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Epidemiology of community-acquired pneumonia in adult patients at the dawn of the 21st century: a prospective study on the Mediterranean coast of Spain

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ABSTRACT

This study presents data from a prospective study of adult patients with community-acquired pneumonia (CAP). Of 493 patients included in the study, 223 (45.2%) were aged ≥65 years, and 265 (53.7%) had one or more underlying diseases, mostly chronic obstructive pulmonary disease, diabetes mellitus or dementia. In total, 281 microorganisms were identified in 250 (50.7%) patients, with two or more pathogens detected in 28 (5.7%) cases. Microbial diagnosis varied according to age, severity, co-morbidity and site-of-care, but there was much overlap among groups. *Streptococcus pneumoniae* was the single most prevalent organism in outpatients, patients admitted to hospital, and patients who died, either as a single pathogen or combined with another organism. Infections caused by 'atypical' pathogens were seen across all groups, including the elderly and patients with co-morbidities. Mortality varied according to the pneumonia severity index (PSI) of the pneumonia patient outcomes research team. Shock (OR 34.48), an age of >65 years (OR 25) and altered mental status (OR 9.92) were factors associated independently with 30-day mortality. Key findings from this study were the advanced age of the population with CAP, and the high prevalence of dementia as an underlying disease. The study also revealed that microbiological diagnosis of CAP remains problematic. Although certain epidemiological features may help to predict the microbial aetiology, the overlap among groups reduces the usefulness of this information in guiding therapeutic decisions. Greater effort should be made to improve identification methods for microbial pathogens causing CAP.

Keywords Aetiology, community-acquired pneumonia, diagnosis, epidemiology, outcome, risk-factors

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INTRODUCTION

Community-acquired pneumonia (CAP) is an acute medical condition that is common worldwide. It remains a major cause of admission to hospital and mortality in developed countries, and contributes significantly to excessive consumption of healthcare resources and related costs [1–4]. Pneumonia has always been an active field of investigation, given its relevance and complexity. In the past decade, significant progress has been made in understanding the aetiology and outcomes of patients with CAP. *Chlamydia pneumoniae* has emerged as a significant independent and co-infecting pathogen [5,6], and epidemiological research has provided prognostic and clinical-decision support tools [7], as well as critical pathways to optimise the healthcare process [8]. In addition, the benefits resulting from immunisation of specific patient groups with pneumococcal polysaccharide have led to recommendations for the use of this vaccine in patients at risk for CAP [9].

In recent years, there have been further significant changes with respect to many aspects of CAP. The selection of empirical therapy has become

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complicated by increasing concern regarding the concurrent presence of 'atypical' pathogens (e.g., *Mycoplasma pneumoniae*, *Chlamydia* spp., *Coxiella burnetii* and *Legionella pneumophila*) in a significant proportion of cases thought previously to be caused by a single pathogen [5,10–18], and by the marked rise of β-lactam and macrolide resistance among *Streptococcus pneumoniae* isolates. While most studies suggest that current levels of β-lactam resistance do not usually result in treatment failures among patients with pneumococcal pneumonia [19,20], therapeutic failures attributable to macrolide-resistant *S. pneumoniae* have been reported among patients treated with an oral macrolide who required admission subsequently with *S. pneumoniae* bacteraemia [21,22]. However, the availability of newer fluoroquinolones with greater activity against *S. pneumoniae* and other respiratory pathogens, as well as novel immunochromatographic assays to detect *S. pneumoniae* and *L. pneumophila* antigens in urine, have facilitated the medical management of CAP [23–25].

Large-scale studies of the epidemiology of CAP are labour-intensive, but the above-mentioned changes and controversies mean that new epidemiological data are required. Most previous studies of CAP have focused either on patients admitted to hospital or on outpatients [6,26–31]. The aim of the present work was to provide a comprehensive overview of the current clinical and epidemiological features of CAP by conducting a prospective population-based study with two major advantages: (1) the inclusion of consecutive patients covering a broad clinical spectrum of CAP; and (2) an extensive microbiological workup, including detection of urinary antigen for *S. pneumoniae* and *L. pneumophila*, and standard serological tests and criteria for atypical and virus pathogens. A previous report evaluated the Binax immunochromatographic assay for detection of *S. pneumoniae* urinary antigen in the same patient cohort [32]. The present study presents a complete analysis of the epidemiological features, microbial diagnosis and outcome for these patients.

PATIENTS AND METHODS

Setting and population studied

This was a prospective observational cohort study conducted between 15 October 1999 and 14 October 2001 at Hospital General Universitario de Elche, a 430-bed university-affiliated teaching hospital serving a population of 239 335 in three municipalities of the Health Authority of Bajo Vinalopó on the Mediterranean coast of Spain. All adult patients (≥ 15 years) from this Health Authority with signs and symptoms compatible with pneumonia over the 24-month study period were eligible for inclusion in the study. The study was approved by the local Ethical Committee. Attending clinicians were asked to consider the possibility of pneumonia in any patient with an acute illness and symptoms suggesting lower respiratory tract infection, including a new cough with high fever or chills, pleuritic chest pain, dyspnoea or prolonged fever. Patients were evaluated clinically and roentgenographically, and those with a provisional diagnosis of CAP were seen by a study investigator to confirm the diagnosis. CAP was defined as an acute illness associated with at least one of the following signs or symptoms: fever, new cough with or without sputum production, pleuritic chest pain, dyspnoea or altered breath sound on auscultation, plus a chest radiograph showing an opacity compatible with the presence of acute pneumonia. Patients who had been hospitalised previously within 2 weeks of a current diagnosis of pneumonia were excluded.

Demographic and clinical data were collected by a study investigator using a written standardised questionnaire. The pneumonia severity index (PSI) of the pneumonia patient outcomes research team (PORT) [7], which classifies patients into five risk classes according to outcome (stage I includes patients with the most favourable prognosis, and stage V includes those with the poorest prognosis), was used to calculate the severity of pneumonia at presentation. A repeat chest radiogram and a blood sample were obtained between 2 and 4 weeks after the initial diagnosis of CAP. Patients were followed for at least 4 weeks or until death. Mortality was defined as death by any cause within 30 days of the diagnosis of pneumonia.

Microbiological investigations

Laboratory investigations for a patient with CAP included sputum samples for Gram's stain and culture (only for patients with productive cough), two blood samples for culture (only for patients with fever ≥38°C), urine sample for detection of *S. pneumoniae* and *L. pneumophila* urinary antigens (all patients, except those from whom a urine sample could not be collected before starting antibiotic therapy), and serum samples for serological testing, drawn during the acute and convalescent phases of illness (all patients, except those who died before the convalescent sample was due to be obtained or failed to attend the follow-up visit). Any bronchoscopic samples obtained were also cultured.

Only qualified sputum samples with >25 white blood cells and <10 squamous cells/low-magnification field (× 10) were evaluated. Hospital staff in charge of patients were asked to collect sputum samples before the start of antibiotic therapy. The Binax immunochromatographic assays (Binax, Portland, ME, USA) were used to detect *S. pneumoniae* antigen and *L. pneumophila* serogroup I antigen in urine samples collected at the time of diagnosis of CAP.

A complement fixation (CF) test was performed to detect antibodies against *M. pneumoniae*, *Chlamydia* spp., *Cox. burnetii*, influenza viruses A and B, respiratory syncytial virus and adenovirus. CF tests followed a standard micromethod in which heat-inactivated sera were titrated at a dilution of 1:64. Four units of commercially available antigens (Institute Virion,

Rüschlikon/Zurich, Switzerland) and 4 U of guinea-pig complement were used. The CF test antibody titre was read as the highest dilution showing 50% haemolysis. An indirect immunofluorescence test was used to detect antibodies against *L. pneumophila* (Vircell, Granada, Spain), and a microimmunofluorescence test was used to detect antibodies against *C. pneumoniae*, *Chlamydia psittaci* and *Chlamydia trachomatis* (Vircell, Granada, Spain).

Criteria for aetiological diagnosis

The following criteria were used to classify a pneumonia as being of known aetiology: (1) a four-fold or greater rise in antibody titre by CF test for *M. pneumoniae*, *C. psittaci*, *Cox. burnetii*, influenza viruses A and B, respiratory syncytial virus and adenovirus; (2) a four-fold rise in antibody titres to ≥1:128, or the presence of IgM antibodies (≥ 1:20) for *C. pneumoniae*; (3) isolation from respiratory samples, or the detection of antigen in urine, or a four-fold or greater rise in immunofluorescence antibody titre for *L. pneumophila*; (4) isolation from blood or from pleural fluid, or the predominant organism isolated from a qualified sputum sample, or antigen for *S. pneumoniae* detected in urine; (5) isolation from blood or from pleural fluid, or the predominant organism isolated from a qualified sputum sample for *Haemophilus influenzae*, *Moraxella catarrhalis*, *Staphylococcus aureus* and other bacteria, including Gram-negative enterobacteria. Cases that did not fulfil these diagnostic criteria were considered to be 'pneumonia of unknown aetiology'. Cases that fulfilled the diagnostic criteria for more than one pathogen were considered to represent 'mixed pneumonia'. Cases with a four-fold antibody rise against more than one species of *Chlamydia* were excluded from the definition of mixed pneumonia because of possible non-specific cross-reactions.

Statistical analysis

Descriptive statistics were computed by standard methods. Differences between specified groups were detected by the chi-square test, or Fisher's exact test where appropriate, for categorical variables, and the Mann–Whitney *U*-test or Student's *t*-test for continuous variables. Multivariable analysis of factors potentially associated with mortality was performed by stepwise logistic regression, including all significant variables in univariate analysis and all clinically important variables, whether significant or not. A two-tailed p value of 0.05 was considered significant. Associations between independent variables and outcomes were assessed by the odds ratio (OR) and its 95% confidence interval (CI). Statistical analyses were performed with SPSS v. 11 software (SPSS Inc., Chicago, IL, USA).

RESULTS

Patient characteristics

Of 516 patients with signs and symptoms compatible with pneumonia, 23 were found subsequently not to have CAP (8 × lower respiratory tract infection without pneumonia; 7 × heart failure; 2 × pulmonary embolism; 2 × lung cancer; 1 × bronchiectasis; 1 × atelectasis; 1 × pulmonary fibrosis; 1 × pulmonary haemorrhage), leaving 493 patients in the study cohort. The main demographic characteristics of these patients are summarised in Table 1. In total, 361 (73.2%) patients were admitted to hospital for a mean (SD) stay of 6.45 (6.46) days. The remaining 132 (26.8%) patients were managed as outpatients. The mean (SD) PSI score in patients admitted to hospital was 80.8 (35.3), compared to 36.3 (19.5) in outpatients ($p < 0.001$). All ambulatory patients were classified within risk classes I and II of the PSI. The distribution of patients admitted to hospital according to PSI risk classes was as follows: I/II 144 (39.9%), III 97 (26.9%), IV 92 (25.5%), and V 28 (7.8%).

Some patient characteristics varied according to age. Co-morbid illnesses were more common in patients aged ≥65 years than in younger patients (73.5% vs. 23.5%; $p < 0.001$). Predisposing factors for aspiration pneumonia (reduced level of consciousness, underlying neurological disease, dysphagia, impaired gag reflex, or severe periodontal disease) were also significantly more frequent in patients aged ≥65 years than in younger patients (22.9% vs. 3.3%; $p < 0.001$).

Table 1. Characteristics of 493 patients with community-acquired pneumonia

Characteristic	No. (%) patients
Age, mean (range), 56.6 years (15–94 years)	
Distribution of cases by age group	
15–44 years	161 (32.7)
45–64 years	109 (22.1)
65–74 years	87 (17.6)
≥ 75 years	136 (27.6)
Male gender	308 (62.5)
Regular cigarette use	111 (22.5)
Heavy alcohol consumption	63 (12.8)
Intravenous drug use	3 (0.6)
Predisposing cause for aspiration[a]	60 (12.2)
Underlying disease	227 (46)
Chronic obstructive pulmonary disease	99 (20.1)
Diabetes mellitus	98 (19.9)
Dementia	52 (10.5)
Immunosuppression	26 (5.3)
Neoplasia	21 (4.3)
Congestive heart failure	20 (4.1)
Chronic renal failure	17 (3.4)
Previous antibiotic therapy[b]	114 (23.1%)
Distribution according to PSI score	
I/II	267 (54.2)
III	103 (20.9)
IV	94 (19.1)
V	29 (5.9)
Admission to hospital	361 (73.2)

PSI, pneumonia PORT (patient outcome research team) severity index.
[a]Reduced level of consciousness, underlying neurological disease, dysphagia, impaired gag reflex, severe periodontal disease.
[b]A wide variety of agents, including β-lactams, macrolides, tetracyclines and quinolones.

Results of microbiological investigations and aetiological agents identified

Specimens obtained included blood cultures from 302 (61.2%) patients, urine from 454 (92.1%), acute and follow-up serum from 401 (81.3%), sputum from 272 (55.2%), and lower respiratory secretions obtained by a bronchoscopic procedure from 14 (2.8%). In total, 280 pathogens (140 bacteria, 110 atypical pathogens and 30 viruses) were identified in 250 (50.7%) patients (Table 2). A single pathogen was detected in 222 (45%) patients and two or more pathogens in 28 (5.7%) patients. The most frequent aetiological agents were *S. pneumoniae* (16.8%), *M. pneumoniae* (7.7%), *Chlamydia* spp. (6.3%), *L. pneumophila* (4.1%), Gram-negative bacilli, including *Pseudomonas* spp. (3.2%), and influenza virus (2.8%). In 243 (49.3%) cases, the microbial aetiology remained unknown. A wide variety of combinations of pathogens was found among patients with CAP of mixed aetiology, with the most frequent combinations being a bacterial pathogen plus an atypical organism (eight cases) and two bacterial pathogens (eight cases). The most common mixed infections were *S. pneumoniae* with *L. pneumophila* (three cases), *S. pneumoniae* with *Pseudomonas* spp. (three cases), *S. pneumoniae* with *M. pneumoniae* (two cases), *S. pneumoniae* with influenza virus (two cases), *M. pneumoniae* with influenza virus (two cases), and *C. pneumoniae* with *L. pneumophila* (two cases).

Table 2. Results of microbiological investigations performed on specimens obtained from 493 patients with community-acquired pneumonia

Microbiological investigation	No. (%) patients with positive result/total no. of patients for whom the test was performed
Serological testing (acute and convalescent samples)	122/401 (30.4)
Mycoplasma pneumoniae	45
Chlamydia spp.[a]	34
Legionella pneumophila	27
Influenza virus	22
Respiratory syncytial virus	5
Coxiella burnetii	4
Varicella-zoster virus	2
Adenovirus	1
Urinary antigen detection	119/454 (26.2)
Streptococcus pneumoniae	104
Legionella pneumophila	15
Gram's stain and culture from respiratory specimens (sputum + bronchoscopic samples)	52/286[b] (18.2)
Streptococcus pneumoniae	15
Pseudomonas spp.	14
Haemophilus influenzae	11
Gram-negative bacilli other than *Pseudomonas* spp.[c]	6
Staphylococcus aureus	4
Moraxella catarrhalis	2
Blood cultures	17/302 (5.6)
Streptococcus pneumoniae	13
Pseudomonas spp.	2
Escherichia coli	1
Listeria monocytogenes	1

[a]*Chlamydia pneumoniae* (18 cases), *Chlamydia psittaci* (10 cases). In six cases, there was a four-fold rise in antibodies against both *Chlamydia psittaci* and *Chlamydia pneumoniae*.
[b]Of the 286 specimens, 272 were expectorated sputum and 14 were bronchoscopic samples.
[c]*Klebsiella* spp. (three cases), *Enterobacter* spp. (one case), *Citrobacter* spp. (one case), *Stenotrophomonas* spp. (one case).

Microbial aetiology by age and co-morbidity

The distribution of the causative microorganisms by age group is shown in Table 3. *S. pneumoniae* was the single most prevalent organism in all groups, except in the youngest patients, where *Mycoplasma* was identified more frequently. Overall, bacterial pathogens accounted for 26.5% (59 of 223 cases) of pneumonias in patients aged ≥65 years, compared with 19.3% (52 of 270 cases) in younger patients (p 0.06). Pneumonias caused by Gram-negative bacilli, including *Pseudomonas* spp., were also more common in older patients; 12 (75%) of the 16 cases were diagnosed in patients aged ≥65 years. Atypical pathogens were more prevalent in younger patients, and showed a declining trend with age. There were no significant trends according to age group in the incidence of pneumonia caused by other pathogens.

Co-morbidity was also related to the aetiology of CAP (Table 4). Overall, infections caused by atypical pathogens were seen more frequently in patients without co-morbidities, whereas bacterial infections tended to occur more commonly in patients with underlying conditions. *S. pneumoniae* was the single most prevalent organism in both groups, but was detected more frequently in patients with underlying disease (21.1% vs. 13.3%; p 0.02). Pneumonias caused by Gram-negative enteric bacilli or *Pseudomonas* spp. were also more common among patients with co-morbid conditions, where they accounted for 5.3% of the cases, compared with 1.5% in patients without co-morbid conditions (p 0.02). Overall, of 111 episodes of bacterial infection, 65 (58.6%) occurred in patients with co-morbidities, compared with 45 (40.5%) in patients without underlying disease (p 0.002). In contrast to bacterial infections, 66 (72.5%) of 91 episodes of atypical infection occurred in patients without underlying disease, compared with 25 (27.5%) in patients with co-morbidities ($p < 0.001$). In patients

Table 3. Distribution of the causative microorganisms identified in 493 patients with community-acquired pneumonia according to age group

Microorganism	Total (*n* = 493) No. (%)	Aged 15–44 years (*n* = 161) No. (%)	Aged 45–64 years (*n* = 109) No. (%)	Aged 65–74 years (*n* = 87) No. (%)	Aged ≥ 75 years (*n* = 136) No. (%)
Bacterial pathogens	111 (22.5)	29 (18.0)	23 (21.1)	23 (26.4)	36 (26.5)
Streptococcus pneumoniae	83 (16.8)	23 (14.3)	17 (15.6)	17 (19.5)	26 (19.1)
Pseudomonas spp.	11 (2.2)	2 (1.2)	2 (1.8)	2 (2.3)	5 (3.7)
Haemophilus influenzae	9 (1.8)	2 (1.2)	4 (3.7)	2 (2.3)	1 (0.7)
Gram-negative bacilli other than *Pseudomonas* spp.[a]	5 (1.0)	0	0	1 (1.1)	4 (2.9)
Staphylococcus aureus	2 (0.4)	2 (1.2)	0	0	0
Moraxella catarrhalis	1 (0.2)	0	0	1 (1.1)	0
Atypical pathogens	91 (18.5)	44 (27.3)[b]	25 (22.9)	12 (13.8)	10 (7.4)
Mycoplasma pneumoniae	38 (7.7)	28 (17.4)[c]	3 (2.8)	4 (4.6)	3 (2.2)
Legionella pneumophila	21 (4.3)	4 (2.5)	10 (9.2)	5 (5.7)	2 (1.5)[d]
Chlamydia spp.[e]	30 (6.1)	10 (6.2)	12 (11.0)	3 (3.4)	5 (3.7)
Coxiella burnetii	2 (0.4)	2 (1.2)			
Virus pathogens	20 (4.1)	5 (3.1)	5 (4.6)	5 (5.7)	5 (3.7)
Influenza virus	14 (2.8)	3 (1.9)	5 (4.6)	3 (3.4)	3 (2.2)
Respiratory syncytial virus	4 (0.8)	0	0	2 (2.3)	2 (1.5)
Adenovirus	1 (0.2)	1 (0.6)	0	0	0
Varicella-zoster virus	1 (0.2)	1 (0.6)	0	0	0
Mixed aetiology[f]	28 (5.7)	10 (6.2)	6 (5.5)	3 (3.4)	9 (6.6)
Unknown	243 (49.3)	73 (45.3)	50 (45.9)	44 (50.6)	76 (55.9)

[a]*Klebsiella* spp. (two cases), *Escherichia coli* (one case), *Citrobacter* spp. (one case), *Stenotrophomonas* spp. (one case).
[b]p 0.001 for the comparison with the rest of the patients.
[c]p < 0.001 for the comparison with the rest of the patients.
[d]p 0.007 for the comparison with the rest of the patients.
[e]*Chlamydia pneumoniae* (15 cases), *Chlamydia psittaci* (nine cases). In six cases, there was a four-fold rise in antibodies against both *C. psittaci* and *C. pneumoniae*.
[f]*S. pneumoniae* and *L. pneumophila* (three cases), *S. pneumoniae* and *Pseudomonas* spp. (three cases), *S. pneumoniae* and *M. pneumoniae* (two cases), *S. pneumoniae* and influenza virus (two cases), *M. pneumoniae* and influenza virus (two cases), *L. pneumophila* and *C. pneumoniae* (two cases), *S. pneumoniae* and *Haemophilus* spp. (one case), *S. pneumoniae* and *S. aureus* (one case), *S. pneumoniae* and *Klebsiella* spp. (one case), *S. pneumoniae* and *Enterobacter* spp. (one case), *S. pneumoniae* and *Moraxella catarrhalis* (one case), *S. pneumoniae* and *Coxiella burnetii* (one case), *M. pneumoniae* and *H. influenzae* (one case), *C. psittaci* and *Listeria monocytogenes* (one case), *C. pneumoniae* and *Cox. burnetti* (one case), *L. pneumophila* and influenza virus (one case), influenza virus and varicella-zoster virus (one case), influenza virus and respiratory syncytial virus (one case), *S. pneumoniae*, *M. pneumoniae* and influenza virus (one case), *M. pneumoniae*, *S. pneumoniae* and *Staphylococcus aureus* (one case).

Table 4. Distribution of the causative microorganisms identified in 493 patients with community-acquired pneumonia according to co-morbidity

Microorganism	Absence of co-morbidity[a] (*n* = 264) No. (%)	Underlying conditions[a] (*n* = 227) No. (%)	COPD (*n* = 99) No. (%)	Diabetes mellitus (*n* = 98) No. (%)	Dementia (*n* = 52) No. (%)
Bacterial pathogens	45 (17.0)	65 (28.6)	29 (29.3)	26 (26.5)	14 (26.9)
Streptococcus pneumoniae	35 (13.3)	48 (21.1)	18 (18.2)	22 (22.4)	11 (21.2)
Pseudomonas spp.	3 (1.1)	8 (3.5)	6 (6.0)[b]	2 (2.0)	1
Haemophilus influenzae	5 (1.9)	4 (1.8)	2	1	0
Gram-negative bacilli other than *Pseudomonas* spp.[c]	1 (0.4)	4 (1.8)	2	1	2
Staphylococcus aureus[d]	1 (0.4)	0	0	0	0
Moraxella catarrhalis	0	1 (0.4)	1	0	0
Atypical pathogens	66 (25.0)[e]	25 (11.0)	10 (10.1)	18 (18.4)	4 (7.7)
Mycoplasma pneumoniae	30 (11.4)[e]	8 (3.5)	2	6	2
Legionella pneumophila	11 (4.2)	10 (4.4)	6	5	1
Chlamydia spp.[f]	23 (8.7)[g]	7 (3.1)	2	6	1
Coxiella burnetii	2 (0.8)	0	0	0	0
Virus pathogens	10 (3.9)	10 (4.4)	2 (2.0)	6 (6.1)	4 (7.7)
Influenza virus	8 (3.0)	6 (2.6)	1	4	3
Respiratory syncytial virus	0	4 (1.8)	1	2	1
Adenovirus	1 (0.4)	0	0	0	0
Varicella-zoster virus	1 (0.4)	0	0	0	0
Mixed aetiology	9 (3.4)	18 (7.9)	7 (7.1)	1 (1.0)	7 (13.5)
Unknown	134 (50.8)	109 (48.0)	51 (51.5)	47 (48.0)	23 (44.2)

COPD, chronic obstructive pulmonary disease.
[a]One or more of the following conditions: diabetes, chronic lung or heart disease, chronic liver disease, chronic renal insufficiency, cancer, immunosuppression, dementia, malnutrition. Information about underlying conditions was unavailable for two patients.
[b]p 0.015 for the comparison with patients without underlying conditions.
[c]*Klebsiella* spp. (two cases), *Escherichia coli* (one case), *Citrobacter* spp. (one case), *Stenotrophomonas* spp. (one case).
[d]Data regarding underlying disease were unavailable for one of the patients.
[e]p 0.001 for the comparison with patients with underlying conditions.
[f]*Chlamydia pneumoniae* (15 cases), *Chlamydia psittaci* (nine cases). In six cases, there was a four-fold rise in antibodies against both *C. psittaci* and *C. pneumoniae*.
[g]p 0.01 for the comparison with patients with underlying conditions.

without co-morbidity, atypical organisms were the most frequent group of pathogens, accounting for 25% of all pneumonia cases. Interestingly, whereas pneumonias caused by *Mycoplasma* and *Chlamydia* spp. were more common among patients without co-morbidity, the prevalence of

L. pneumophila was the same in patients with or without co-morbidities. The overall frequency of virus infections was also similar in patients with or without underlying disease, but all pneumonias caused by respiratory syncytial virus were seen in patients with co-morbidities.

The aetiological distribution found in patients with the three major underlying diseases is shown in Table 4. Of particular note is the leading position of *S. pneumoniae* in all groups, and the significant association of *Pseudomonas* spp. with chronic obstructive pulmonary disease.

Aetiology by severity and site-of-care

Microbial diagnosis of CAP also varied according to severity and site-of-care, but *S. pneumoniae* was the single most prevalent organism in all specified groups. In patients classified into low-severity risk classes (I–III) of the PSI, *S. pneumoniae* (14.9%), *M. pneumoniae* (8.9%) and *C. pneumoniae* (4.9%) were the pathogens detected most frequently (Table 5). Compared to patients in high-severity risk classes, those classified in low-severity classes had a higher prevalence of atypical pathogens (20.8% in classes I–III vs. 11.4% in classes IV/V; p 0.02). The main aetiological agents identified in the high-severity risk classes (IV/V) were *S. pneumoniae* (22.8%), *L. pneumophila* (4.1%) and *M. pneumoniae* (4.1%). *Chlamydia* spp. were very rare among patients in high-severity risk classes (Table 5).

The distribution of aetiological agents by site-of-care mimicked the distribution according to severity (Table 6). *S. pneumoniae* was the organism detected most frequently in both inpatients and outpatients. The only significant difference between inpatients and outpatients was in the prevalence of infections caused by atypical pathogens; these occurred more frequently in outpatients than in patients admitted to hospital (27.3% vs. 15.2%; p 0.004). Fifteen (93.7%) of the 16 cases of pneumonia caused by Gram-negative bacilli or *Pseudomonas* spp. were diagnosed in patients who were admitted to hospital.

Outcomes and factors associated with mortality

Analysis of different variables showed a lower rate of hospital admission for patients with atypical aetiology (60.4%) compared with bacterial (79.1%; p 0.005) and unknown (74.9%; p 0.01) aetiology. The hospitalisation rate was highest for patients infected with Gram-negative bacilli, including *Pseudomonas* spp. (93.3%), followed by those infected with more than one organism (82.2%), pneumococci (77.1%), unidentified organisms (74.9%), viruses (70%) and *M. pneumoniae* (55.3%). Excluding patients who died, the mean (range) hospital stay was 8.87 (1–52) days. The mean period of hospitalisation was longer for patients with bacterial pneumonia (11.44 ± 8.95 days) than for those with atypical pathogens (7.36 ± 4.21 days; p 0.001) and viral pneumonia (7.64 ± 3.57 days; p 0.009).

Table 5. Distribution of the causative microorganisms identified in 493 patients with community-acquired pneumonia according to severity

Microorganism	Low-severity risk classes (I–III) of the PSI (n = 370) No. (%)	High-severity risk classes (IV/V) of the PSI (n = 123) No. (%)	p
Bacterial pathogens	74 (20.0)	37 (30.1)	0.02
Streptococcus pneumoniae	55 (14.9)	28 (22.8)	0.05
Pseudomonas spp.	7 (1.9)	4 (3.3)	NS
Haemophilus influenzae	7 (1.9)	2 (1.6)	NS
Gram-negative bacilli other than *Pseudomonas* spp.[a]	2 (0.5)	3 (2.4)	NS
Staphylococcus aureus	2 (0.5)	0	NS
Moraxella catarrhalis	1 (0.3)	0	NS
Atypical pathogens	77 (20.8)	14 (11.4)	0.02
Mycoplasma pneumoniae	33 (8.9)	5 (4.1)	0.08
Legionella pneumophila	15 (4.1)	6 (4.9)	NS
Chlamydia spp.[b]	27 (7.3)	3 (2.4)	0.05
Coxiella burnetii	2 (0.5)	0	NS
Virus pathogens	15 (4.1)	5 (4.1)	NS
Influenza virus	11 (3.0)	3 (2.4)	NS
Respiratory syncytial virus	2 (0.5)	2 (1.6)	NS
Adenovirus	1 (0.3)	0	NS
Varicella-zoster virus	1 (0.3)	0	NS
Mixed pneumonia	17 (4.6)	11 (8.9)	NS
Unknown	187 (50.5)	56 (45.5)	NS

PSI, pneumonia patient outcomes research team (PORT) severity index; NS, not significant.
[a]*Klebsiella* spp. (two cases), *Escherichia coli* (one case), *Citrobacter* spp. (one case), *Stenotrophomonas* spp. (one case).
[b]*Chlamydia pneumoniae* (15 cases), *Chlamydia psittaci* (nine cases). In six cases, there was a four-fold rise in antibodies against both *C. psittaci* and *C. pneumoniae*.

Table 6. Distribution of the causative microorganisms identified in 493 patients with community-acquired pneumonia according to site-of-care

Microorganism	Patients admitted to hospital (n = 361) No. (%)	Outpatients (n = 132) No. (%)	p
Bacterial pathogens	88 (24.4)	23 (17.4)	NS
Streptococcus pneumoniae	64 (17.7)	19 (14.4)	NS
Pseudomonas spp.	10 (2.8)	1	NS
Haemophilus influenzae	6 (1.7)	3 (2.3)	NS
Gram-negative bacilli other than *Pseudomonas* spp.[a]	5 (1.4)	0	NS
Staphylococcus aureus	2	0	NS
Moraxella catarrhalis	1	0	NS
Atypical pathogens	55 (15.2)	36 (27.3)	0.004
Mycoplasma pneumoniae	21 (5.8)	17 (12.9)	0.009
Legionella pneumophila	17 (4.7)	4 (3.0)	NS
Chlamydia spp.[b]	17 (4.7)	13 (9.8)	0.05
Coxiella burnetti	2	0	NS
Virus pathogens	14 (3.9)	6 (4.5)	NS
Influenza virus	10 (2.8)	4 (3.0)	NS
Respiratory syncytial virus	4 (1.1)	0	NS
Adenovirus	0	1	NS
Varicella-zoster virus	0	1	NS
Mixed aetiology	23 (6.4)	5 (3.8)	NS
Unknown	175 (48.5)	62 (46.9)	NS

NS, not significant.
[a]*Klebsiella* spp. (two cases), *Escherichia coli* (one case), *Citrobacter* spp. (one case), *Stenotrophomonas* spp. (one case).
[b]*Chlamydia pneumoniae* (15 cases), *Chlamydia psittaci* (nine cases). In six cases, there was a four-fold rise in antibodies against both *C. psittaci* and *C. pneumoniae*.

Of 490 patients for whom treatment information was available, 223 (45.5%) received combined therapy with a macrolide plus a β-lactam antibiotic, 106 (21.6%) received monotherapy with a β-lactam, 46 (9.4%) received a macrolide alone, 85 (17.3%) received a 'respiratory' fluoroquinolone, and 30 (6.1%) received other antibiotics. The antibiotics prescribed varied according to site-of-care. Monotherapy with macrolides was prescribed predominantly in the outpatient setting (30 (65.2%) of 46 prescriptions), whereas combined therapy was given mostly to patients admitted to hospital (191 (85.7%) of 223 prescriptions). Forty-three (50.6%) of 85 courses of fluoroquinolones were administered to outpatients, and 42 (49.4%) to hospitalised patients.

Of 361 patients admitted to hospital, 24 died within the 4-week follow-up period, with a mortality rate of 6.6% (95% CI, 4.40–9.87). Causative pathogens identified in 11 (45.8%) of the 24 patients who died were *S. pneumoniae* (n = 6), *Pseudomonas* spp. (n = 1), *Escherichia coli* (n = 1) and mixed infections (*S. pneumoniae* with *Pseudomonas* spp. in two cases, and *S. pneumoniae* with *Staph. aureus* in one case). Five (3.8%) of the 132 ambulatory patients eventually required hospital admission, but all five had a favourable outcome.

The overall mortality rate, including both inpatients and outpatients, was 4.8% (95% CI, 3.21–7.26). Mortality according to the PSI risk classes was as follows: (1) classes I/II, 0.75% (two of 266 cases); (2) class III, 1.96% (two of 102 cases); (3) class IV, 11.82% (11 of 93 cases); and (4) class V, 32.14% (nine of 28 cases). In addition to PSI risk class, the following variables were associated significantly with mortality by univariate analysis: age >65 years, presence of co-morbidity, shock, altered mental status at admission, increased respiratory rate (> 30/min), respiratory failure (PO_2/F_IO_2 < 300), renal failure (creatinine >150 mmol/L), bacteraemia, aspiration pneumonia, and antibiotic therapy not including a macrolide or a fluoroquinolone (Table 7). No association was found between gender, previous antibiotic therapy, immunodepression, temperature at presentation, white blood cell count, multilobar involvement, Gram-negative pneumonia or infection with *Pseudomonas* spp., and mortality.

In the multivariate analysis, shock (OR 34.48), age >65 years (OR 25) and altered mental status (OR 9.92) were the only independent predictors of mortality that were statistically significant.

The potential association between antimicrobial regimens and either complications or mortality was explored by univariate and multivariate analysis in different subgroups of patients. There was no association between combined antimicrobial therapy and either complications or mortality in patients with any particular aetiology of CAP, including bacterial pneumonia, mixed pneumonia, pneumococcal pneumonia, or Gram-negative pneumonia. Although an association was found between combined antimicrobial therapy,

Table 7. Variables associated with mortality in 493 patients with community-acquired pneumonia by univariate analysis

Characteristic	Survived (n = 469) No. (%)	Died (n = 24) No. (%)	OR	95% CI	p
Age > 65 years	194/469 (41.4)	22/24 (91.7)	15.62	3.62–66.66	< 0.001
Predefined underlying conditions[a]	203/467 (43.5)	24/24 (100%)	1.12	1.07–1.17	< 0.001
Shock	5/465 (1.1)	6/24 (25)	30.30	8.55–111.11	< 0.001
Altered mental status at admission	36/432 (7.7)	16/24 (66.7)	24.0	9.62–59.88	< 0.001
Increased respiratory rate (> 30/min)	38/468 (8.1)	9/24 (37.5)	6.80	2.79–16.67	< 0.001
Respiratory failure (PO_2/F_iO_2 < 300)	172/381 (45.1)	18/21 (85.7)	7.30	2.11–25	< 0.001
Renal failure (creatinine > 150 mmol/L)	33/465 (7.1)	6/23 (26.1)	4.59	1.69–12.35	0.007
Bacteraemia	13/465 (2.8)	3/24 (12.5)	4.98	1.31–18.87	0.03
Aspiration pneumonia	15/455 (3.3)	12/24 (50)	29.41	11.36–76.92	< 0.01
Antibiotic therapy not including a macrolide or a fluoroquinolone	124/466 (26.6)	12/24 (50)	2.75	1.21–6.29	0.01

Data are no. patients/no. for whom data were available (%), unless otherwise indicated.
[a]One or more of the following conditions: diabetes, chronic lung or heart disease, chronic liver disease, chronic renal insufficiency, cancer, immunosuppression, dementia, malnutrition.

including either a macrolide or a fluoroquinolone, and reduced mortality by univariate analysis, the association was not confirmed by multivariate analysis.

DISCUSSION

This prospective study provides comprehensive data for a large cohort of patients with CAP and offers updated epidemiological information that may be especially relevant in light of recent developments in many aspects of this disease. The uniform sampling in all groups of patients, the comprehensive search for microorganisms, and the use of standard diagnostic tests and criteria to establish the aetiological diagnosis form an important addition to our present knowledge of the epidemiology of CAP.

Among the most interesting observations from the cohort were the older age of the population, compared with previous population-based studies [33–39], and the high prevalence of dementia as an underlying disease. The older age of the population may have accounted in part for the higher proportion of patients admitted to hospital compared with other population-based studies carried out in the last decade. In the present study, dementia emerged as a significant co-morbid illness in patients with CAP, ranking after chronic obstructive pulmonary disease and diabetes mellitus. Pneumonia is one of the most serious medical conditions seen in late-stage dementia, and is a common cause of death in these patients [40]. The high prevalence of dementia observed in the present study is probably related to population ageing, which was also reflected in the older age of the patients included in the study. Although Alzheimer's disease is an increasing problem in the elderly, affecting 4.5 million individuals in the USA alone [41], the presence of dementia was not found to be a major risk factor for CAP in epidemiological studies published in the last decade. However, a recent study of CAP in patients aged ≥80 years admitted to hospital found that dementia was the fourth most common underlying disease after chronic obstructive pulmonary disease, chronic heart disease and diabetes mellitus [42]. Patients with dementia may be particularly susceptible to pneumonia because of their swallowing difficulties and the use of sedative medications, which are factors that have been found to increase the risk of pneumonia in elderly patients living in long-term care facilities [43,44]. The problem of pneumonia in patients with dementia may be more serious in the future in view of forecasts of a continued increase in the number of individuals with Alzheimer's disease [41].

A disappointing finding of the study was the fact that, despite the introduction of urinary antigen testing for *S. pneumoniae* and *L. pneumophila*, and the extensive serological tests performed, the aetiology remained unidentified for half of the cases, confirming that microbial diagnosis of CAP remains problematic. However, neither non-serological tests for viruses (e.g., immunofluorescence, virus culture) nor nucleic acid amplification techniques were used, and no attempt was made to look for emerging viruses, such as coronavirus, human metapneumovirus or hantavirus. The results obtained showed a high proportion of patients with pneumococcal CAP. *S. pneumoniae* was the most frequent organism identified, both in outpatients and in patients requiring admission to hospital, and it was also the most frequent pathogen involved in mixed infections and in fatal cases. This finding concurs with the results of previous studies of

hospitalised patients [8], but the frequency of *S. pneumoniae* in outpatients has varied widely [6,27–29,35,38,45]. Some studies have identified atypical organisms, such as *M. pneumoniae* [6,28] and *C. pneumoniae* [35], or viruses [46], more frequently than *S. pneumoniae*, but these differences probably reflect the different populations studied and the types of diagnostic test performed.

The results of the present study support the high prevalences of CAP caused by atypical pathogens reported previously [5,6,29,30,47], reaching 36% of all diagnosed cases in the present cohort, with *M. pneumoniae* accounting for 41.8% of all atypical pathogens. This observation agrees with the results of other studies in which *M. pneumoniae* has accounted for up to 60% of all atypical pathogens [5,29,47], reinforcing the pivotal role of this organism in CAP. In contrast, the importance of C. *pneumoniae* is not yet completely understood. In the last few years, *C. pneumoniae* has been identified with increasing frequency in some studies, reaching a proportion comparable to and ever higher than that of *Mycoplasma* [34,47], but has been found rarely in other cohorts [28,29]. The lack of a reference standard for diagnosis, combined with the occurrence of epidemic outbreaks during some studies, may account in part for the wide variations in the reported incidence rates. In order to determine the significance of *C. pneumoniae* as a cause of pneumonia in a population, it is critical to use standard diagnostic tests and criteria, and to perform studies for a sufficient length of time to avoid any seasonal bias. The present study used CDC criteria [48] for diagnosing definite acute infection by serology, and patients were recruited over a 2-year period. According to the results, *C. pneumoniae* is a significant pathogen in CAP, but its frequency is lower than that of *M. pneumoniae*, and much lower than that found in other pneumonia studies [6,34,47].

On comparison of aetiology by age group and co-morbidity, there were many similarities, but also some differences. Overall, the prevalence of CAP caused by atypical organisms was highest among young adults and patients without co-morbidities, reflecting the epidemiological pattern of *Mycoplasma* and *Chlamydia* infections. In contrast, pneumonias caused by *Legionella* were seen with similar frequency in young and older individuals, and in patients with or without co-morbidities. Although *Mycoplasma* and *Chlamydia* infections were more common in the youngest patients, 22% of all cases of pneumonia caused by these organisms occurred in patients aged >65 years. These findings agree with other studies reporting significant incidence rates of CAP caused by atypical pathogens in the elderly [49] and in patients with co-morbidities [50]. With regard to the aetiological distribution according to underlying diseases, *S. pneumoniae* held the leading position in all groups, while there was a significant association between *Pseudomonas* spp. and chronic obstructive pulmonary disease. Cases of staphylococcal pneumonia among diabetic patients were not observed.

On analysis of aetiology by site-of-care and severity, *S. pneumoniae* was again the single most prevalent organism both in patients admitted to hospital and in outpatients, and in low- and high-severity risk classes, emphasising that empirical antibiotic therapy should always be active against pneumococci. The incidence of CAP caused by atypical pathogens, including *M. pneumoniae* and *C. pneumoniae*, was highest among outpatients, but was also high among hospitalised patients. The importance of *M. pneumoniae*, *C. pneumoniae* and *Legionella* in pneumonias requiring hospitalisation has been highlighted in several previous studies of CAP [30,51,52]. Although atypical pathogens other than *Legionella* spp. have usually been associated with mild-to-moderate illness, severe cases requiring admission to an intensive care unit have also been reported [53]. In the CBPIS study [30], pneumonia caused by *M. pneumoniae* and *C. pneumoniae* accounted for between 8% (using criteria for definite diagnosis) and 35% (using criteria for possible diagnosis) of all patients with pneumonia who required hospitalisation. A recent study found that CAP patients aged ≥60 years with *Chlamydia* infection had the highest hospitalisation rate, leading to the suggestion that pneumonia caused by *Chlamydia* can rival even pneumococcal pneumonia for severity [47]. However, little information was actually available on the severity at presentation of atypical pneumonia using a validated prognostic tool. The results of the present study, using the validated PORT prediction rule for 30-day mortality and medical complications to quantify severity of illness at presentation, suggest that the severity of CAP caused by atypical organisms may have been overestimated. Indeed, most

patients with CAP caused by *M. pneumoniae* or *C. pneumoniae* had a disease of low severity, and all such patients had a favourable outcome. According to current recommendations [2], most of these cases should probably have been treated at home.

Legionella spp. have long been considered to be some of the most common pathogens causing severe CAP. However, the frequency with which *Legionella* spp. have been identified in case series of severe CAP has ranged from 21.8% [54] to 5% [55], and these organisms were found only rarely in large French studies [56,57]. Recent population-based data show that most cases of *Legionella* infection probably present as mild-to-moderate disease, rather than severe pneumonia [58,59]. In the largest outbreak of Legionnaires' disease to date, with more than 800 cases reported, one-third of the patients were managed as outpatients and a case fatality rate of only 1.1% was observed [58]. In the present population-based study using the PORT classification, of 21 cases of Legionnaires' disease, 15 (71.4%) were classified within 'low-severity' and six (28.6%) within 'high-severity' risk classes. Four (19%) of the 21 cases were managed as outpatients, only one (6%) of the 17 patients admitted required treatment in the intensive care unit, and none of these patients died.

The importance of epidemiological data in guiding empirical therapeutic decisions for patients with CAP has been recognised in different guidelines from specialist scientific societies [1–3]. Thus, patients with CAP are often classified into groups, each with a list of likely pathogens and a suggested empirical therapy, based on stratification according to age, place of therapy, co-morbidity and severity [1–3]. The present data confirmed that microbial diagnosis varies according to epidemiological factors, but there was too much overlap between groups for this information to be used as a guide for therapeutic decisions. Selection of empirical therapy is complicated further by the marked increase in β-lactam and macrolide resistance among isolates of *S. pneumoniae*, and by the increasing concern about mixed infections [5,10–14]. A low proportion of cases of CAP in the present study were considered to be of mixed aetiology. Mixed infections were seen across all age groups, including elderly patients, and in both hospitalised patients and outpatients [29,30,34].

Although the importance of treating multiple infecting pathogens has not been established, several observational studies indicate that the use of a macrolide with a cephalosporin, as part of an initial empirical regimen for patients with CAP admitted to hospital, may be associated with a shorter length of hospital stay and a lower mortality rate than treatment with a cephalosporin alone [60–63]. In addition, recent data suggest an advantage in using an empirical β-lactam–macrolide combination, rather than monotherapy, for the treatment of CAP that is associated subsequently with pneumococcal bacteraemia [16,17,64]. However, all of these investigations were retrospective, with design limitations and several sources of bias [65]. In the present study, combined therapy was not associated with a better outcome in the multivariate analysis when compared with monotherapy. Although the frequent involvement of pneumococci in mixed pneumonias would support a role for dual therapy in pneumococcal infection, no association was demonstrated between combined antibiotic therapy and outcome in patients with pneumococcal pneumonia. Although these findings may argue against the use of dual therapy in patients with pneumococcal pneumonia, the results should be interpreted with caution because the relatively small size of the groups affects the power and general applicability of the findings. In addition, as stated in the updated guidelines for CAP from the Infectious Diseases Society of America [2], until such time as a prospective, randomised trial clarifies this issue, identification of pneumococci should not prevent clinicians from pursuing other diagnostic possibilities (e.g., an 'atypical' co-pathogen), especially when the pneumonia is not responding to treatment.

The overall mortality rate in the present study was 4.8%, which is a figure similar to that found in other recent community-based studies of CAP [34,35,47]. For patients requiring hospitalisation, the 6.6% mortality rate resembles the rate of 8.8% in the CBPIS study [30], but is lower than other figures reported previously, which have averaged 12% [3]. Age, disease severity and underlying disease, as reflected by the PSI prediction rule, were factors that affected outcome. Indeed, mortality varied according to the PSI, with most fatal cases occurring in patients classified within risk classes IV and V. Although several variables were associated with mortality in the univariate analysis, only shock, an age >65 years and an altered mental status were associated independently with

increased mortality. As stated above, no association was found in multivariate analysis between mortality and either monotherapy or combination antibiotic therapy.

In summary, this study of CAP, conducted at the beginning of the 21st century, has confirmed many epidemiological features known from previous studies, but has also disclosed interesting and novel aspects of this disease. The study confirmed that microbial diagnosis of CAP remains problematic, and that the aetiology still cannot be identified in a considerable proportion of cases. Although certain epidemiological features may help to predict the microbial aetiology, the overlap between groups reduces the usefulness of this information in guiding therapeutic decisions. New microbiological techniques are required to improve the ability of laboratories to detect microbial pathogens causing CAP.

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