Intensive Care Med (1996) 22: 387–394

ORIGINAL

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ICU-Acquired Pneumonia
Study Group

Modification of empiric antibiotic treatment in patients with pneumonia acquired in the intensive care unit

Received: 17 October 1994
Accepted: 8 November 1995

Supported by a grant from Bristol-Myers-Squibb. The results of this study were presented in part at the 4th Panamerican and Iberic Congress on Intensive Care, Rio de Janeiro, Brazil, 1991

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Abstract *Objective:* To assess the frequency of and the reasons for changing empiric antibiotics during the treatment of pneumonia acquired in the intensive care unit (ICU).
Design: A prospective multicenter study of 1 year's duration.
Setting: Medical and surgical ICUs in 30 hospitals all over Spain.
Patients: Of a total of 16 872 patients initially enrolled into the study, 530 patients developed 565 episodes of pneumonia after admission to the ICU.
Results: Empiric antibiotics were administered in 490 (86.7%) of the 565 episodes of pneumonia. The antimicrobials most frequently used were amikacin in 120 cases, tobramycin in 110, ceftazidime in 96, and cefotaxime in 96. Monotherapy was indicated in 135 (27.6%) of the 490 episodes, a combination of two antibiotics in 306 episodes (62.4%), and a combination of three antibiotics in 49 episodes (10%). The empiric antibiotic treatment was modified in 214 (43.7%) cases because of isolation of a microorganism not covered by treatment in 133 (62.1%) cases, lack of clinical response in 77 (36%), and development of resistance in 14 (6.6%). Individual factors associated with modification of empiric treatment identified in the multivariate analysis were microorganism not covered (relative risk (RR)) 22.02; 95% confidence interval (CI) 11.54 to 42.60; $p < 0.0001$), administration of more than one antimicrobial (RR 1.29; 95% CI 1.02 to 1.65; $p = 0.021$), and previous use of antibiotics (RR 1.22; 95% CI 1.08 to 1.39; $p = 0.0018$). Attributable mortality was 16.2%

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in patients with appropriate initial therapy and 24.7% in patients with inappropriate treatment ($p = 0.034$).
Conclusions: A high percentage of patients (43.7%) required modification of empiric antibiotic treatment for pneumonia acquired in the ICU. In 62.1% of cases the main reason for changing antibiotic treatment was inadequate antibiotic coverage of microorganisms. Attributable mortality was significantly higher in patients with inappropriate initial antibiotic therapy. Rapid and accurate diagnostic methods are needed to initiate appropriate antibiotic treatment as soon as pneumonia is suspected.

Key words Nosocomial pneumonia · Empiric antibiotic therapy · Intensive care unit · Modification of antibiotic treatment · Attributable mortality

Introduction

Pneumonia in an artificially ventilated patient is usually associated with hemodynamic alterations, worsening gas exchange, and increased catabolism; occasionally it may cause progressive multiple organ failure. Management of such patients includes early initiation of antibiotic treatment as well as other support measures. Antibiotic treatment of patients with nosocomial pneumonia is usually initiated empirically before the results of bacterial cultures are available [1, 2]. Several reasons have been given to justify this policy, including the severity of the patient's underlying condition prior to infection, the low sensitivity and specificity of some procedures used to obtain clinical specimens [3, 4], delay in getting microbiological results, and an increase in the attributable mortality of pneumonia [5, 6].

There are several guidelines [1, 2, 7, 8] for choosing empiric antibiotic therapy, such as knowledge of microorganisms (and their sensitivity patterns) that cause pneumonia in patients needing assisted ventilation, understanding of the properties of the antibiotics used against these organisms in each hospital (i.e., the policy on antibiotic treatment), and evaluation of characteristics of individual patients that may suggest the type of infecting organism.

Different treatment schedules have been used for pneumonia acquired during mechanical ventilation [1, 2, 7–10]. For instance, in non-neutropenic patients admitted to an intensive care unit (ICU), combinations of a third-generation cephalosporin or ureidopenicillin with aminoglycosides [9, 10] have been used in recent years. Since the introduction of potent broad-spectrum antibiotics with high activity against gram-negative bacilli, monotherapy has been recommended, particularly when the causative microorganism is identified [10–14].

Although initial antibiotic regimens are sometimes modified during the course of the infection, as far as we are aware the frequency of the changes and the reasons for changing empiric antibiotic therapy in patients with pneumonia acquired in hospital have not been previously reported in the literature. The aim of this study was to assess the cause of changes to empiric antibiotic therapy during treatment of pneumonia acquired in the ICU based on data obtained from a Spanish multicenter study.

Patients and methods

Between November 1988 and October 1989, all patients admitted to any medical or surgical ICU in 30 different hospitals in Spain were prospectively followed up for 72 h after discharge from the ICU. Patients were included in the study if they developed ICU-acquired pneumonia and fulfilled the Centers for Disease Control (CDC) definitions for nosocomial infection [15]. Clinical suspicion of pneumonia was based on the presence of one or more of the following criteria: (1) new and/or progressive chest X-ray infiltrates, purulent secretions, fever, leukocytosis or leukopenia; (2) new and/or persistent chest X-ray infiltrates, positive blood culture, and absence of another primary focus; (3) progression of chest X-ray infiltrates, recurrence of fever, and increase in purulent secretions; and (4) bilateral chest X-ray infiltrates, positive cultures of blood or pleural fluid for the same microorganism as that isolated from respiratory secretions. Pneumonia was considered to have been acquired in the ICU when: (1) diagnosed at least 48 h after admission to the ICU and not present in the incubation period before admission, or (2) diagnosed within 72 h of discharge from the ICU.

The etiological diagnosis of pneumonia was established if at least two cultures of sputum or endotracheal aspirates were positive for the same pathogen; quantitative cultures of protected-brush specimens yielded 10^3 colony-forming units (CFU) /ml; quantitative cultures of bronchoalveolar lavage yielded 10^5 CFU/ml; isolation of definite pathogens such as *Legionella* spp; positive blood or pleural fluid cultures for the same microorganism isolated from respiratory secretions; histopathological evidence of pneumonia; positive serology for *Legionella pneumophila* (fourfold increase in dilution titer over time).

The patient's underlying condition was classified according to grades described by McCabe and Jackson [16]. The severity of illness was assessed at the time of admission to the ICU and pneumonia was assessed by means of the Acute Physiology and Chronic Health Evaluation (APACHE II) score [17]. Previous antibiotic use was defined as intravenous antibiotic administration for more than 24 h prior to the diagnosis of pneumonia.

Empirical antibiotic therapy was initially instituted according to the criteria of physicians in charge in each hospital. No common therapeutic regimens were recommended in any case. The reasons for subsequent changes in antibiotic treatment included poor clinical response, microorganism not covered by antibiotic treatment, or detection of a resistant strain during treatment. Poor clinical response was defined as the persistence and/or worsening of clinical signs or symptoms of pneumonia 72 h after treatment was initiated. "Uncovered" microorganism was considered when isolated microorganisms were not susceptible to any of the antibiotics administered. Appropriate antibiotic coverage was considered when at least one effective drug was included in the antibiotic treatment. Modification of empirical antibiotic treatment was made independently of the patients' clinical response; therefore, it was possible that a patient with a good clinical response and an "uncovered" organism in cultures had a change in treatment.

Shock was considered in a patient with a systolic blood pressure of < 90 mmHg or there was a decrease of > 30 mmHg in a hypertensive patient associated with signs of systemic hypoperfusion (lactic acidosis, oliguria or altered consciousness). Disseminated intravascular coagulation was defined as a platelet count of $< 10 \times 10^9$/l, a decrease in serum fibrinogen levels, a prolonged prothrombin time, thrombin time and partial thromboplastin time, and an increase in serum levels of fibrin degradation products. Acute renal failure was defined as a serum creatinine concentration of > 2 mg/100 ml or a 50% reduction in previous creatinine clearance. Respiratory failure was considered when a $FIO_2 > 0.6$ and/or a positive end-expiratory pressure of > 10 cmH_2O was needed to maintain a $PaO_2 > 60$ mmHg. Multiple organic failure syndrome was defined by three or more organ system failures during the course of pneumonia. Septic metastatis was defined by the development of a septic complication other than the source of infection that was not present at the time of diagnosis of pneumonia.

Evolution was classified as "resolution" (disappearance of clinical manifestations during treatment and no recurrence within 48 h after antibiotics were withdrawn), "attributable mortality" (death associated with the occurrence of pneumonia-related complications), and "crude mortality" (death due to any cause).

Statistical analysis

Student's *t*-test, the Mann-Whitney test for continuous variables and the chi-square test (Fisher exact test when needed) for discrete data were used. The nonparametric Wilcoxon signed rank test was used to compare scores of severity because the distribution of data departed from normal. For comparisons between groups with empirical treatment (yes/no), and changes in empirical treatment (yes/no), we used a bivariate analysis including Mantel–Haenszel statistics, levels of significance, the relative risks and their confidence intervals. All univariate associations with $p < 0.10$ were tested using logistic regression to identify variables independently associated with changes in empirical antibiotic treatment. For multivariate analysis, a forward stepwise logistic regression procedure was used with $p < 0.05$ as a limit for entering or removing new terms. The dependent variable was the presence or absence of antibiotic changes. The following variables were tested in the logistic regression model: number of empiric antibiotics (one or $>$ one), previous use of antibiotics (yes/no), uncovered microorganism (yes/no), duration of mechanical ventilation prior to pneumonia (< 5 or > 5 days), and respiratory infection on admission (yes/no). Collinearity was assessed by means of a correlation matrix. No factors in the models correlated. As for influential observations, no patients with outlier values in any variable were detected. All reported *p* values are two-tailed [18].

Results

Of all the patients ($n = 16\,872$) admitted to the ICU during the study period, 530 developed 565 episodes of pneumonia. The incidence of ICU-acquired pneumonia was 3.3/100 ICU discharges. Incidence rates for the different participating ICUs varied between 0.53 and 7.69%. The overall incidence in patients on mechanical ventilation for more than 24 h was 8.7%. The mean length of hospital stay for all patients was 7.26 ± 2.1 days compared with 18.9 ± 13.1 days for patients with pneumonia.

The diagnosis of pneumonia was established by culture of sputum or endotracheal aspirates in 57.7% of the cases, protected-brush specimens in 19.6%, blood samples in 10.6%, bronchoalveolar lavage in 9.2%, and pleural fluid in 3.9%. Positive serological tests were obtained in 0.7% of the cases.

Of the 565 episodes of pneumonia, 490 (86.7%) were initially treated with empirical antibiotics, 56 were treated when results of antibiotic sensitivity testing were available, and in the remaining 19 no antibiotics were given (either because the diagnosis was made at autopsy or the patient was in a terminal phase). In the univariate analysis, empirical antibiotic treatment was significantly associated with a first episode of pneumonia ($p = 0.017$), a non-fatal underlying condition ($p < 0.001$), fewer days on mechanical ventilation before the diagnosis of pneumonia ($p < 0.001$), absence of diffuse chest X-ray infiltrates ($p = 0.049$), presence of unilateral chest X-ray infiltrates ($p = 0.023$), and shorter length of hospital stay before the first episode of pneumonia ($p = 0.027$) (Table 1).

In the 490 empirically treated episodes of pneumonia, a total of 894 antibiotics were administered (Table 2). The drugs most frequently used were amikacin, tobramycin, ceftazidime, and cefotaxime, which accounted for 47% of all antimicrobials prescribed. In the 135 (27.6%) cases of monotherapy, ciprofloxacin, imipenem/cilastatin and cefotaxime were most commonly used. A combination of two antibiotics was given in 306 (62.4%) cases, the most frequent being combinations of third-generation cephalosporins with aminoglycosides (41.8%) and ureidopenicillins with aminoglycosides (17.6%). Finally, three antibiotics were administered in 49 (10%) episodes of pneumonia. Vancomycin (34.7%), cloxacillin (30.6%) and clindamycin (20.4%) were the agents most frequently combined with two other agents.

The initial regimen was modified in 214 (43.7%) of the 490 episodes of empirically treated pneumonia (Table 3). In the remaining 276 episodes in which the

Table 1 Patients' characteristics according to the type of therapeutic regimen in 565 episodes of ICU-acquired pneumonia. Values expressed as means ± standard deviation

	Empirically treated ($n = 490$)	Not empirically *treated* ($n = 75$)	p value
Age[a]	47.75 ± 19.72	49.64 ± 18.26	NS
APACHE II at ICU admission	17.49 ± 6.15	17.95 ± 7.03	NS
APACHE II at diagnosis	17.34 ± 6.14	18.02 ± 6.53	NS
Attributable mortality	92(18.8%)	21 (28.0%)	NS
Crude mortality	153 (33.5%)	33 (44.0%)	NS
Diagnostic criteria			NS
X-ray plus clinical features	375 (76.5%)	54 (72.0%)	
2nd episode of pneumonia	71 (14.5%)	15 (20.0%)	
X-ray plus blood culture	28 (5.7%)	1 (1.3%)	
Blood culture plus pulmonary microbiology	13 (2.7%)	3 (4.0%)	
Mechanical ventilation	448 (91.4%)	71 (94.7%)	NS
MV prior to pneumonia (days)	9.18 ± 9.82	14.38 ± 14.99	< 0.001
First episode of pneumonia ($n = 529$)	466 (95.1%)	63 (84.0%)	0.017
Days in hospital prior to 1st episode	13.43 ± 14.27	17.73 ± 18.86	0.027
Diffuse X-ray infiltrates	196/489 (40.1%)	42/73 (57.6%)	0.049
Unilateral X-ray infiltrates	290/489 (59.3%)	33/73 (45.2%)	0.023
Nonfatal underlying disease	361/467 (77.3%)	41/72 (56.9%)	< 0.001
Previous antibiotic use	337 (68.8%)	58/73 (79.4%)	NS
Surgery	162 (33.1%)	19/73 (26.0%)	NS
Neoplasia	35 (7.1%)	6/73 (8.2%)	NS
Immunosuppressive treatment	140 (28.6%)	22/73 (30.1%)	NS
Respiratory infection at ICU admission	70 (14.3%)	16/73 (21.9%)	NS

[a] Calculated for 530 patients (empirically treated, $n = 457$; not empirically treated, $n = 73$)

Table 2 Antibiotics used for initial empiric therapy in 490 episodes of ICU-acquired pneumonia

Agent	Monotherapy ($n = 135$)	Two drugs ($n = 306$)	Three drugs ($n = 49$)	Total ($n = 490$)
Amikacin		98	22	120
Tobramycin	3	91	16	110
Ceftazidime	8	68	20	96
Cefotaxime	21	72	3	96
Piperacillin	6	46	6	58
Gentamicin	2	49	3	54
Ciprofloxacin	31	18	3	52
Imipenem	26	16	2	47
Vancomycin	2	17	17	36
Netilmicin		26		26
Clindamycin		15	10	25
Cloxacillin		7	15	22
Cefuroxime	7	11	3	21
Cefoxitin	5	12	3	20
Aztreonam	3	10	2	15
Azlocillin	2	11	2	15
Erythromycin	1	6	6	13
Others	15	39	14	68

initial regimen was not modified, 34 episodes were excluded from the analysis because the patient died within 48 h of initiation of empirical antibiotic therapy. In the univariate analysis, modification of initial therapy was significantly associated with an uncovered microorganism ($p < 0.0001$), administration of more than one drug ($p = 0.0011$), previous antibiotic use ($p = 0.0018$), more days on assisted ventilation prior to the diagnosis of pneumonia ($p = 0.0226$), and respiratory infection on admission ($p = 0.059$) (Table 3).

In the 214 episodes of pneumonia in which initial empiric antibiotic therapy was changed, isolation of

Table 3 Characteristics of the study population according to modification of initial empiric antibiotic therapy in 456 episodes of ICU-acquired pneumonia. Values expressed as means ± standard deviation

	Change of empiric antibiotics ($n = 214$)	No change of empiric antibiotics ($n = 242$)	p value
Age	46.19 ± 19.8	48.71 ± 19.3	NS
APACHE II at ICU admission	17.87 ± 6.0	17.00 ± 6.3	NS
APACHE II at diagnosis	17.39 ± 5.8	17.24 ± 6.5	NS
Attributable mortality[a]	38/207 (18.4%)	43/237 (18.1%)	NS
Crude mortality[a]	63/207 (30.4%)	76/237 (32.1%)	NS
Diagnostic criteria			NS
X-ray plus clinical features	157 (73.4%)	190 (78.5%)	
2nd episode of pneumonia	35 (16.4%)	31 (12.8%)	
X-ray plus blood culture	16 (7.5%)	10 (4.1%)	
Blood culture plus pulmonary microbiology	5 (2.3%)	8 (3.3%)	
Mechanical ventilation	201 (93.9%)	218 (90.1%)	NS
MV prior to pneumonia (days)	9.44 ± 8.44	9.21 ± 11.15	0.023
First episode of pneumonia	199 (93.0%)	233 (96.3%)	NS
Days in hospital prior to 1st episode	13.56 ± 13.31	13.45 ± 14.42	NS
Diffuse X-ray infiltrates	90/213 (42.3%)	92/241 (38.2%)	NS
Unilateral X-ray infiltrates	117/213 (454.9%)	150/241 (62.2%)	NS
Nonfatal underlying disease	153 (71.5%)	181 (74.8%)	NS
Previous antibiotic use	161 (75.2%)	149 (61.6%)	0.002
Surgery	75 (35.0%)	74 (30.6%)	NS
Neoplasia	13 (6.1%)	21 (8.7%)	
Corticoids	67 (31.3%)	63 (26.0%)	NS
Antibiotic therapy			0.001
Monotherapy	50 (23.4%)	79 (32.6%)	
Two antibiotics	139 (65.0%)	146 (60.3%)	
Three antibiotics	25 (11.7%)	17 (7.0%)	
Respiratory infection at ICU admission	37 (17.3%)	27 (11.2%)	0.059
Inappropriate antibiotic coverage ($n = 365$)	128/190 (67.4%)	15/175 (8.6%)	< 0.0001

[a] Calculated for 444 patients (change of empiric therapy in 207; no change of empiric therapy in 237)

Table 4 Reasons for changing initial empiric antibiotic therapy in 214 episodes of ICU-acquired pneumonia in relation to the number of agents administered

Reason for changing	Monotherapy ($n = 50$)	Two drugs ($n = 139$)	Three drugs ($n = 25$)	Total ($n = 214$)
Poor clinical response	26	44	7	77
Microorganism not covered	29	96	8	133
Resistance during treatment	1	11	2	14
Other reasons	3	13	9	25
Total[a]	59	164	26	249

[a] More than one reason for changing initial empiric antibiotic therapy in 35 episodes of ICU-acquired pneumonia

uncovered microorganisms was the most frequent reason for modifications (62.1%), followed by poor clinical response (36%) and detection of a resistant strain during treatment (6.6%). In 35 cases there were two reasons for modification of empirical therapy. With regard to the number of antimicrobials given, a change to other agents occurred significantly less frequently when monotherapy was given ($p = 0.0107$) (Table 4).

The multivariate analysis showed that the presence of uncovered microorganisms (RR 22.02; 95% CI 11.54 to 42.60; $p < 0.0001$), the administration of more than one drug (RR 1.29; 95% CI 1.02 to 1.65; $p = 0.021$), and previous use of antibiotics (RR 1.22; 95% CI 1.08 to 1.39; $p = 0.0018$) were individual factors associated with modification of initial empirical antibiotic therapy.

Among the 565 episodes of ICU-acquired pneumonia, the appropriateness of antibiotic treatment was assessed in 430 cases (no diagnosis in 116, no treatment with antibiotics in 19). Antibiotic coverage was considered appropriate in 284 episodes and inappropriate in 146 (34%). Coverage in relation to the number of

Table 5 Most frequently isolated microorganisms in 565 episodes of ICU-acquired pneumonia according to appropriate or inappropriate antibiotic coverage

Microorganism isolated	Total no.	Appropriate antibiotic	Inappropriate antibiotic	Not covered by antibiotic (%)
Pseudomonas aeruginosa	174	110	64	36.8
Staphylococcus aureus	102	72	30	29.4
Acinetobacter spp	56	28	28	50.0
Klebsiella spp	21	19	2	9.5
Streptococcus pneumoniae	21	18	3	14.3
Haemophilus influenzae	21	20	1	4.8
Escherichia coli	16	12	4	25.0
Enterobacter spp	16	8	8	50.0
Proteus mirabilis	15	11	4	26.7
Serratia marcescens	14	9	5	35.7

Table 6 Pneumonia-related complications and mortality in relation to appropriate or inappropriate antibiotic coverage

	Appropriate ($n = 284$)	Inappropriate ($n = 146$)	p value
Attributable mortality	46 (16.2%)	36 (24.7%)	0.0385
Crude mortality	92 (32.4%)	51 (34.9%)	NS
No. of complications per patient	1.73 ± 1.82	2.25 ± 1.98	< 0.001
Shock	17.1%	28.8%	< 0.005
Disseminated intravascular coagulation	2.1%	3.4%	NS
Renal failure	18.9%	22.6%	NS
Barotrauma	8.9%	8.9%	NS
Respiratory failure	24.9%	32.2%	NS
Empyema	3.6%	4.1%	NS
Septic metastases	3.6%	1.4%	NS
Extrapulmonary infection	13.2%	17.1%	NS
Cavitation	1.8%	3.4%	NS
Gastrointestinal bleeding	10.7%	21.2%	= 0.003
Multiple organ failure	12.5%	21.2%	NS

antibiotics ranged from 73.2% for monotherapy to 61.2% and 76.9% for treatment with combinations of two or three antibiotics, respectively ($p = 0.039$). The pathogens not covered by antibiotic treatment are shown in Table 5.

Episodes of pneumonia with inappropriate antibiotic coverage had a significantly higher attributable mortality and number of related complications (particularly shock and gastrointestinal bleeding) than those with appropriate coverage (Table 6).

Discussion

The main finding of the study is that empirical antibiotic treatment for pneumonia acquired in the ICU was modified in 43.7% of cases. Unfortunately, to our knowledge there are no studies that allow comparison with this result.

The incidence of ICU-acquired pneumonia in our study (3.3%) is lower than that reported in studies with selected populations (e.g., > 48 h of mechanical ventilation, type of underlying disease, length of stay in ICU > 72 h, etc.). In our study, all ICU patients prospectively followed up during the study period were included in the calculation of the incidence rate. However, in patients mechanically ventilated for more than 24 h, our incidence rate was 8.7%. In a European multicenter study, in which patients with pneumonia at the time of admission to the ICU were excluded, incidence rates of 12.6% versus 4.6% were found according to the need for mechanical ventilation on admission to the ICU [19]. In patients admitted to the ICU for more than 72 h, Joshi et al. [20] reported pneumonia in

12.8%. Wenzel et al. [21], in a 5-year surveillance in one hospital, reported pneumonia in 9% of patients admitted to burns units, in 0.5% admitted to coronary units and in 1.5% to 2.5% admitted to the remaining medical or surgical ICUs.

As expected, initial empiric treatment was established in 86.7% of the patients. In the remaining patients, no such treatment was initiated because of fatal underlying disease, presence of diffuse or bilateral chest X-ray infiltrates, a firm diagnosis after 10 days of mechanical ventilation, and a second or third episode of pneumonia. These factors occur more frequently in patients in whom the diagnosis of pneumonia is more difficult to make [22].

Although some monotherapies were inappropriate, especially those including aminoglycosides, it should be noted that the selection of initial agents was based on the criteria of the physicians participating in this multicenter study. Nevertheless, a change in initial empirical antibiotic therapy was significantly associated with the administration of more than one drug.

The administration of aminoglycosides in combination with other antimicrobials, in particular third-generation cephalosporins or ureidopenicillins, has been the regimen most widely used over the past few years [9, 10]. In the present study, aminoglycosides were included in over 75% of combined empiric antibiotic regimens. These results are in accordance with those reported by Fagon et al. [23], who analyzed the treatment of nosocomial pneumonia in the patients of seven physicians from the same institution and found that in 77% of cases an aminoglycoside plus a second- or third-generation cephalosporin, or vancomycin, or both, was indicated as initial empirical antibiotic therapy. However, the role of aminoglycosides is still controversial. The aim of its use is to increase the antimicrobial spectrum in order to delay the emergence of resistant bacterial strains and to promote synergism with other antibiotics. Nevertheless, when aminoglycosides are used as monotherapy, a high incidence of failure has been observed despite its adequate in vitro activity [24]. Reasons for the lack of efficacy of aminoglycosides include inadequate serum concentrations in critically ill patients [25], poor alveolar penetration in the range 10–45% of serum concentrations, which leads to low minimal inhibitory concentrations for most of Enterobacteriaceae and nonfermenting gram-negative bacilli, and decreased activity of acidic pH. Pennington [26] found an eightfold reduction in aminoglycoside activity when pH decreased from 7.4 to 6.4. According to Bodem et al. [27], the pH of bronchial secretions in patients with pneumonia is about 6.5. On the other hand, Moore et al. [28] showed an association between serum concentrations of aminoglycosides during the first 24 h of treatment and therapeutic success in pneumonia caused by gram-negative microorganisms. Despite arguments against the use of aminoglycosides, a recent multicenter study [11], in which ciprofloxacin and imipenem were randomly administered as monotherapy, showed that these regimens were unable to eradicate nonfermenting gram-negative bacilli. At present, the combination of two or more agents that include an aminoglycoside can be recommended, especially when *Pseudomonas aeruginosa* or *Acinetobacter* spp. are the organisms involved.

The most common reason for modifying the initial empirical antibiotic therapy was isolation of microorganisms not covered by the treatment. This occurred in 62% of cases and was mostly attributable to isolation of *Acinetobacter* spp., *Enterobacter* spp., *Serratia* spp., and *P. aeruginosa*. These microorganisms are common agents in nosocomial infections and are associated with the development of late-onset pneumonia [29] and prior antibiotic treatment [30]. Fagon et al. [23] showed that 33% of 133 empirical therapeutic regimens were inappropriate. In most of the cases this was due to failure to establish the diagnosis of pneumonia and hence not treating it. On the other hand, when pneumonia was correctly diagnosed, the failure rate was 46.9% [23]. The failure rate in the present study was 43.7%.

Conclusions

In a high percentage of patients with ICU-acquired pneumonia their initial empiric antibiotic treatment had to be modified. The main reason for the change was inadequate antibiotic coverage of microorganisms. Although it has recently been proposed that invasive procedures improve the isolation of causative organisms, these techniques do not represent an accepted standard for routine use and need validation that they actually improve outcome and survival [31, 32]. Further work should be directed toward the development of rapid and accurate methods for the diagnosis of nosocomial pneumonia in order to allow antibiotics to be given as soon as a diagnosis of pneumonia is made. At present, antibiotic therapy is based on speculative knowledge.

Acknowledgements The authors are indebted to M. El-Ebiary, M.D., for reviewing this article and helpful suggestions, and to Marta Pulido, M.D., for editing the manuscript and editorial assistance.

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