Eur Respir J 2002; 20: 1254–1262
DOI: 10.1183/09031936.02.01942001
Printed in UK – all rights reserved


European Respiratory Journal
ISSN 0903-1936

# Factors associated with unknown aetiology in patients with community-acquired pneumonia

S. Ewig*, A. Torres#, M. Ángeles Marcos+, J. Angrill#, A. Rañó#, A. de Roux#, J. Mensa¶, J.A. Martínez¶, J.P. de la Bellacasa+, T. Bauer§

*Factors associated with unknown aetiology in patients with community-acquired pneumonia. S. Ewig, A. Torres, M.Ángeles Marcos, J. Angrill, A. Rañó, A. de Roux, J. Mensa, J.A. Martínez, J.P. de la Bellacasa, T. Bauer. ©ERS Journals Ltd 2002.*

**ABSTRACT: Despite comprehensive diagnostic work-up, the aetiology of community-acquired pneumonia (CAP) remains undetermined in 30–60% of cases. The authors studied factors associated with undiagnosed pneumonia.**

**Patients hospitalised with CAP and being evaluated by two blood cultures, at least one valid lower respiratory tract sample, and serology on admission were prospectively recorded. Patients who had received antimicrobial pretreatment were excluded. Patients with definite or probable aetiology were compared to those with undetermined aetiology by uni- and multivariable analysis.**

**A total 204 patients were eligible for the study. The aetiology remained undetermined in 82 (40%) patients, whereas a definite aetiology could be established in 89 (44%) and a probable one in 33 (16%). In multivariable analysis, factors associated with undetermined aetiology included age >70 yrs, renal and cardiac comorbidity, and nonalveolar infiltrates on the chest radiograph. There was no association of undiagnosed pneumonia with mortality.**

**Age and host factors were associated with unknown aetiology of community-acquired pneumonia. Some of these cases may also represent fluid volume overload mimicking pneumonia.**

*Eur Respir J 2002; 20: 1254–1262.*

*Medizinische Universitäts-Poliklinik Bonn, Germany. #Serveis de Pneumologia, ¶Malalties Infeccioses, +Microbiologia, Hospital Clinic Universitat de Barcelona, Spain. §Berugsgenossenschaftliche Klinik Bergmannsheil-Universitätskliniken Innere Medizin, Bochum, Germany.

Correspondence: A. Torres, Hospital Clinic i Provincial, UVIR Servei de Pneumologia, Villarroel 170, 08036 Barcelona.
Fax: 34 932275454
E-mail: atorres@medicina.ub.es

Keywords: Aetiology, epidemiology, pneumonia

Received: October 22 2001
Accepted after revision: June 5 2002

This study was supported by Commisionat per a Universitats i Recerca de la Generalitat de Catalunya,1997 SGR 00086, IDIBAPS Hospital Clinic Barcelona, and FISS 98/0138.

The aetiology of community-acquired pneumonia (CAP) has been studied in various regions and settings. While these studies differ considerably in patient populations, diagnostic methodology, and presence of confounders, one intriguing constant finding is the failure to detect a pathogen in ~30–60% of cases [1–9]. Among the factors which may explain this observation, ambulatory antimicrobial pretreatment is the most attractive. Accordingly, there is evidence from the literature that the majority of cases of unknown aetiology may be caused by *Streptococcus pneumoniae*, a pathogen which is easily missed after one single dose of antimicrobial treatment [1, 10]. Conversely, the recognition *of Legionella pneumophila* and *Chlamydia pneumoniae* has taught that unrecognised pathogens may represent important causes of CAP. Finally, comorbid conditions may represent important diagnostic confounders, either associated with distinct pathogens or as mimics of pneumonia.

A prospective study was therefore conducted in patients with CAP in order to identify factors associated with unknown aetiology. Since the authors were particularly interested in factors other than antimicrobial pretreatment, only previously untreated patients were selected. The prognostic implications of failure to detect microbial aetiology were also studied.

## Methods

### *Eligibility criteria*

All patients who presented to the emergency department of the Hospital Clinic I Provincial, a 1,000-bed tertiary care teaching hospital in Barcelona (Spain) during a 2-yr period were prospectively studied. Emergency care physicians were instructed to identify patients with pulmonary infiltrates and to report these patients immediately to a respiratory or infectious disease specialist on call for the purpose of this study.

In order to be eligible for this study, the following entry criteria had to be fulfilled: 1) CAP, as defined by a new infiltrate on the chest radiograph, symptoms compatible with a lower respiratory tract infection, and no alternative diagnosis emerging during follow-up; 2) absence of severe immunosuppression, as defined by a condition associated with a significant risk of opportunistic infection (solid organ or bone

marrow transplantation, neutropenia $<1\times10^9$ $L^{-1}$, treatment with oral corticosteroids in daily doses $\geq$20 mg prednisolone-equivalent and/or $\geq$2 weeks of treatment with azathioprine, cyclosporin or cyclophosphamide); 3) absence of human immunodeficiency virus (HIV) infection regardless of immune status; 4) the need for hospitalisation according to the judgment of the physician in charge; 5) the absence of previous hospitalisation for >48 h within 30 days of the present hospital admission; 6) the absence of ambulatory antimicrobial pretreatment as defined by any antimicrobial treatment administered within 30 days of the present hospital admission; and 7) the presence of an aetiological work-up, consisting of two blood cultures, at least one valid lower respiratory tract sample, and serology on admission.

The following lower respiratory tract samples were accepted as valid: 1) sputum sample with >25 granulocytes and <10 epithelial cells per low power field total magnification ×100 in the Gram stain; 2) protected specimen brush (PSB); 3) bronchoalveolar lavage (BAL); and 4) tracheobronchial aspirate (TBAS, retrieved *via* the endotracheal tube in intubated patients).

### *Data recording*

The following parameters were recorded at admission: age, sex, smoking and alcohol habits, comorbidity, residence in nursing home, probable aspiration, current medication, clinical symptoms (cough, dyspnoea, chest pain, body temperature, respiratory rate, cardiac frequency, arterial systolic and diastolic blood pressure, blood gas analysis (oxygen and carbon dioxide tensions in arterial blood ($P_{a,O_2}$, $P_{a,CO_2}$), inspiratory oxygen fraction ($F_{I,O_2}$)), chest radiograph pattern (alveolar, interstitial or mixed infiltrate, number of lobes affected, pleural effusion), and serum creatinine. At the clinical end-points of hospital discharge or death, the following parameters were additionally retrieved: definite microbial aetiology, type of sample the definite microbial diagnosis was based on (sputum, serology, antigen-detection, culture of blood or pleural effusion, and other lower respiratory tract specimen), antimicrobial treatment administered during hospital stay, admission to the intensive care unit (ICU), and 30 day in-hospital outcome.

### *Definitions*

The following definitions were applicable to the study: 1) comorbid illnesses: cardiac (treatment for coronary artery disease or congestive heart failure or presence of valvular heart disease), pulmonary (treatment for asthma or chronic obstructive pulmonary disease or presence of interstitial lung disorders), renal (pre-existing renal disease with documented abnormal serum creatinine outside the pneumonia episode), hepatic (pre-existing viral or toxic liver disease), central nervous system disorders (presence of symptomatic acute or chronic vascular or nonvascular brain disease, with or without dementia), diabetes mellitus (intolerance to glucose and treatment with oral antidiabetics or insulin), neoplastic (any solid tumour active at the time of presentation or requiring antineoplastic treatment within the last year); 2) alcohol abuse: the ingestion of >80 g of alcohol per day at least during the last year or prior abuse; 3) current smokers: those who smoked at least 10 cigarettes·$day^{-1}$ during the last year at least; 4) probable aspiration: witnessed aspiration or presence of risk factors for aspiration (severely altered consciousness, abnormal gag reflex or abnormal swallowing mechanism) [11]; 5) medication with $H_2$-blockers: ranitidine or similar in a dose of at least 150 mg·$day^{-1}$ for at least 30 days prior to hospital admission; 6) severe sepsis or septic shock: systemic inflammatory response to infection (presence of $\geq$2 of the following: temperature >38°C or <36°C, cardiac frequency >90 beats·$min^{-1}$, respiratory rate >20 $min^{-1}$ or $P_{a,CO_2}$ <32 mmHg, and leucocyte count >12,000 $mm^{-3}$ or >10% band forms) in addition to hypotension (systolic blood pressure <90 mmHg or diastolic blood pressure <60 mmHg), with or without end organ damage [12]; and 7) acute respiratory failure: presence of respiratory rate >30 breath·$min^{-1}$, $P_{a,O_2}/F_{I,O_2}$ <250, or the requirement for mechanical ventilation.

### *Microbiological evaluation*

Sampling included sputum, two blood cultures, and paired serology. Pleural puncture, TBAS, and flexible bronchoscopy with PSB or BAL were additional diagnostic techniques, applied according to the clinical judgment of the physician in charge. Urine samples were investigated for *L. pneumophila* serogroup I antigen titres.

Validated sputum, blood culture samples, pleural fluid, and undiluted and serially diluted TBAS, PSB, and BAL fluid samples were plated on the following media: blood-sheep agar, Centers for Disease Control agar, chocolate agar as well as Sabouraud agar. The identification of microorganisms was performed according to standard methods [13].

The aetiology was regarded to be probable when the causative organism was identified in sputum. It was considered to be definite if one of the following criteria were met: 1) blood cultures yielding a bacterial or fungal pathogen (in the absence of an apparent extrapulmonary focus); 2) bacterial growth in cultures of TBAS $\geq10^5$ colony forming units (cfu)·$mL^{-1}$, in PSB $\geq10^3$ cfu·$mL^{-1}$, and in BAL fluid $\geq10^4$ cfu·$mL^{-1}$; 3) seroconversion (four-fold rise in immunoglobulin (Ig)G-titres) for: *C. pneumoniae* ($\geq$1:512), *C. psittaci* ($\geq$1:64), *L. pneumophila* ($\geq$1:128), *Coxiella burnetii* ($\geq$1:80), respiratory viruses (Influenza virus A and B, Parainfluenza virus 1–3, respiratory syncytial virus, adenovirus); and 4) a rise in IgM-titre for: *C. pneumoniae* ($\geq$1:32), C. burnetii ($\geq$1:80), and *Mycoplasma pneumoniae* (any titre).

In addition to these criteria, pleural fluid cultures yielding a bacterial pathogen, and a positive urinary antigen for *L. pneumophila* were accepted as definitely diagnostic.

Growth of fungi in respiratory samples was only

considered diagnostic in case of positive blood cultures for *Candida* spp., or isolation of *Histoplasma capsulatum or Aspergillus fumigatus* from lower respiratory tract cultures.

*Statistical analysis*

In a first step, all patients included in the analysis were grouped according to the aetiology into probable or definite aetiology or no aetiology according to the definitions given above. The second step involved univariable analysis for the candidate variables. An unpaired t-test was used for the comparison of quantitative variables between patient groups. Proportions were compared by the Chi-squared test or Fisher′s exact test in comparisons with an expected cell frequency of less than five.

For multivariable analysis, a logistic regression model with forward stepwise selection was employed. The problems associated with multivariable analysis were addressed as follows. Stringent entry criteria ($p<0.10$ in univariable analyses) reduced the number of candidate variables to avoid over-fitting. To minimise the possibility of including two highly correlated variables into the statistical model a stepwise forward model was chosen ($p<0.05$). Interactions were analysed pairwise by entering an interaction term into the logistic regression analysis. Results are reported separately when interaction was found ($p<0.05$). All variables remained in their original dimension in the initial analysis to avoid bias induced by arbitrary cut-offs. Results of all multivariable analyses are reported as adjusted odds ratio, 95% confidence intervals (CI) and exact p-values.

The initial multivariable model was repeated in a larger population that fulfilled all criteria except the completeness of the diagnostic sampling to control for bias induced by the selection criteria.

Results are expressed as mean±SD. All p-values presented refer to two-tailed analyses.

## Results

*Patients*

Overall 719 episodes were entered into the initial database. The following patients were excluded: no or previous hospital admission (n=50), severe immunosuppression (n=47), HIV-infection (n=50), alternative diagnosis (n=13), previous antimicrobial treatment (n=135). The remaining population (n=424) formed the larger population. Of these, the following had to be excluded additionally: no blood cultures at admission (n=127), no valid respiratory tract sample (n=72), no paired serology (n=21). Thus, after the application of all exclusion criteria, 204 of 719 episodes were selected for this analysis (28%).

*Aetiology*

Overall, a probable or definite aetiology could not be established in 82 of 204 included cases (40%). The group of patients that remained without an aetiology was the largest single patient group.

The aetiologies as they were identified according to the given definitions as well as the corresponding diagnostic criteria are summarised in table 1.

Table 1. – Bacteriological findings of the 122 patients with either probable or definite aetiology of the episode of community-acquired pneumonia

| | Total | Sputum | Blood culture | TBAS | PSB, BAL | Pleural fluid | Serology, urinary antigen |
|---|---|---|---|---|---|---|---|
| *Streptococcus pneumoniae* | 38/204 (19) | 19/38 (50) | 17/38 (45) | 1/38 (50) | | 1/38 (3) | |
| *Haemophilus influenzae* | 12/204 (6) | 9/12 (75) | 2/12 (17) | | | 1/12 (8) | |
| *Moraxella catarrhalis* | 2/204 (1) | 1/2 (50) | | 1/2 (50) | | | |
| *Staphylococcus aureus* | 4/204 (2) | | 3/4 (75) | 1/4 (25) | | | |
| *Streptococcus viridans* | 3/204 (2) | | 3/3 (100) | | | | |
| *Streptococcus pyogenes* | 1/204 (0.5) | | 1/1(100) | | | | |
| *Pseudomonas aeruginosa* | 9/204 (4) | 3/9 (33) | 1/9 (11) | 3/3 (33) | 2/9 (22) | | |
| *Klebsiella pneumoniae* | 1/204 (0.5) | | 1/1 (100) | | | | |
| *Escherichia coli* | 4/204 (2) | | 3/4 (75) | 1/4 (25) | | | |
| *Chlamydia pneumoniae* | 21/204 (10) | | | | | | 21/21 (100) |
| *Chlamydia psittaci* | 1/204 (0.5) | | | | | | 1/1 (100) |
| Mycoplasma | 3/204 (2) | | | | | | 3/3 (100) |
| Coxiella | 3/204 (2) | | | | | | 3/3 (100) |
| *Legionella pneumophila* | 11/204 (5) | | | | | | 11/11 (100) |
| *Mycobacterium tuberculosis* | 1/204 (0.5) | 1/1 (100) | | | | | |
| *Aspergillus fumigatus* | 1/204 (0.5) | | | 1/1 (100) | | | |
| *Eikenella corrodens* | 1/204 (0.5) | | | | | 1/1 (100) | |
| Virus | 6/204 (3) | | | | | | 6/6 (100) |
| Total | 204/204 (100) | 33/122 (27) | 31/122 (25) | 8/122 (7) | 2/122 (2) | 3/122 (3) | 45/122 (37) |

Data are presented as n/total n (%). Percentages in the first column refer to the total number of patients in the study (n=204) to yield comparability to other diagnostics studies on community-acquired pneumonia. Probable: n=33; definite: n=89; community-acquired pneumonia: n=122. TBAS: tracheobronchial aspirate (quantitative bacterial cultures $\geq 10^5$ colony forming units (cfu)·mL$^{-1}$); PSB: protected specimen brush (quantitative bacterial cultures $\geq 10^3$ cfu·mL$^{-1}$); BAL: bronchoalveolar lavage.

Table 2. – Demographic characteristics of patients with a successful diagnostic procedure compared to patients without aetiology

| Parameter | No aetiology | Probable or definite aetiology | p-value | 95% CI of the difference |
|---|---|---|---|---|
| Patients n | 82/204 (40) | 122/204 (60) | | |
| Age yrs mean±SD | 71±18 | 66±16 | 0.019 | 1.0–0.4 |
| Sex male | 50/82 (61) | 92/122 (75) | 0.028 | 0.9–21.7 |
| Current smokers | 19/82 (23) | 44/122 (36) | 0.051 | 0.5–25.5 |
| Alcohol abuse | 8/82 (10) | 25/122 (21) | 0.041 | 1.3–20.7 |
| Nursing home admission | 4/81 (5) | 4/121 (3) | 0.560 | -3.6–7.6 |
| Probable aspiration | 9/79 (11) | 5/111 (5) | 0.073 | -2.0–14.0 |
| $H_2$-blockers | 7/81 (9) | 7/120 (6) | 0.443 | -4.5–10.5 |
| Comorbidity present | 65/82 (79) | 122/122 (68) | 0.078 | -1-1–23.1 |
| Type of comorbidity | | | | |
| Cardiac | 22/82 (27) | 12/122 (10) | 0.001 | 6.0–28.0 |
| Pulmonary | 44/82 (54) | 67/122 (55) | 0.859 | -12.9–4.9 |
| Chronic Bronchitis | 10/82 (12) | 13/122 (11) | 0.733 | -8.0–0.0 |
| COPD | 29/82 (35) | 38/122 (31) | 0.529 | -9.2–7.2 |
| Bronchiectasis | 0/82 (0) | 3/122 (3) | 0.211# | 0.0–6.0 |
| Asthma | 0/82 (0) | 5/122 (4) | 0.073# | 0.7–7.5 |
| Others | 5/82 (6) | 8/122 (7) | 0.918 | -5.8–7.8 |
| Renal | 10/82 (12) | 4/122 (3) | 0.014 | 1.3–16.7 |
| Hepatic | 2/81 (3) | 10/122 (8) | 0.090 | -1.1–1.1 |
| CNS | 12/82 (15) | 15/122 (12) | 0.888 | -6.6–12.6 |
| Diabetes mellitus | 14/82 (17) | 17/122 (14) | 0.540 | -7.2–13.2 |
| Neoplastic | 5/82 (6) | 11/122 (9) | 0.461 | -4.2–10.2 |

Data are presented as n/total n (%), unless otherwise stated. CI: confidence interval; COPD: chronic obstructive pulmonary disease; CNS central nervous system. # Fisher's exact test. The exact numbers are given for each parameter, since information was not available for all patients.

A probable aetiology was established in 33 of 122 cases (27%). A definite aetiology was identified in 89 of 122 cases (73%), based on serology or antigen-testing in 45 of 122 cases (37%), on blood cultures in 31 of 122 cases (25%), on TBAS in eight of 122 cases (7%), on pleural fluid in three of 122 cases (3%) or on either PSB or BAL in two of 122 cases (2%). No differences in the number of diagnostic procedures performed were found when patients with aetiology of their episode of CAP were compared to patients without: sputum (97 of 122 (80%) *versus* 57 of 82 (70%); p=0.104), TBAS (19 of 122 (16%) *versus* nine of 82 (11%); p=0.349), PSB, BAL (10 of 122 (8%) *versus* four of 82 (5%); p=0.358), and pleural fluid (12 of 122 (10%) *versus* five of 82 (6%); p=0.343), respectively.

*S. pneumoniae* was identified as the causative microorganism in 38 of 204 patients (19%), whereas "atypical" microorganisms (*Chlamydia* spp., *Mycoplasma* spp., or *Coxiella* spp.) were the second largest diagnostic group (28 of 204 patients, 14%). *H. influenzae* was identified in 12 of 204 cases (6%) and other Gram-negative bacteria (*Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, or *Escherichia coli*) were recovered in 14 of 204 patients (7%).

### *Analysis of patients with unknown aetiology*

*Demographic characteristics.* The results of the comparison between patients with a probable or definite aetiology and patients without aetiology are summarised in table 2. Patients without aetiology were older (nondiagnostic: 71±18 *versus* diagnostic: 66±16 yrs, p=0.019), were less likely to be male (nondiagnostic: 50 of 82 (61%) *versus* diagnostic: 92 of 122 (75%), p=0.028) and reported less alcohol abuse (nondiagnostic: eight of 82 (10%) *versus* diagnostic: 25 of 122 (21%), p=0.041). There was a trend towards fewer smokers (nondiagnostic: 19 of 82 (23%) *versus* diagnostic: 44 of 122 (36%), p=0.051) and more cases with probable aspiration (nondiagnostic: nine of 79 (11%) *versus* diagnostic: five of 111 (5%), p=0.073) in the group of patients with an undefined aetiology.

*Comorbidity.* The presence of a comorbidity seemed to lower the diagnostic yield (nondiagnostic: 65 of 82, 79% *versus* diagnostic: 83 of 122 (68%), p=0.078; table 2). This was especially evident when the different types of comorbidities were analysed separately. A cardiac (nondiagnostic: 22 of 82 (27%) *versus* diagnostic: 12 of 122 (10%), p=0.001) and renal comorbidity (nondiagnostic: 10 of 82 (12%) *versus* diagnostic: four of 122 (3%), p=0.014) were more frequent in the group of patients with unknown aetiology, whereas the diagnostic yield was higher in the group of patients with hepatic comorbidity (nondiagnostic: two of 81 (3%) *versus* diagnostic: 10 of 122 (8%), p=0.090). A pulmonary comorbidity did not influence this comparison (nondiagnostic: 44 of 82 (54%) *versus* diagnostic: 67 of 122 (55%), p=0.859).

*Clinical data on admission and chest radiographs.* No significant differences were present in the comparison of the clinical symptoms on admission. However, there was a nonsignificant trend towards a lower percentage of patients who reported pleuritic chest pain (nondiagnostic: 25 of 82 (31%) *versus* diagnostic: 53 of 122 (44%), p=0.056) or chills (nondiagnostic: 29 of 82

Table 3. – Clinical characteristics and symptoms on admission of patients with a successful diagnostic procedure compared to patients without aetiology

| Parameter | No aetiology | Probable or definite aetiology | p-value | 95% CI of the difference |
|---|---|---|---|---|
| Patients n | 82/204 (40) | 122/204 (60) | | |
| $P_{a,O_2}/F_{I,O_2}$ mmHg | 262±66 | 264±66 | 0.840 | -21.7–17.6 |
| Body temperature °C | 37.6±1.1 | 37.8±1.1 | 0.124 | -0.5–0.1 |
| Respiratory rate bpm | 31.4±8.0 | 30.0±9.6 | 0.285 | -1.2–4.0 |
| Duration of symptoms days | 4.5±4.0 | 4.7±6.6 | 0.751 | -1.9–1.4 |
| Acute respiratory failure | 55/82 (67) | 72/122 (59) | 0.244 | -5.4–21.4 |
| Septic shock | 12/82 (15) | 28/122 (23) | 0.142 | -2.7–18.7 |
| Serum creatinine $mg \cdot dL^{-1}$ | 1.5±1.5 | 1.2±0.8 | 0.081 | -0.1–0.6 |
| Serum albumin $mg \cdot dL^{-1}$ | 33.1±4.5 | 33.1±7.4 | 0.995 | -2.0–2.0 |
| ICU admission | 9/82 (11) | 20/122 (16) | 0.277 | -4.4–14.4 |
| Mechanical ventilation | 6/82 (7) | 16/122 (13) | 0.191 | -2.1–14.1 |
| Type of radiological infiltrate | | | | |
| Bilateral | 28/82 (34) | 40/122 (33) | 0.840 | -12.2–14.2 |
| Alveolar | 48/78 (62) | 91/121 (75) | 0.040 | -0.3–26.3 |
| Interstitial | 6/78 (8) | 10/121 (8) | 0.884 | -7.7–7.7 |
| Mixed | 24/78 (30) | 20/121 (17) | 0.018 | 0.8–25.2 |
| Pleural effusion | 14/79 (18) | 16/116 (14) | 0.455 | -6.6–14.6 |
| Cough | 63/82 (78) | 92/122 (75) | 0.697 | -8.8–14.8 |
| Dyspnoea | 63/82 (77) | 84/122 (69) | 0.213 | -4.3–20.3 |
| Pleuritic chest pain | 25/82 (31) | 53/122 (44) | 0.056 | -0.3–26.3 |
| Chills | 29/82 (35) | 60/122 (49) | 0.051 | 0.4–27.6 |
| Preceding symptoms of upper airways infections | 33/81 (41) | 37/118 (31) | 0.173 | -3.6–23.6 |

Data are presented as n/total n (%) or mean±SD. CI: confidence interval; $P_{a,O_2}$: oxygen tension in arterial blood; $F_{I,O_2}$: inspiratory oxygen fraction; ICU: intensive care unit. Clinical characteristics and symptoms on admission of patients. The exact numbers are given for each parameter, since information was not available for all patients.

(35%) *versus* diagnostic: 60 of 122 (49%), p=0.051) on admission in the nondiagnostic group (table 3). There was also a trend towards a higher serum creatinine in the undiagnosed group (nondiagnostic: 1.5±1.5 *versus* diagnostic: 1.2±0.8 $mg \cdot dL^{-1}$, p=0.081; table 3).

The analysis of the radiographs on admission showed that alveolar appearance of the infiltrate was less common (nondiagnostic: 48 of 78 (62%) *versus* diagnostic: 91 of 121 (75%), p=0.040), whereas a mixed pattern was significantly more often in the group of patients with undetermined aetiology (nondiagnostic: 24 of 78 (30%) *versus* diagnostic: 20 of 121 (17%), p=0.018; table 3).

*Multivariable analysis.* In order to avoid interactions in the statistical model the authors did not include the presence of a comorbidity and serum creatinine because these confounding factors were covered by other variables (single comorbidities and renal comorbidity, respectively). According to the entry criteria for the multivariable analysis ($p<0.10$) the following 13 variables were then entered: age, sex, current smoker, alcohol abuse, probable aspiration, asthma, cardiac comorbidity, renal comorbidity, hepatic comorbidity, alveolar pulmonary infiltrate, mixed pulmonary infiltrate, pleuritic chest pain, and chills.

Overall, 21 cases had at least one missing value. Thus, 183 of 204 (90%) of the patients could be included into the multivariable analysis (table 4). The risk of an episode of CAP without aetiology in the present study increased with age and the presence of a renal or cardiac comorbidity. The likelihood of unknown aetiology increased in the presence of something other than alveolar pulmonary infiltrate on the chest radiograph on admission (table 4).

Patients aged $\geqslant$70 yrs had a two-fold risk of remaining without an aetiology when age was

Table 4. – Results of the multiple logistic regression analysis for qualified candidate variables

| | Adjusted odds ratio | p-value | 95% CI |
|---|---|---|---|
| Age (continuous) | 1.02¶ | 0.026 | 1.0–1.04 |
| Renal comorbidity | 5.1 | 0.057 | 1.0–26.7 |
| Cardiac comorbidity | 2.7 | 0.028 | 1.1–6.4 |
| Infiltrate other than alveolar | 2.5 | 0.008 | 1.3–5.0 |
| Age $\geqslant$70 yrs | 2.0 | 0.033 | 1.1–3.9 |
| Renal comorbidity | 5.0 | 0.057 | 1.0–26.5 |
| Cardiac comorbidity | 2.9 | 0.014 | 1.2–6.9 |
| Interaction analysis# | | | |
| Age *versus* renal¶ | | 0.114 | |
| Age *versus* cardiac¶ | | 0.004 | |
| Age *versus* infiltrate¶ | | 0.008 | |
| Renal *versus* cardiac¶ | | 0.110 | |
| Renal *versus* infiltrate¶ | | 0.657 | |
| Cardiac *versus* infiltrate¶ | | 0.055 | |

CI: confidence interval. Adjusted odds ratios are reported for the risk of undiagnosed episode of community-acquired pneumonia. #: for categorised variable age; ¶: odds ratio for continuous variable.

categorised for further analysis according to the group median (table 4). However, the effects of the other variables remained virtually unchanged by this measure. The interaction analysis revealed a significant interaction between age $\geqslant$70 yrs and the presence of a cardiac comorbidity. This interaction is explained by the fact that the patients with both risk factors were more likely to remain without aetiology (nondiagnostic: 17 of 82 (21%) *versus* diagnostic: eight of 122 (7%), p=0.002). An age $\geqslant$70 yrs also interacted with variables other than alveolar infiltrates. This interaction was also due to the disproportionally high percentage of patients with both risk factors in the undiagnosed group (nondiagnostic: 19 of 78 (24%) *versus* diagnostic: 12 of 121 (10%), p=0.006).

*Aetiology according to identified risk groups.* Table 5 summarises the aetiological agents according to the risk groups identified in the multivariable analysis. The proportion of patients with an isolate of *Moraxella catarrhalis* or atypical agents was higher in the group of patients who presented with CAP in combination with a cardiac comorbidity. No other significant differences were found for this comparison.

*Analysis in the larger population.* A total of 424 of the 719 patients included in the database qualified for the larger population (60%). In this group, 188 of 424 patients remained without probable or definite aetiology (44%). Overall, 384 of 424 (95%) were entered into the multivariable analysis. Cardiac comorbidity was the most important confounding factor for the sampling effort in this analysis (nondiagnostic: 52 of 188 (28%) *versus* diagnostic: 31 of 236 (13%), p<0.001, adjusted odds ratio: 2.6, 95% CI: 1.6–4.4, p<0.001).

### *Antimicrobial treatment*

Overall 175 patients (102 with and 73 without aetiology) were treated on the regular ward, and 29 (20 with and nine without aetiology) were admitted to the ICU. There were no significant differences in antimicrobial treatment regimens between patients with and without defined aetiology (table 6).

*Outcome.* The 30-day in-hospital mortality of patients with CAP included in this study was 12 of 204 (6%), without differences between the diagnostic groups (nondiagnostic: three of 82 (4%) *versus* diagnostic: nine of 122 (7%), 95% CI -3.2–9.2; p=0.368, Fisher's exact test). The 30-day in-hospital mortality in the larger population was undistinguishable from mortality in the investigated population (44 of 424 (10%), 95% CI -0.3–8.8%; p=0.824). No differences in mortality were found between the diagnostic groups in the larger population (nondiagnostic: 17 of 188 (9%) *versus* diagnostic: 27 of 236 (11%), 95% CI: -3.7–7.7; p=0.522).

## Discussion

The main findings of this study were: 1) in the population investigated a total 82 of 204 (40%) patients with CAP remained without aetiology, despite a substantial diagnostic effort; 2) multivariable analysis revealed age, renal and cardiac comorbidity, and nonalveolar radiological pattern as independent risk factors for an unknown aetiology; 3) the confounding role of cardiac comorbidity could be confirmed in a larger analysis; and 4) mortality was not different between patients with and without aetiology of CAP.

An important confounder which may have accounted for part of the undiagnosed cases is incomplete diagnostic work-up. A more extensive and aggressive diagnostic approach including antigen detection and polymerase chain reaction (PCR) may have increased the diagnostic yield. However, available evidence from the literature suggests that the diagnostic yield approaches a "ceiling effect" by ~70–80% even when using a most comprehensive diagnostic approach [4, 6–8]. In the present study, it was ensured that every patient included was evaluated by at least two blood cultures, one valid sample of the lower respiratory tract, and serology, with additional testing performed according to clinical needs. This approach is unique in the literature since other studies included significant variations in the diagnostic testing applied to the individual patient. At the very least, the present study

Table 5. – Recovered microorganisms according to the risk factors identified in multivariate analysis

| | Age $\geqslant$70 yrs | p-value# | Renal comorbidity | p-value# | Cardiac comorbidity | p-value# | Infiltrates other than alveolar | p-value* | Total population |
|---|---|---|---|---|---|---|---|---|---|
| With aetiology | 52/100 (52) | | 4/14 (29) | | 12/34 (35) | | 30/60 (50) | | 122/204 (60) |
| *Streptococcus pneumoniae* | 17/52 (33) | 0.840 | 3/4 (75) | 0.100¶ | 2/12 (17) | 0.509¶ | 5/30 (17) | 0.114 | 38/122 (31) |
| *Haemophilus influenzae* | 5/52 (10) | 0.966 | 0/4 (-) | 1.0 | 0/12 (-) | 0.597¶ | 4/30 (13) | 0.522 | 12/122 (10) |
| *Moraxella catarrhalis* | 1/52 (2) | 1.0¶ | 0/4 (-) | 1.0¶ | 2/12 (17) | 0.046¶ | 0/30 (-) | 1.0¶ | 2/122 (2) |
| Gram-positive cocci+ | 3/52 (6) | 1.0¶ | 0/4 (-) | 1.0¶ | 1/12 (8) | 0.581¶ | 2/30 (7) | 1.0¶ | 8/122 (7) |
| Gram-negative rods§ | 5/52 (10) | 0.718 | 0/4 (-) | 1.0¶ | 0/12 (-) | 0.367¶ | 3/30 (10) | 1.0¶ | 14/122 (12) |
| Atypical$^f$ | 10/51 (20) | 0.628 | 1/4 (25) | 1.0¶ | 6/12 (50) | 0.049 | 8/30 (27) | 0.668 | 28/122 (23) |
| *Legionella pneumophila* | 4/52 (8) | 1.0¶ | 0/4 (-) | 1.0¶ | 1/12 (8) | 1.0¶ | 4/30 (13) | 0.479¶ | 11/122 (9) |
| Others** | 4/52 (8) | 1.0¶ | 0/4 (-) | 1.0¶ | 0/12 (-) | 1.0¶ | 4/30 (13) | 0.287¶ | 9/122 (7) |

Data are presented as n/total n (%). #: p-value compared to the larger population; ¶: Fisher's exact test; +: *Staphylococcus aureus*, *Streptococcus viridans*, and *Streptococcus pyogenes*; §: *Pseudomonas* spp., *Klebsiella pneumoniae*, and *Escherichia coli*; $^f$: *Chlamydia* spp., *Coxiella* spp., and *Mycoplasma pneumoniae*; **: *Mycobacterium tuberculosis*, *Aspergillus fumigatus*, *Eikenella corrodens*, and viruses.

Table 6. – Initial antimicrobial treatment in patients with community-acquired pneumonia

| Non-ICU patients | Aetiology | | p-value |
|---|---|---|---|
| | With | Without | |
| Patients n | 102 | 73 | |
| Monotherapy | 13 (13) | 15 (21) | 0.165 |
| Aminopenicillin | 1 | 2 | 0.376 |
| Aminopenicillin±β-lactamase inhibitor | | 5 | 0.007 |
| Macrolide | 1 | 1 | 0.811 |
| Cephalosporin III | 11 | 7 | 0.797 |
| Dual combination therapy | 88 (86) | 58 (79) | 0.231 |
| Cephalosporin III+macrolide | 80 | 50 | 0.138 |
| Cephalosporin III+clindamycin | 5 | 6 | 0.372 |
| Cephalosporin IV+macrolide | 1 | 1 | 0.811 |
| Cephalosporin IV+aminoglycoside | 1 | 1 | 0.811 |
| Carbapenem+aminoglycoside | 1 | | 0.396 |
| Triple combination therapy | 1 (1) | | 0.396 |
| Cephalosporin III+macrolide+aminoglycoside | 1 | | 0.396 |
| ICU patients n | 20 | 9 | |
| Dual combination therapy | 16 (80) | 6 (67) | 0.437 |
| Cephalosporin III+macrolide | 14 | 6 | 0.857 |
| Cephalosporin+clindamycin | 2 | | 0.325 |
| Triple combination therapy | 4 (20) | 3 (33) | 0.437 |
| Cephalosporin III+macrolide+aminoglycoside | 2 | 1 | 0.927 |
| Cephalosporin III+macrolide+clindamycin | 1 | 1 | 0.547 |
| Cephalosporin III+macrolide+vancomycin | 1 | | 0.494 |
| Carbapenem+macrolide+aminoglycoside | | 1 | 0.129 |

Data are presented as n (%) or n. Data are reported separately for patients with and without definite aetiology and according to intensive care unit admission (ICU). The p-values were calculated using a Chi-squared test.

succeeded in providing sufficiently homogeneous groups for comparison.

The rate of undiagnosed cases of CAP closely resemble those reported in prior studies *e.g.* two studies including >500 patients could not identify a pathogen in 50 and 45%, respectively [2, 3]. Likewise, in a previous study by the authors group, they failed to establish an aetiology in 54% of pateints [9]. Without any doubt, prior antimicrobial treatment is an important factor which decreases the diagnostic yield. FANG *et al.* [14] clearly showed the decline in diagnostic yield in the presence of such treatment. In another large series, no diagnosis was made in 45% of the cases. With adjustment for antimicrobial therapy before admission and for other logistical considerations, it was estimated that the aetiology could have been ascertained in 65% of the cases [5]. The effect of antimicrobial treatment was analysed in more detail in the British Thoracic Society multicentre study. In this study, the rate of patients with evidence for pneumonia due to *S. pneumoniae* was more than twice as high in patients not given antimicrobial treatment before admission. Accordingly, ~55% of 150 cases with undetermined aetiology could have been accounted for by this pathogen [1]. Thus, it seems that most of the reduction in diagnostic yield by antimicrobial pretreatment was due to a failure to identify *S. pneumoniae*. This view is further supported by studies showing that using diagnostic techniques which are insensitive for antimicrobial pretreatment, such as antigen testing, increase the rate of pneumococcal aetiologies by ⩽50%. For example, in a British study, 63% of all pneumococcal aetiologies were exclusively established by pneumococcal antigen detection [15]. In a Dutch study, antigen was present in 12 of 25 patients with pneumonia of unknown aetiology who produced representative sputum [16]. Similar findings have also been reported by others [17, 18]. Therefore, the lack of antigen-testing represents a limitation of the present study. On the other hand, antigen detection is not an irrefutable diagnostic tool, and, therefore, does not mount definite evidence that positive testing in otherwise undiagnosed patients truly represents pneumococcal infection in every case. Corresponding considerations with regards to the role of *S. pneumoniae* in undiagnosed patients as well as limitations in accuracy are also true for new diagnostic tools such as PCR [19].

In the present study, the confounding factor of antimicrobial pretreatment was excluded. Nevertheless, it may still remain difficult to demonstrate a pneumococcal aetiology in nonbacteraemic pneumococcal pneumonia. Indirect evidence for a leading role of *S. pneumoniae* in undiagnosed patients was provided by a British study. In this report, the microbial aetiology was correctly predicted by a discriminant function analysis in 42% of cases. When a similar discriminant function analysis was applied to the one-third of patients in whom the microbial aetiology was never determined, most of these cases were predicted to be due to *S. pneumoniae* [10]. However, the present results suggest that after exclusion of the confounding factor of antimicrobial pretreatment, nonpneumococcal aetiologies and host factors play an important role in undiagnosed patients.

First, an unknown aetiology was more frequent in elderly patients, a cut-off of 70 yrs being associated

with a two-fold increase in risk. Studies addressing elderly patients with CAP tended to have undiagnosed cases at the higher extreme of the reported range (57 and 58%, respectively) [20, 21]. Accordingly, in a previous study by ÖRTQUIST *et al.* [4] age was also significantly associated with an undetermined aetiology. However, sputum, blood cultures, and paired sera were significantly less often obtained, and thus, the significance of this finding remained uncertain. The present results confirm the independent association of undetermined aetiology with age. This is an important finding, yet difficult to interpret. The most likely hypothesis is that elderly patients may be at higher risk for pathogens which are difficult to demonstrate. Among these, anaerobic pathogens involved in pneumonia due to silent (not gross) aspiration as well as viruses may be leading candidates. In fact, silent aspiration is a frequent event in elderly patients with CAP [22]. Moreover, these pathogens would be compatible with the nonalveolar radiographic pattern which was found to predominate in these patients.

Secondly, renal and cardiac comorbidity were independent predictors of an undetermined aetiology. Both volume overload due to renal failure as well as bronchial congestion due to congestive heart failure are risk factors for CAP [23]. However, whether these conditions predispose to specific pathogens is largely unknown. It was found that *M. catarrhalis* as well as atypical pathogens (*C. pneumoniae*, *M. pneumoniae*, and *Coxiella* spp.) were significantly associated with cardiac comorbidity. These pathogens may easily be missed by the usual diagnostic approach. Alternatively, part of this association may be due to the fact that volume overload may mimic pneumonia. This may occur not only by confounding radiographic findings but also by a noninfectious inflammatory response to bronchial congestion. However, only approximately one-third of the infiltrates were bilateral in both groups, which substantially reduces the probability that volume overload was the leading cause of failure to obtain an aetiology. Conversely, parameters other than those specified such as echocardiography- or nonpneumonia-related treatment were not recorded, these may have provided additional evidence for the relative role of fluid overload. This issue clearly should be assessed more specifically in a future study.

Finally, the nonalveolar radiographic pattern predominating in patients with undetermined aetiology strongly hints at pathogens other than pyogenic bacteria. LEVY *et al.* [24] demonstrated that alveolar patterns were due to pyogenic bacteria in >90% of cases, whereas mixed patterns had a very heterogeneous aetiology including atypical bacterial and viral pathogens.

The role of diagnostic work-up in terms of outcome of CAP remains controversial. So far, no study has demonstrated a beneficial effect of establishing an aetiology on any outcome measure [25]. The only hint, with regards to the advantage of diagnostic tools, originates from a study of elderly patients. In this study, the outcome was better when blood cultures were performed within 24 h of admission [26]. However, for this finding to be conclusive there should be an excess mortality in patients with undetermined aetiology. In the present study, although antimicrobial treatment was comparable in patients with and without defined aetiology, a corresponding difference was not found, and the authors were not aware of any other study which might have found such an association.

The intention of this study was hypothesis generating and the results presented have to be interpreted accordingly. The statistical methods employed yielded results that were relevant to the population investigated therefore, they may change in different samples [27]. In order to give the reader an idea about the stability of the conclusions reached on a selected sample, the analyses were repeated in a large less selected population (referred to as the larger population) with the same results. This fact together with the clinical plausibility of the results presented supports the importance of the hypothesis and should stimulate future studies on the repeatibility of the predictors presented.

To conclude, age and host factors were found to be independent predictors of undetermined aetiology in community-acquired pneumonia. The predominance of a nonalveolar pattern in chest radiographs, leads the authors to believe that most undiagnosed cases may be due to pathogens which may be difficult to determine, particularly anaerobes involved in silent aspiration and atypical pathogens. Some of these cases may also have represented volume overload mimicking pneumonia. Although excess mortality in undiagnosed patients was not found, further efforts should be made to test the hypothesis generated from this study.

## References


1. British Thoracic Society. Community-acquired pneumonia in adults in British hospitals in 1982–1983: a survey of aetiology, mortality, prognostic factors, and outcome. *Q J Med* 1987; 239: 195–220.
2. Marrie TJ, Dunant H, Yates L. Community-acquired pneumonia requiring hospitalization: 5-year prospective study. *Rev Infect Dis* 1989; 11: 586–599.
3. Blanquer J, Blanquer R, Borras R, *et al.* Aetiology of community acquired pneumonia in Valencia, Spain: a multicentre propspective study. *Thorax* 1991; 46: 508–511.
4. Örtquist A, Hedlund J, Grillner L, *et al.* Aetiology, outcome and prognostic factors in patients with community-acquired pneumonia requiring hospitalization. *Eur Respir J* 1990; 3: 1105–1113.
5. Bohte R, van Furth R, van den Broek PJ. Aetiology of community-acquired pneumonia: a prospective study among adults requiring admission to hospital. *Thorax* 1995; 50: 543–547.
6. Mundy LM, Auwaerter PG, Oldach D, *et al.* Community-acquired pneumonia: impact of immune status. *Am J Respir Crit Care Med* 1995; 152: 1309–1315.
7. Lieberman D, Schlaeffer F, Boldur I, *et al.* Multiple pathogens in adult patients admitted with community-acquired pneumonia: a one year propspective study of 346 consecutive patients. *Thorax* 1996; 51: 179–184.

8. Neill AM, Martin IR, Weir R, *et al.* Community acquired pneumonia: aetiology and usefulness of severity criteria on admission. *Thorax* 1996; 51: 1010–1016.
9. Ruiz M, Ewig S, Marcos MA, *et al.* Aetiology of community-acquired pneumonia: impact of age, comorbidity, and severity. *Am J Respir Crit Care Med* 1999; 160: 397–405.
10. Farr BM, Kaiser DL, Harrison BDW, Connolly C. Prediction of microbial aetiology at admission to hospital for pneumonia from the presenting clinical features. *Thorax* 1989; 44: 1031–1035.
11. Leroy O, Vandenbussche C, Coffinier C, *et al.* Community-acquired aspiration pneumonia in intensive care units. Epidemiological and prognosis data. *Am J Respir Crit Care Med* 1997; 156: 1922–1929.
12. Bone RC, Balk RA, Cerra FB, *et al.* Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. *Chest* 1992; 101: 1644–1655.
13. Balows A, Harsler WJ Jr. Manual of Clinical Microbiology. 5th edn. Washington DC, American Society for Microbiology, 1991; pp. 209–553.
14. Fang GD, Fine M, Orloff J, *et al.* New and emerging etiologies for community-acquired pneumonia with implications for therapy. A prospective multicenter study of 359 cases. *Medicine* 1990; 69: 307–316.
15. Macfarlane JT, Finch RG, Ward MJ, Macrae AD. Hospital study of adult community-acquired pneumonia. *Lancet* 1982; II: 255–258.
16. Boersma WG, Lowenberg A, Holloway Y, Kuttschrutter H, Snijder JA, Koeter GH. Pneumococcal capsular antigen detection and pneumococcal serology in patients with community acquired pneumonia. *Thorax* 1991; 46: 902–906.
17. Ruiz-Gonzalez A, Falguera M, Nogues A, Rubio-Caballero M. Is Streptococcus pneumoniae the leading cause of pneumonia of unknown aetiology? A microbiologic study of lung aspirates in consecutive patients with community-acquired pneumonia. *Am J Med* 1999; 106: 385–390.
18. Bella F, Tort J, Morera MA, Espaulella J, Armengol J. Value of bacterial antigen detection in the diagnostic yield of transthoracic needle aspiration in severe community-acquired pneumonia. *Thorax* 1993; 48: 1227–1229.
19. Menendez R, Cordoba J, de La Cuadra P, *et al.* Value of the polymerase chain reaction assay in noninvasive respiratory samples for diagnosis of community-acquired pneumonia. *Am J Respir Crit Care Med* 1999; 159: 1868–1873.
20. Venkatesan P, Gladman J, Macfarlane JT, *et al.* A hospital study of community acquired pneumonia in the elderly. *Thorax* 1990; 45: 254–258.
21. Riquelme R, Torres A, El-Ebiary M, *et al.* Community-acquired pneumonia in the elderly. A multivariate analysis of risk and prognostic factors. *Am J Respir Crit Care Med* 1996; 154: 1450–1455.
22. Kikuchi R, Watabe N, Konno T, Mishina N, Sekizawa K, Sasaki H. High incidence of silent aspiration in elderly patients with community-acquired pneumonia. *Am J Respir Crit Care Med* 1994; 150: 251–253.
23. Farr BM, Woodhead MA, Macfarlane JT, *et al.* Risk factors for community-acquired pneumonia diagnosed by general practitioners in the community. *Respir Med* 2000; 94: 422–427.
24. Levy M, Dromer F, Brion N, Leturdu F, Carbon C. Community-acquired pneumonia. Importance of initial noninvasive bacteriologic and radiographic investigations. *Chest* 1988; 92: 43–48.
25. Sanyal S, Smith PR, Saha AC, Gupta S, Berkowitz L, Homel P. Initial microbiologic studies did not affect outcome in adults hospitalized with community-acquired pneumonia. *Am J Respir Crit Care Med* 1999; 160: 346–348.
26. Meehan TP, Fine MJ, Krumholz HM, *et al.* Quality of care, process, and outcomes in elderly patients with pneumonia. *JAMA* 1997; 278: 2080–2084.
27. Concato J, Feinstein AR, Holford TR. The risk of determining risk with multivariate models. *Ann Intern Med* 1993; 118: 201–210.