Eur. J. Clin. Microbiol. Infect. Dis., 1997, 16: 863–870

Pneumococcal Community-Acquired Pneumonia in 148 Hospitalized Adult Patients

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In a previous prospective study, *Streptococcus pneumoniae* was identified as the causative agent in 148 (42.8%) of 346 adult patients hospitalized over the course of one year with community-acquired pneumonia (CAP) in the Soroka Medical Center, Beer-Sheva, Israel. The present study characterizes those cases in which *Streptococcus pneumoniae* was the only pathogen and those in which additional etiological agents were identified. Pneumococcal CAP was diagnosed by standard blood cultures or positive serological tests by one of two laboratory methods. In 100 (67.6%) patients, at least one other etiological agent of CAP was identified in addition to *Streptococcus pneumoniae*. Compared with patients who were not infected by *Streptococcus pneumoniae*, patients with *Streptococcus pneumoniae* CAP were older and had a higher rate of comorbidity (39.5% vs. 29.8%). *Streptococcus pneumoniae* CAP had a more severe clinical course and a higher mortality rate, especially when *Streptococcus pneumoniae* was the only pathogen. Community-acquired pneumonia due to *Streptococcus pneumoniae* only was more similar in its clinical manifestations to classic typical pneumococcal pneumonia. When an additional etiological agent was identified, the clinical characteristics could not be distinguished from those of atypical pneumonia. It is concluded that *Streptococcus pneumoniae* remains the principal cause of CAP in this region. The frequency of additional etiological agents of CAP and the difficulty in differentiating clinically between cases due to *Streptococcus pneumoniae* only and those due to *Streptococcus pneumoniae* plus other organisms necessitates initial empirical treatment that covers *Streptococcus pneumoniae* as well as other causative agents of atypical pneumonia.

The addition of many recently identified pathogens to the list of etiological causes of community-acquired pneumonia (CAP) has made it difficult to characterize this common syndrome (1,2). In addition, regional variance in causative agents necessitates ongoing reassessment of therapeutic strategies. Although the list of etiological agents of CAP has been regularly updated over recent years, *Streptococcus pneumoniae* remains the principal pathogen, despite the availability of an effective immunization (3–5).

Three hundred forty-six adult patients hospitalized with CAP were included in a prospective study conducted over the course of one year in the Soroka Medical Center in Beer-Sheva, Israel. We previously reported the etiological distribution of CAP in this study population (6). Evidence for *Streptococcus pneumoniae* as the etiological agent of CAP was found in 148 (42.8%) patients. In the present report, we analyze and describe the epidemiological and clinical features of this group of patients and the clinical course of *Streptococcus pneumoniae* CAP. Differences between patients with *Streptococcus pneumoniae* as the only etiological agent and patients with additional pathogens are emphasized.

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Patients and Methods

All 346 adult patients who were hospitalized with CAP at the Soroka Medical Center in Beer-Sheva, Israel between 1 November 1991 and 31 October 1992 were included in the study which was approved by the review board for human research

Table 1: Method of diagnosis of *Streptococcus pneumoniae* infection in patients with and without concomitant infection by other organisms.

	Bacteremic	Serology only	Total
Pneumococcal infection only	11	37	48
Pneumococcal plus other infection	14	86	100
Total	25	123	148

(the Helsinki committee) of the Soroka Medical Center. All participants gave their informed consent to participate. The mean age of the patients was 49.3 ± 19.5 years (range, 17–94). One hundred eighty-seven (54%) patients were male. Sixteen patients (4.6%) died in the hospital. All other patients were alive at least six weeks after admission to the hospital. During their hospitalization, the patients were diagnosed and treated by the medical staff of the internal medicine wards, without intervention by the investigators. Upon discharge, the patients were referred to the investigators at the pulmonary disease clinic of the hospital for clinical and radiological follow-up.

Community-acquired pneumonia was diagnosed in the presence of an acute febrile illness with an acute pulmonary infiltrate on chest radiograph and a clinical and radiological course that confirmed this diagnosis. Exclusion criteria included patients with blood tests positive for the human immunodeficiency virus (HIV), patients with lung malignancies, and patients who had been discharged from the hospital less than 21 days before their present hospitalization with pneumonia.

In addition to routine hospital blood tests (complete blood count, biochemistry, and blood cultures), we drew blood within the first 48 h of admission for serological testing. A second serum was obtained from 308 (89%) patients, usually at the follow-up appointment in the pulmonary clinic. The mean interval between the two serum samples was 31.7 ± 12.1 days (range, 17–45). All sera were separated immediately and stored at –70 °C until serum testing was performed.

Etiological Diagnoses. Pneumococcal etiology was diagnosed by standard blood cultures and by two serological techniques. Community-acquired pneumonia was considered to be of pneumococcal etiology if a blood or pleural fluid culture was positive for *Streptococcus pneumoniae* or if either serological test was positive. Immunoglobulin G (IgG) antibodies to a pneumococcal protein toxin, pneumolysin, were measured by enzyme immunoassay (EIA) utilizing pneumolysin produced in *Bacillus subtilis* as antigen (7). A twofold rise in antibody titer between paired sera was considered for pneumococcal infection (7, 8). *Pneumococcus*-specific immune complexes were determined in all 654 (paired and unpaired) sera by measuring antibodies to pneumolysin and to the mixture of 23 capsular polysaccharides present in the vaccine (9, 10). The cutoff value for the presence of pneumococcal immune complexes was based on the testing of serum samples from 40 healthy elderly people. All serological testing was conducted at the Finnish National Public Health Institute at Helsinki and at Oulu, Finland.

The serological tests for *Haemophilus influenzae* and *Moraxella catarrhalis* were conducted by EIA, for *Mycoplasma pneumoniae* by microparticle agglutination and the antibody capture EIA method, for *Chlamydia pneumoniae* and *Coxiella burnetii* by microimmunofluorescence, for *Legionella* spp. by indirect immunofluorescence, and for six respiratory viruses (influenza A, influenza B, adenovirus, respiratory syncytial virus, parainfluenza 1, and parainfluenza 3) by complement fixation. These methods have been further detailed in the literature (6).

Data Analyses. The chi-square test was used to determine the significance of differences in proportions between groups. Analysis of variance (ANOVA) was used to determine whether the means of continuous variables were significantly different between the study groups. A p value of < 0.05 was considered statistically significant.

Table 2: Sociodemographic characteristics and comorbidity in 279 patients with community-acquired pneumonia, according to etiology.

Characteristic	Etiology of community-acquired pneumonia			P value
	Sp only (n = 48)	Sp + other pathogen (n = 100)	Non-Sp (n = 131)	
Male (%)	62.5	53.0	47.3	0.192
Mean age in years ± SD	59.4 ± 19.1	47.8 ± 20.3	47.3 ± 18.1	0.0005
Age > 75 years (%)	29.2	13.0	7.6	0.0008
New immigrant (%)*	6.3	17.0	11.5	0.158
Bedouin (%)	18.8	27.0	21.4	0.451
Comorbidity (%)				
Pulmonary disease	45.8	39.0	35.1	0.420
COPD	8.3	12.0	8.4	0.636
Asthma	12.6	6.0	3.1	0.012
Present smoking	29.2	26.0	26.0	0.377
Cardiovascular disease	22.9	10.0	14.5	0.110
Diabetes mellitus	24.3	10.3	17.0	0.161
Cirrhosis	4.2	2.0	–	0.097
Extrapulmonary malignancy	4.2	2.0	3.1	0.749
Influenza immunization	12.5	7.0	10.7	0.442

* Less than two years in Israel.
COPD, chronic obstructive pulmonary disease; Sp, *Streptococcus pneumoniae*.

Table 3: Clinical and laboratory data upon admission for 279 patients hospitalized for community-acquired pneumonia (CAP).

Parameter	Etiology of community-acquired pneumonia			P value
	Sp only (n = 48)	Sp + other pathogen (n = 100)	Non-Sp (n = 131)	
Mean duration of illness prior to hospitalization (days) ± SD	4.2±3.5	5.8±5.1	5.4±3.7	0.124
Antibiotic therapy prior to hospitalization (%)	25.0	41.0	48.1	0.097
Impaired consciousness (%)*	10.4	7.0	5.3	0.301
Systolic blood pressure < 90 mmHg (%)*	6.3	6.0	6.1	0.636
Cough (%)	70.8	64.0	74.0	0.423
Dyspnea (%)	27.1	32.0	21.4	0.356
Sputum (%)	47.9	42.0	36.6	0.092
Chest radiograph findings				
Pleural effusion (%)	6.3	7.0	2.3	0.237
Homogeneous infiltrate (%)	60.0	53.3	50.8	0.581
Bilateral infiltrate (%)	4.3	9.4	6.9	0.557
Multi-lobar infiltrate (%)	20.8	19.0	12.2	0.237
Mean temperature (°C)* ± SD	38.6±0.8	38.7±1.0	38.6±1.2	0.730
Mean respiratory rate (/min)* ± SD	27.0±13.6	21.2±6.5	22.9±8.5	0.005
Mean pulse rate (bpm)* ± SD	103.4±18.3	107.6±20.4	104.1±15.5	0.261
Mean leukocyte count (x 1000)* ± SD	14.4±7.8	12.5±6.6	10.3±4.9	0.0002
Mean BUN (mg/dl) ± SD	52.3±42.4	33.7±23.6	32.4±20.0	0.0001
Mean creatinine (mg/dl)* ± SD	1.30±0.90	1.00±0.34	1.00±0.36	0.001
Mean PO_2 (mmHg)* ± SD	69.0±19.1	72.3±19.4	74.6±25.0	0.451
Mean APACHE II score ± SD	12.3±6.0	8.6±5.7	8.3±6.2	0.0005

* These parameters are included in the APACHE II score.
BUN, blood urea nitrogen; Sp, *Streptococcus pneumoniae*.

Results

In 279 of 346 (80.6%) patients with CAP, at least one etiological agent of CAP was identified. In 146 (42.4%) of these patients, a single pathogen was identified; in 133 (38.4%), at least two causative agents were found; and in 67 (19.4%), no etiological agent was identified. The frequency distribution of CAP etiologies for the 346 patients in our study was reported previously (6).

Streptococcus pneumoniae, the most common etiological agent of CAP, was identified in 148 (42.8%) patients (Table 1). In 48 (32.4%) patients *Streptococcus pneumoniae* was the sole causative agent, whereas in the other 100 (67.6%) patients, the following pathogens were identified in addition to *Streptococcus pneumoniae: Mycoplasma pneumoniae* in 43, *Chlamydia pneumoniae* in 34, *Legionella* spp. in 23, viruses in 17, *Coxiella burnetii* in ten, *Haemophilus influenzae* in eight, other bacteria in five, *Mycoplasma tuberculosis* in six, and *Moraxella catarrhalis* in three (149 etiological agents identified in all).

Table 2 shows sociodemographic data and comorbidity for the three etiological groups: *Streptococcus pneumoniae* only CAP, *Streptococcus pneumoniae* CAP with an additional pathogen, and non-*Streptococcus pneumoniae* CAP. Compared with the other groups, the *Streptococcus pneumoniae* only patients were older and had a higher rate of comorbidity, including pulmonary, cardiovascular, and hepatic disease and diabetes mellitus. However, other than age, none of these differences reached statistical significance. Bedouins and new immigrant Jews were found more frequently in the group with *Streptococcus pneumoniae* plus an additional pathogen. The higher prevalence of patients from these lower social status population groups in this infection category can be explained, in part, by the social factors that influenced the decision to hospitalize some patients with a relatively mild illness. The percentage of patients who were immunized against influenza was low in all three groups.

Table 3 presents clinical, laboratory, and radiological data for study patients on admission to the hospital and during the course of hospitalization. In the *Streptococcus pneumoniae* only CAP group, the pre-hospitalization period was shorter and the patients received less antibiotic therapy in the community (differences not statistically significant). Neither the classic manifestations of cough, sputum production, and pleuritic pain nor the radiological

Table 4: Number of patients treated with various antibiotics prior to hospitalization and on the first day of hospitalization, according to patient group.

	Before hospitalization		Day 1 of hospitalization	
Antibiotic	Sp only CAP (n = 48)	Sp CAP + other pathogen (n = 100)	Sp only CAP (n = 48)	Sp CAP + other pathogen (n = 100)
Beta-lactam agent	8	21	40	66
Macrolide	3	12	8	31
Other	1	8	3	5
None	36	59	3	10

Sp, *Streptococcus pneumoniae*; CAP, community-acquired pneumonia.

findings distinguished between the etiological groups at the time of admission to the hospital. However, patients in the *Streptococcus pneumoniae* only CAP group suffered from a significantly more severe disease as determined by the APACHE II score (11). Compared with patients in the other groups, those with *Streptococcus pneumoniae* only CAP had higher respiratory rates and higher total leukocyte counts; furthermore, rates of impaired renal function were higher among this group. Mortality in this group was significantly higher (10.4%). Survivors recovered quicker and were discharged sooner from the hospital.

Table 4 presents data on the antibiotic therapy that the patients in the *Streptococcus pneumoniae* only CAP group and those with *Streptococcus pneumoniae* and another pathogen received before hospitalization and on the first day of hospitalization. The differences between the two groups were not statistically significant (p=0.34). It is noteworthy that on the first day of hospitalization many patients were treated with more than one antibiotic, and a significant proportion received additional or different antibiotics during the course of their hospitalization.

Eight (5.4%) patients died, five of whom were in the *Streptococcus pneumoniae* only CAP group and three of whom were in the group with *Streptococcus pneumoniae* CAP plus an additional pathogen. Table 5 shows the characteristics of the patients who died. These patients were older and had more comorbidity with cardiovascular diseases and cancer. Their condition on admission to the hospital was severe, with systolic blood pressure of < 90 mmHg, hyperglycemia, tachypnea, impaired renal function, and a high APACHE II score. The patients who died received less antibiotic therapy at home before hospitalization, had higher respiratory rates and higher rates of posi-

Table 5: Comparison of patients with *Streptococcus pneumoniae* community-acquired pneumonia who died versus those who survived.

Characteristic	Died (n = 8)	Survived (n = 140)	P value
Mean age (years)* ± SD	72.5±11.9	50.4±20.3	0.003
Male (%)	75.0	55.0	0.267
Cardiovascular disease (%)	50.0	12.1	0.002
Pulmonary disease (%)	37.5	41.4	0.826
Diabetes mellitus (%)	50.0	10.7	0.217
Extrapulmonary malignancy (%)	37.5	0.7	0.0001
Antibiotics received at home (%)	25.0	36.4	0.702
Systolic blood pressure < 90 mmHg*	25.0	5.0	0.0001
Mean respiratory rate (/min)* ± SD	31.3±16.5	23.1±9.3	0.097
Multilobar pulmonary infiltrate (%)	37.5	18.6	0.189
Mean urea (mg/dl) ± SD	95.0±68.7	37.1±27.3	0.0001
Mean creatinine (mg/dl)* ± SD	1.28±1.00	0.97±0.66	0.197
Mean glucose (mg/dl) ± SD	248.8±185.3	130.6±54.2	0.0001
Mean APACHE II score ± SD	10.5±6.6	5.3±3.5	0.0009
Blood culture positive for *S. pneumoniae* (%)	25.0	16.4	0.529
Blood culture positive for *S. pneumoniae* only (%)	62.5	30.7	0.061

* These parameters are included in the APACHE II score.

tive blood cultures, and tended to be in the *Streptococcus pneumoniae* only CAP group, but these differences were not statistically significant.

Discussion

Pneumococcal CAP is still a common and potentially fatal disease, despite the availability of an effective vaccine and potent antibiotic therapy that can be administered in the community and in the hospital. Many patients with CAP are hospitalized, even when the indication for hospitalization is not clear (12). Initial therapeutic strategies are usually based on the severity of the disease at the time of hospitalization and on the presence of risk factors and chronic comorbidity. This approach is supported by guidelines that have been developed and published by scientific organizations (13, 14). Identification of the etiological agent is an important element in selecting appropriate therapy, but empirical antibiotic therapy is usually chosen due to physicians reluctance to carry out sputum examinations, the delay in obtaining laboratory test results, the availability of broad-spectrum antibiotics, and the need to begin antibiotic therapy quickly, before the etiological agent of CAP can be determined definitively (15). Regional epidemiology plays an important role in the selection of initial empirical therapy, especially in light of the increasing number of reports on atypical and multiple etiologies of CAP (5, 16, 17). The new array of diagnostic tests, mostly serological, available to physicians makes it possible to reach an etiological diagnosis in most cases (18, 19).

We, like Bates et al. (3), did not depend on sputum cultures in this study, as they are unreliable and their diagnostic value has diminished in recent years (20–22). They can, however, be of important diagnostic use in some cases. In our prospective study we relied on several new laboratory techniques and succeeded in identifying the etiological agent in 80% of patients on the basis of intensive serological testing at follow-up and the large percentage of paired sera that were collected.

Streptococcus pneumoniae was the most common pathogen causing CAP. We identified it in 42.8% of our cases, a result that is consistent with the range of 16 to 60% reported in the literature (5, 17, 23–26). Similar to previous reports, only 16.9% of the infections with *Streptococcus pneumoniae* were identified by culture (27). In 83% of the 148 patients with pneumococcal infection, the diagnosis was based on the results of serological testing. Serology plays a role in the diagnosis of pneumococcal infection, even though questions relating to the sensitivity and specificity of these modern methods remain (18, 28–30). Furthermore, in 100 (67.6%) of the patients with pneumococcal infection, there was evidence of at least one other etiological agent, usually an "atypical" pathogen (*Mycoplasma pneumoniae, Chlamydia pneumoniae,* and *Legionella* spp.). The identification of more than one pathogen has been reported in other studies (5) and was discussed by us previously (6).

We are aware that our results raise questions as to the specificity of the serological tests that we used for the diagnosis of streptococcal infection in our study. These questions are important in regard to the clinical and epidemiological uses of these tests. In the absence of a gold standard for the diagnosis of nonbacteremic pneumococcal infection, it is impossible to answer these specific questions convincingly. The sensitivity of the tests can be estimated accurately by the number of bacteremic patients in whom the serological test was positive. Of 25 bacteremic patients, 22 had at least one positive serological test for *Streptococcus pneumoniae*, yielding a sensitivity of 88%. This high sensitivity rate, taken together with the bacteremia rate of 17% among all patients diagnosed with *Streptococcus pneumoniae* CAP, was similar to the results obtained by indirect calculations, thus adding considerable weight to our contention that these tests should be considered useful and reliable.

Patients with *Streptococcus pneumoniae* only CAP tended to have a more severe course with more serious clinical and laboratory manifestations, including tachypnea, leukocytosis, and impaired renal function, which contributed significantly to the high APACHE II score, as has been reported by other investigators (31). In addition, common clinical symptoms such as fever, cough, sputum production, and lung infiltrate on chest radiograph did not distinguish between etiological groups or between *Streptococcus pneumoniae* only CAP patients and those coinfected with an additional pathogen.

Patients coinfected with *Streptococcus pneumoniae* and an additional pathogen had clinical and laboratory manifestations similar to those of patients with atypical etiologies such as *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, and *Legionella* spp. Patients infected with the latter two pathogens were characterized by a relatively low age. Similar prevalences were found among new

immigrants to Israel and Bedouin Arabs, populations living under crowded conditions and at high risk for infection with these pathogens.

The significance of coinfection is problematic and may be associated with regional epidemiologic factors, nonspecific serological tests during acute infection (despite the meticulous use of these tests), or a combination of these factors. The finding that patients with *Streptococcus pneumoniae* CAP and coinfection with an additional pathogen had a milder clinical condition raises the possibility that these patients had atypical pneumonia with a nonspecific serological reaction to *Streptococcus pneumoniae*. An alternative possibility is that these patients represent a subpopulation with a different clinical course in whom coinfection results from a combination of epidemiological and host factors. These considerations have been discussed by us and others (6, 14, 25, 26).

The empirical therapy was similar for patients in the two groups with *Streptococcus pneumoniae* CAP, and most patients received treatment with antibiotics that are effective against *Streptococcus pneumoniae*. The major difference was that patients with *Streptococcus pneumoniae* CAP and coinfection with an additional pathogen received more macrolide preparations than those with *Streptococcus pneumoniae* only CAP (31% and 17%, respectively), even though the treating physicians did not know the etiology when treatment was initiated.

Eight (5.4%) of the 148 patients with *Streptococcus pneumoniae* CAP died. Mortality was significantly higher (10.4%) among patients with *Streptococcus pneumoniae* only CAP. The range of mortality rates reported in the literature is 6 to 24% (32). All the prognostic factors found in our study (increased age, cancer, systolic blood pressure > 90 mmHg, tachypnea, and impaired renal function) have been reported previously (33–35). We found associations between mortality and positive cultures for *Streptococcus pneumoniae*, and between mortality and *Streptococcus pneumoniae* only CAP, but neither association was statistically significant. The patients who died did not live long enough to have a second serological test for atypical organisms, which may explain the high number of deaths in the *Streptococcus pneumoniae* only CAP group. It is noteworthy that the patients who died were treated with cephalosporins, but none of the three patients who died in the group with *Streptococcus pneumoniae* CAP and coinfection with an additional pathogen received a macrolide antibiotic. It is difficult to determine whether an association exists between the empirical antibiotic therapy administered in these cases and their outcome.

The age range of our patients (mid-50s to late 60s) is similar to that previously reported for CAP patients (24, 25, 36). The clinical manifestations and rates of chronic comorbidity are also similar to those reported in the literature, except for alcoholism, which is rare in our area, and HIV-positive patients, who were not included in our study (2, 24, 25, 36, 37). *Streptococcus pneumoniae* CAP occurred in our region throughout the year, without significant seasonal variations except for a mild peak in the spring, much like CAP caused by other etiological agents.

In summary, because of the therapeutic implications, we attempted to determine whether CAP due to coinfection with *Streptococcus pneumoniae* and an additional pathogen is different from CAP due solely to *Streptococcus pneumoniae*. The clinical characteristics of the patients with CAP due to *Streptococcus pneumoniae* only more closely resembled those typical for pneumonia caused by *Streptococcus pneumoniae* (age, chronic comorbidity, leukocytosis), while the group with CAP due to *Streptococcus pneumoniae* and an additional pathogen resembled patients with CAP caused by atypical pathogens such as *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* (younger age, fewer cases of chronic comorbidity, and lower leukocyte counts). The clinical message for physicians in our region is that the prevalence of patients infected with *Streptococcus pneumoniae* and an additional pathogen as etiological agents of CAP is high. This finding justifies empirical combination therapy with an β-lactam agent and a macrolide, regardless of whether the clinical presentation is typical of *Streptococcus pneumoniae* CAP.

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