Pneumonic vs Nonpneumonic Acute Exacerbations of COPD*

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Study objective: To describe and compare the background, clinical manifestations, disease course, and infectious etiologies of pneumonic acute exacerbations (PNAE) vs nonpneumonic acute exacerbations (NPAE) of COPD.
Design: A prospective, observational study.
Setting: A tertiary university medical center in southern Israel.
Patients: Twenty-three hospitalizations for PNAE and 217 hospitalizations for NPAE were included in the study. Paired sera were obtained for each of the hospitalizations and were tested serologically for 12 pathogens. Only a significant change in antibody titers or levels was considered diagnostic.
Results: No significant differences were found between the two groups for any of the parameters related to COPD or comorbidity. The clinical type of the exacerbation was not significantly different between the groups. Compared to NPAE, patients with PNAE had lower Po_2 values at hospital admission ($p = 0.004$) but higher rates of abrupt onset ($p = 0.005$), ICU admissions ($p = 0.006$), invasive mechanical ventilation ($p = 0.01$), mortality ($p = 0.007$), and longer hospital stay ($p = 0.001$). In 22 PNAE hospitalizations (96%) and in 153 NPAE hospitalizations (71%), at least one infectious etiology was identified ($p = 0.001$). Mixed infection was found in 13 patients with PNAE (59%) and in 59 patients with NPAE (39%; not significant [NS]). Viral etiology was identified in 18 patients with PNAE (78%) compared with 99 patients with NPAE (46%; $p = 0.003$). Pneumococcal etiology was found in 10 patients with PNAE (43%) and in 38 patients with NPAE (18%; $p = 0.006$). An atypical etiology was identified in 8 patients with PNAE (35%) and 64 patients with NPAE (30%; NS).
Conclusions: Community-acquired pneumonia is common among patients hospitalized for an acute exacerbation of COPD and is generally manifested by more severe clinical and laboratory parameters. In PNAE, compared to NPAE, viral and pneumococcal etiologies are more common, but the rate of atypical pathogens is similar. The therapeutic significance of these findings should be investigated further. *(CHEST 2002; 122:1264–1270)*

Key words: COPD; exacerbation; pneumonia, community-acquired

Abbreviations: AECOPD = acute exacerbation of COPD; CAP = community-acquired pneumonia; NPAE = non-pneumonic acute exacerbations; NS = not significant; PNAE = pneumonic acute exacerbations

COPD is a common disease. Over the prolonged, chronic course of the disease, episodes of acute exacerbation often occur. These episodes have a deleterious effect on the patient's quality of life and necessitate utilization of health-care services, including hospitalization some of the time. Although the definition of an acute exacerbation of COPD (AE-COPD) is problematic,[1] it is generally diagnosed and categorized on the basis of clinical criteria of increasing shortness of breath, and/or an increase in the

amount or purulence of sputum.[2] Community-acquired pneumonia (CAP) is an infectious disease with a broad spectrum of severity. Among CAP patients with the highest severity of disease who require hospitalization, COPD is the most common comorbidity.[3–5]

These two diagnoses, CAP and AECOPD, come together when COPD patients acquire AECOPD

caused by CAP. The clinical manifestations of these episodes meet the accepted criteria for the diagnosis of AECOPD, and CAP is determined only in those cases in which a chest radiograph is obtained and a pulmonary infiltrate is found. The number of published articles on CAP in patients with COPD is very small. In a prospective, multicenter Spanish study, 124 hospitalizations for CAP among patients with COPD were investigated.[6] Despite the importance of this study, the acute episodes were investigated from the viewpoint of CAP and not AECOPD, so there was no comparison between these cases and cases of AECOPD without CAP.

In the context of a large study on infectious etiologies in patients hospitalized with AECOPD, a database was created for 240 hospitalizations and a broad range of infectious etiologies, which were diagnosed serologically in these hospitalizations. The frequency distribution of all infectious etiologies found in that study have been presented and discussed in a previous publication.[7] The aim of the present study was to use the same database to evaluate episodes of CAP in patients with COPD from the aspect of AECOPD, by describing and comparing the background, clinical manifestations, diseases course, and infectious etiologies of these episodes in patients with pneumonic acute exacerbations (PNAE) and nonpneumonic acute exacerbations (NPAE) of COPD.

MATERIALS AND METHODS

Patients

All patients hospitalized for AECOPD during the period between November 1, 1997, and March 15, 1999, in the internal medicine and intensive care wards of the Soroka Medical Center in Beer-Sheva, Israel, who met the inclusion criteria, and gave consent to participate, were included in the study. All first hospitalizations in the study period were included as well as repeat hospitalizations for AECOPD of patients in the study population, if the hospitalization took place at least 6 months after the initial one for which the patient was recruited into the study. No more than one repeat hospitalization was included in the study data for any particular patient. The study was approved by the Helsinki Committee for research on human beings of the Soroka Medical Center, and all participants gave informed consent to participate.

Inclusion criteria for the study group were the fulfillment of all the following five conditions: (1) age > 40 years; (2) chronic airway obstruction as determined by spirometry (6 months prior to hospitalization or within 1 to 2 months following hospitalization) with an FEV_1 value < 70% of expected and an FEV_1/FVC ratio < 0.7; (3) smoking history of at least 20 pack-years; (4) increased shortness of breath, a significant increase in sputum production, or a new expectoration of purulent sputum or increased sputum purulence in the week prior to hospitalization; and (5) no hospitalizations during the 3-week period prior to the present hospitalization.

Study Protocol

All patients with AECOPD were hospitalized by decision of the emergency department physicians, without intervention on the part of the investigators. Every 24 to 48 h, a research assistant visited each of the internal medicine and intensive care wards and identified patients hospitalized in the interim who met the inclusion criteria for the study. After the patient agreed to participate in the study, he or she was interviewed concerning their respiratory disease and the regular treatment they received for it, smoking habits, and complaints and symptoms of their current acute episode. During the first meeting, a blood sample of 5 mL was drawn for serologic testing. The blood sample was centrifuged shortly after being drawn, and the serum was frozen at a temperature of − 20°C until serologic tests were conducted. Additional relevant medical and administrative data were collected from the medical records.

On discharge from hospitalization, the patient was invited to a follow-up appointment at the pulmonary clinic of the Soroka Medical Center 3 to 5 weeks after admission to the hospital. At that clinic, follow-up data were collected on the course of the convalescence and abnormal events that may have occurred following discharge from the hospital. At this meeting, an arterial blood sample was obtained at ambient pressure and spirometry was performed. Each of the patients had a second (convalescence-phase) serum sample obtained at this meeting for serologic testing. This sample was handled in exactly the same manner as the previous acute-phase sample. Patients whose hospitalization period extended for > 3 weeks, or who were rehospitalized at the time of scheduled follow-up appointments, had the serum sample drawn during the hospitalization. Patients who were not considered to be in stable condition at the first follow-up appointment (3 to 5 weeks after hospitalization) were invited to an additional follow-up appointment including spirometry and arterial blood gas testing a month later.

Spirometry and Arterial Blood Gases

In order to analyze the results of the spirometric measurements with the patients in stable respiratory condition as well as to diagnose permanent obstructive disturbances by spirometry as an inclusion criterion, the definitive spirometry was conducted for these purposes, in the vast majority of patients, at the clinic follow-up appointment 3 to 5 weeks after hospitalization. When the test could not be performed at this occasion, or when the patient was not in stable condition, the criteria for permanent airway obstruction was assessed on the basis of previous spirometry performed on the patient, in stable condition, within 6 months prior to hospitalization, or at a further follow-up 1 month later. Patients in whom spirometry at the follow-up did not demonstrate a sufficient degree of airway obstruction were withdrawn from the study. In patients who underwent more than one spirometric test during the period beginning 6 months before hospitalization and ending 2 months after discharge, the best result was used. All spirometric tests were conducted by an experienced technician using the Vitalograph Compact instrument (Vitalograph, Buckingham, UK), which was calibrated at the beginning of each work day. Predicted values of FEV_1 were calculated in accordance with accepted European values.[8]

Arterial blood gas determinations presented in the "Results" were also conducted with the patient in stable condition and were obtained at the same time the definitive spirometry test was done. Arterial blood was obtained by puncturing the brachial or radial artery, and it was tested immediately with the Blood Gas System 520 (Radiometer; Copenhagen, Denmark).

Radiographic Diagnosis of Pneumonia

In each hospitalization, a chest radiograph was obtained while the patient was still in the emergency department. For study purposes, each week all radiographs were analyzed separately by a senior pulmonologist and a senior radiologist. All radiographs that were interpreted by at least one of the experts as pneumonia were classified, at this stage, as "suspected pneumonia," and only those patients underwent repeat radiographs at the clinic follow-up 3 to 5 weeks after hospitalization. The paired radiographs of these patients (acute phase and convalescence phase) were again interpreted separately by the same experts. Pneumonia was diagnosed only if both experts independently reported a pulmonary infiltrate in the acute-phase radiograph that disappeared or retreated significantly in the follow-up radiograph. Those cases in which the two experts did not agree were not considered pneumonia for the purpose of the study. In patients who died in the hospital, pneumonia was diagnosed by the presence of a typical infiltrate on the admission chest radiograph that was not present in a previous radiograph.

Etiologic Tests

The etiologic workup in this study was based exclusively on serologic testing. Serologic tests were conducted to identify 12 pathogens known to be infectious agents in the upper and lower respiratory tract that can be diagnosed by serologic methods. The paired sera for each patient were tested in the same run in all cases. Serologic tests for seven respiratory tract viruses, *Mycoplasma pneumoniae*, *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis* were conducted using the enzyme immunoassay method. Microimmunofluorescence serology was used for identification of Legionella spp. Only a significant change in the antibody level or titer for a specific pathogen between the acute-phase and convalescence-phase serum samples was considered diagnostic for infection with that pathogen. In light of this requirement, only patients for whom paired sera were obtained were included in the final data analyses. The methods, kits, and criteria used for serologic diagnoses were described in detail in our previous publication.[7]

Data Analysis

The results were analyzed using statistical software (Epi Info, Epidemiology Program Office, Centers for Disease Control and Prevention, Atlanta, GA). The χ^2 test or its equivalent served to compare proportions between groups, and analysis of variance was done to compare continuous variables among two or more groups. Statistical significance was set at $p < 0.05$.

Results

The study consisted of 250 hospitalizations for AECOPD among 219 different COPD patients during the 16.5-month period. In 241 cases (96.4%), a convalescence-phase serum sample was obtained at a mean $\pm$ SD interval of 24.7 ± 5.6 days (range, 17 to 53 days) after the first sample was obtained at the beginning of the hospitalization. Since the etiologic diagnoses in this study were based on changes in antibody level/titer between the acute-phase and convalescence-phase sera, we did not include in the final analyses of the study the nine hospitalizations for which no convalescence-phase serum was obtained. One other hospitalization was not included because we found a polyclonal response to all of the pathogens tested. In all, 240 hospitalizations of 213 patients were included in the final analyzed study population. In all 240 hospitalizations, the patients were treated during the course of their hospitalization with systemic corticosteroids.

In 37 hospitalizations (15%), chest radiographs were classified by acute-phase imaging as suspected pneumonia, but only 28 of these radiographs (12%) were classified as "pneumonia" by one of the experts on the basis of the paired radiographs (acute phase and convalescence phase). In 23 hospitalizations (10%), paired chest radiographs were classified by the two examiners as pneumonia and were considered such for study purposes. These 23 hospitalizations were for 23 different patients, who were designated as the "PNAE group" of the study. In 13 patients, the pneumonia was right sided; in 8 patients, it was left sided; and in 2 patients, it was bilateral. In 13 patients, the pneumonic infiltrate was homogeneous; in 10 patients, it was nonhomogenous; and in 3 patients, more than one lobe was involved in the pneumonic process. The other 217 hospitalizations were among 190 different patients with COPD, who were designated as the "NPAE group" of the study.

Table 1 presents a comparison of data between the 23 patients with PNAE and the 190 patients with

Table 1—Comparison of Data Between the Pneumonic AECOPD and Nonpneumonic AECOPD Groups*

Variables	Pneumonic AECOPD (n = 23)	Nonpneumonic AECOPD (n = 190)	p Value
Male gender	18 (78)	161 (85)	NS
Mean age, yr	66.4 ± 9.6	67.2 ± 8.7	NS
Baseline FEV_1, % of expected†	41.6 ± 17.6	40.7 ± 16.4	NS
Baseline Po_2, mm Hg†	65.2 ± 11.4	67.8 ± 13.1	NS
Baseline Pco_2, mm Hg†	45.7 ± 9.2	44.8 ± 9.4	NS
Home oxygen	10 (43)	72 (38)	NS
Chronic oral steroid therapy	3 (13)	59 (31)	NS
Complications of COPD‡	17 (74)	116 (61)	NS
Influenza vaccination	6 (26)	80 (42)	NS
Pneumococcal vaccination	4 (17)	25 (13)	NS
Diabetes mellitus	8 (36)	55 (29)	NS
Ischemic heart disease	2 (9)	38 (20)	NS
Left-sided heart failure	1 (4)	17 (9)	NS

*Data are presented as No. (%) or mean ± SD.
†Baseline FEV_1, Po_2, and Pco_2 values were determined 6 months prior to hospitalization, or within 1 to 2 months posthospitalization, at room air with the patient in stable condition.
‡Documentation of at least one of the following: chronic hypoxemia ($Po_2 < 60$ mm Hg), hypercapnea ($Pco_2 > 50$ mm Hg), polycythemia (hematocrit $> 50\%$), pulmonary hypertension (> 40 mm Hg).

NPAE. These include demographic data, baseline spirometry, and arterial blood gas test results in patients in stable condition, rate of chronic steroid therapy, rate of COPD complications, rates of influenza and pneumococcal vaccination, and rates of chronic comorbidity. No significant difference was observed for any of these variables between the two groups.

Table 2 presents a comparison of clinical expressions of the exacerbation and arterial Po_2 and Pco_2 levels at admission between the two study groups. Compared to the NPAE group, the PNAE group had significantly higher rates of abrupt onset of acute exacerbation, fever during the acute exacerbation, crepitations on lung auscultation, and severe hypoxemia. There was no significant difference in the distribution of the exacerbations according to the classification of Anthonisen et al[2] between the two groups, but there was a clear trend to a higher rate of type 1 exacerbation in then PNAE group.

Table 3 presents a comparison of the rates of invasive mechanical ventilation, admission to intensive care, duration of hospitalization, mortality, and the course of recovery following discharge from the hospital between the two groups. In all of the first four parameters, which are markers of severity of the acute exacerbation, the PNAE group had significantly more severe results. In contrast, no significant difference was found between the two groups in the

two parameters that relate to the course of recovery from the acute exacerbation following discharge from the hospital.

In 22 of the PNAE hospitalizations (965) and in 153 of the NPAE hospitalizations (71%), at least one infectious etiology for the AE was identified by serologic testing. There was a significantly higher rate of viral etiologies in the PNAE group, especially in relation to parainfluenza virus type 2 and adenovirus. The PNAE group also had a significantly higher rate of bacterial etiologies, particularly pneumococcal. There was no difference between the groups in the rate of atypical bacterial etiologies. Compared to the NPAE group, a vary small and significantly lower percentage of patients in the PNAE group had no infectious etiology identified by serologic tests. More than one etiologic agent (mixed etiology) was found in 13 patients with PNAE patients and in 59 patients with NPAE, who represent 59% and 39%, respectively, of the patients in whom at least one etiologic agent was identified (p = not significant [NS]).

In two hospitalizations, blood culture findings were positive at admission. One patient with PNAE had a blood culture finding positive for *S pneumoniae* and also had a positive serology for that pathogen. This patient also had positive serologic test results for parainfluenza virus type 1, adenovirus, and *M pneumoniae*. One patient in the NAPE group had a blood culture finding positive for *Streptococcus mitis*. In this patient, serologic testing results were also positive for adenovirus (Table 4).

DISCUSSION

The combination of clinical symptoms typical of AECOPD that develop because of CAP brings up the question as to whether it is justified to diagnose such an episode as AECOPD. The name of this

Table 3—Comparison of Hospital Factors Between Pneumonic AECOPD and Nonpneumonic AECOPD Groups*

Variables	Pneumonic AECOPD (n = 23)	Nonpneumonic AECOPD (n = 217)	p Value
Invasive ventilation	4 (17)	10 (5)	0.01
Admission to intensive care	6 (26)	14 (7)	0.006
Mortality	3 (13)	2 (1)	0.007
Hospitalization, d	7.9 [8.3]	4.6 [4.1]	0.001
Readmission	2 (10)	36 (17)	NS
Recovery within 30 d	16 (80)	166 (77)	NS

*Data are presented as No. (%) or No. [SD].

Table 2—Comparison of Clinical Expressions of the Exacerbation and Arterial Po_2, Pco_2, and pH Between the Pneumonic AECOPD and Nonpneumonic AECOPD Groups*

Variables	Pneumonic AECOPD (n = 23)	Nonpneumonic AECOPD (n = 217)	p Value
Clinical type of AECOPD†			
1	16 (70)	110 (51)	NS
2	1 (4)	37 (17)	NS
3	6 (26)	70 (32)	NS
Abrupt onset of exacerbation‡	11 (48)	47 (22)	0.005
Mental status change	3 (13)	12 (6)	NS
Feeling of shaking chills	12 (52)	72 (33)	NS
Fever during exacerbation	21 (91)	148 (68)	0.02
Crepitations on lung auscultation	15 (65)	47 (22)	0.0001
Po_2 at hospital admission (room air)	50.3 [10.3]	56.9 [10.2]	0.004
Pco_2 at hospital admission (room air)	46.5 [15.2]	46.8 [13.9]	NS
PH at hospital admission	7.39 [0.08]	7.39 [0.07]	NS

*Data are presented as No. (%) or No. [SD].
†In accordance with the classification of Anthonisen et al.[2]
‡Development of all symptoms of exacerbation within < 12 h.

Table 4—Comparison of the Frequency Distribution of Infectious Etiologies Between Pneumonic AECOPD and Nonpneumonic AECOPD Groups*

Etiology	Pneumonic AECOPD (n = 23)	Nonpneumonic AECOPD (n = 217)	p Value
Viral agents			
Influenza virus type A	0 (0)	23 (11)	NS
Influenza virus type B	3 (13)	12 (6)	NS
Parainfluenza virus type 1	3 (13)	16 (7)	NS
Parainfluenza virus type 2	9 (39)	29 (13)	0.004
Parainfluenza virus type 3	1 (4)	6 (3)	NS
Adenovirus	5 (22)	15 (7)	0.03
Respiratory syncytial virus	2 (9)	14 (7)	NS
At least one of the above	18 (78)	99 (46)	0.003
Bacterial agents			
S pneumoniae	10 (43)	38 (18)	0.006
H influenzae	3 (13)	7 (3)	NS
M catarrhalis	1 (4)	8 (4)	NS
At least one of the above	10 (43)	48 (22)	0.02
Atypical bacterial agents			
Legionella spp.	5 (22)	35 (16)	NS
M pneumoniae	3 (13)	31 (14)	NS
At least one of the above	8 (35)	64 (30)	NS
Agent not identified	1 (4)	64 (30)	0.001

*Data are presented as No. (%).

article expresses the position we take on this question, even though the issue is controversial. According to American Thoracic Society standards, CAP is not excluded from the diagnosis of AECOPD,[1] but according to the British Thoracic Society guidelines, COPD patients with CAP do not receive a diagnosis of AECOPD.[9] In a recent review of treatment for AECOPD[10] and in other studies related to AECOPD,[11,12] pneumonia was excluded; in the studies by Anthonisen et al[2] and Connors et al,[13] pneumonia was not excluded; and in still another study,[14] only severe pneumonia was excluded. Finally, in one study, pneumonia was listed as excluded, but the study was conducted on an outpatient basis and chest radiographs were not obtained routinely on every patient with AECOPD.[15] This semantic controversy has led to a state in which CAP in a patient with COPD with clinical manifestations of AECOPD will be called pneumonic AECOPD by some and CAP in a patients with COPD by others. Our decision to prefer the approach that does not exclude patients with CAP from the diagnosis of AECOPD stemmed from the two following primary considerations: (1) in a patient in whom the clinical expression of the episode completely meets the accepted criteria for AECOPD and only by chest radiography does one know that CAP is present, there is no justification to eliminate the diagnosis of AECOPD and it is appropriate to note that the patient has a pneumonic exacerbation,

thereby strengthening the therapeutic significance of this combination of events; (2) most AECOPD episodes take place and are treated in the community framework on an outpatient basis.[16] In this framework, chest radiographs are not routinely obtained and exclusion of CAP is not a practical alternative.

The comparison of demographic data and clinical background between the PNAE group and the NPAE group shows that there is no significant difference between them in parameters that reflect the severity of the baseline airway obstruction and baseline gas exchange, nor is there any significant difference between them in chronic comorbidity. In contrast, a statistically significant difference was found in most of the parameters that reflect the clinical and laboratory severity of the acute episode. As expected, this difference demonstrated a more severe exacerbation in the PNAE group. It should be noted that these differences are based on group means. A patient-by-patient analysis of these same parameters shows that a substantial number of patients in the NPAE group had more severe values than some of the PNAE patients. The significance of this finding, in our opinion, is that the clinical and laboratory severity of AECOPD cannot serve as a reliable predictor of CAP in these acute episodes. Similarly, the clinical type of the exacerbation cannot predict whether the acute disease was caused by CAP.

The important finding of this study is the frequency distribution of infectious etiologies in the two groups. The issue of the preferred method to determine the infectious etiology in respiratory infections in general and in CAP and AECOPD in particular is very complicated, and a detailed discussion would be beyond the scope of this article. The factors that brought us to choose the serologic method as the diagnostic method in this study have been detailed and discussed in our previous publication.[7] Among the etiologies tested for, two viruses known to cause infection in patients with COPD are missing. These are coronavirus and rhinovirus (the cause of the common cold). The serologic diagnosis of these two viruses is particularly difficult, so they were not included in this study. However, at least concerning rhinovirus, the rate of patients with COPD with this infection who require hospitalization is very low compared to other viruses.[17] Another respiratory pathogen that is conspicuously missing from the list of etiologies is *Chlamydophila (Chlamydia) pneumoniae*. This pathogen is recognized as an important etiological agent in CAP[18] and was included in the original list of etiologies tested for in this study. However, in the data-analysis stage, there was no case, in any of the 240 hospitalizations, in which the antibody titer for *C pneumoniae* changed signifi-

cantly between the paired sera for any of the antibody types tested. We believe that the feasibility of diagnosing an acute infection with this pathogen on the basis of a high, unchanging titer is particularly problematic in patients with COPD who are known to have a high prevalence of chronic infection with this pathogen, as diagnosed by a high antibody titer.[19] In these circumstances, we preferred to exclude this etiology, despite the obvious problems associated with this solution. It is reasonable to assume that at least some of the patients who were defined in this study as "agent not identified" were infected by one of these pathogens that are missing from the list of etiologies for AECOPD infections.

As expected, pneumococcal etiology, identified in 43% of the PNAE group, was the most common etiology in that group. It is interesting that this rate of 43% for pneumococcal etiology is identical to the rate found in our previous study in which similar methods were used to test 346 hospitalized patients with CAP, only a few of whom were patients with COPD.[20] Even more surprising and interesting is the identity between this finding in the present study and the rate of pneumococcal etiology of 43% reported in the Spanish study that evaluated CAP etiologies in patients with COPD.[6] This identity was found even though that study used a spectrum of diagnostic methods that are totally different from those used in the present study. In our opinion, this identity in the rates of pneumococcal etiology in the two studies lends support to the robustness of the finding. Furthermore, we see in this identity indirect, but convincing, proof of the reliability of the serologic method for diagnosing pneumococcal infections. Comparison of the other findings in our study with the Spanish studies points to a substantial difference in the viral etiologies that were identified in 78% of patients in our study compared to a miniscule rate in the Spanish study. Atypical bacterial agents were also found at much lower rates in the Spanish study compared to ours. Based on our knowledge of the sensitivity of the various methods that were used in both studies, we assume that the differences relating to viral and atypical bacterial etiologies stem from the high sensitivity of the methods used in our study. In addition, a convalescence serum sample was obtained from all patients in our study, which has great importance in the serologic diagnosis of viral and atypical bacterial etiologies.

Two important bacterial etiologies, *H influenzae* and *M catarrhalis*, were identified in this study at much lower rates than previously published studies in which the culture methodology was used to identify causative organisms for AECOPD. In those studies these two bacteria, especially *H influenzae*,

were identified as the predominant organisms. The explanation for these results in the present study is that the immunologic/serologic reaction to these two bacteria is strain specific.[21,22] The serologic assay for the two bacteria utilized antigens derived from non-homologous strains and therefore underestimated the role of infections with these two bacteria in the exacerbations. This limitation of the serologic method in relation to these two bacteria is particularly important from the point of view of the frequency distribution of all etiologies for AECOPD found in our study and for any therapeutic conclusions that may be derived from it.

From the point of view of the frequency distribution of etiologies in the PNAE group compared to the NPAE group, there is a significant difference in prevalence for some of the etiologies, but not to the extent that would justify basing a different therapeutic strategy for AECOPD on the presence or absence of CAP. The American Thoracic Society guidelines for the management of adults with CAP that were recently published[23] were based, among others, on two important observations that have been confirmed in a number of studies over the past decade. One observation is the relatively high prevalence of atypical pathogens among the causes of CAP, and the other observation is the not-uncommon possibility that more than one pathogen (mixed infection) participated in the pathogenesis of CAP. From the viewpoint of these two observations, the findings of the present study indicate a similar rate of atypical etiologies in both groups and the absence of a significant difference in the rate of mixed infections between the two groups, even though the rate is higher in the PNAE group. These findings raise the speculative question of whether it does not make sense to recommend the same antibiotic therapy for patients with AECOPD with and without CAP? This important question should be tested in further studies designed to specifically address this issue.

We conclude that CAP is common among patients hospitalized with AECOPD and usually causes the exacerbation to have more severe clinical and laboratory parameters, but the rate of atypical etiologies is similar in both groups. The therapeutic implications of these findings should be investigated further.

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