Prospective epidemiologic survey of patients with community-acquired pneumonia requiring hospitalization in Switzerland

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Background: Community-acquired pneumonia (CAP) is a common problem and the principal infection requiring hospitalization, but its treatment is complicated by the difficulty in microbiological diagnosis and the increasing incidence of antibiotic resistance among respiratory pathogens. The purpose of this paper is to present the main epidemiologic features of patients with CAP requiring hospitalization in our country.

Methods: We enrolled three hundred and eighteen adult patients with CAP requiring hospitalization in seven large medical centers in Switzerland during two winter periods. The patients' mean age was 70.4 years. This study describes the epidemiology of these patients. Clinical, radiologic and microbiological evaluations were performed at study entry during treatment, and at 4 weeks post-therapy. For microbiological diagnostic purposes, sputum culture, throat swab culture, PCR, blood cultures, *Legionella* urinary antigen and serologic evaluations were also performed.

Results: Despite the higher mean age, the overall mortality rate was 8%, lower than in other comparable studies. The most common underlying diseases present at study entry were cardiac failure (23%), chronic obstructive pulmonary disease (20%), renal failure (15%), and diabetes (12%); 40% of the patients were smokers. Although dyspnea, cough and positive pulmonary auscultation findings were present in about 90% of patients, fever >38°C was present in only 64%. The most frequently isolated respiratory pathogens were *Streptococcus pneumoniae* (12.6%), *Haemophilus influenzae* (6%), *Staphylococcus aureus* (1.6%), and *Moraxella catarrhalis* (1.6%). Atypical pathogens were frequently found, with the following distribution: *Mycoplasma pneumoniae*, 7.5%; *Chlamydia pneumoniae*, 5.3%; and *Legionella pneumophila*, 4.4%. The mean duration between onset of symptoms and hospital admission was 4.8 days, and the mean treatment duration was 12.1 days. Two weeks after the start of therapy, although clinical symptoms were absent, radiologic infiltrates were still present in 24% of patients.

Conclusions: The microbiological diagnosis in CAP can be established in only about 50% of cases with the combination of several diagnostic tools. Epidemiologic surveys of CAP should be performed on a regular basis, regionally, as a way to improve the management of these infections.

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INTRODUCTION

Respiratory infections are among the illnesses most frequently encountered by physicians in the USA and Europe in both outpatient and hospital practice. In particular, community-acquired pneumonia (CAP) has an estimated annual incidence of 4 million cases among ambulatory patients, or 12 cases per 1000 persons in the USA. Pneumonia, in general, is the sixth leading cause of death in the USA, and is responsible for more than 600 000 hospital admissions per year.[1] Mortality rates approximate 13.7% among all cases of CAP requiring hospital admission,[2] and appear to be even higher in the elderly population.

The most common microbes associated with CAP are *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Mycoplasma pneumoniae*.[3–5] However, during the last decade, pathogens such as *Moraxella catarrhalis*, *Legionella pneumophila* and *Chlamydia pneumoniae* have been identified more frequently, and several studies have demonstrated the importance of these newly recognized pathogens.[2]

Diagnosis of infections caused by atypical pathogens is often limited by the lack of routine and easy-to-perform tests for these agents. In addition, the growing

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incidence of β-lactam and/or macrolide resistance in common respiratory bacterial pathogens such as *Streptococcus pneumoniae* and *Haemophilus influenzae* complicates the selection of an appropriate antibiotic for initial empirical treatment.[6–9] Initial empirical therapy should inhibit *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis*, and atypical pathogens.

The initial management of CAP requires a decision as to the need for patient hospitalization. In selected circumstances, the severity of illness[10] will necessitate hospital admission and the administration of intravenous antibiotics. Once the patient has improved, intravenous antibiotics may be replaced with oral agents, depending on the availability of an efficacious and safe oral agent to treat the infecting pathogen(s).

We have performed a prospective, randomized, open-label, comparative, controlled study on CAP requiring hospitalization in Switzerland.

The original study was a randomized, phase III, multicenter, blind (open when patient was included) study to compare the quinolone trovafloxacin 200 mg/day intravenously, and then orally once a day, with amoxicillin–clavulanic acid 4 × 1.2 g/day intravenously, and then orally with optional clarithromycin, for the treatment of CAP. The intravenous treatment was given for a minimum of 48 h, followed by oral treatment, to complete at a course of treatment of at least 7 days.

The purpose of this paper is to present the main epidemiologic features of patients with CAP requiring hospitalization in our country, and not to compare the results of the two different treatments.

MATERIALS AND METHODS

The study was a multicenter, prospective, randomized, blind (open-label when patient was included), comparative, controlled study conducted at seven Swiss medical centers (Basel-Bruderholz, Biel, Fribourg, Geneva, La Chaux-de-Fonds, Saint-Gall, and Zoug). The institutional review board of each center approved the study, and all patients provided written informed consent.

Patients who fulfilled inclusion criteria were randomized according to a computer-generated, blinded randomization list, and assigned to one treatment arm to complete at least 7 days of therapy.

Patient characteristics

Patients eligible for inclusion in the study met the following criteria: older than 18 years and hospitalized with a primary diagnosis of CAP; a medical and clinical history of pneumonia; a new pulmonary infiltrate revealed by chest X-ray compatible with pneumonia; and two or more signs and symptoms associated with a lower respiratory tract infection (i.e. body temperature >38°C or <36.1°C, new or increased cough, production of purulent sputum, findings on examination such as rales or evidence of pulmonary consolidation, blood leukocyte count >10 000/mm^3 or <4000/mm^3, or >10% bands, hypoxemia (defined as: pO_2 <70 mmHg at FiO_2= 21% or a decrease of >25% from an initial value)).

Patients excluded were: pregnant women, nursing mothers, or women of childbearing potential not practicing adequate contraception; patients with known or suspected hypersensitivity or intolerance to the study drugs; and those who had received antimicrobial therapy for 24 h or longer within 72 h prior to the baseline visit, unless there was documented evidence of resistance or clinical failure. Also excluded were the following subjects: those with AIDS, suspected *Pneumocytis carinii* pneumonia, or a known infection with fungi or mycobacteria; those with neutropenia, defined as a total of white blood cells of less than 1000 leukocytes/mm^3, or an absolute neutrophil count of less than 1000/mm^3; those receiving immunosuppressive therapy, defined as chronic treatment with known immunosuppressive agents; those with a diagnosis of cystic fibrosis, known lung cancer, emphysema or aspiration pneumonia, cavitary lung diseases confirmed by chest X-ray at baseline, or a history of seizures; those who had received any investigational agent within the month prior to the baseline visit; those who had been enrolled in this study previously; those with evidence of recent drug or alcohol abuse or dependence; and those with an underlying condition that might give them a life expectancy <1 week, or who had been hospitalized during the past week.

Microbiological investigations

From all patients, a sputum specimen for routine culture and Gram stain was obtained prior to study entry. If a satisfactory specimen or expectorated sputum was not obtained, the investigator could carry out induction of sputum with nebulized hypertonic or physiotherapy or, if medically indicated, could use other techniques such as transtracheal aspiration, bronchoalveolar lavage, bronchial brushings, or biopsy. In addition, blood cultures were performed by standard procedures at study entry and during other visits, if clinically indicated. Identification of causative organisms and testing for aerobic susceptibility to study drugs by disk and broth microdilution MIC methods was performed according to the National Committee for Clinical Laboratory Standards procedures.[11] Serologic testing for *Mycoplasma pneumoniae* (complement fixation), *L. pneumophila* (enzyme-linked immunosorbent assay) and *Chlamydia pneumoniae* (microimmunofluorescence test) was performed in all patients at baseline and 4 weeks after study entry (results were positive when there was a fourfold rise in the titer of Ig or the Ig titer was >1/256 in a simple serum sample). A urine antigen assay for *Legionella* spp. was also performed at the time of admission (Binax, S. Portland, Maine, USA).[12]

Identification of typical and atypical pathogens was performed at the bacteriologic laboratories of the indicated centers, and, when necessary, by a reference

laboratory. Standard respiratory pathogens, when isolated from purulent respiratory secretions, were considered to be the microorganism responsible for the infection. Throat swabs and sputum specimens were used at study entry for PCR assays for *Mycoplasma pneumoniae* (gene amplification with primers MPP 10 and MPP 12)[13] and *Chlamydia pneumoniae* (amplification by Pst with primers HM-1 and HR-1).[14]

RESULTS

Three hundred and twenty-three patients were enrolled during the 19-month study period (from November 1997 to May 1999) at seven Swiss hospital centers. Five patients did not meet the entry criteria and were excluded from the study due to protocol violations (hospital-acquired pneumonia, bronchial aspiration pneumonia, acute bronchitis, and two cases of urinary sepsis). The numbers of patients included in the different centers were as follows: Basel-Bruderholz, 6; Biel, 60; Fribourg, 51; Geneva, 102; La Chaux-de-Fonds, 42; Saint Gall, 47; and Zoug, 10. The total number of patients was 318.

Study population

The mean age of the adult patients was 70.4 years. Baseline demographic data are presented in Table 1.

The most frequent underlying diseases present at study entry were cardiac failure (71, 23%), chronic obstructive pulmonary disease (63, 20%), renal failure (45, 15%), diabetes (39, 12%), asthma (17, 5%), and hepatic failure(16, 5%). One hundred and twenty-four patients (40%) were smokers. The mean time from onset of symptoms to admission was 4.8 days (SD 4.39) (median 3.5). The mean total duration of treatment for clinically evaluable patients was 12.1 days (±4.95).

The proportions of patients with different clinical symptoms and signs of pneumonia at study entry are presented in Table 1.

The relatively low frequency of fever was probably due to the advanced age of the patients. The high mean age of the study population and the high percentage of co-morbidities allow the classification of patients as class III according to the Fine criteria.[15]

Radiologic results

The most common localization of radiologic infiltrates at study entry comprised lesions on the right lung (49%), with a significant difference ($P<0.05$) compared to localization on the left lung (34%). Bilateral infiltrates were found in 81 patients (18%). Pleural effusion was present in 86 patients (27%). Other radiologic data are shown in Table 2.

Two weeks after the start of treatment, radiologic success (defined as resolution or improvement of abnormal pre-therapy radiographic findings) was observed in 188 patients (76%), whereas radiologic failure (failure of resolution or improvement of abnormal pre-therapy radiographic findings) was observed at the same time in 62 patients (24%).

At the end of the study period (28 days after study entry), among evaluable patients, radiologic resolution (no abnormal radiographic findings) was observed in 102, and persistence of radiologic infiltrates in 13.

Bacteriologic findings

One hundred and twenty-four pathogens (39%) were identified at baseline among the patients. The most common typical bacterial pathogens isolated from sputum specimens of the study population patients were *Streptococcus pneumoniae* (40), *Haemophilus influenzae* (19), *Staphylococcus aureus* (8), and *Moraxella catarrhalis* (5). Other microorganisms isolated from sputum cultures are listed in Table 3. For 28 patients, sputum could not

Table 1. Patients' demographic characteristics and clinical symptoms and signs of pneumonia at study entry

Demographic	
Total number of patients	318
Male (no. (%))	188 (59%)
Female (no. (%))	130 (41%)
Age (years)	70.4 (±16.2)
Patients over 65 years (no. (%))	212 (67%)
Body weight (kg)	80 (37–123)
Height (cm)	168.5 (145–195)
Signs and symptoms (no. (%))	
Pulmonary auscultation findings	291 (92%)
Cough	287 (90%)
Dyspnea	280 (88%)
Respiratory rate	
≥20/min	249 (78%)
≥30/min	95 (30%)
Increased sputum volume	215 (68%)
Temperature ≥38°C	202 (64%)
Heart rate ≥95/min	173 (54%)
Chills	173 (54%)
Pleuritic chest pain	168 (53%)
Pleural effusion	86 (27%)

Table 2. Radiologic findings in the study population at study entry

	Number	*%*
Presence of lung infiltrates (n=478)		
In right lung	235	49
In left lung	162	34
Bilateral lung	81	17
In right lung lobes (n=308)		
Lower	138	45
Middle	77	25
Upper	55	18
Bi-lobe	34	11
Tri-lobe	4	1
In left lung lobes (n=170)		
Lower	126	74
Upper	31	18
Both	13	8

Table 3. Respiratory tract pathogens detected by sputum culture and nonculture methods in the study population

Microorganisms	*Number of patients*	*Percentage*
Streptococcus pneumoniae	40	12.6
Haemophilus influenzae	19	6.0
Mycoplasma pneumoniae	24	7.5
Chlamydia pneumoniae	8	2.5
Legionella spp.	17	5.3
Staphylococcus aureus	14	4.4
Moraxella catarrhalis	5	1.6
Klebsiella pneumoniae	2	0.6
Streptococcus beta-haemolyticus	1	0.3
Mycobacterium (non-tuberculosis)	1	0.3
Pasteurella multocida	1	0.3

For *L. pneumophila*, seven serology conversion, six cases diagnosed by positive urinary antigen, and one by culture.
For *Mycoplasma pneumoniae*, seven serology conversion and 17 diagnosed by PCR.
For *Chlamydia pneumoniae*, nine serology conversion and eight diagnosed by PCR.

be obtained at study entry. No penicillin-, erythromycin- or clarithromycin-resistant isolates of *Streptococcus pneumoniae* were identified.

Other microorganisms isolated from sputum cultures at study entry which are not usually considered to be respiratory pathogens were: *Pseudomonas aeruginosa*, *Escherichia coli*, *Enterobacter cloacae*, *Acinetobacter* spp., *Corynebacterium diphtheriae*, *Pseudomonas fluorescens*, *Stenotrophomonas maltophilia*, *Serratia marcescens*, *Enterobacter aerogenes*, *Hafnia alvei*, *Candida albicans*, and *Aspergillus fumigatus*. None of the patients was subjected to invasive techniques to obtain sputum samples.

Serologic samples were taken from 83% (264) of the patients at study entry, and from 53% (169) patients 4 weeks later for serology control.

Legionella urinary antigen testing was performed in 95% of the patients at study entry, and was positive in six cases. Positive PCR in throat specimens was observed in 17 cases for *Mycoplasma pneumoniae*, and in eight cases for *Chlamydia pneumoniae*. An etiologic diagnosis of CAP was possible in 130 patients (41%). The overall mortality rate at 30 days in this patient population was 8%.

Blood cultures

At study entry, 56 (19.2%) patients had positive blood cultures. The most common bacterial pathogens isolated from blood cultures and presumed to be involved in the etiology of pneumonia were: *Streptococcus pneumoniae* (n=32) (10%) (57% of all positive blood cultures), *Haemophilus influenzae*, *Staphylococcus aureus*, *Escherichia coli* (n=3) (5.3%), *Morganella morganii*, and *Streptococcus agalactiae* (n=1) (1.8%). Other microorganisms isolated without evidence of a pathogenic role in pneumonia or considered to be contaminants were coagulase-negative *Staphylococcus* (n=7), *Propionibacterium* spp. (n=2) and, with one case each, *Enterococcus aerogenes*, *Pseudomonas pancinoli*, *Streptococcus mitis*, and *Oligella urethralis*.

Analysis of all microorganisms isolated from blood cultures (56) and all microorganisms isolated from sputum (124) showed that matching of similar pathogens (blood cultures/sputum) was achieved in only nine cases. In 29 cases with positive blood cultures, no microorganisms were found in sputum. Finally, in 18 cases with positive blood cultures, the microorganisms isolated in sputum were different but did not fit the standard purulent criteria with Gram stain. These results demonstrate the importance of blood cultures for the establishment of the etiology of CAP, and give an indication of how frequently blood or sputum samples may contaminate pathogens.

DISCUSSION

CAP is a common condition, and its treatment poses new challenges because of the growing incidence of antibiotic resistance among traditional respiratory pathogens and the increasing recognition of pneumonia caused by atypical respiratory pathogens.[16]

Rapid diagnosis of the etiologic agents causing respiratory infections is difficult, and the treatment of patients with CAP is often empirical. Therefore, selection of an appropriate antibacterial agent should be, in large part, based on its antimicrobial activity and the local epidemiologic setting. Local sensitivity patterns need to be considered in particular, because there are different rates of pneumococci penicillin resistance in different countries.

In this study, we achieved a precise etiology for the causative pathogens, with the use of different diagnostic techniques such as sputum culture, PCR, serology, blood cultures, and *Legionella* urine antigen, in a total of 41% of the study population. The etiology was unknown for the other patients, but this proportion is comparable with the results of other studies.[2,17] Antibiotics given before admission probably decreased the possibility of isolating a specific pathogen, even though antibiotic treatment was administered for less than 24 h in our study.

The most frequent typical respiratory pathogens isolated were: *Streptococcus pneumoniae* (the predominant pathogen in our study, as in other published studies[2,18,19]), *Haemophilus influenzae*, *Staphylococcus aureus*, *Moraxella catarrhalis*, and *Klebsiella pneumoniae*. Infection rates with the three atypical pathogens *Chlamydia pneumoniae*, *Legionella pneumophila* and *Mycoplasma pneumoniae* were comparable to those in the series published by Halm et al,[20] but lower than in other series.[1,21]

In the present study, we did not observe antibiotic resistance of *Streptococcus pneumoniae*, as reported elsewhere.[9] The resistance of *Streptococcus pneumoniae* in the Alexander project during the same period ranged between 3% and 6% in Switzerland (from 1996 to 1999). The absence of resistant pneumococci in our patients is

probably due to differences between overall specimen collection in some large microbiological centers when compared to our prospective clinical study.

In some other European countries, such as Italy, Austria and Belgium, the frequency of resistance in *Streptococcus pneumoniae* remains quite low, but not in France or Greece, where it was much higher during the same time period (32–40%). In the study by Plouffe et al,[22] from the USA, incidences of 8% of *Streptococcus pneumoniae* resistance to penicillin and 2.8% to ofloxacin were reported. We did not observe *Streptococcus pneumoniae* resistance to erythromycin and clarithromycin, whereas in another study, performed in Providence (USA), 5% of isolates of *Streptococcus pneumoniae* from bacteremic patients were resistant to erythromycin and clarithromycin.[23]

The most common localization of radiologic infiltrates comprised lesions on the right lung, with significant differences to localization on the left lung. Bilateral infiltrates were found in 81 patients. Radiologic resolution was not observed in 13 patients.

The studies listed in Table 4 were comparable to the present study. They were multicenter and randomized studies with similar sample sizes. Most of the studies were performed in North America; therefore, it is interesting to have recent epidemiologic data from Switzerland. Some of these studies looked for concomitant diseases, clinical signs and clinical symptoms at study entry. In our patient population, the most important differences, compared to these other studies, were a higher patient mean age, a higher proportion of smokers, and a more accurate description of respiratory symptoms and clinical signs. In our series, careful auscultation revealed positive signs in 92% of the cases. By contrast, fever was observed in only 64% of cases.

The mortality rate of 8% among our hospitalized patients was lower than those previously reported in most other studies,[2] despite the fact that the severity of disease and the age at hospitalization were high. This probably reflects a better standard of care, and perhaps earlier treatment in the ambulatory setting preventing a progressive severe infection. The microbiological diagnosis in CAP can only be established in about 50% of cases. In spite of the combined use of several diagnostic tools, about 50% of patients are treated with no identification of the microorganisms involved. We recommend that epidemiologic surveys of CAP should be performed on a regular basis, regionally, as a way to improve the management of these frequent infections requiring hospitalization.

Table 4. Comparison with other studies

	Sarbino, present report	*Mandell and Donowitz*[24]	*Halm et al*[20]	*Fang et al*[2]	*Plouffe et al*[21]	*File et al*[17]	*Bartlett and Mundy*[1]
Study design							
Multicenter	X		X	X	X	X	
Randomized	X		X	X	X	X	
Mean age (years)	70	50–60	58	63	57–58	50	
Number of patients	318			359	298	456	
Etiology							
Known etiology (%)	41	50–70	27	37	64	46	35–70
Positive blood cultures (%)	17.6			7.70			11
Streptococcus pneumoniae (%)	12	16–60	8	15.3	8	13.5	5–18
Haemophilus influenzae (%)	6	4–15	4	10.9	10	11.2	3–18
Gram-negative pathogens (%)	7.9	7–18	3	5.9			3–10
Atypical pathogens (%)	4	1–10	2		26		10–20
Concomitant diseases							
COPD (%)	19.8		21	31.4			
Cardiac failure (%)	22		19	29			
Renal failure (%)	14.1		8	7			
Diabetes (%)	12.2		13				
Hepatic failure (%)	5						
Smoker (%)	38.9						
Asthma (%)	5		9				
Symptoms (%)							
Heart rate >95/min	55	45	56	45.1			
Temperature >38°C	64	68–78	46				80
Respiratory rate >25/min	78	69	71	47.2			>85
Cough	90	80		88.4		49.4	
Dyspnea	88			60.2		57.8	
Chills	54	40–50		47.8		49.4	
Pleural effusion	27	20					30–50
Increased sputum production	68	60–80		70.8		67.9	
Pulmonary auscultation	92						80

COPD, chronic obstructive pulmonary disease.

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