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Community-acquired pneumonia in outpatients: aetiology and outcomes

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ABSTRACT: The purpose of this study was to establish the microbial aetiology and outcomes of patients with community-acquired pneumonia (CAP) treated as outpatients after presenting to a hospital emergency care unit.

A prospective observational study was carried out in the Hospital Clinic of Barcelona (Barcelona, Spain). All consecutive cases of CAP treated as outpatients were included.

568 adult outpatients with CAP were studied (mean±SD age 47.2±17.6 yrs; 110 (19.4%) were aged ⩾65 yrs). Aetiological diagnoses were established in 188 (33.1%) cases. *Streptococcus pneumoniae* was the most frequent pathogen followed by *Mycoplasma pneumoniae* and respiratory viruses. *Legionella* was detected in 13 (2.3%) cases. More than one causative agent was found in 17 (9.0%) patients. Mortality was low (three (0.5%) patients died) and other adverse events were rare (30 (5.2%) patients had complications, 13 (2.3%) were re-admitted and treatment failed in 13 (2.3%)). Complications were mostly related to pleural effusion and empyema, and re-admissions and treatment failures to comorbidities.

Outpatients with CAP have a characteristic microbial pattern. Regular antipneumococcal coverage remains mandatory. Treatment failures and re-admissions are rare and may be reduced by increased attention to patients requiring short-term observation in the emergency care unit and in the presence of pleural effusion and comorbidities.

KEYWORDS: Community-acquired pneumonia, outpatients, respiratory infection

In both the USA and Europe, community-acquired pneumonia (CAP) is the most frequent cause of death due to infection and has considerable implications for healthcare systems worldwide [1–3].

Selection of the initial site of care is one of the most important clinical decisions made in the treatment of CAP and directly affects the intensity of laboratory testing, microbiological evaluation and antibiotic therapy [4]. The microbiology and outcomes of hospitalised patients with CAP is very well known [5–7]. A variety of severity assessment tools have been developed for the identification of patients at low risk in order to guide decisions on hospitalisation [8, 9]. Previous studies have been performed outside the hospital [10–12]. Surprisingly, there are no data from patients visiting the emergency department, and treated as outpatients and followed up for 1 month. The purpose of this study was to establish the aetiology and outcomes of a large series of nonhospitalised patients with CAP who initially visited the emergency department.

METHODS

Study setting and design

Prospective observational study carried out in the Hospital Clinic of Barcelona (Barcelona, Spain), an 800-bed, third-level hospital covering an urban population of 540,000 inhabitants. All consecutive cases of CAP visiting the emergency department and treated as outpatients from January 2000 to July 2010 were included.

Study population

The study population consisted of adults aged ⩾16 yrs consecutively admitted to the emergency department with a diagnosis of CAP and discharged for ambulatory treatment. Pneumonia was

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defined in the presence of a new infiltrate on the chest radiograph (evaluated by the attending physician prior to deciding treatment and site of care), together with symptoms suggestive of a lower respiratory tract infection and the absence of an alternative diagnosis during follow-up. Exclusion criteria were: severe immunosuppression, such as in solid-organ or bone-marrow transplantation or AIDS, or receiving chemotherapy or other immunosuppressive drugs (>20 mg prednisone-equivalent per day for ⩾2 weeks); active tuberculosis; healthcare-associated pneumonia; and cases with a confirmed alternative diagnosis at the end of follow-up.

This study was approved by the ethical committee of the Hospital Clinic of Barcelona (registration number 2009/5451). Patient data were anonymised and informed consent was waived due to the observational nature of the study.

Data collection and follow-up

Data collected at the time of hospital admission has been reported previously [6]. All surviving patients were re-examined or at least contacted by telephone ⩾30 days after discharge from the emergency care unit. Pneumonia Severity Index (PSI) and CURB-65 (confusion of new onset, urea >7 mmol·L^{-1}, respiratory rate ⩾30 breaths·min^{-1}, blood pressure <90 mmHg systolic or diastolic blood pressure ⩽60 mmHg, and age ⩾65 yrs) score classes were assigned according to the original authors' designations [8, 9].

Definitions

Outpatient treatment was defined as discharge from the emergency care observation unit to any outpatient setting or discharge from an emergency care observation unit within 24 h of presentation [13].

Current smokers were defined as anyone who had at some time smoked at least one cigarette per day or one cigar or pipe per week for ⩾1 yr; an ex-smoker was defined as a smoker who had given up the habit ⩾1 yr before the diagnosis of CAP [14]. Alcohol abuse was considered in cases with a current intake of ⩾80 g of alcohol per day in males and 60 g per day in females [15].

Appropriateness of empirical antibiotic treatment in all patients was defined according to the treatment guidelines of the Spanish Society of Pulmonology and Thoracic Surgery (SEPAR) [4]. Appropriateness of empirical antimicrobial treatment in patients with known aetiology was defined when the isolated pathogens were susceptible *in vitro* to at least one of the antimicrobial agents administered.

Treatment failure was defined as clinical deterioration within 72 h of treatment resulting from one or more of the following causes: haemodynamic instability; appearance or impairment of respiratory failure; radiographic progression; or the appearance of new metastatic infectious foci (modified from the criteria used by MENENDEZ *et al*. [16]).

Microbiological evaluation

Regular sampling included sputum specimens, two blood cultures, urine samples for detection of *Streptococcus pneumoniae* (Binax Now *S. pneumoniae* Urinary Antigen Test; Emergo Europe, The Hague, the Netherlands) and *Legionella pnemophila* serogroup 1 (Binax Now *L. pneumophila* Urinary Antigen Test; Trinity Biotech, Bray, Ireland), and nasopharyngeal swabs for respiratory virus detection. Diagnosis of the following microorganisms was performed by means of paired serology at admission and during the third or sixth week thereafter: 1) atypical microorganisms, including *L. pneumophila* serogroup 1, *Chlamydophila pneumoniae, Chlamydia psittaci*, *Mycoplasma pneumoniae* and *Coxiella burnetii*; 2) respiratory viruses, *i.e.* influenza virus (A and B), parainfluenza virus (1, 2 and 3), respiratory syncytial virus and adenovirus. High titres of immunoglobulin (Ig)M antibodies in the serum during the acute phase was accepted for the diagnosis of atypical microorganisms, such as *C. pneumoniae* (⩾1:32), *C. burnetii* (⩾1:80) and *M. pneumoniae* (any positive titre).

Diagnostic criteria

The aetiology of pneumonia was classified as presumptive if a valid sputum sample yielded one or more predominant bacterial strain. The aetiology was considered definite if one of the following criteria was met: 1) blood culture yielding a bacterial or fungal pathogen (in the absence of an apparent extrapulmonary focus); 2) seroconversion (*i.e.* a four-fold increase in IgG titre for *L. pneumophila* (⩾1:128), *C. pneumoniae* IgG (⩾1:512), *C. psittaci* IgG (⩾1:64), *C. burnetii* (⩾1:80) and respiratory viruses (*i.e.* influenza viruses A and B, parainfluenza virus 1 to 3, respiratory syncytial virus and adenovirus); 3) a single IgM titre for *C. pneumoniae* (⩾1:32), *C. burnetii* (⩾1:80) and *M. pneumoniae* (any titre); 4) a single titre (⩾1:128) or a positive urinary antigen test for *L. pneumophila* serogroup 1; 5) a positive urinary antigen test for *S. pneumoniae*. For the purpose of this study, presumptive and definitive diagnoses were analysed together.

Strains were initially screened for susceptibility to antimicrobial agents using Sensititre (Trek Diagnostic Systems Ltd, East Grinstead, UK). Penicillin and other antibiotic susceptibilities were defined according to the 2008 breakpoints of the Clinical Laboratory Standards Institute (Wayne, PA, USA).

Statistical analysis

Categorical variables were described as frequencies and percentages. Continuous variables were expressed as means and standard deviations or medians and interquartile ranges for data that were not normally distributed (Kolmogorov–Smirnov test).

Categorical variables were compared with Fisher's exact test where appropriate. All tests were two-tailed and significance was set at 5%. All analyses were performed with SPSS version 16.0 for Windows (SPSS Inc., Chicago, IL, USA).

RESULTS

Patient characteristics

During the study period, a total of 3,223 adult patients with CAP were admitted to our hospital; of these, 2,655 (82.4%) were hospitalised and 568 (17.6%) were treated as outpatients. The annual percentage of outpatients with CAP ranged between 9% and 23% during the study period (2000–2010). We analysed a total of 568 adult outpatients. There were 301 (53.0%) males and 267 (47.0%) females, with a mean age of 47.2±17.6 yrs; 110 (19.4%) were aged ⩾65 yrs. We re-examined 550 (97%) patients in ambulatory setting and contacted only 18 (3%) patients by telephone. The main clinical characteristics and radiological findings are summarised in tables 1 and 2.

TABLE 1 Clinical characteristics of outpatients

Patients n	568
Demographic	
Age yrs	47.2±17.6
Age ⩾65 yrs	110 (19.4)
Male	301 (53.0)
Current smoking	214 (37.9)
Current alcohol abuse	71 (12.6)
Previous antibiotic	139 (25.0)
Influenza vaccine	97 (19.6)
Pneumococcal vaccine	25 (5.1)
Comorbidity	185 (32.6)
Chronic respiratory disease	125 (22.0)
Neurological disease	38 (6.7)
Diabetes mellitus	30 (5.3)
Chronic cardiovascular disease	15 (2.6)
Chronic liver disease	15 (2.6)
Chronic renal disease	4 (0.7)
Bacteraemia	21 (5.8)#
Multilobar infiltration	36 (6.5)
Pleural effusion	30 (6.2)
PSI	
I–III	551 (97.0)
IV	17 (3.0)
CURB-65	
0–1	538 (94.7)
2	30 (5.3)
30-day mortality	3 (0.5)

Data are presented as mean± SD or n (%), unless otherwise stated. PSI: Pneumonia Severity Index; CURB-65: confusion of new onset, urea >7 mmol·L^{-1}, respiratory rate ⩾30 breaths·min^{-1}, blood pressure <90 mmHg systolic or diastolic blood pressure ⩽60 mmHg, and age ⩾65 yrs. #: percentage was calculated in patients with blood culture (n=362).

TABLE 2 Clinical presentation and laboratory data on admission

Patients n	568
Symptoms	
Previous ''common cold'' symptoms	224 (40.1)
Fever	505 (88.9)
Chills	314 (56.6)
Cough	454 (80)
Purulent sputum	300 (52.8)
Pleuritic pain	292 (52.5)
Dyspnoea	199 (35.4)
Nausea/vomiting	85 (20.9)
Radiographic features	
Alveolar infiltrate pattern	510 (89.8)
Interstitial infiltrate pattern	40 (7.0)
Mixed infiltrate pattern	18 (3.2)
Pleural effusion	35 (6.3)
Atelectasis	15 (2.7)
Lobes affected	
1	532 (93.7)
⩾2	36 (6.3)
Vital signs	
Respiratory rate breaths·min^{-1}	20.0±6.0
Heart rate beats·min^{-1}	92.0±22.0
Systolic blood pressure mmHg	120.0±26.0
Diastolic blood pressure mmHg	72.0±12.0
Laboratory findings median (IQR)	
C-reactive protein mg·dL^{-1}	12.2 (15.4)
Creatinine mg·dL^{-1}	0.9 (0.3)
WBC count ×10^9 cells·L^{-1}	10.9 (7.6)
Platelet count ×10^9 platelets·L^{-1}	248.5 (114.3)

Data are presented as n (%) or mean± SD, unless otherwise stated. IQR: interquartile range; WBC: white blood cell.

A total of 139 (25.0%) patients had received previous antimicrobial treatment prior to the emergency department visit as follows: β-lactams in 79 (56.8%), fluoroquinolones in 24 (17.3%), macrolides in 18 (12.9%) and other antimicrobial agents in 18 (12.9%) patients.

The distribution of groups by severity scores (PSI and CURB-65) is shown in table 1. In the emergency department, both scores placed most of the patients in the low-risk group (PSI 97.0%; CURB-65 94.7%).

Microbial aetiology

A complete or partial microbiological investigation was possible in 527 (92.8%) patients while no microbiological test was performed in 41 (7.2%). Aetiological diagnoses were established in 188 (33.1%) cases. Of the 380 (66.9%) patients without a defined aetiology, one-quarter (25.0%) had received antimicrobial treatment in the previous 30 days.

As shown in tables 3 and 4, the most frequent pathogens isolated were *S. pneumoniae* (n=66; 35.1%), *M. pneumoniae* (n=29; 15.4%), respiratory viruses (n=25; 13.3%), *L. pneumophila* (n=13; 6.9%), *C. burnetii* (n=11; 5.9%), *C. pneumoniae* (n=10; 5.3%) and *Haemophilus influenzae* (n=9; 4.8%). Unfortunately we did not record or investigate the possible source of *C. burnetii* infection in our series. More than one causative agent was found in 17 (9.0%) patients and *S. pneumoniae* was the most frequent microorganism involved in mixed infections (14 out of 17; 82.4%).

21 (3.7%) patients had bacteraemia (due to *S. pneumoniae* in 16 patients, *H. influenzae* in two, *Streptococcus viridans* in one, *Escherichia coli* in one and *P. aeruginosa* in one) (table 4). Patients with bacteraemia were re-evaluated when blood was drawn for culture in a daytime hospital setting to assess patients' clinical conditions (except for the case of *P. aeruginosa* bacteraemia that was lost at follow-up) and after 1 month in the outpatient clinic for follow-up. 34 isolates of *S. pneumoniae* were tested for susceptibility, with 30 (88.2%) being susceptible to penicillin and four (11.7%) resistant to penicillin. 28 (82.3%) were sensitive to erythromycin and six (17.6%) were resistant. Four (11.7%) were sensitive to cefotaxime and one (2.9%) was resistant.

Seven patients with positive blood cultures for *S. pneumoniae* also presented positive urinary antigen tests and three patients with positive pleural fluid also presented positive urinary antigen tests.

TABLE 3 Distribution of the causative microorganisms identified in community-acquired pneumonia outpatients

	Total population	Population with defined aetiology
Patients n	568	188
Streptococcus pneumoniae	66 (11.6)	66 (35.1)
Streptococcus viridans	2 (0.4)	2 (1.1)
Staphylococcus aureus	1 (0.2)	1 (0.5)
Haemophilus influenzae	9 (1.58)	9 (4.8)
Escherichia coli	1 (0.2)	1 (0.5)
Pseudomonas aeruginosa	1 (0.2)	1 (0.5)
Others	3 (0.5)	3 (1.6)
Atypical	63 (11.1)	63 (33.5)
Legionella pneumophila	13 (2.3)	13 (6.9)
Mycoplasma pneumoniae	29 (5.1)	29 (15.4)
Coxiella burnetii	11 (1.9)	11 (5.9)
Chlamydophila pneumoniae	10 (1.8)	10 (5.3)
Respiratory virus	25 (4.4)	25 (13.3)
Rhinovirus	6 (1.1)	6 (24.0)
Influenza virus A	14 (2.5)	14 (56.0)
Influenza virus B	2 (0.4)	2 (8.0)
Adenovirus	1 (0.2)	1 (4.0)
Respiratory syncytial virus	1 (0.2)	1 (4.0)
Parainfluenza virus 2	1 (0.2)	1 (4.0)
Mixed	17 (3.0)	17 (9.0)
S. pneumoniae + influenza A virus	9 (1.6)	9 (52.9)
H. influenzae + influenza virus A	2 (0.4)	2 (11.7)
S. pneumoniae + *H. influenzae*	2 (0.4)	2 (11.7)
S. pneumoniae + adenovirus	1 (0.2)	1 (5.8)
S. pneumoniae + *P. aeruginosa*	1 (0.2)	1 (5.8)
S. pneumoniae + rhinovirus	1 (0.2)	1 (5.8)
L. pneumophila + rhinovirus	1 (0.2)	1 (5.8)

Data are presented as n (%), unless otherwise stated.

The distribution of aetiology according to comorbidity is shown in table 5. Atypical pathogens, particularly *M. pneumonia*e, were more frequently present in patients without comorbidities, whereas *S. pneumoniae* and *Legionella* were more frequently present in patients with comorbidities. We also analysed the distribution of aetiologies according to smoking and alcohol habits, and the only significant result was that *L. pneumophila* and *H. influenzae* were more frequent in alcohol abusers (table S1a and b).

Initial empirical antimicrobial treatment

The initial antimicrobial treatment was fluoroquinolone monotherapy (n=315; 55.5%), a β-lactam plus a macrolide (n=133; 23.4%), β-lactam monotherapy (n=40; 7.0%), fluoroquinolones plus a β-lactam (n=34; 6.0%), macrolide monotherapy (n=31; 5.5%), a fluoroquinolone plus a macrolide (n=11; 1.9%) or other combinations (n=4; 0.7%). The initial empiric antimicrobial treatment followed the SEPAR guidelines in 496 (87.3%) patients and was adequate according to the aetiology in 172 (91.4%) out of 188 patients with a defined aetiology.

Outcomes

Mortality

The 30-day mortality was 0.5% (n=3) (two patients were re-admitted to hospital due to pneumonia and one patient was re-admitted for another cause). Two patients had comorbid chronic respiratory disease and another had acute leukaemia. The aetiology was established in two patients (*Streptococcus viridans* (n=1) and adenovirus (n=1)). The complications in these patients were bacteraemia and multilobar infiltration. Empirical antibiotic treatment was inadequate in two patients. Patients who were re-admitted were treated in the respiratory intensive care unit and were not subject to treatment restrictions.

Complications

Pleural effusion as a pulmonary complication was observed in 30 (5.3%) patients, with five (16.6%) of these patients developing empyema due to *S. pneumoniae* (n=3) or *S. viridans* (n=2). All patients with empyema required re-admission. One patient was diagnosed with acute leukaemia during the first visit in the emergency department and discharged according to clinical stability and the patient's preference; unfortunately, the patient died later during the re-admission episode. Autopsy showed extensive pulmonary necrosis due to *S. viridans*. Most of the patients with pleural effusion were classified into risk classes I and II (n=22; 73.3%) by PSI score and into risk class 0 (n=19; 63.3%) by the CURB-65 score. None of the patients with a pulmonary complication demonstrated treatment failure.

None of the patients with bacteraemia (n=21; 5.8%) was re-admitted or died. 19 (90.4%) of these patients received adequate empirical antibiotic treatment.

Re-admissions

13 (2.3%) patients were re-admitted to hospital within 30 days; nine (69.2%) had comorbidities (chronic respiratory disease, neurological disease, diabetes mellitus, chronic cardiovascular disease and chronic liver disease). The PSI score placed these patients into risk classes II and III and the CURB-65 score into risk classes 0, 1 and 2.

The empirical antimicrobial treatment was adequate in 11 (84.6%) of the patients who were re-admitted. Seven (53.8%) patients were re-admitted because of respiratory problems (complicated pleural effusion, slow-responding pneumonia and chronic obstructive pulmonary disease exacerbation) and six (46.1%) patients were readmitted for other causes not related to pneumonia. The mean time for readmission was 2 weeks, independent of the cause. Three patients died after re-admission.

Treatment failure

Treatment failure occurred in 13 (2.3%) patients, being related to pneumonia in seven (53.8%) patients and noninfectious in six (46.1%). The PSI score classified the seven patients with infectious causes into risk classes I, II and III, while the CURB-65 score placed these patients in risk classes 0, 1 and 2.

The microorganisms most frequently isolated in patients with infectious treatment failure were *M. pneumoniae* (n=3), *S. pneumoniae* (n=2) (both isolates being resistant to penicillin and erythromycin), *P. aeruginosa* plus *S. pneumoniae* (n=1) and *S. viridans* (n=1). Five out of the six cases of noninfectious treatment failure were patients who developed systemic complications after

TABLE 4 Aetiology and diagnostic methods

	Isolates	Blood culture	Sputum culture	Urinary antigen	BAL/BAS	Pleural effusion culture	Nasopharyngeal swab	Serology
Patients n	188	362	193	532	3	12	112	120
Typical	80 (42.6)							
Streptococcus pneumoniae	66 (35.1)	16 (4.41)	26 (13.5)	34 (6.4)	1 (33.3)	3 (25.0)	NA	NA
Streptococcus viridans	2 (1.1)	1 (0.27)		NA		2 (16.6)	NA	NA
Staphylococcus aureus	1 (0.5)		1 (0.5)	NA			NA	NA
Haemophilus influenzae	9 (4.8)	2 (0.55)	9 (4.7)	NA			NA	NA
Escherichia coli	1 (0.5)	1 (0.27)		NA			NA	NA
Pseudomonas aeruginosa	1 (0.5)	1 (0.27)	1 (0.5)	NA			NA	NA
Atypical	63 (33.5)							
Mycoplasma pneumoniae	29 (15.4)	NA	NA	NA	NA	NA	NA	29 (24.1)
Coxiella burnetii	11 (5.9)	NA	NA	NA	NA	NA	NA	11 (9.2)
Chlamydophila pneumoniae	10 (5.3)	NA	NA	NA	NA	NA	NA	10 (8.3)
Legionella pneumophila	13 (6.9)	NA	NA	13 (2.4)	NA	NA	NA	4 (3.3)
Respiratory viruses	25 (13.3)	NA	NA					
Influenza virus A	14 (7.4)	NA	NA	NA	NA	NA	10 (8.9)	4 (3.3)
Rhinovirus	6 (24.0)	NA	NA	NA	NA	NA	6 (5.3)	
Influenza virus	2 (1.1)	NA	NA	NA	NA	NA	2 (1.8)	
Adenovirus	1 (0.5)	NA	NA	NA	NA	NA	1 (0.9)	
Respiratory syncytial virus	1 (0.5)	NA	NA	NA	NA	NA		1 (0.8)
Parainfluenza virus 2	1 (0.5)	NA	NA	NA	NA	NA		1 (0.8)
Mixed	17 (9.0)							
S. pneumoniae + influenza virus A	9 (52.9)		1 (0.5)	8 (1.5)			9 (8.0)	
S. pneumoniae + rhinovirus	1 (5.8)			1 (0.2)			1 (0.9)	
H. influenzae + influenza virus A	2 (11.7)		2 (1.0)				2 (1.8)	
S. pneumoniae + *P. aeruginosa*	1 (5.8)		1 (0.5)	1 (0.2)				
L. pneumophila + rhinovirus	1 (5.8)			1 (0.2)			1 (0.9)	
S. pneumoniae + *H. influenzae*	2 (11.7)		2 (3.2)	2 (0.4)				
S. pneumoniae + adenovirus	1 (5.8)			1 (0.2)			1 (0.9)	
Others	3 (1.6)		3 (1.5)					

Data are presented as n (%), unless otherwise stated. BAL: bronchoalveolar lavage; BAS: broncho-aspirate; NA: not applicable.

pneumonia (cardiac arrhythmia, endocarditis, pyelonephritis and acute renal failure) and two were hospitalised for other causes not related to the episode of pneumonia.

Higher risk patients

The PSI score classified 17 (3.0%) patients into risk class IV. Five out of 17 patients had an aetiological diagnosis, the pathogens of these patients being *S. pneumoniae*, *Staphylococcus aureus*, *L. pneumophila*, respiratory virus and mixed aetiology (one case each). According to the SEPAR guidelines, 15 (88.2%) patients received appropriate empirical antimicrobial treatment and according to their aetiologies, all patients were adequately treated. The CURB-65 score did not assign patients to high-risk classes (3–5).

No patients considered as having higher risk according to PSI and CURB-65 required re-admission or died. Six (35.3%) patients presented complications, *i.e.* multilobar infiltration (n=4), pleural effusion (n=1) and bacteraemia (n=1).

DISCUSSION

The most important findings of our study are as follows. 1) Outpatients with CAP had a characteristic microbial pattern, with *S. pneumoniae* as the leading pathogen, followed by *M. pneumoniae* and respiratory viruses; *L. pneumophila* was present in 6.9% of cases with known aetiology. 2) Initial antimicrobial treatment was adequate according to guidelines in 87.3% and according to the aetiology in 91.4% of the cases. 3) The mortality rate was very low (0.5%) and other adverse events were infrequent (complication rate 5.3%, readmission rate 2.3% and treatment failure rate 2.3%). 4) Deaths and adverse events occurred in low-risk patients but in not in the 3% of patients at higher risk according to the severity scores.

Several issues are crucial to adequately interpret studies on the aetiology of CAP in outpatients. First, it is very important to define the setting of treatment. On one hand, there are true primary care studies of patients referred to general practitioners [11, 17–19], while on the other there are hospital-based studies including patients initially examined at the emergency department [10, 12]. Secondly, some studies are based on patients with ''lower respiratory tract infections'' [17, 18], not necessarily requiring a chest radiograph for confirmation of an infiltrate [17, 20], while others exclude patients without a new infiltrate [10–12]. In fact, these might be very different entities. In one

TABLE 5 Distribution of aetiology according to comorbidity

	No comorbidity	Comorbidity	Chronic respiratory disease	Neurological disease	Diabetes mellitus	Chronic cardiovascular disease	Chronic liver disease	Chronic renal disease	p-value
Patients n	383	185	122	36	31	15	14	4	
Typical	46 (12.0)	34 (18.4)	26 (21.3)	6 (16.6)	7 (22.6)		3 (21.4)		0.053
Streptococcus pneumoniae	38 (9.9)	28 (15.1)	20 (16.3)	5 (13.8)	5 (16.1)		2 (14.3)		0.093
Streptococcus viridans	1 (0.3)	1 (0.5)	1(0.8)				1 (7.1)		0.55
Staphylococcus aureus		1 (0.5)	1 (0.8)						0.33
Haemophilus influenzae	6 (1.6)	3 (1.6)	3 (2.5)		2 (6.5)				1.00
Escherichia coli		1 (0.5)	1 (0.8)	1 (2.7)					0.33
Pseudomonas aeruginosa	1 (0.3)								1.00
Atypical	49 (12.8)	14 (7.6)	9 (7.4)	3 (8.3)	1 (3.2)	1 (6.7)			0.065
Mycoplasma pneumoniae	24 (6.3)	5 (2.7)	2 (1.6)	1 (2.7)	1 (3.2)	1 (6.7)			0.10
Coxiella burnetii	10 (2.6)	1 (0.5)	1 (0.8)	1 (2.7)					0.11
Chlamydophila pneumoniae	7 (1.8)	3 (1.6)	2 (1.6)						1.00
Legionella pneumophila	8 (2.1)	5 (2.7)	4 (3.3)	1 (2.7)					0.77
Respiratory viruses	17 (4.4)	8 (4.3)	8 (6.5)	1 (2.7)	2 (6.5)		1 (7.1)		0.95
Influenza virus A	9 (2.3)	5 (2.7)	5 (4.1)		1 (3.2)		1 (7.1)		0.78
Rhinovirus	5 (1.3)	1 (0.5)	1 (0.8)	1 (2.7)					0.67
Influenza virus B	2 (0.5)								1.00
Adenovirus		1 (0.5)	1 (0.8)						0.33
Respiratory syncytial virus	1 (0.3)								1.00
Parainfluenza virus 2		1 (0.5)	1 (0.8)		1 (3.2)				0.33
Mixed	12 (3.1)	5 (2.7)	2 (1.6)	2 (5.6)	1 (3.2)	1 (6.7)			1.00
S. pneumoniae + influenza virus A	8 (2.1)	1 (0.5)	1 (0.8)	1 (2.7)					0.28
S. pneumoniae + rhinovirus		1 (0.5)			1 (3.2)				0.33
H. influenzae + influenza virus A	2 (0.5)								1.00
S. pneumoniae + *H. influenzae*		2 (1.1)	1 (0.8)	1 (2.7)					0.11
S. pneumoniae + adenovirus	1 (0.3)								1.00
S. pneumoniae + *P. aeruginosa*		1 (0.5)				1 (6.7)			0.33
L. pneumophila + rhinovirus	1 (0.3)								1.00
Others	1 (0.3)	2 (1.1)	1 (0.8)	1 (2.7)					0.25

Data are presented as n (%), unless otherwise stated.

study including 364 adult patients with lower respiratory tract infections, pneumonia was radiologically verified in only 48 (13%) patients [18]. However, due to the limited reliability of radiographic diagnosis of mild pneumonia [21], excluding patients without radiographic infiltrates may miss a proportion of patients with pneumonia. Finally, to date, few studies have included follow-up investigations in order to confirm the validity of CAP diagnosis and aetiology [22]. These differences are important, particularly because of the heavy impact of patient selection linked to the treatment setting. Our study is unique in that: 1) it is the only hospital-based study with patients being evaluated in an emergency department with high expertise in the treatment of acute respiratory tract infections, 2) all cases required a chest radiograph for confirmation of pneumonia, and 3) all survivors were re-evaluated within 30 days. This treatment setting clearly implies that only patients with confirmed CAP and carefully judged severity by both clinical means and severity tools were included [23]. Thus, the analysis presented is based on the most distinctive and valid data on outpatient CAP.

Several pitfalls must be recognised in studies evaluating the aetiology of CAP. The predefined set of diagnostic samples is usually incompletely recovered due to the many problems related to the retrieval of such samples, particularly with regard to sputum. For example, urinary antigens were not available the first years of our study. Antimicrobial pre-treatment clearly reduces and characteristically affects the diagnostic yield of culture-based investigations [24]; in fact, of those without aetiology defined in our study, 72.6% had received previous antimicrobial treatment. Thus, relating aetiologies to the total population underestimates the incidence, whereas the reverse is true when these are related to the population with a defined aetiology. We provide both ratios and argue that the true incidence might be anywhere within these two. Another important potential bias is the presence of comorbidities which might affect the resulting microbial pattern. Therefore, we provided an analysis of aetiology in relation to comorbidity and found a trend for *S. pneumoniae* to occur more frequently in comorbid patients and *M. pneumoniae* in patients without comorbidity.

Overall, *S. pneumoniae* was the most common pathogen, followed by *M. pneumoniae* and respiratory viruses. This is comparable to other studies [11, 19, 20]. Several authors have reported a high frequency of *M. pneumonia* [10, 12], even being more frequent than *S. pneumoniae* in outpatients [12]. In fact, age is the main host factor related to the incidence of *M. pneumoniae* [25] and the mean age of the patients in this series was remarkably low. Regardless of the differences reported, initial anti-pneumococcal coverage remains mandatory. *L. pneumophila* was the cause of CAP in 6.9% of cases. This finding is important for empirical antibiotic treatment in our setting.

Establishing the aetiology only marginally (by 4.1%) increased the proportion of patients receiving adequate treatment as compared with those treated according to guidelines. In addition, an established aetiology was obviously not crucial in managing patients with adverse outcomes. However, a small but relevant number of patients had resistance to penicillin (n=4; 11.7% of isolates tested) and two cases had unexpected pathogens (*E. coli* and *P. aeruginosa*). Moreover, nine out of 13 patients with mild *L. pneumonia* were not adequately treated, which might cause prolonged morbidity. Patients requiring short-term observation in an emergency care unit and/or presenting with pleural effusion and/or significant comorbidity might be candidates for microbial investigation, particularly for pyogenic pathogens and *L. pneumophila*.

Overall, mortality and other adverse outcomes were rare. In line with previous reports, pleural effusion (16.6% progressed to empyema) was the most frequent cause of complications [26]. Interestingly, bacteraemia had no impact on any outcome measure. Re-admission was mostly related to comorbidity (in 69.2% of cases) and, actually, was the only cause of re-admission in roughly half of these patients. Treatment failure was rare (2.3%) and only half of the cases were related to infection. Again, comorbidity was the main driver behind this adverse outcome. These outcomes compare favourably to other reports [11, 22].

Both severity scores correctly identified the patients at low risk in the vast majority of cases. None of the cases at increased risk according to the severity scores had an adverse outcome. Thus, the few patients dying and experiencing other adverse outcomes were all in the low-risk group. Our data indicate that a closer view on patients with pleural effusions and comorbidities might reduce underestimations of risks according to clinical judgment and severity scores. It has previously been shown that ambulatory treatment in low-risk patients is equivalent to hospitalisation in the absence of respiratory failure, unstable comorbidity, pleural effusions and social problems [22].

In conclusion, most patients managed as outpatients after presenting in a hospital emergency department can be safely treated based on the current guidelines. Antimicrobial pneumococcal coverage in all patients remains crucial. *L. pneumophila* cannot be disregarded. Patients presenting with pleural effusions and/or comorbidities should probably be more closely observed if not admitted to hospital.

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STATEMENT OF INTEREST

A statement of interest for A. Torres can be found at www.erj.ersjournals.com/site/misc/statements.xhtml

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