suction catheters entering the tracheal tube, investigators have examined closed suctioning systems (Table 7) (194–196). Closed versus open suctioning systems were compared for 104 mechanically ventilated patients and a nonsignificantly lower prevalence rate of VAP was found for patients managed with the closed system compared with those with the open system (7.3 versus 15.9 per 1,000 patient-days; p = 0.07) without demonstrating any adverse effect (196). In an earlier study, not only did the investigators not show a statistically significant protective effect of the closed system on the incidence of VAP (26 versus 29%), they observed a higher frequency of endotracheal colonization associated with the closed device (67 versus 39%; p < 0.02) (194).

Mechanical ventilators with humidifying cascades often have high levels of tubing colonization and condensate formation that may also be risk factors for pneumonia. The rate of condensate formation in the ventilator circuit is linked to the temperature difference between the inspiratory-phase gas and the ambient temperature and may be as high as 20 to 40 ml/h (197–199). Examination of condensate colonization in 20 circuits detected a median level of 2.0×10^5 organisms/ml, and 73% of the 52 gram-negative isolates present in the patients' sputum samples were subsequently isolated from condensates (198). Because most of the tubing colonization was derived from the patients' secretions, the highest bacterial counts were present near the endotracheal tube. Simple procedures, such as turning the patient or raising the bed rail, may accidentally spill contaminated condensate directly into the patient's tracheobronchial tree. Inoculation of large amounts of fluid with high bacterial concentrations is an excellent way to overwhelm pulmonary defense mechanisms and cause pneumonia. Heating ventilator tub-

ing markedly lowers the rate of condensate formation, but heated circuits are often nondisposable and are expensive. Inline devices with one-way valves to collect the condensate are probably the easiest way to handle this problem; they must be correctly positioned into disposable circuits and emptied regularly. Furthermore, to date, no scientific evidence has confirmed that heated circuits reduce the rate of VAP (199).

To decrease condensation and moisture accumulation in ventilator circuits, several studies have investigated the use of heat–moisture exchangers (HMEs) in place of conventional heated-water humidification systems. Slightly lower VAP rates were observed in four studies and a significant difference was observed in a fifth study, suggesting that HMEs are at least comparable to heated humidifiers and may be associated with lower VAP rates than heated humidifiers (Table 7) (200–204). Changing the HME every 48 hours did not affect ventilator circuit colonization, and the authors concluded that the cost of MV might be substantially reduced without any detriment to the patient by prolonging the time between HME changes from 24 to 48 hours (205). Furthermore, using HMEs may decrease the nurses' workload (no need to refill cascades, to void water traps on circuits, etc.), decrease the number of septic procedures (it was clearly shown that respiratory tubing condensates must be handled as an infectious waste), and reduce the cost of MV, especially when used for prolonged periods without change. However, because some observational studies have documented an increased resistive load and a larger dead space associated with exchangers (206, 207), their use should be discouraged in patients with ARDS ventilated with a low tidal volume and in patients with COPD during the weaning period, when pressure support, and not T-piece trials, are used.

There is no apparent advantage to changing ventilator circuits frequently for VAP prevention. This holds true whether circuits are changed every 2 days or every 7 days compared with no change at all and whether they are changed weekly as opposed to three times per week (208–210). A policy of no circuit changes or infrequent circuit changes is simple to implement and the costs are likely lower than those generated by regular, frequent circuit changes; thus, such a policy is strongly recommended by the 1997 CDC guidelines (23).

Sinusitis. Whereas many studies have compared the risk of nosocomial sinusitis as a function of the intubation method used and the associated risk of VAP (211–227), only a few were adequately powered to give a clear answer. In 1 study of 300 patients who required MV for at least 7 days and were randomly assigned to undergo nasotracheal or orotracheal intubation, computed tomographic evidence of sinusitis was observed slightly more frequently in the nasotracheal group than in the oral endotracheal group (p = 0.08), but this difference disappeared when only bacteriologically confirmed sinusitis was considered (223). The rate of infectious maxillary sinusitis and its clinical relevance were also prospectively studied in 162 consecutive critically ill patients, who had been intubated and mechanically ventilated for 1 hour to 12 days before enrollment (221). All had a paranasal computed tomography scan within 48 hours of admission, which was used to divide them into three groups (no, moderate, or severe sinusitis), according to the radiologic appearance of the maxillary sinuses. Patients who had no sinusitis at admission (n = 40) were randomized to receive endotracheal and gastric tubes via the nasal or oral route and, on the basis of radiologic images, respective sinusitis rates were 96 and 23% (p < 0.03); yet, no differences in the rates of infectious sinusitis were documented according to the intubation route. However, VAP was more common in patients with infectious sinusitis, with 67% of them developing lung infection in the days following the di-

agnosis of sinusitis (221). Therefore, whereas it seems clear that infectious sinusitis is a risk factor for VAP, no studies have yet been able to definitively demonstrate that orotracheal intubation decreases the infectious sinusitis rate compared with nasotracheal intubation, and thus no firm recommendations on the best route of intubation to prevent VAP can be advanced.

Intrahospital patient transport. A prospective cohort study conducted with 531 mechanically ventilated patients evaluated the impact of transporting the patient out of the ICU to other sites within the hospital (171). Results showed that 52% of the patients had to be moved at least once for a total of 993 transports and that 24% of the transported patients developed VAP compared with 4% of the patients confined to the ICU (p < 0.001). Multiple logistic regression analysis confirmed that transport out of the ICU was independently associated with VAP (OR = 3.8; p < 0.001).

DIAGNOSIS

Unlike community-acquired pneumonia, it may be difficult to determine whether pneumonia has developed in a hospitalized ventilator-dependent patient.

Clinical Evaluation Combined with Microscope Examination and Culture of Tracheal Secretions

The diagnosis of VAP is usually based on three components: systemic signs of infection, new or worsening infiltrates seen on the chest roentgenogram, and bacteriologic evidence of pulmonary parenchymal infection (53). The systemic signs of infection, such as fever, tachycardia, and leukocytosis, are nonspecific findings and can be caused by any condition that releases cytokines (228). In trauma and other surgical patients, fever and leukocytosis should prompt the physician to suspect infection, but during the early posttraumatic or postoperative period (i.e., during the first 72 hours), these findings usually are not conclusive. However, later, fever and leukocytosis are more likely to be caused by infection, but even then, other events associated with an inflammatory response (e.g., devascularized tissue, open wounds, pulmonary edema, and/or infarction) can be responsible for these findings.

Although the plain (usually portable) chest roentgenogram remains an important component in the evaluation of hospitalized patients with suspected pneumonia, it is most helpful when it is normal and rules out pneumonia. When infiltrates are evident, the particular pattern is of limited value for differentiating among cardiogenic pulmonary edema, noncardiogenic pulmonary edema, pulmonary contusion, atelectasis (or collapse), and pneumonia. Because atelectasis is common among patients in the ICU, the contribution of repeating the chest X-ray after vigorous pulmonary physiotherapy was emphasized to differentiate infiltrates caused by atelectasis from those due to infection (229). Few studies have examined the accuracy of the portable chest radiograph in the ICU (53, 230–235). In a review of 24 patients with autopsy-proven pneumonia who were receiving MV, no single radiographic sign had a diagnostic accuracy greater than 68% (230). The presence of air bronchograms was the only sign that corresponded well with pneumonia, correctly predicting 64% of pneumonias in the entire group. When the group was divided into patients with and without ARDS, however, a significant difference was noted. The presence of air bronchograms or alveolar opacities in patients without ARDS correlated with pneumonia, whereas no such correlation was found for patients with ARDS. A variety of causes other than pneumonia can explain asymmetric consolidation in patients with ARDS, for example, atelectasis,

emphysema, pulmonary edema, and thromboembolic disease. Marked asymmetry of radiographic abnormalities has also been reported in patients with uncomplicated ARDS (236).

Microscopy evaluation and culture of tracheal secretions and/or expectorated sputum are also frequently inconclusive for patients clinically suspected of having pneumonia, because the upper respiratory tract of most patients in the ICU is colonized with potential pulmonary pathogens, whether or not parenchymal pulmonary infection is present (96, 117, 237–239). On the basis of specimens simultaneously obtained from the deep trachea and lung for culture from 48 patients with respiratory failure undergoing open-lung biopsy, culture results agreed for only 40% of these paired samples (240). For patients with histologically documented pneumonia, endotracheal aspirate sensitivity was 82%, but its specificity was only 27%. Microscope examination of tracheal aspirates may, however, be of some potential value in the diagnosis of patients with VAP. Indeed, specimens from intubated patients with pneumonia showed higher semiquantitative grading of neutrophils and bacteria including intracellular organisms than did those from patients without pneumonia (41). Nine of the 11 patients with pneumonia experienced rapid rises in bacterial counts at an average of 5 days before the appearance of a new or progressive pulmonary infiltrate. In the same study, elastin fibers seen on KOH-treated preparations of endotracheal aspirates had a sensitivity of 52% and a specificity of 100% for detecting pneumonia. However, in patients with ARDS, elastin fibers have only a 50% positive-predictive value for pneumonia because noninfectious lung necrosis is common in this context (41, 241, 242).

A study conducted with 84 ventilated patients suspected of having lung infection prospectively compared the diagnostic predictions independently formulated by each member of a team of physicians aware of all clinical, radiologic, and laboratory data, including the results of gram-stained bronchial aspirates, with those resulting from a complete work-up including quantitative culture results of PSB specimens (243). Only 27 of the 84 clinically suspected pneumonias were indeed present and only 62% of the predictions accurately diagnosed lung infection. The mean values of temperature; blood leukocytes and blood lymphocytes; Pa_{O_2}/Fi_{O_2} and radiologic scores; and changes in temperature, blood leukocytes, and radiologic score during the 3 days preceding suspicion of pneumonia did not differ between patients who had pneumonia and those who did not, thereby confirming previous conclusions that no objective clinical criteria exist for differentiating patients who have pneumonia from those who do not. A postmortem study established 69% sensitivity and 75% specificity for a diagnostic rule consisting of new and persistent infiltrates on chest radiographs and two of the following three criteria: (1) fever > 38.3° C; (2) leukocytosis > 12×10^9/ml, and/or (3) purulent tracheobronchial secretions (235). Thus, available evidence indicates that clinical diagnosis of VAP is associated with about 30 to 35% false-negative and 20 to 25% false-positive results (244). Even when the clinical diagnosis of pneumonia is accurate, results of gram staining and culture of tracheal aspirates can be misleading for the choice of the appropriate antibiotics. In the prospective study comparing predicted with PSB-documented VAP (243), only 33% of the treatments prescribed for patients subsequently diagnosed as having pneumonia proved to be effective, despite the fact that the physicians who contributed their predictions usually used combination antibiotic regimens, which are currently considered to be standard therapy for nosocomial pneumonia.

In 1991, a composite clinical score was proposed, based on seven variables (temperature, blood leukocyte count, volume

and purulence of tracheal secretions, oxygenation, pulmonary radiography, and semiquantitative culture of tracheal aspirate) accorded zero, one, or two points (245). That study of 28 patients requiring prolonged MV showed a good correlation (r = 0.84, p < 0.0001) between this clinical score and quantitative bacteriology of BAL samples, with a threshold value of 6 enabling identification of patients with infection. However, this scoring system is tedious to calculate and difficult to use in clinical practice, because several variables, such as progression of pulmonary infiltrates and results of semiquantitative cultures of tracheal secretions, can lead to different calculations depending on the observer. Furthermore, its value remains to be validated in a large prospective study, especially in patients with bilateral pulmonary infiltrates.

The potential usefulness of routine culture of endotracheal aspirates for monitoring the response to antibiotic treatment in patients with VAP is also questionable, because the upper respiratory tract of most patients with pneumonia remains colonized with multiple potential pathogens, even when the clinical course is favorable. These cultures contribute indisputably to the diagnosis of VAP only when they are completely negative for a patient with no modification of prior antimicrobial treatment. In such a case, the negative-predictive value is high and the probability of the patient having pneumonia is close to null (31).

Microbiologic Diagnosis of Ventilator-associated Pneumonia Using Nonbronchoscopic Techniques

Bacteremia and positive pleural effusion cultures are generally considered to be able to identify the organisms causing the pneumonia, if no other source of infection is found. Therefore, most experts recommend that investigation of suspected VAP should include taking two sets of blood samples for culture and tapping pleural effusions > 10 mm, even though spread to the blood or pleural space occurs in < 10% of VAP (2, 33, 39, 246).

Quantitative cultures of endotracheal aspirates. While the simple qualitative culture of endotracheal aspirates is a technique with a high percentage of false-positive results due to bacterial colonization of the proximal airways observed in most patients in the ICU, some studies using quantitative culture techniques suggest that endotracheal aspirate cultures may have an acceptable overall diagnostic accuracy, similar to that of several other more invasive techniques (29, 241, 247–251). In one study, the operating characteristics of endotracheal aspirate quantitative cultures, using 10^6 cfu/ml of respiratory secretions as the interpretative cutoff point, compared favorably with those of the PSB technique, with slightly higher sensitivity (82 versus 64%) and lower specificity (83 versus 96%) (247). To assess the reliability of that method, FOB with PSB and BAL was used to study 57 episodes of suspected lung infection in 39 ventilator-dependent patients with no recent changes of antimicrobial therapy (250). The operating characteristics of endotracheal aspirate cultures were calculated over a range of cutoff values (from 10^3 to 10^7 cfu/ml) and the threshold of 10^6 cfu/ml appeared to be the most accurate, with a sensitivity of 68% and a specificity of 84%. However, when this threshold was applied to the study population, almost one-third of the patients with pneumonia were not identified. Furthermore, only 40% of microorganisms cultured in endotracheal aspirate samples coincided with those obtained from PSB specimens. Other authors have emphasized that, although quantitative endotracheal aspirate cultures can correctly identify patients with pneumonia, microbiologic results cannot be used to infer which microorganisms present in the trachea are really present in the lungs. In a study comparing quantitative endotracheal aspirate culture results with postmortem quantitative lung bi-

opsy cultures, only 53% of the microorganisms isolated from the former samples at concentrations greater than 10^7 cfu/ml were also found in the latter cultures (252).

Therefore, quantitative endotracheal aspirate cultures may be an adequate tool for diagnosing pneumonia when no fiberoptic techniques are available. But it must be kept in mind that this technique has several potential pitfalls. First, many patients may not be identified by using the cutoff value of 10^6 cfu/ml. Second, as soon as a lower threshold is used, specificity declines sharply and overtreatment becomes a problem. Finally, selecting antimicrobial therapy solely on the basis of endotracheal aspirate culture results can lead to either unnecessary antibiotic therapy or overtreatment with broad-spectrum antimicrobial agents.

Sampling of distal airways. Secretions in the distal airways can be collected through a bronchoscope or blindly, using an endobronchial catheter that is wedged in the tracheobronchial tree. The nonbronchoscopic techniques are used in mechanically ventilated patients essentially because the endotracheal tube, which bypasses the proximal airways, permits easy access to the lower airways. At least 15 studies have described a variety of nonbronchoscopic techniques for sampling lower respiratory tract secretions (30, 60, 121, 245, 253–265). Inherent advantages of these techniques are less invasiveness, availability to nonbronchoscopists, lower initial cost than FOB, the lack of potential contamination by the bronchoscopic channel, less compromise of patient gas exchange during the procedure, and availability to patients with small endotracheal tubes. Disadvantages include the potential sampling errors inherent in a blind technique and the lack of airway visualization.

Apparently acceptable results were, however, obtained by several investigators using nonbronchoscopic methods (30, 60, 245, 254, 256–258, 261–265). For example, a study of 78 suspected episodes of nosocomial pneumonia in 55 patients found that a protected telescoping catheter gave results similar to those obtained with the PSB technique for 74% of the cases (254). To assess the accuracy of a protected telescoping catheter inserted blindly into the respiratory tract, 27 patients who died after receiving MV for at least 72 hours were included in a comparative prospective postmortem study (266). Microbiologic sampling procedures were performed immediately after death, using either simple distal protected suction or instillation of sterile saline, that is, protected mini-BAL, and the results were compared with histologic postmortem lung examination or biopsies. When bacterial VAP was defined by the association of histologic signs and positive lung tissue culture, both techniques provided good specificity (86 and 100% for mini-BAL and protected distal suction, respectively) with an acceptable sensitivity (78%) for the diagnosis of bacterial VAP.

Although autopsy studies indicate that pneumonia in ventilator-dependent patients has often spread into every pulmonary lobe and predominantly involves the posterior portion of the lower lobes (30, 267–269), two clinical studies of ventilated patients with pneumonia contradict those findings, as some patients had sterile cultures of PSB specimens from the noninvolved lung (50, 270). Furthermore, although the authors of most studies concluded that the sensitivities of nonbronchoscopic and bronchoscopic techniques were comparable, the overall concordance was only $\sim$ 80%, emphasizing that, in some patients, the diagnosis could be missed by this technique, especially in the case of pneumonia involving the left lung, as demonstrated by Jorda and coworkers (256) and Meduri and coworkers (50).

Microbiologic Diagnosis of Ventilator-associated Pneumonia Using Bronchoscopic Techniques

Procedure. FOB provides direct access to the lower airways for sampling bronchial and parenchymal tissues at the site of lung inflammation. To reach the bronchial tree, however, the bronchoscope must traverse the endotracheal tube and proximal airways, where contamination is likely to occur. Therefore, distal secretions directly aspirated through the bronchoscope suction channel are frequently contaminated, thereby limiting their clinical specificity (271). Modifications of specimen retrieval, discussed below, and quantitative cultures are used to control for this contamination. However, poor technique during FOB can negate the benefit of these modifications. Therefore, to obtain meaningful results with FOB, it is extremely important to follow a precise methodology, as summarized in the Memphis International Consensus Conference report (272).

One major technical problem with all bronchoscopic techniques is proper selection of the sampling area in the tracheobronchial tree. Almost all intubated patients have purulent-looking secretions and the first secretions seen may represent those aspirated from another site in gravity-dependent airways or upper airway secretions aspirated around the endotracheal tube. Usually, the sampling area is selected on the basis of the location of the infiltrate on the chest radiograph or the segment visualized during FOB as having purulent secretions (272). In patients with diffuse pulmonary infiltrates or minimal changes in a previously abnormal chest film, determining the correct airway to sample may be difficult. In these cases, sampling should be directed to the area where endobronchial abnormalities are maximal. However, when in doubt, and because autopsy studies indicate that VAP frequently involves the posterior portion of the right lower lobe, this area should probably be sampled as a first priority (29, 30, 267, 269). While bilateral sampling has been advocated in the immunosuppressed host with diffuse infiltrates, there is no convincing evidence that multiple specimens are more accurate than single specimens for diagnosing VAP (236).

Complications. The risk inherent in FOB appears slight, even for critically ill patients requiring MV, although the associated occurrence of cardiac arrhythmias, hypoxemia, or bronchospasm is not unusual (60, 273–275). Careful methodical attention to the anesthesia protocol, with addition of a short-acting neuromuscular blocking agent, and monitoring of patients during FOB should permit rapid correction and more frequent prevention of hypoxemia in this setting, and therefore should further decrease the morbidity associated with this procedure. In a study that was conducted with 110 patients with ARDS, only 5% of them had arterial oxygen saturation less than 90% during FOB, although many suffered severe prebronchoscopy hypoxemia (274).

Although bacteremia does not appear to occur after PSB (276), release of tumor necrosis factor-α has been documented in patients undergoing BAL (277, 278). Transbronchial spread of infection is also an extremely remote possibility (272, 278, 279).

Specimen types and laboratory methods. A variety of bronchoscopic techniques can be used to diagnose bacterial pneumonia but, among them, two have been considered to be of particular value in establishing a specific diagnosis of VAP: (*1*) the use of a double-lumen catheter with a PSB to collect and calibrate uncontaminated specimens directly from the affected area in the lower respiratory tract (280); and (*2*) BAL, because this technique is a safe and practical method for obtaining cells and secretions from a large area of the lung that can be examined microscopically immediately after the procedure and are also suitable for culture by quantitative techniques (281).

Using BAL, infusion of at least 120 ml of saline in several (3 to 6) aliquots is needed to sample secretions in the distal respiratory bronchioles and alveoli (239, 272). It is estimated that the alveolar surface area distal to the wedged bronchoscope is 100 times greater than that of the peripheral airway

and that ~ 1 million alveoli (1% of the lung surface) are sampled, with ~ 1 ml of actual lung secretions retrieved in the total lavage fluid (281). The fluid return on BAL varies greatly and may affect the validity of results. In patients with emphysema, collapse of airways with the negative pressure needed to aspirate fluid may limit the amount of fluid retrieved. A small return may contain only diluted material from the bronchial rather than alveolar level and thus give rise to false-negative results (281).

Specimen handling. Regardless of the bronchoscopic technique used, rapid processing of specimens for culture is desirable to prevent loss of viability of pathogens or overgrowth of contaminants in these unfixed specimens (239, 280, 282). Although no absolute guideline exists, it is generally accepted that a delay of more than 30 minutes should not elapse before specimens are processed for microbiologic analysis (272, 279, 282). According to some investigators, refrigeration may be used to prolong transport time, and thus may permit the procedure to be performed even when the microbiology laboratory cannot immediately handle the specimens, for instance, during the weekend or night shift (279, 283).

Once bronchoscopic specimens are received in the laboratory, they should be processed according to clearly defined procedures (see Baselski [239] and Baselski and Wunderink [279] for complete description). Because of the inevitable oropharyngeal bacterial contamination that occurs in the collection of all bronchoscopic samples, quantitative culture techniques are always needed to differentiate oropharyngeal contaminants present at low concentration from higher concentration infecting organisms. Several investigators have confirmed that, in pneumonia, pathogens are present in lower respiratory tract inflammatory secretions at concentrations of at least 10^5 to 10^6 cfu/ml, and contaminants are generally present at less than 10^4 cfu/ml (267, 284–288). The diagnostic thresholds proposed for PSB and BAL are a confirmation of this concept. Because PSB collects between 0.001 and 0.01 ml of secretions, the presence of more than 10^3 bacteria in the originally diluted sample (1 ml) actually represents 10^5 to 10^6 cfu/ml of pulmonary secretions. Similarly, 10^4 cfu/ml for BAL, which collects 1 ml of secretions in 10 to 100 ml of effluent, represents 10^5 to 10^6 cfu/ml (239, 282).

Although PSB samples can be subjected to direct microscopy, the optimal method for smear preparation has not yet been established. Methods used include direct smearing of the secretions retrieved by the brush and cytocentrifugation of the material suspended in the diluent used for quantitative cultures. Although more sensitive, the former method has the disadvantages of decreasing the amount of secretions available for quantitative cultures and possibly contaminating the specimen. Reported sensitivities and specificities for PSB gram staining range from 20 to 100% and from 95 to 100%, respectively (239, 282, 289–291).

For BAL, it is recommended that a total cell count be performed to assess adequacy and a differential count be performed to assess cellularity. For quality assessment, the percentages of squamous and bronchial epithelial cells may be used to predict heavy upper respiratory contamination, with more than 1% of the total cells being proposed as a rejection criterion, even if only a few studies have directly assessed this point (292). Modified Giemsa staining (e.g., Diff-Quik; Baxter Scientific Products, McGaw Park, IL) is recommended, as it offers a number of advantages over Gram staining, including better visualization of host cell morphology, improved detection of bacteria, particularly intracellular bacteria, and detection of some protozoan and fungal pathogens (e.g., *Histoplasma*, *Pneumocystis*, *Toxoplasma*, and *Candida* spp.) (239, 293).

Usefulness of the protected specimen brush technique. The potential contribution of the PSB technique to evaluate ventilated patients suspected of having developed VAP has been extensively investigated in both human and animal studies, including eight investigations in which the accuracy of this culture technique was determined by comparison of both histologic features and quantitative cultures from the same area of the lung (29, 30, 267, 286–288, 294, 295). Despite the need for cautious interpretation, the results of those studies indicated that the PSB technique offers a sensitive and specific approach to identifying the microorganisms involved in pneumonia in critically ill patients, and to differentiate between colonization of the upper respiratory tract and distal lung infection. Pooling the results of 18 studies evaluating the PSB technique in a total of 795 critically ill patients showed the overall accuracy of this technique for diagnosing nosocomial pneumonia to be high, with a sensitivity of 89% (95% CI, 87 to 93%) and a specificity of 94% (95% CI, 92 to 97%) (29, 235, 238, 241, 257, 263, 266, 270, 288, 293, 294, 296–305).

Nevertheless, some controversy persists in the literature concerning the sensitivity of this technique, especially for detecting some pneumonias in patients already receiving antimicrobial treatment (269, 306). Although several studies have shown that, once bacterial infection of the lung is clinically apparent, there are at least 10^4 microorganisms/g of tissue, this assumption is valid only when patients have not received appropriate antimicrobial treatment after the onset of lung infection but before obtaining lung specimens (98, 307–309). Furthermore, the relationships between histology and quantitative cultures are highly complex, and investigation in this field is hampered by several unresolved methodologic problems. Thus, the reference standard shifts from one study to another and there is certainly no "gold standard." Even diagnosis based on histologic examination of open-lung biopsies has been called into question lately by studies such as the one showing that VAP diagnosis ranged from 18 to 38% among four different pathologists (28).

For 30 patients who died while receiving MV after having received prior antibiotic treatment, quantitative bacterial cultures of lung biopsies using 10^3 cfu/g of tissue as the cutoff point had low sensitivity (40%) and low specificity (45%), and could not differentiate between the histologic absence and presence of pneumonia (235). Pertinently, however, the operating characteristics of the PSB technique were similar to those obtained with lung cultures. Studies of experimental VAP in miniature pigs have also raised some concerns about the validity of the quantitative culture technique. Whereas higher lung tissue bacterial counts were found in the presence of pneumonia as compared with mere bronchial infection or absence of infection, it was not possible to define a threshold that would identify the presence or absence of pneumonia (268, 310). However, it remains unclear to what extent these findings obtained in experimental VAP and/or autopsied patients can be extended to patients in the ICU. From a practical point of view, it should be kept in mind that a diagnostic method based on microbiologic culture techniques only documents, qualitatively and quantitatively, the bacterial burden present in the lung tissue that was sampled. In no way can these bronchoscopic techniques retrospectively identify resolving pneumonia, or when antimicrobial treatment and lung antibacterial defenses might have been successful in suppressing microbial growth in lung tissue.

Even when PSB is performed before any antimicrobial treatment is given for suspected pneumonia, three major drawbacks are still inherent in this technique. First, even using the most accurate threshold of 10^3 cfu/ml to distinguish patients

with airway colonization from those with deep lung infection, a small number of false-positive results may be observed (249). Second, results of such cultures require 24 to 48 hours, and, therefore, no information is available to guide initial decisions concerning the appropriateness of antimicrobial therapy and which antibiotics should be prescribed. Finally, the PSB technique can yield negative results in patients with pneumonia in the following situations: (1) FOB performed at an early stage of infection when the bacterial burden is below the concentration necessary to reach diagnostic significance; (2) specimens obtained from an unaffected segment (which is probably crucial in patients with diffuse lung injury, in whom it is sometimes difficult to be sure to have selected the proper site for sampling); (3) incorrectly processed specimens; and/or (4) specimens obtained after initiation of a new class of antimicrobial agents.

Many technical factors, including the medium, adequacy of incubation and antibiotic or other toxic components, may influence microbiologic test results. Two groups evaluated the reproducibility of PSB sampling (299, 301) and concluded that, although *in vitro* repeatability is excellent and *in vivo* qualitative recovery is 100%, quantitative results are more variable. For 14 to 17% of patients, results of replicate samples fell on both sides of the 10^3 cfu/ml threshold and cfu counts varied by more than 10-fold for 59 to 67% of samples. This variability presumably reflects both the irregular distribution of organisms in secretions and the small volume actually sampled by PSB. It was concluded that, as with all diagnostic tests, borderline PSB quantitative culture results should be interpreted with caution and the clinical circumstances considered before any therapeutic decision can be made. FOB should be repeated in persistently symptomatic patients with an initially negative (less than 10^3 cfu/ml) concentration (311).

Usefulness of bronchoalveolar lavage. Although providing a broader image of lung content than PSB, BAL is subject to the same risk of contamination as bronchoscopic aspirates. Many groups have now investigated the value of quantitative BAL culture for the diagnosis of pneumonia in mechanically ventilated patients (29, 58, 96, 235, 241, 245, 248, 249, 257, 262, 272, 292–296, 300, 302, 303, 312–322). Although some investigators have concluded that BAL provides the best reflection of the lung's bacterial burden, both quantitatively and qualitatively, others have reported mixed results with poor specificity of BAL fluid cultures for patients with high tracheobronchial colonization. Analysis of postmortem lung biopsy samples showed quantitative cultures of BAL fluid to be as useful as those of PSB cultures (294). Although a few more microorganisms not detected in lung tissue were grown from BAL specimens than PSB specimens, the concentrations of organisms grown in cultures of BAL fluid and lung tissue specimens were strongly correlated ($\rho = 0.75$, $p < 0.0001$). Using more than 10^4 bacteria/ml of BAL fluid as the discriminative value for differentiating between infected lung segments with at least 10^4 cfu/g of tissue (n = 11) and noninfected lung segments (n = 9), only one false-negative and two false-positive results were observed, giving a sensitivity of 91% and a specificity of 78%. When the results of the 11 studies evaluating BAL fluids from a total of 435 ICU patients suspected of having developed VAP were pooled, the overall accuracy of this technique was close to that of the PSB, with a Q value of 0.84 (Q represents the intersection between the summary receiver operating characteristics [ROC] curve and a diagonal from the upper left corner to the lower right corner of the ROC space) (296). Similar conclusions were drawn in another meta-analysis when the results of 23 studies were pooled, with a sensitivity of 73 ± 18% and a specificity of 82 ± 19% (312).

The repeatability of BAL was assessed in 44 mechanically ventilated patients with suspected VAP (323). Two BALs were performed by the same physician in the same lung area during two FOB within a 30-minute interval. For the 44 patients studied, the qualitative repeatability (i.e., presence or absence of bacteria) was excellent (95%). For the 16 patients who had at least one positive culture, however, the results were more controversial. The quantitative repeatability for bacteria (same $\log_{10}$ for both BALs from the same patient) was lower (53%). The authors of that study concluded that BAL seems to have excellent repeatability when sterile, but that its repeatability when positive needs further assessment (323).

Because BAL harvests of cells and secretions from a large area of the lung and specimens can be microscopically examined immediately after the procedure to detect the presence or absence of intracellular or extracellular bacteria in the lower respiratory tract, it is particularly well adapted to provide rapid identification of patients with pneumonia. Several studies have confirmed the diagnostic value of this approach (56, 103, 245, 291, 293, 294, 320, 324–330). In each study, either the Giemsa or Gram staining was positive (more than 1 or 5% of BAL cells containing intracellular bacteria) for most patients with pneumonia and negative for those without pneumonia. Furthermore, in patients with pneumonia, the morphology and Gram staining of these bacteria were closely correlated with bacterial culture results, enabling early formulation of a specific antimicrobial therapy before the culture results became available. In one study in which the diagnostic accuracy of direct microscope examination of BAL cells could be directly assessed with both histologic and microbiologic postmortem lung features in the same segment, a high correlation could be established among the percentage of BAL cells containing intracellular bacteria, the total number of bacteria recovered from the corresponding lung samples, and the histologic grades of pneumonia ($p < 0.001$) (294). However, assessment of the degree of qualitative agreement between BAL Gram staining and PSB quantitative cultures for a series of 51 patients with VAP showed the correspondence to be complete for 51%, partial for 39%, and nonexistent for 10% of the cases (326).

Because measurement of endotoxin in BAL fluid may permit the rapid diagnosis of GNB pneumonia, the potential value of this technique was evaluated by several investigators (331–334). On the basis of 170 patients clinically suspected of having VAP and considering that an endotoxin level equal to or greater than 4 endotoxin units/ml distinguished patients with a significant GNB count from colonized patients, a sensitivity of 82 to 93%, a specificity of 81 to 95%, and a correct classification rate of 85 to 90% were found. Gram staining of BAL fluid for the presence of GNB, although much less expensive, yielded slightly inferior operating characteristics (334). These findings suggest that determination of endotoxin in BAL fluid could become an acceptable adjunct for the rapid diagnosis of GNB pneumonia in the near future.

Arguments for Bronchoscopy for the Diagnosis of Ventilator-associated Pneumonia

The use of invasive techniques, such as FOB, coupled with quantitative cultures of PSB or BAL specimens help guide the choice of antibiotic therapy in addition to confirming the actual diagnosis of VAP, while culture results precisely identify the offending organisms and their susceptibility patterns (Figure 1). Such data are invaluable for optimal antibiotic selection. They also increase the confidence and comfort level of health care workers in managing patients with suspected noso-

comial pneumonia (335). Antibiotic therapy that is selected on the basis of quantitative culture results may be more effective than empiric treatment. It is clear that the inappropriate initial management of VAP is associated with higher mortality (Table 3) and evidence suggests that the clinical recognition of treatment failure may be delayed. Indeed, initial, empiric antibiotic treatment often requires modification when quantitative culture results become available (21, 59, 61, 62, 74, 243). What is less clear is whether this delayed modification of initial treatment affects outcome (58, 98). The results of gram-stained bronchoscopic specimens, especially of BAL fluid, may provide an earlier guide to antibiotic management, but the impact of this information on physician practice and patient outcomes has not been fully investigated (103).

The second most compelling argument for invasive bronchoscopic techniques is that they can reduce excessive antibiotic use. There is little disagreement that the clinical strategy too readily opts for a diagnosis of VAP and leads to the unnecessary administration of broad-spectrum antibiotics. Because of their potentially greater specificity, bronchoscopic techniques should reduce antibiotic selection pressure in the ICU, thereby limiting the emergence of drug-resistant strains and the resulting higher risks of superinfection (45, 336–340). Indeed, most epidemiologic investigations have clearly demonstrated that the indiscriminate administration of antimicrobial agents to patients in the ICU have immediate as well as long-term consequences, which contribute to the emergence of multiresistant pathogens and increase the risk of severe superinfections (336, 340). This enhanced risk is not limited to one patient but may raise the risk of colonization or infection by multidrug-resistant bacterial strains in patients throughout the ICU and even the entire hospital (148). Therefore, policies regarding the empiric use of antibiotics do matter in the control of antimicrobial resistance. Virtually all reports empha-

size that better antibiotic control programs to limit bacterial resistance are urgently needed in the ICU and that patients without true infection should not receive antimicrobial agents (339–344).

The more targeted use of antibiotics could also reduce overall costs, despite the expense of FOB and quantitative cultures, and minimize antibiotic-related toxicity (298). This possibility is particularly true for patients who develop late-onset VAP, in whom expensive combination therapy is recommended by most experts in the field. A conservative cost analysis performed in a trauma ICU suggested that the discontinuation of antibiotics on the return of negative bronchoscopic quantitative culture results could lead to a savings of more than US$1,700 per patient suspected of having VAP (345).

Finally, and probably the most important risk of not performing FOB for the patient, is that another site of infection may be missed. The major benefit of negative FOB findings may indeed be to direct attention away from the lungs as the source of fever. Many hospitalized patients with negative bronchoscopic cultures have other potential sites of infection that can be identified via a simple diagnostic protocol. A study of 50 patients with suspected VAP who were subjected to a systematic diagnostic protocol, designed to identify all potential causes of fever and pulmonary densities, confirmed the presence of lung infection in only 42% of them, and that the frequent occurrence of multiple infectious and noninfectious processes justifies a systematic search for the source of fever in this setting (231). This search is in general greatly facilitated by the absence of an empiric antimicrobial therapy that can mask the true diagnosis (346).

Other than decision analysis studies (347, 348), only five trials have assessed the impact of a diagnostic strategy on antibiotic use and outcome of patients suspected of having VAP (Table 8) (61–63, 104, 335). No differences in mortality and
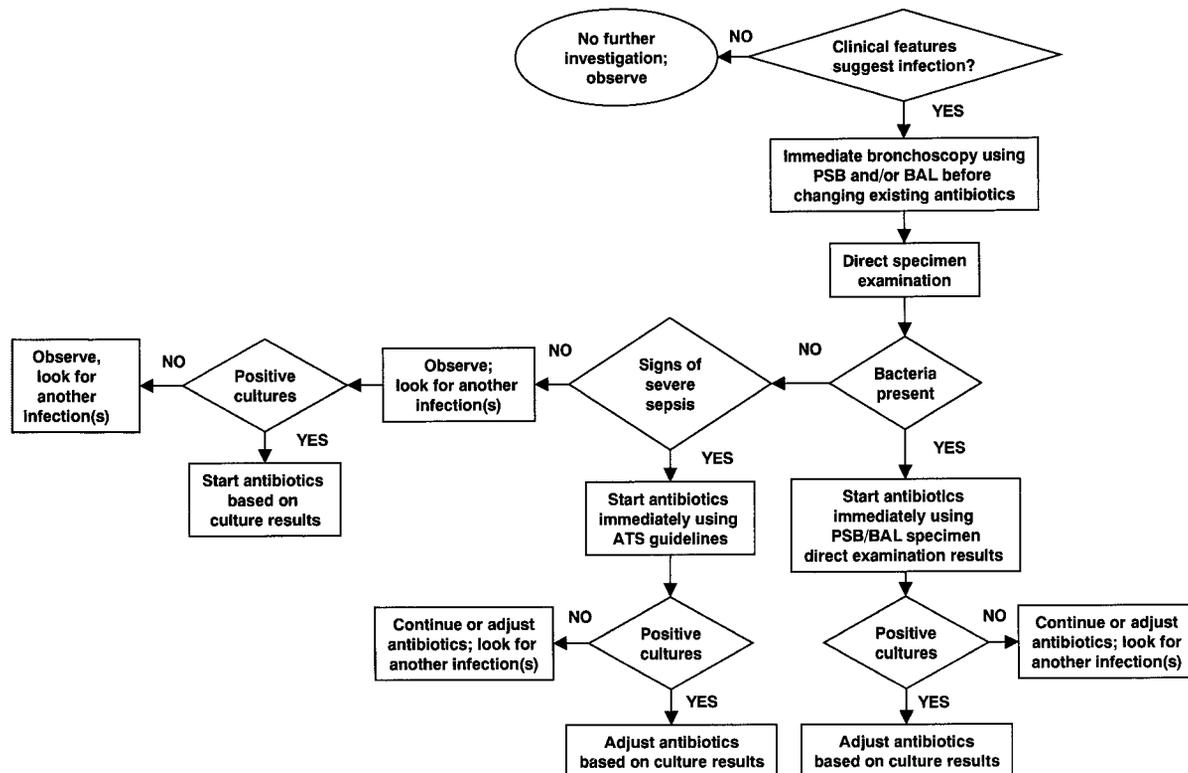

Figure 1. Diagnostic and therapeutic strategy applied to patients managed according to the "invasive" strategy.

morbidity were found when either invasive (PSB and/or BAL) or noninvasive (quantitative endotracheal aspirate cultures) techniques were used to diagnose VAP in three Spanish randomized studies (61, 62, 104). However, those studies were based on relatively few patients (51, 76, and 88, respectively) and antibiotics were continued in all patients despite negative cultures, thereby neutralizing one of the major potential advantages of any diagnostic test in patients clinically suspected of having VAP. Concerning the latter, it was shown, on the basis of 138 patients investigated by bronchoscopic specimen collection, that antibiotics can indeed be stopped in patients with negative quantitative cultures with no adverse effects on the recurrence of VAP and mortality (59). Authors of other studies have also concluded that antibiotics can be safely stopped in patients with negative quantitative cultures (21, 102, 298, 311, 335).

One of the first studies to clearly demonstrate a benefit in favor of invasive techniques was a prospective cohort study conducted in 10 Canadian tertiary care ICUs (335). The investigators compared antibiotic use, duration of MV, duration of ICU stay, and mortality for 92 mechanically ventilated patients clinically suspected of having VAP who underwent FOB and 49 patients who did not. Although mortality among patients undergoing FOB was lower than for control subjects (19 versus 35%, p = 0.03), the strength of that observation is somewhat diluted because control patients were those suspected of having VAP who did not undergo the intended FOB. The reasons that led their physicians to forego FOB may explain the higher mortality rate of these patients. However, once FOB results had become available to the physicians treating the study patients, the diagnosis of VAP was deemed much less likely (p < 0.001), confidence in the diagnosis increased (p = 0.03), and the level of comfort with the management plan rose (p = 0.02). Furthermore, patients in the FOB group received fewer antibiotics (31of 92 versus 9 of 49; p = 0.05) and more patients had all their antibiotics discontinued (18 of 92 versus 3 of 49; p = 0.04) compared with the no-FOB group. Invasive diagnostic testing may thus increase physician confidence in the diagnosis and management of VAP, and allows for greater flexibility to limit or discontinue antibiotic treatment.

A large, prospective, randomized trial compared noninvasive versus invasive diagnostic management of 413 patients suspected of having VAP (63). For the noninvasive group (n = 209), empiric antimicrobial therapy was based on the presence of bacteria in the gram-stained endotracheal aspirates, and

therapy could be adjusted or discontinued according to the results of endotracheal aspirate qualitative cultures. In the case of severe sepsis, empiric therapy was started without the laboratory result. With this schedule, which resembles clinical practice in most ICUs, 91% of the patients (191 of 209) received empiric therapy for suspected VAP and only 9% did not. The invasive work-up (n = 204) consisted of FOB with direct microscope examination of BAL and/or PSB specimens and empiric therapy was started only when results were positive. A definitive diagnosis based on quantitative culture results of specimens obtained with a PSB or by BAL was awaited before starting, adjusting, or discontinuing therapy (Figure 1). This strategy resulted in treatment of 52% (107 of 204) of the patients with suspected VAP, whereas 47% (97 of 204) did not immediately receive antibiotics. Compared with patients managed clinically, those receiving invasive management had a lower mortality rate on Day 14 (16 and 25%; p = 0.02), lower mean sepsis-related organ failure assessment scores on Days 3 and 7 (p = 0.04), and less antibiotic use (mean number of antibiotic-free days, 5 ± 5 and 2 ± 3; p < 0.001). At 28 days, the invasive management group had significantly more antibiotic-free days (11 ± 9 versus 7 ± 7; p < 0.001), and only multivariate analysis showed a significant difference in mortality (hazards ratio, 1.54 [CI, 1.10 to 2.16]; p = 0.01) (63).

Thus, implementation of bronchoscopic techniques for the diagnosis of VAP may reduce antibiotic use and improve patient outcome. Pertinently, in that study, invasive group patients had 22 infections at other sites that required specific therapeutic measures versus only five in the clinical group (63). This difference suggests that reliance on noninvasive techniques and the consequent overestimation of VAP may mean that diagnoses of nonpulmonary infections are missed. Many hospitalized patients with negative bronchoscopic specimen cultures have other potential sites of infection that can more readily be identified in the absence of antibiotic interference (13, 231, 349, 350). Delaying diagnosis or definitive treatment of the true infection site may lead to prolonged antibiotic therapy, more antibiotic-associated complications, and induction of additional organ dysfunctions (102, 345, 351–353).

Arguments against Bronchoscopy for the Diagnosis of Ventilator-associated Pneumonia

Reasons not to use invasive diagnostic techniques include the following: (*1*) their accuracy is questionable for patients who received prior antibiotics, especially when new antibiotics have been introduced after the onset of the symptoms suggestive of

TABLE 8. RESULTS OF TRIALS COMPARING A FIBEROPTIC BRONCHOSCOPY–BASED "INVASIVE" STRATEGY WITH A CLINICAL EVALUATION-BASED STRATEGY FOR PATIENTS CLINICALLY SUSPECTED OF HAVING VENTILATOR-ASSOCIATED PNEUMONIA

First Author	Ref.	Year of Publication	Total No. of Patients	Study Design	Mortality: No. of Patients Who Died/Total No. (%)		p Value
					"Invasive" Strategy	"Clinical" Strategy	
Sanchez-Nieto	61	1998	51	Monocenter, randomized	11/24 (46)	7/27 (26)	NS
Ruiz	62	2000	76	Monocenter, randomized	14/37 (38)	18/39 (46)	NS
Sole Violan	104	2000	88	Monocenter, randomized	10/45 (22)	9/43 (21)	NS
Heyland	335	1999	141	Multicenter, nonrandomized, prospective cohort	17/92 (18)	17/49 (35)	0.03
Fagon	63	2000	413	Multicenter, randomized	63/204 (31)	81/209 (39)	0.07*

Definition of abbreviation: NS = not significant.
* p = 0.01, using multivariate analysis.

nosocomial pneumonia but before collection of pulmonary secretions; (2) FOB may transiently worsen the patient's status, although the results of several studies indicate that the frequency of such complications is low; (3) an invasive approach to diagnosing nosocomial pneumonia may increase the costs of caring for critically ill patients, at least at some institutions where fees for FOB are high; and (4) although patient management may change on the basis of results of invasive tests, data suggesting that these changes lead to an improvement of patient outcome are limited (306).

The appropriateness of diagnostic tools may also differ depending on whether the goal is to prevent the spread of resistant organisms, compare the rates of pneumonia, or prescribe treatment for a patient. For example, to calculate the frequency, a definition that is applicable to all patients over prolonged time periods should be used. Infection control personnel should be able to make the diagnosis on the basis of common clinical and laboratory findings. Definitions that require the performance of specialized diagnostic tests are not sufficiently universal to provide comparable rates in most health care settings.

The presence of prior antimicrobial treatment in patients clinically suspected of nosocomial pneumonia is frequently cited as a major limitation to accurate diagnosis, because it may lead to a high number of false-negative results. In fact, as demonstrated by several investigative teams, the results of respiratory secretion cultures are usually not modified when pneumonia develops as a superinfection in patients who have been receiving systemic antibiotics for several days before the appearance of the new pulmonary infiltrates, because the bacteria responsible for the new infection have become resistant to the antibiotics being given (98, 267). To evaluate further the effects of antibiotic treatment received before the suspicion of pneumonia on the diagnostic yield of PSB and direct examination and culture of BAL fluid, two groups of ventilated patients with suspected nosocomial pneumonia were studied: 65 patients who had received antibiotics for an earlier septic episode and 96 patients who had not (308). FOB was always performed before any treatment for suspected pneumonia was given. The sensitivity and specificity of each test did not differ between the two groups, thereby confirming that the antibiotics used to treat an earlier septic episode unrelated to suspected pneumonia do not affect the diagnostic yield of PSB and BAL.

On the other hand, cultures of pulmonary secretions for diagnostic purposes after initiation of new antibiotic therapy in patients suspected of having developed VAP can clearly lead to a high number of false-negative results, regardless of the way in which these secretions are obtained. In one study, in which follow-up cultures of PSB samples were obtained 24 and 48 hours after the onset of antimicrobial treatment for 43 cases of proven VAP, nearly 40% of the cultures were negative after only 24 hours of treatment and 65% were negative after 48 hours (354). Similar results were obtained for a series of 76 consecutive patients with VAP evaluated by FOB after 3 days of treatment (98). In a series of 63 episodes of suspected VAP (307), when therapy had recently been initiated, the sensitivities of the invasive diagnostic methods, using traditional thresholds, were only 38% for BAL and 40% for PSB (307). Using a lower threshold to define a positive PSB or BAL result in such a setting may be inaccurate, because follow-up cultures can be completely negative in at least 40% of true cases of VAP (98, 354). Pulmonary secretions therefore need to be obtained before new antibiotics are administered, as is the case for all microbiologic samples.

Several investigators argue that the use of FOB to evaluate VAP is limited by the lack of standardized, reproducible methods and diagnostic criteria (306, 355). There is no doubt that the literature is replete with variations on this theme: BAL versus PSB; whether to collect secretions with the PSB under direct observation or wedge it distally; what volume of saline to use for BAL; which transport medium to use; whether to set up cultures using quantitative loops or serial dilutions; and whether to express the results in colony-forming units per milliliter or construct a bacterial index composed of the sum of the exponents from each quantitated isolate. Although a general consensus has emerged on the use of 10^3 cfu/ml as the cutoff for a PSB culture, and 10^4 cfu/ml for BAL specimens, concern has been raised about their reproducibility, particularly near the diagnostic thresholds (299, 301, 323). Whether the clinical suspicion of VAP should influence the interpretation of quantitative culture results also has not been entirely resolved (347). It is likely that no single method will emerge as superior to others. What is most important is that physicians using these techniques establish a protocol that is supported by the literature and within the capabilities of the local microbiology laboratory. Many microbiology laboratories may not be able to promptly and accurately process quantitative cultures, even though the techniques used can be similar to those applied routinely to urine cultures (279).

Others have suggested that any potential value of FOB in the management of nosocomial pneumonia would be limited to late-onset infections, as infections that occur within 4 days of admission often are caused by community-acquired pathogens, and are easier to diagnose and manage than pneumonia occurring later in the hospital stay (355, 356). Although it is true that community-acquired pathogens are often identified in early-onset pneumonia, hospital-acquired pathogens cannot be excluded during the early time frame (106, 107, 110). Furthermore, early-onset pneumonia may be a less common problem than late-onset infection in many medical ICUs, as the cumulative risk of pneumonia (and the risk of infection with hospital-acquired pathogens) increases with the duration of hospitalization.

Some experts also doubt the willingness of physicians to stop antibiotic therapy when confronted with a negative bronchoscopic culture. Indeed, as cited above, there is evidence that physicians are reluctant to discontinue antibiotics for suspected VAP solely because of a negative culture (356). The development of algorithms incorporating clinical suspicion into the interpretation of culture results may improve the acceptability of and responsiveness to negative results. However, the potential benefit of an invasive strategy can be obtained only when physicians accept the basing of their antibiotic prescription on the results of bronchoscopic specimen cultures and, thus, to withdraw antimicrobial therapy from patients with negative results (347, 348).

Because VAP in the ICU has substantial attributable mortality, there is justification, albeit unwarranted at times, to use antibiotics for patients with pulmonary infiltrates, despite a low likelihood of infection. A randomized study proposed to minimize excessive use of antibacterial agents, but still allow clinicians flexibility in managing patients with a perceived treatable infection (Figure 2) (357). Patients with a Clinical Pulmonary Infection Score (CPIS) ≤ 6 (implying low likelihood of pneumonia) were randomized to receive either standard therapy (choice and duration of antibiotics at the discretion of physicians) or ciprofloxacin monotherapy with reevaluation on Day 3; ciprofloxacin was discontinued when the CPIS remained ≤ 6. Antibiotics were continued beyond 3 days for 90% (38 of 42) of the patients receiving standard therapy compared with 28% (11 of 39) in the ciprofloxacin group (p = 0.0001). Mortality and length of ICU stay did not differ de-

spite the shorter duration (p = 0.0001) and lower cost (p = 0.003) of antimicrobial therapy in the monotherapy arm than in the standard-therapy arm. Antimicrobial resistance, super-infections, or both developed in 15% of the patients in the ciprofloxacin group versus 35% of the patients in the standard therapy group (p = 0.017). Such an approach may thus lead to significantly lower antimicrobial therapy costs, antimicrobial resistance, and superinfections without adversely affecting the length of stay or mortality and merits prospective analysis in a large study sample. However, it should be emphasized that this strategy was tested in relatively few patients (n = 81) and that only 42% of patients included in the study did not require MV. Thus, it remains to be precisely determined whether this strategy can perform as well when it is applied to mechanically ventilated patients.

Recommendations

The diagnosis of bacterial pneumonia in the severely ill, mechanically ventilated patient remains a difficult dilemma for the clinician. Our personal bias is that the use of bronchoscopic techniques to obtain PSB and/or BAL specimens from the affected area in the lung of ventilated patients with signs suggestive of pneumonia allows definition of a therapeutic strategy superior to that based exclusively on clinical evaluation (Figure 1). When performed before introduction of new antibiotics, these bronchoscopic techniques enable physicians to identify most patients who need immediate treatment and help to select optimal therapy, in a manner that is safe and well tolerated by patients. Furthermore, these techniques prevent resorting to broad-spectrum drug coverage in all patients who develop a clinically suspected infection. Although the true impact of this decision tree on patient outcome remains controversial, available data clearly suggest that being able to withhold antimicrobial treatment from some patients without infection may constitute a distinct advantage in the long term, by minimizing the emergence of resistant microorganisms in the ICU and redirecting the search for another (the true) infection site.

Despite broad clinical experience with the PSB and BAL techniques, it remains, nonetheless, unclear which one should be used in clinical practice. As discussed above, their operating characteristics for diagnosing VAP are probably similar, with only small differences in their sensitivities and specificities. Most investigators prefer to use BAL rather than PSB to diagnose bacterial pneumonia, because BAL (*1*) has a slightly higher sensitivity to identify VAP-causative microorganisms, (*2*) enables better selection of an empiric antimicrobial treatment before culture results are available, (*3*) is less dangerous for many critically ill patients, (*4*) is less costly, and (*5*) may provide useful clues for the diagnosis of other types of infections. However, it must be acknowledged that a small return on BAL may contain only diluted material from the bronchial rather than the alveolar level and thus give rise to false-negative results, particularly for patients with severe COPD. In these patients, the diagnostic value of BAL techniques is greatly diminished and the PSB technique should be preferred. Therefore, the choice of procedure(s) may eventually depend on the preferences and experiences of individual physicians and the patient's underlying disease(s).

In patients with clinical evidence of severe sepsis with rapidly deteriorating organ dysfunction, hypoperfusion, or hypotension, the initiation of antibiotic therapy should not be delayed while awaiting FOB and patients should be treated immediately with antibiotics. It is probably in this latter situation that simplified nonbronchoscopic diagnostic procedures could be most justified, because distal pulmonary secretions can be obtained on a 24-hour basis, just before starting new antimicrobial therapy. Because several studies have indicated that delays in the administration of effective antibiotic therapy may impact on VAP outcome, antibiotic therapy should not be postponed for more than a few hours (less than 6 hours) pending performance of FOB, even when the patient is clinically stable.

When FOB is not available to physicians treating patients clinically suspected of having VAP, we recommend using either a simplified nonbronchoscopic diagnostic procedure, replacing FOB in the algorithm depicted in Figure 1 by one of these techniques, or following the strategy described by Singh and coworkers (357), in which decisions regarding antibiotic therapy are based on a clinical score constructed from seven variables, the CPIS. Using this algorithm (Figure 2), patients with CPIS > 6 are treated as having VAP with antibiotics for 10 to 21 days, whereas antibiotics are discontinued when the
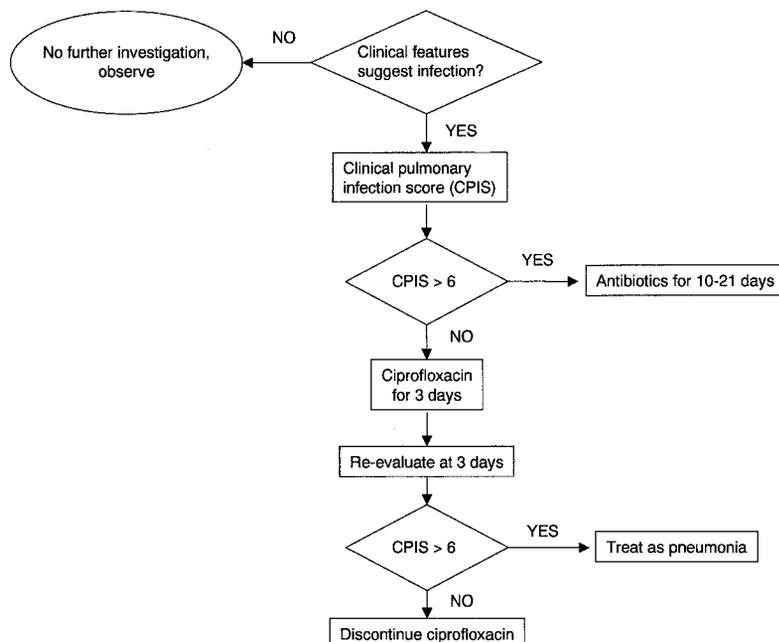

Figure 2. Diagnostic and therapeutic strategy applied to patients managed according to the strategy proposed by Singh and coworkers (357).

CPIS remains ≤ 6 at 3 days. Such an approach avoids prolonged treatment of patients with a low likelihood of infection, while allowing immediate treatment of patients with VAP. However, two conditions must rigorously be respected when implementing this strategy. First, selection of the initial antimicrobial therapy should be based on predominant flora responsible for VAP at each institution. It is highly probable that ciprofloxacin would not be the right choice in numerous institutions because of the high prevalence of MRSA infections in many of them (358). Second, it should be made clear to physicians that antimicrobial treatment should be reevaluated on Day 3, when susceptibility patterns of the microorganism(s) considered to be VAP causative are available, to select treatment with a narrower spectrum.

TREATMENT

Evaluation of Current Antimicrobial Strategies

Successful treatment of patients with VAP remains a difficult and complex undertaking. Despite broad clinical experience with this disease, no consensus has been reached concerning issues as basic as the optimal antimicrobial regimen or its duration. In fact, to date, evaluation of various antimicrobial strategies for the treatment of bacterial VAP has been difficult for several reasons.

First, as indicated above, the criteria for a definitive diagnosis of VAP in critically ill patients remain to be established. Although it is difficult to clinically distinguish between bacterial colonization of the tracheobronchial tree and true nosocomial pneumonia, nearly all previous therapeutic investigations have relied solely on clinical diagnostic criteria and, therefore, have probably included patients who did not have pneumonia. Second, most of those studies used tracheal secretions as the major source of specimens for microbiologic cultures, despite the fact that the upper respiratory tract of most ventilated patients is usually colonized with multiple potential pathogens. Finally, the lack of an adequate technique to directly sample the infection site in the lung has hampered the study of the ability or inability of antibiotics to eradicate the causative pathogens from the lower respiratory tract and, therefore, to predict their bacteriologic efficacy.

Newer methods for a more precise microbiologic diagnosis of pneumonia, such as the use of quantitative cultures of protected endoscopic brushings, appear promising in this context. Follow-up PSB sample cultures were used to assess directly the infection site in the lung in 76 patients with bacteriologically proven VAP and results demonstrated that the administration of antimicrobial therapy combining, in most cases, two effective agents was able to sterilize or contain the lower respiratory tract infection, after only 3 days of treatment, in 67 (88%) of the patients (98). The only two bacteriologic failures were observed in patients who did not receive appropriate treatment due to errors in the selection of antimicrobial drugs. Early superinfection due to bacteria resistant to the initial antibiotics was, however, documented in seven (9%) patients, thus emphasizing the need to carefully monitor the impact of treatment on the initial microbial flora for optimal management of such patients, when the clinical response is suboptimal. Furthermore, results of cultures of follow-up PSB samples correlated well with the clinical outcome noted during the 15-day observation period, making this test a good prognostic indicator for patients with VAP (98).

Antibiotic Treatment: General Considerations

Whereas VAP carries significant added mortality and morbidity, as previously demonstrated (6, 51, 81, 89, 359), tracheo-bronchitis alone does not seem to be associated with a poor prognosis and, therefore, antimicrobial treatment of mechanically ventilated patients with only tracheobronchitis is probably not justified (41, 81, 311, 360). Several investigative teams analyzed the outcome of patients who were clinically suspected of having VAP but in whom this diagnosis was finally excluded and found that the mortality rate was lower for these patients than for those with documented pneumonia, and that their death rate was the same as that observed for patients not suspected of having pneumonia (81, 311, 360). These findings support the conclusion that it is pneumonia per se that is associated with poorer survival, not the presence of acute tracheobronchitis with purulent tracheal secretions. Not all studies, however, have generated the same results. For example, the prognostic multivariate analysis based on 387 patients who required MV for more than 48 hours indicated that confirmation of VAP using PSB and/or BAL in patients clinically suspected of having lung infection added no prognostic information (46).

Patient survival may improve if pneumonia is correctly diagnosed and treated (Table 3) (11, 14, 21, 22, 74, 361). Using multiple logistic regression analysis to study risk factors for death of ventilated patients who developed pneumonia, it was demonstrated that inappropriate therapy was strongly associated with fatality, with a relative OR of 5.8 (14). Similar results were obtained by logistic regression analysis, which selected six independent risk factors for death: advanced age, ultimately or rapidly fatal underlying disease, high-risk microorganisms, bilateral infiltrates on the chest radiograph, presence of respiratory failure, and inappropriate antibiotic therapy, with this last factor having the most impact on prognosis (11).

Two other Spanish studies (Table 3) examined the influence of the adequacy of initial empiric antibiotic therapy on the outcomes of patients with VAP (21, 74). The first monitored 530 patients who developed 565 episodes of pneumonia (92% during MV in the ICU setting) (74). Attributable mortality and numbers of patients who developed shock after the onset of pneumonia were significantly higher for patients with inappropriate initial antimicrobial therapy than for other patients. The second study included 113 ventilated patients judged to have VAP on the basis of clinical criteria and cultures of either blood, pleural fluid, or lower airway secretions obtained bronchoscopically by BAL or PSB (21). The crude and VAP-associated mortality rates for the patients with inappropriate therapy were found to be significantly higher than the respective mortality rates for patients receiving adequate initial empiric antibiotics. Similar results were obtained for a series of 130 mechanically ventilated patients with clinically identified VAP in a medical ICU (361). The hospital mortality rate for the 51 patients who required new or modified antibiotic therapy after identification of causative pathogens by mini-BAL cultures was significantly higher than those for patients requiring no change of their antibiotic management (n = 51) and patients whose antibiotics were discontinued (n = 28). Multiple logistic regression analysis demonstrated that being immunocompromised and receiving inadequate antibiotic therapy (i.e., the presence of a microorganism in the mini-BAL culture resistant to the initially prescribed empiric antibiotic regimen) were independently associated with the likelihood of hospital mortality.

Two factors appear to render the choice of antibiotics particularly difficult in critically ill patients. First, VAPs are likely to result from highly resistant organisms, especially in patients who were previously treated with antibiotics (5, 107, 362–364). Second, multiple organisms are frequently cultured from the pulmonary secretions of patients considered to have pneumonia (12, 16, 18, 19, 77, 96, 106). Because of the emergence of

multiresistant, extended spectrum β-lactamase-producing GNB in many institutions and the increasing role played by gram-positive bacteria, such as MRSA, even a protocol combining ceftazidime or imipenem and amikacin would not ensure adequate coverage of all cases of VAP in these ICUs. Therefore, no "magic bullet" exists to cover all the microorganisms potentially responsible for VAP.

Finally, although appropriate antibiotics may improve survival of patients with VAP, use of empiric broad-spectrum antibiotics in patients without infection is potentially harmful, as it facilitates colonization and superinfection with multiresistant microorganisms. The results of many epidemiologic investigations have clearly demonstrated a direct relationship between the use of antimicrobial agents and increased resistance of Enterobacteriaceae and other pathogens (336, 338, 340, 365). The indiscriminate administration of antimicrobial agents to patients in the ICU may have immediate but also long-term consequences, contributing to the emergence of multiresistant pathogens and increasing the risk of severe superinfections (336, 339). Therefore, it should be made clear to physicians confronted with ICU patients clinically suspected of having VAP that prescribing new antimicrobial agents to all these patients may lead to overtreatment of many of them and, thus, possibly to the rapid emergence of multiresistant pathogens, not only in the treated patients but also in other patients hospitalized in the same unit or elsewhere in the same hospital.

Factors Contributing to Selection of Treatment

Important factors to be considered for the optimal selection of initial antibiotic therapy include the following: (*1*) putative etiologic agents and their antibiotic susceptibility patterns, as observed in previous cases of VAP, based on local epidemiologic studies and data obtained by surveillance cultures from the same patient; (*2*) the clinical setting and, in particular, the prior duration of hospitalization and/or MV before the onset of pneumonia, and the absence or presence of prior antibiotic use; (*3*) information obtained by direct microscope examination of pulmonary secretions; (*4*) intrinsic antibacterial activities of antimicrobial agents; and (*5*) other pharmacokinetic considerations.

Etiologic agents. Even though the exact prevalence of each infecting microorganism may vary as a function of country, hospital, and ward concerned, precise knowledge of the distribution of pathogens most frequently reported to be associated with VAP greatly facilitates the selection of appropriate therapy, as does information about their antibiotic susceptibility patterns, as determined by continuous collection of surveillance data. The authors of several epidemiologic studies of nosocomial pneumonia in patients receiving MV have reported increased rates of multiresistant bacteria (5, 106, 107). Many *P. aeruginosa* and *A. baumannii* strains have become class I cephalosporinase producers and are resistant to piperacillin, aztreonam, and ceftazidime. *Klebsiella pneumoniae* and other Enterobacteriaceae strains are also increasingly being recognized as producers of transferable extended spectrum β-lactamases, which confer resistance to third-generation cephalosporins (42, 362, 363, 366). Other multiresistant, aerobic GNB include *Xanthomonas* (*Stenotrophomonas*) *maltophilia* and *Alcaligenes* spp. Unfortunately, MRSA is also being implicated more and more frequently as a causative pathogen in ICU patients who required MV for a prolonged period (107, 142). Therefore, the microbiologic trends of VAP are evolving toward more resistant and more difficult-to-treat pathogens (5, 142, 367).

Several investigators have recommended routine surveillance cultures of patients in the ICU because they may be predictive of patients who are at high risk of invasive disease and, furthermore, should invasive disease develop, empiric therapy can be selected on the basis of the predominant pathogens identified in these cultures (33, 121, 368). However, the accuracy of this approach for selecting initial antimicrobial treatment for ICU patients requiring new antibiotics for VAP has not yet been established (121, 369, 370). This hypothesis was retested in a prospective study conducted with 125 patients, who required MV for more than 48 hours, and for whom strict bronchoscopic criteria were applied to diagnose pneumonia and identify the causative pathogens (371). Although a large number of various prior microbiologic specimen culture results (mean, 45 ± 43 per episode) were obtained before FOB for each VAP episode, only 73 (33%) of the 220 VAP-causative microorganisms were isolated by these routine analyses and their susceptibility patterns made available to guide initial antimicrobial treatment. When the analysis focused on VAP episodes for which prior (within 72 hours) respiratory secretion culture results were available, on the hypothesis that this microbiologic information might be particularly useful for identifying the responsible organisms in the case of subsequent pneumonia, results were still disappointing because all causative pathogens were recovered for less than 60% of them (371).

Several factors may explain the lack of accuracy of routine microbiologic specimen culture results for predicting the causative microorganisms of pneumonia in ICU patients requiring MV. First, the role played by colonization of some of the sites sampled before VAP onset, such as the nares, skin, and/or urine, in the pathogenesis of nosocomial lung infection is probably limited, thus explaining the absence of concordance between these microorganisms and those responsible for VAP. Second, a large number of different bacterial species are recovered from specimens obtained before VAP onset, whereas only a much smaller number of microorganisms is responsible for the infection, making identification of the "true" VAP pathogen(s) difficult. Finally, even when bacteria are isolated from a site likely to play a role in lung infection, such as the tracheobronchial tree, the interval between prior specimen culture results and VAP onset is frequently long enough to permit the development of lung infection caused by microorganism(s) other than the one(s) previously isolated (17, 133, 372).

Although tracheal colonization by potentially pathogenic microorganisms precedes lung infection in a majority of, but not all, ventilated patients (117, 133, 373), data have also emphasized that the pattern of tracheobronchial colonization, and especially the types of microorganisms involved, reflect a dynamic process that is rapidly modified by the flora present at that level and influenced by factors such as prior duration of MV and prior antibiotics (372, 374). In one study in which lower respiratory tract colonization and infection were prospectively evaluated in 30 patients with severe ARDS, using repeated quantitative cultures of plugged telescopic catheter specimens taken blindly via the endotracheal tube every 48 to 72 hours after ARDS onset, colonization preceded BAL-microbiologically confirmed VAP, and VAP was microbiologically confirmed in only 67% of the VAP episodes (17). Therefore, careful evaluation of distal airway colonization can fail to document at least one-third of VAP episodes. Such a strategy may also considerably increase the workload of the microbiology laboratory without having any positive impact on patient management.

Colonization with potentially drug-resistant pathogens, such as MRSA or extended spectrum β-lactamase-producing strains of *K. pneumoniae* or other Enterobacteriaceae, is associated with an increased risk of infection caused by the corresponding

microorganism (368, 375–377). These results were confirmed in the study by Hayon and coworkers (371), with positive-predictive values of recovering such a microorganism from a specimen of 62, 52, or 24% for VAP caused by MRSA, *P. aeruginosa*, or *A. baumannii*, respectively. However, because the sensitivity of prior microbiologic culture results for identifying bacteria causing VAP does not exceed 70%, selection of initial antimicrobial therapy for patients with VAP can hardly be based only on these results, especially for deciding to use (or not use) vancomycin and/or a broad-spectrum β-lactam effective against *P. aeruginosa* and/or *A. baumannii*. However, when one of the three microorganisms (or any pathogen) is isolated from respiratory secretions within 72 hours of VAP, it should probably be covered by the antimicrobial regimen selected, even though predictive values do not exceed 50 to 60% (371).

Clinical setting. As indicated in the section EPIDEMIOLOGY (above), underlying diseases may predispose patients to infection with specific organisms (33). In a study that prospectively included only VAP episodes documented by positive PSB samples, the risk factors for patients who developed nosocomial MRSA or MSSA infection in the lower respiratory tract were compared (82). The former were more likely to have received corticosteroids before developing infection (RR = 3.45), to have been ventilated for > 6 days (RR = 2.03), to be > 25 years old (RR = 1.50), or to have COPD (RR = 2.76). On the other hand, head trauma was more frequent among MSSA-infected persons (RR = 1.94). The most striking finding was that all patients with MRSA infections had previously received antibiotics, compared with only 21% of those with MSSA infections. These observations are consistent with earlier reports on VAP due to multiresistant pathogens and strongly support the notion that duration of MV and prior antibiotic use are two key factors selecting for such microorganisms (107).

Taking into account these epidemiologic characteristics allows the definition of a more rational decision tree for selecting initial treatment in this setting. In 1996, the American Thoracic Society published a Consensus Statement that provides guidelines based on assessments of disease severity, the presence of risk factors for specific organisms, and time of on-set of pneumonia to guide initial antibiotic selection (33). Once these determinations are made, patients suspected of having nosocomial pneumonia fall into one of three groups, each with its own set of likely pathogens: (*1*) patients without unusual risk factors who present with mild-to-moderate pneumonia with onset at any time during hospitalization or severe pneumonia of early onset; (*2*) patients with specific risk factors who present with mild-to-moderate pneumonia occurring any time during hospitalization; and (*3*) patients with severe pneumonia, either of early onset with specific risk factors or of late onset. Recommended therapeutic regimens for ICU ventilated patients or patients with risk factors for pneumonia due to *P. aeruginosa* are given in Table 9. Because the guidelines have not been updated since their publication in 1996, they do not include newer therapies (e.g., cefepime, meropenem, and newer fluoroquinolones) that may be effective and/or associated with less resistance. Furthermore, they fail to distinguish among some compounds with different antibacterial activities or to recommend specific antibiotics.

On the basis of the results of a French prospective study in which the responsible microorganisms for infection in 135 consecutive episodes of VAP observed in the ICU were documented with bronchoscopic specimens, the distribution of infecting pathogens was markedly influenced by prior duration of MV and prior antibiotic use (107). Whereas early-onset pneumonias in patients who had not received prior antimicrobial treatment were mainly caused by susceptible Enterobacteriaceae, *Haemophilus* spp., MSSA, or *S. pneumoniae*, early-onset pneumonias in patients who had received prior antibiotics were commonly caused by nonfermenting GNB, such as *P. aeruginosa*, in addition to streptococci and *Haemophilus* spp. On the other hand, late-onset pneumonias that occurred without antibiotics during the 15 days preceding the onset of infection were essentially caused by streptococci, MSSA, or Enterobacteriaceae; however, some of these GNB were class I cephalosporinase producers, which may require treatment with a new cephalosporin, such as cefepime or cefpirome, for optimal therapy. Late-onset pneumonias in patients having recently received antibiotics were caused by multiresistant patho-

TABLE 9. CORE ORGANISMS RESPONSIBLE FOR VENTILATOR-ASSOCIATED PNEUMONIA AND RECOMMENDED ANTIMICROBIAL THERAPY

Core Organisms	Core Antibiotics
Early-onset VAP, no specific risk factor	
Enteric gram negative (nonpseudomonal)	Cephalosporin
Enterobacter spp.	Second generation
Escherichia coli	Nonpseudomonal third generation
Klebsiella spp.	or
Proteus spp.	β-Lactam–β-lactamase inhibitor combination
Serratia marcescens	
Haemophilus influenzae	If allergic to penicillin:
MSSA	Fluoroquinolone
	or
Streptococcus pneumoniae	Clindamycin + aztreonam
Late-onset VAP	
Core organisms *plus*	Aminoglycoside or ciprofloxacin *plus* one of the following:
Pseudomonas aeruginosa	Antipseudomonal penicillin
Acinetobacter baumannii	β-Lactam–β-lactamase inhibitor combination
	Ceftazidime or cefoperazone
	Imipenem
	Aztreonam
Consider MRSA	± Vancomycin

Definition of abbreviations: MRSA = methicillin-resistant *S. aureus;* MSSA = methicillin-sensitive *S. aureus;* VAP = ventilator-associated pneumonia.
Adapted from the American Thoracic Society (33).

gens, such as *P. aeruginosa*, *A. baumannii*, or MRSA in more than 40% of cases. Taking these epidemiologic characteristics into account allowed the authors to devise a rational decision tree for selecting initial treatment in this setting that prevents resorting to broad-spectrum drug coverage in all patients. For example, monotherapy with a second-generation cephalosporin (cefuroxime, cefamandole, or cefotetan), or a third-generation cephalosporin with no antipseudomonal activity (cefotaxime or ceftriaxone), or therapy combining the β-lactamase inhibitor clavulanic acid with amoxicillin would generally be an appropriate choice for most patients with early-onset VAP who have not received prior antimicrobial treatment. In contrast, for patients who have required prolonged MV and antimicrobial treatment, three-antibiotic therapy with a combination of aminoglycoside or ciprofloxacin plus a broad-spectrum anti-*Pseudomonas* β-lactam, such as piperacillin–tazobactam or imipenem, plus vancomycin should be started, keeping in mind that even such a regimen will not ensure complete coverage of all putative pathogens. For the two intermediate groups, early-onset episodes with previous antibiotic therapy and late-onset episodes without previous antibiotic therapy, in which a mixed distribution of pathogens is frequently observed, including some nonfermenting GNB, such as *P. aeruginosa*, but practically no MRSA and no multiresistant *A. baumannii*, treatment should be based on a combination of aminoglycoside or ciprofloxacin and an anti-*Pseudomonas* β-lactam, but without vancomycin.

However, because the range of bacteria that cause VAP and their susceptibility patterns vary widely among hospitals in the same or different countries, selection of initial antimicrobial therapy needs to be tailored to each institution's local patterns of antimicrobial resistance (106, 358). A computerized decision support program linked to computer-based patient records can facilitate the dissemination of such information to physicians for immediate use in therapy decision-making and improve the quality of care (378–381). Use of such a program for 545 patients in the ICU led to significantly fewer orders for drugs to which the patients had reported allergies (35 versus 146 during the preintervention period; p < 0.01), fewer excess drug doses (87 versus 405; p < 0.01), and fewer antibiotic-susceptibility mismatches (12 versus 206; p < 0.01) than for the 1,136 patients admitted to the same unit during the 2 years before the intervention period (379). In comparison with patients who did not always receive the recommended regimens (n = 195) and those in the preintervention cohort (n = 766), patients who always received the regimens recommended by the computer program (n = 203) had significantly lower costs for anti-infective agents (adjusted means, US$427 and US$340 versus US$102, respectively; p < 0.001), total hospital costs (adjusted means, US$44,865 and US$35,283 versus US$26,315; p < 0.001), and fewer hospital-stay days (adjusted means, 16.7 and 12.9 versus 10.0; p < 0.001) (379).

Information provided by direct examination of pulmonary secretions. Direct microscopy of pulmonary secretions is extremely important not only to identify patients with true VAP but also to select appropriate treatment, especially when BAL specimens are used to prepare cytocentrifuged gram-stained smears. In patients with pneumonia, the morphology and Gram staining of bacteria are closely correlated to the results of bacterial cultures, enabling early formulation of a specific antimicrobial regimen before the culture results are available. In a study assessing the potential value of bronchoscopic techniques, only 1 patient, among the 204 who underwent the invasive-sampling procedure and (of these) the 107 treated, received inappropriate initial empiric therapy, compared with 24 of the 191 patients in the clinical group, probably because of

the additional information obtained by direct specimen examination (63). Similar results were obtained in a study of 94 mechanically ventilated patients with suspected VAP who underwent FOB with BAL and PSB (103). Direct BAL fluid examination results were available within 2 hours, BAL and PSB culture results after 24 hours, and antibiotic susceptibility after 48 hours. At each step in the strategy, the senior physician and the resident in charge of the patient were asked their diagnoses and their therapeutic plans based on the available data. Using a threshold of 1% infected cells, direct BAL examination discriminated well between patients with VAP and those without VAP (sensitivity, 94%; specificity, 92%; area under the ROC curve, 0.95). In contrast, the senior clinical judgment before FOB was correct for only 71% of the cases, compared with the definitive diagnosis and final antibiotic susceptibility test results. In addition, the therapeutic prediction was correct for 65% using clinical judgment (15 untreated patients, 3 ineffective treatments, 15 unnecessary treatments), 66% using airway visualization (14 untreated VAP, 4 ineffective treatments, 14 unnecessary treatments), and 88% using direct BAL examination results (1 untreated patient, 6 ineffective treatments, 4 unnecessary treatments) (103). Therefore, a strategy based on bronchoscopy and direct examination of BAL fluid may lead to more rapid and appropriate treatment of VAP than a strategy based only on clinical evaluation.

Intrinsic antibacterial activities of antimicrobial agents. The interactions between bacteria and antimicrobial agents, as tested *in vitro* by means of standard techniques, are highly contributive to therapeutic decision-making, even if a wide variety of local factors at the pulmonary site of infection may affect the antibacterial activities of most antibiotics.

The role of aminoglycosides in treating VAP deserves further comment because of conflicting data. Evidence exists that aminoglycosides are more active than β-lactams against certain resistant GNB (2, 157, 364). Their bactericidal mode of action, concentration-dependent killing rate, and postantibiotic effect, and their synergism with β-lactam compounds, are clear advantages. However, because the therapeutic activity ratios for aminoglycosides in serum are low, the penetration of circulating aminoglycosides into the infected lung tissues may be insufficient to eradicate infecting organisms and the low pH of infected airways has the potential to inactivate them (382, 383). Consequently, aminoglycosides are now used essentially in combination with β-lactam antibiotics (33).

To improve antibiotic concentrations in respiratory secretions and tissues without increasing toxicity, alternative administration routes have also been investigated, such as direct instillation of aminoglycosides in the bronchial tree or use of a single, high daily dose. Direct aminoglycoside instillation in the respiratory tract via the endotracheal tube or tracheostomy enables high drug concentrations to be attained directly at the site of infection, while possibly avoiding systemic toxicity. In a prospective, randomized study comparing systemic treatment alone versus systemic treatment plus sisomicin deposition in the respiratory tract, more patients receiving local aminoglycoside treatment improved (384). In a subsequent, double-blind, randomized trial (385), patients with endobronchial tubes or tracheostomies in place and documented GNB pneumonia were assigned to receive conventional parenteral antibiotics (β-lactam plus aminoglycoside) and intratracheal instillation of tobramycin (40 mg) in solution every 8 hours versus the same parenteral regimen with intratracheal saline instillation every 8 hours. Among the 85 patients enrolled, only 41 could be evaluated. GNB were eradicated from sputum more frequently in the group receiving endobronchial tobramycin (68 versus 31% of control subjects). However, clini-

cal improvement was virtually identical for the endobronchial tobramycin group (80%) and the placebo group (81%). Further investigation of local aminoglycoside therapy for VAP is therefore required before the relative risks and benefits of this approach can be definitively defined or approved.

Third- and fourth-generation cephalosporins can be divided into two groups depending on their activity against *P. aeruginosa*. For example, ceftazidime, cefoperazone, and cefsulodin exhibit excellent *in vitro* anti-*P. aeruginosa* activity but, unfortunately, are considerably less active against *S. aureus* than other cephalosporins. Conversely, cefotaxime, ceftriaxone, and cefpirome exhibit acceptable or good *in vitro* anti-*S. aureus* activity but relatively weak *in vitro* activity against *P. aeruginosa*. Thus, if one is hoping to achieve monotherapy coverage of the appropriate gram-positive and gram-negative bacterial spectrum for VAP, not all cephalosporins fit the bill.

The *in vitro* spectrum of imipenem exceeds that of any other single agent. It provides bactericidal activity against most gram-positive cocci (except MRSA and enterococci), most GNB, including *P. aeruginosa*, and also most pathogenic anaerobes. Drawbacks for this agent, however, include reports of the emergence of resistant organisms during therapy and seizures when high doses are given to patients with renal dysfunction. Furthermore, the frequency of *Pseudomonas* strains resistant to imipenem is increasing (362, 367, 386).

Meropenem is a new carbapenem already available in some, but not all, countries. Its spectrum of antibacterial activity is similar to that of imipenem, with potent activity against a variety of gram-positive species, gram-negative aerobes, and anaerobic strains. It is slightly less active against gram-positive bacteria, but more active against GNB, including some imipenem-resistant strains of *P. aeruginosa*. The toxicity profile of meropenem is similar to that of imipenem, except that data from animal experiments suggest that meropenem is less epileptogenic and less nephrotoxic. Clinical experience with meropenem is, however, limited and single-drug therapy of severe *P. aeruginosa* infections has been accompanied by the emergence of resistance (387).

Three randomized trials evaluated piperacillin–tazobactam, a new combination of ureidopenicillin plus a β-lactamase inhibitor with excellent activity against *P. aeruginosa* (with or without an aminoglycoside) as therapy for VAP (388–390). One study from 27 French ICUs randomized 127 patients with VAP to be treated with amikacin plus either piperacillin–tazobactam, 4.5 g four times daily, or ceftazidime, 1 g four times daily (388). Bacteriologic failures were more common in the ceftazidime-treated patients (51%) compared with those treated with piperacillin–tazobactam (33%). However, 28-day mortality rates were similar (16 and 20%, respectively). When *P. aeruginosa* was isolated, success rates were 40 or 39% with piperacillin–tazobactam or ceftazidime, respectively. Lower respiratory tract superinfections were significantly more common with ceftazidime (21%) than with the piperacillin–tazobactam plus amikacin combination (9%).

A multicenter American trial randomized 300 patients with VAP to combination therapy with tobramycin plus either piperacillin–tazobactam, 3.375 g every 4 hours, or ceftazidime, 2 g every 8 hours (389). The aminoglycoside could be discontinued at the discretion of the investigator once the pathogen was identified. Among assessable patients, final clinical responses, overall microbiologic response rates, and *P. aeruginosa* eradication were higher with piperacillin–tazobactam than ceftazidime. Mortality was 7.7% in the former group compared with 17% in the latter (p = 0.03). A Swiss trial randomized patients with hospital-acquired pneumonia to receive monotherapy with piperacillin–tazobactam, 4.5 g four times daily, or imi-

penem–cilastatin, 0.5 g four times daily (390). Among 154 assessable patients, clinical success rates were similar for both groups. However, among 45 patients with pseudomonal VAP, a higher percentage of patients responded to piperacillin–tazobactam than to imipenem–cilastatin (90 versus 50%; p = 0.004). Antimicrobial resistance developed in six patients treated with imipenem–cilastatin but in only one patient treated with piperacillin–tazobactam. Taken together, all these results suggest that piperacillin–tazobactam is at least as effective as (and possibly more effective than) ceftazidime or imipenem–cilastatin for VAP, particularly when *P. aeruginosa* is isolated.

Among available fluoroquinolones, ciprofloxacin is the most active against GNB, including *P. aeruginosa*. MSSA is also susceptible to these agents; however, resistance has developed rapidly in MRSA and now most of these strains are no longer susceptible to fluoroquinolones (364). Concerning norfloxacin, ciprofloxacin, ofloxacin, lomefloxacin, and enoxacin, activity against *S. pneumoniae*, enterococci, streptococci, and many anaerobes is limited, even though these agents are concentrated intracellularly in most tissues including bronchial mucosa, neutrophils, and alveolar macrophages, which may enhance their effectiveness against pathogens with intermediate susceptibility. Some newer quinolones, such as trovafloxacin, levofloxacin, sparfloxacin, clinafloxacin, gatifloxacin, tosufloxacin, and moxifloxacin, have excellent *in vitro* activities against streptococci and anaerobic species, but only trovafloxacin and sparfloxacin have been released in the United States.

A randomized, double-blind, multicenter study compared monotherapy with ciprofloxacin or imipenem for severe pneumonia in a series of 405 patients (391). Bacteriologic eradication rates were higher for ciprofloxacin-treated than imipenem-treated patients (69 versus 59%; p = 0.07) as were clinical response rates (69 versus 56%; p = 0.02). However, when *P. aeruginosa* was recovered from initial respiratory tract cultures, failure to achieve bacteriologic eradication and development of resistance during therapy were common in both treatment groups (respectively, 67 and 33% for ciprofloxacin, and 59 and 53% for imipenem), emphasizing that monotherapy, even with a potent antibiotic, can lead to more failures when *P. aeruginosa* is present.

Pharmacokinetic considerations. Effective antibiotic treatment of bacterial pneumonia depends on adequate delivery of antibacterial agents to the infection site and, therefore, scrupulous attention must be given to optimal doses, routes of administration, and pharmacodynamic characteristics of each agent used to treat this infection. Antibiotic levels in infected tissues are considered to be therapeutic when free drug concentrations equal at least the *in vitro* minimal inhibitory concentration (MIC) for the infecting pathogen(s). Because of major methodologic problems, published data concerning the penetration of most antibiotics into the lung should probably be viewed with caution, and only general trends concerning concentrations achievable at the infected site in lung tissue can be derived from those studies (382, 383, 392).

For penicillins and cephalosporins, the bronchial secretion-to-serum drug concentration ratios range between 0.05 and 0.25. Fluoroquinolones have better penetration characteristics, and bronchial secretion concentrations are between 0.8 and 2 times those in serum. Aminoglycosides and tetracyclines have ratios of 0.2 to 0.6. Host-related as well as drug-related factors may, however, influence the penetration of antimicrobial drugs across the blood–bronchus and alveolar–capillary barriers. Thus, for those drugs, such as the β-lactams and glycopeptides, which do not cross membranes readily, penetration might increase in the presence of inflammation because of enhanced membrane permeability (393).

Several published reports have demonstrated a relationship among serum concentrations of β-lactams or other antibiotics, the MIC of the infecting organism, and the rate of bacterial eradication from respiratory secretions in patients with lung infection, thereby emphasizing that clinical and bacteriologic outcomes can be improved by optimizing the therapeutic regimen according to pharmacokinetic properties of the agent(s) selected for treatment (394–400). Most investigators distinguish between antimicrobial agents that kill by a concentration-dependent mechanism (e.g., aminoglycosides and fluoroquinolones) and those that kill by a time-dependent mechanism (e.g., β-lactams and vancomycin). Multivariate analyses based on 74 acutely ill patients, most with VAP, who were treated with intravenous ciprofloxacin (200 mg twice daily to 400 mg three times daily), demonstrated that the most important independent factor for probability of cure was a pharmacodynamic variable, that is, the 24-hour area under the concentration–time curve divided by the MIC (AUIC) (394). For AUIC < 125, the probabilities of clinical and microbiologic cures were 42 and 26%, respectively, but with AUIC > 125, the probabilities were 80 and 82%, respectively.

Pharmacokinetic–pharmacodynamic models have also been used to optimize aminoglycoside therapy for VAP caused by GNB (395). Seventy-eight patients with VAP were analyzed, and the investigators reported an 89% success rate for temperature normalization by Day 7 of therapy for C_{max}/MIC > 4.7 and an 86% success rate for leukocyte count normalization by Day 7 of therapy for C_{max}/MIC > 4.5. Logistic regression analysis predicted a 90% probability of temperature and leukocyte count normalizations by Day 7, if a C_{max}/MIC > 10 was achieved within the first 48 hours of aminoglycoside administration. Aggressive aminoglycoside doses immediately followed by pharmacokinetic monitoring for each patient would ensure that C_{max}/MIC target ratios are achieved early during therapy.

These findings confirm the need to adjust the target dose of antimicrobial agents used to treat severe pulmonary infection to an individual patient's pharmacokinetics and the susceptibilities of the putative bacterial pathogens. Development of *a priori* dosing algorithms based on the MIC, patient creatinine clearance and weight, and the clinician-specified AUIC target might therefore be a valid way to improve treatment of these patients, leading to a more precise approach than current guidelines for optimal use of antimicrobial agents (396–400).

Monotherapy versus Combination Therapy

Several studies have examined the use of a single antibiotic, for example, a third-generation cephalosporin, imipenem–cilastatin, or a fluoroquinolone, to treat VAP (401–412). In general, monotherapy has proven to be a useful alternative to combination therapy, with the same success rate and no more superinfections or colonizations by multiresistant pathogens. It should, however, be pointed out that most of those studies included patients with VAP diagnosed on clinical grounds alone, and that treatment efficacy was assessed using information provided by sputum or tracheal aspirate cultures and not by more specific techniques. Most industry-sponsored studies excluded the sickest patients and were designed to demonstrate therapeutic equivalence rather than superiority. Indeed, a more rigorous comparison of these two regimens, performed on the basis of follow-up PSB sample or BAL fluid cultures, is required before monotherapy can be strongly recommended to treat VAP (98).

Furthermore, for patients with severe infection due to *P. aeruginosa* or other multiresistant bacteria, such as *Klebsiella* spp. or *Acinetobacter* spp., combining an antipseudomonal β-lactam with an aminoglycoside or ciprofloxacin is likely to obtain a much better outcome than monotherapy, as previously shown (413–416). In a prospective clinical study of 200 patients with *P. aeruginosa* bacteremia, mortality rates for patients with pneumonia receiving monotherapy or combination therapy as the initial empiric treatment were 88% (7 of 8 patients) or 35% (7 of 20 patients), respectively (p = 0.03) (413). Similarly, for the subgroup of 55 patients who experienced hypotension within 72 hours of or on the day of the positive blood culture in a prospective observational study of 230 *Klebsiella* bacteremias, the mortality rate was significantly lower for those patients who received combination therapy (24%) than those given monotherapy (50%) (415). It should be noted, however, that the β-lactam agents used in those studies were older agents, with less potent activity than the advanced cephalosporins or the carbapenems available today.

A controlled, multicenter, randomized European trial including 129 patients with cancer, granulocytopenia, and gram-negative bacteremia supported an adjunctive role for an aminoglycoside (416). In that study, patients were randomized to one of three treatment arms (azlocillin plus amikacin, ceftazidime plus amikacin for 3 days, or ceftazidime plus amikacin for 9 days). Clinical response rates were highest with ceftazidime plus long-course (9 days) amikacin treatment. The benefit of the aminoglycoside was more pronounced when *P. aeruginosa* was implicated. Among patients with pseudomonal bacteremias, only 5 (38%) of 13 patients responded to ceftazidime–short-course amikacin treatment, whereas 8 (89%) of 9 patients responded to ceftazidime–long-course amikacin treatment. These data, although derived from a study not without methodologic flaws, suggest that combination therapy is the preferred therapeutic regimen for severe infections for which at least one of these difficult-to-treat bacteria is likely to be the causative organism.

To reassess the need for β-lactam–aminoglycoside combinations to treat severe infections, a prospective, randomized, controlled study compared imipemem alone with imipenem plus netilmicin as the empiric regimen for nosocomial pneumonia and other severe infections in nonneutropenic patients (411). Among the 280 patients enrolled in the study, 48% had pneumonia and required MV. The success rate was not significantly improved by adding an aminoglycoside to imipenem, and the failure rates and numbers of superinfections were similar for both groups. While the addition of netilmicin increased nephrotoxicity, neither colonization with imipenem-resistant *P. aeruginosa* strains nor clinical treatment failures due to the emergence of resistant *P. aeruginosa* were prevented. Another randomized study of 140 ICU patients with suspected pneumonia or bacteremia found imipenem to be as effective as cefotaxime plus amikacin (409). Meropenem was also demonstrated to be as effective as ceftazidime when given alone or in combination with amikacin (417, 418).

Because those studies included nonhomogeneous populations of patients with different types of infections and given the potential inaccuracy of using only clinical criteria to diagnose lung infection, further trials are needed to clarify these uncertainties. In the meantime, it is probably safer to use a β-lactam antibiotic in combination with an aminoglycoside or a quinolone for patients with severe VAP, at least for the first days of therapy, while culture results of pulmonary secretions are pending. It may be that monodrug therapies for nosocomial pneumonia would best be reserved for infections in which *P. aeruginosa* or other multiresistant microorganisms, such as *Klebsiella*, *Enterobacter*, *Citrobacter*, *Serratia*, or *Acinetobacter* spp., have been excluded as the etiologic agents (33, 75, 157, 413, 415).

Duration of Antimicrobial Therapy

Despite the thoroughness of some guidelines, the treatment durations proposed by the American Thoracic Society remain

rather imprecise (33). Those experts recommend that the duration be adapted to the severity of the disease, the time to clinical response, and the microorganism(s) responsible. A "long" treatment, that is, a minimum of 14 to 21 days, is prescribed for the following situations: multilobar involvement, malnutrition, cavitation, gram-negative necrotizing pneumonia, and/or isolation of *P. aeruginosa* or *Acinetobacter* spp. This duration is essentially justified by the high theoretical risk of relapse. A "short" treatment, lasting 7 to 10 days, is recommended for *S. aureus* or *H. influenzae* pneumonia.

In many trials comparing the efficacies of diverse antimicrobial agents, although the scheduled duration of treatment was 14 days, the observed time of administration was often about 10 days (388, 389, 391, 411, 419). However, it must be noted that this duration is an average that includes those patients who died early. In addition, in numerous studies, the diagnostic methods did not include quantitative techniques with, as a corollary, uncertainty as to the reality of the pneumonia.

From a conceptual point of view, there are three potential disadvantages for using "long-duration" antimicrobial therapy: effects on bacterial "ecology," antibiotic toxicity, and increased cost. As mentioned above, a relationship exists between antibiotic use and the selection of resistant bacteria (336, 338, 340, 365). It is widely accepted that antibiotic therapy plays a major role in this selection at an individual level, either by selecting strains naturally resistant to the administered antibiotic (e.g., *P. aeruginosa*, yeasts) or by selecting resistant bacteria by chromosomal mutation within an initially sensitive population. The causal relationship between antibiotic administration (and also its duration) and the frequency of resistance is more difficult to demonstrate at a collective level. However, strong arguments exist that support the concept that the total amount of antibiotics prescribed in a given hospital influences the level of resistance within that institution (336, 365, 420). In a study in which 102 consecutive patients with VAP were prospectively evaluated before and after the application of a clinical guideline restricting the total duration of antimicrobial therapy to 7 days in selected patients (those who were not bacteremic and not neutropenic, and who experienced defervescence in response to therapy), no statistically significant differences in hospital mortality and hospital lengths of stay were found between the two study groups; however, patients in the before-evaluation group, for whom the mean duration of treatment was 14.8 days, were more likely to develop a second episode of VAP compared with those in the after-evaluation group (358).

Antibiotics represent ∼ 20 to 50% of a hospital's drug expenditures (excluding antiretroviral agents) (379, 421). Bacteria isolated from nosocomial pneumonias occurring late in patients already receiving antibiotics are often multiresistant and necessitate the use of molecules with broad spectra of activity that are often expensive (107). It can reasonably be thought that, should a "short" duration of antibiotic therapy prove acceptable, the consequences in financial terms would be beneficial.

However, a regimen of insufficient duration can be the source of therapeutic failure or relapse, defined as the reappearance of signs of pneumonia and isolation of the same pathogen(s), which may or may not have acquired resistance. The risk is probably small for bacteria considered susceptible but might be high for certain strains, especially *P. aeruginosa* and MRSA, which are particularly difficult to eradicate from the respiratory tract (422). This situation is even further aggravated in certain immunocompromised patients. Thus, at present, a short-term regimen is rarely prescribed, despite the potential major advantages it could have in terms of bacterial ecology, the prevention of the emergence of multiresistant bacteria,

and, obviously, lower costs. Lowering the amount of antibiotics administered to patients in the ICU is indeed a primary objective of every strategy aimed at preventing the emergence and dissemination of such bacteria (340, 423).

Antibiotic Rotation

Many studies have shown that alterations of antibiotic prescription patterns, such as restricting the use of a particular antibiotic or changing the empiric antibiotic of choice for a particular diagnosis, are associated with declines in antibiotic resistance (344, 359, 424–426). Theoretically, this decline is due to diminished selection pressure favoring resistance. Continuous modifications of selection pressure by rotating antibiotic therapy, therefore, might reduce the emergence of resistance and the associated morbidity. To date, however, the impact of predetermined, scheduled changes of empiric antibiotic therapy, rather than changes in response to the proliferation of any given pathogen, has not been fully tested in patients with VAP. In one study during which ciprofloxacin was used in place of ceftazidime for the empiric treatment of suspected GNB infections, VAP occurred significantly less frequently during the after period compared with the before period (7 versus 12%; p = 0.03) but no outcome differences were noted between the two groups of patients (427).

During a before–after study conducted over a 4-year period with 3,455 ICU patients to evaluate a new strategy of antibiotic use combining rotation of antibiotics and restricted use of ceftazidime and ciprofloxacin, the investigators observed a decrease from 231 (22%) to 161 (16%) VAP episodes in patients who received MV for more than 48 hours (p < 0.01), particularly for VAP occurring within the first 7 days of MV. In addition, they demonstrated significantly increased susceptibilities of *P. aeruginosa*, *Burkholderia cepacia*, and *S. aureus* (428).

A similar decline in the rates of infection caused by multiple classes of resistant bacteria was demonstrated by Raymond and coworkers when they tested antibiotic rotation in 1,456 consecutive admissions to the ICU (429). Furthermore, outcome analysis revealed a significant reduction of the mortality associated with infection (2.9 deaths per 100 admissions versus 9.6 deaths per 100 admissions; p < 0.0001) during rotation, which was confirmed by logistic regression analysis, with antibiotic rotation being an independent predictor of survival (OR, 6.3; 95% CI, 2.8 to 14.2). Further study in this area, including multicenter trials, evaluation of rotation intervals, evaluation of single versus multiple drug rotations, and long-term effects of antibiotic rotation is, however, necessary to understand these effects more completely. Whether antibiotic rotation can maintain lower levels of antimicrobial resistance and mortality over time remains to be seen.

To conclude, effective antimicrobial therapy and adequate supportive measures remain the mainstay of treatment for VAP. Persistently high mortality rates for pneumonia in the ICU argue, however, for the continued reassessment of our current therapeutic modalities and design of better protocols. More active and less toxic antibacterial agents are still needed, especially for some problematic pathogens, such as multiresistant nonfermenting GNB or MRSA. However, it should be emphasized that, in the event that one or several specific etiologic agents are identified by a reliable diagnostic technique, the choice of antimicrobial drugs is much easier, because the optimal treatment can be selected in light of the susceptibility pattern of the causative pathogens without resorting to broad-spectrum drugs or risking inappropriate treatment. Every possible effort should therefore be made to obtain, before new antibiotics are administered, reliable pulmonary specimens for

direct microscope examination and cultures from each patient clinically suspected of having developed VAP.

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