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Source / Izvornik: **Epidemiology and Infection, 2006, 134, 548 - 555**

Journal article, Accepted version
Rad u časopisu, Završna verzija rukopisa prihvaćena za objavljivanje (postprint)

https://doi.org/10.1017/S0950268805005522

Permanent link / Trajna poveznica: https://urn.nsk.hr/urn:nbn:hr:105:261478

Puljiz, I., Kuzman, I., Đaković-Rode, O., Schonwald, N., Miše, B. (2006) *Chlamydia pneumoniae and Mycoplasma pneumoniae pneumonia: comparison of clinical, epidemiological characteristics and laboratory profiles.* Epidemiology and Infection, 134 (3). pp. 548-555.

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Chlamydia pneumoniae and *Mycoplasma pneumoniae* pneumonia:

Comparison of clinical, epidemiological characteristics and laboratory profiles

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Short running head: *C. pneumoniae* and *M. pneumoniae* pneumonia

SUMMARY

The purpose of our retrospective three-year-study was to analyse and compare clinical and epidemiological characteristics in hospitalized patients older than six years with community-acquired pneumonia (CAP) caused by *Chlamydia pneumoniae* (87 patients) and *Mycoplasma pneumoniae* (147 patients). *C. pneumoniae* and *M. pneumoniae* infection was confirmed by serology. *C. pneumoniae* patients were older (42.12 year vs. 24.64 year), and were less likely to have a cough, rhinitis, and hoarseness ($p<0.001$). *C. pneumoniae* patients had higher levels of C-reactive protein (CRP), and aspartate aminotransferase (AST) than *M. pneumoniae* patients ($p<0.001$). Pleural effusion was recorded more frequently in patients with *M. pneumoniae* (8.84% vs.3.37%). There were no characteristic epidemiological and clinical findings that would distinguish CAP caused by *M. pneumoniae* from *C. pneumoniae*. However, some factors are indicative for *C. pneumoniae* such as older age, lack of cough, rhinitis, hoarseness, and higher value of CRP, and AST.

KEY WORDS: Community-acquired pneumonia, *Chlamydia pneumoniae, Mycoplasma pneumoniae*

INTRODUCTION

Atypical pneumonia agents such as *Chlamydia pneumoniae* and *Mycoplasma pneumoniae* are an important cause of community-acquired pneumonia (CAP) [1]. The prevalence of CAP caused by *C. pneumoniae* and *M. pneumoniae* varies from 3-43% of all CAP cases [2-7]. These organisms share similar epidemiological and clinical characteristics in human infection and disease [8]. Pneumonia caused by these pathogens is usually associated with low severity but this may vary with the patient′s age, the presence of co-pathogens, or the existence of co-morbidity [9]. The diagnosis of *C. pneumoniae* and *M. pneumoniae* CAP has been made by several diagnostic techniques: antibody tests, culture, antigen detection, and identification of specific DNA sequences by polymerase chain reaction (PCR) [10]. The isolation and identification of *C. pneumoniae* and *M. pneumoniae* is difficult, time consuming, not routinely available and expensive [11]. Serology remains the main diagnostic tool in clinical practice.

C. pneumoniae has been associated with atherosclerotic cardiovascular disease including coronary artery disease [12]. However, *C. pneumoniae* may cause acute exacerbation of chronic obstructive pulmonary disease (COPD) [13]. The microbiological eradication of *C. pneumoniae* may be difficult with effective antimicrobial therapy even when good clinical response occurs [14]. Failure to eradicate may have significant clinical consequences such as reactivation of COPD, most concerning in association with coronary artery disease [15, 16].

M. pneumoniae is responsible for producing a wide spectrum of non-pulmonary manifestations including neurological, hepatic, cardiac, and hematological manifestations [17]. Central and peripheral nervous system manifestations are common complications associated with *M. pneumoniae* infection [18]. The outcome of CNS involvement ranges from normal to severe residual deficits [19].

We studied a group of 89 patients with CAP caused by *C. pneumoniae* and compared them with 147 patients with CAP caused by *M. pneumoniae*. Serological tests are regarded as

diagnostic, although the results are usually not available in a timely manner. The hypothesis is that clinical, radiological, and laboratory manifestations of the pneumonia caused by *C. pneumoniae* closely resemble those of *M. pneumoniae*. The goal of this study was to determine whether we may distinguish pneumonia caused by *C. pneumoniae* from *M. pneumoniae* on the basis of epidemiological, clinical, laboratory and radiological characteristics before serological confirmation of infection. The goal was also to establish a presumptive diagnosis of pneumonia that can be useful for both prognostic and therapeutic purposes.

METHODS

We analyzed retrospectively patients with CAP caused by *C. pneumoniae* and *M. pneumoniae* hospitalized at the University Hospital for Infectious Diseases Zagreb, during the three year period from January 1, 1998 to December 31, 2000. The University Hospital for Infectious Diseases Zagreb serves a population of 1,000.000 inhabitants of Croatia's capital, Zagreb, and its surrounding region. Annually, 600 to 800 patients of all ages are hospitalized with CAP, accounting for about 10% of all hospitalized patients.

Patients who met the following criteria were included in the study: age older than six years, clinical findings suggestive of pneumonia (cough, fever, rales), evidence of a new pulmonary infiltrate on chest X-ray, and confirmed acute infection of *C. pneumoniae* and *M. pneumoniae*. Exclusion criteria included nosocomial pneumonia, patients with active tuberculosis, HIV positive patients, and patients who were discharged from hospital less than 21 days prior to their current hospitalization due to pneumonia.

The diagnosis of *C. pneumoniae* and *M. pneumoniae* infection was based on serological testing of antibodies. *C. pneumoniae* was diagnosed by microimmunofluorescence (MIF) based on *C. pneumoniae* elementary bodies (Savyon Diagnostics LTD, Israel) as antigen to detect specific IgG, IgA and IgM antibodies. Evidence of acute infection was defined as four-fold rise in *C. pneumoniae* antibody titre between acute and convalescent serum samples or an IgM antibody titre of ≥ 16. Patients with a serum IgG titre of ≥ 512 in both acute and convalescent serum samples without a four-fold rise in titre in convalescent serum were excluded.

Serum antibodies to *M. pneumoniae* were assayed by enzyme-linked immunosorbent assay (ELISA) by using P1 membrane protein as antigen (Savyon Diagnostics LTD, Israel). Evidence of infection was defined as either a single positive serum IgM titre (≥ 10) in any serum sample or four-fold increase in IgG titre in paired sera.

Paired serum samples were tested for antibodies to *Chlamydia psittaci, Legionella pneumophila* and *Coxiella burnetii*. In addition, urine samples from patients were tested for *L. pneumophila* serogroup-1 antigen. Also we performed blood culture specimens and in selected patients sputum culture prior to antibiotic therapy.

We analysed epidemiological data (age, gender, and cluster of patients, seasonal variations, date of onset of present illness, underlying comorbidity), clinical signs and symptoms (fever, cough, headache, chest pain, hoarseness, sore throat, rhinitis, myalgias/arthralgias, vomiting, diarrhoea), and laboratory findings (erythrocyte sedimentation rate, white blood cell count, sodium, aspartate aminotransferase, alanine aminotransferase, C-reactive protein, alpha-2 globulin, urine, electrocardiogram).

A chest radiograph was obtained on admission to hospital. The radiological manifestations of pulmonary infiltrates were described as: interstitial infiltrate, bronchopneumonia or alveolar infiltrate.

Statistical analysis

Means and standard deviations were calculated to summarize continuous variables. For categorical variables, group percentages were calculated. Differences between patient groups were calculated using the Fisher`s exact one-tailed test for categorical variables and Student`s t-test for continuous variables. Results were considered significant at p value <0.05. All tests were performed with the STATISTICA for Windows software package [20].

RESULTS

From January 1 1998 to December 31 2000, we studied 89 patients with CAP caused by *C. pneumoniae* and 147 caused by *M. pneumoniae* treated at the University Hospital for Infectious Diseases Zagreb. These were chosen out of a larger group of 1,285 hospitalized patients with CAP older than six years including 774 (60.73%) patients whose serum samples were tested for evidence of infection. *C. pneumoniae* was confirmed in 89 patients, accounting for 6.93 % of all patients with CAP, and 11.5 % of patients whose serum samples were tested. Of these, 11 patients had more than one pathogen identified as a cause of pneumonia. *S. pneumoniae*, as a copathogen, was confirmed in six, *M. pneumoniae* in three, and *L. pneumophila* in two patients. *M. pneumoniae* infection was confirmed in 147 patients, accounting for 11.44 % of all CAP patients, and 18.99 % of patients whose serum samples were tested. Ten patients with *M. pneumoniae* infection had a copathogen. *S. pneumoniae* was confirmed in five, *C. pneumoniae* in three, and *L. pneumophila* in one patient.

The patients with *C. pneumoniae* infection and *M. pneumoniae* infection are presented in Table 1. The majority of patients were males in both study groups (p= 0.022). The mean age in the *C. pneumoniae* group was 42.12±17.92 years, significantly higher compared to the *M. pneumoniae* group (24.64±13.59 years; p<0.028). There were significant differences between *C. pneumoniae* patients and *M. pneumoniae* patients in terms of comorbidity (14/89 vs. 9/147; p=0.016). Nearly one third of patients in both groups were smokers (p=0.426). The duration of symptoms prior to admission to hospital was similar (6.24 vs. 6.53 days; p=0.989). A lower incidence of *C. pneumoniae* than *M. pneumoniae* patients had a history of contact with a person with similar symptoms (12/89 vs. 45/147; p=0.002). Most cases of mycoplasma outbreaks occured in schools (22), among family members (13), and military recruits (10). Six patients with *C. pneumoniae* CAP but none with *M. pneumoniae* infection came from nursing homes.

The oldest patient with *C. pneumoniae* CAP was 85 years of age (Table 2). CAP caused by *C. pneumoniae* was uncommon in school-age children, and its occurrence increased with age. Eighty patients (20.22%) were in the 20-29 age group, nine (10.11%) were aged 30-39, 21 (23.60%) were aged 40-49, 14 (15.73%) were aged 50-59, and 17 (19.10%) were 60 years or older. *Mycoplasma pneumoniae* most frequently affected older children and younger adults (ages 15 to 30 years). The oldest patient with *M. pneumoniae* CAP was 65 years old.

The seasonal distribution of *C. pneumoniae* infections is showed in Table 3. A higher proportion of *C. pneumoniae* patients was recorded in summer months, between June and October while *M. pneumoniae* was more frequent between August and November.

Patients in both groups had similar signs and symptoms on admission to hospital (Table 4). The most common symptoms in patients with *C. pneumoniae* and *M. pneumoniae* infection were fever (97.75 vs. 97.96%), cough (82.02% vs. 97.28), and headache (53.06 vs. 59.55%), respectively. Patients with *C. pneumoniae* CAP were less likely to have a cough on admission ($p<0.001$). Upper respiratory tract symptoms were less commonly associated with *C. pneumoniae* CAP than with *M. pneumoniae* CAP. Gastrointestinal tract symptoms such as vomiting ($p=0.029$) and diarrhoea ($p=0.056$) were more commonly associated with *C. pneumoniae*. Patients in both groups had similar laboratory results (Table 5 and 6). The mean erythrocyte sedimentation rate (ESR) did not significantly differ between the *Chlamydia* and *Mycoplasma* group ($p=0.900$), but more patients in the *Chlamydia* group had accelerated ESR ($p=0.047$). The mean leucocyte count was similar in both groups of patients ($10.32x10^9$/L vs. $9.87x10^9$/L; $p=0.310$). Fifty one patients (57.3 %) from the *C. pneumoniae* group and 86 (58.50%) from *M. pneumoniae* group had normal leucocyte count ($p=0.481$). The major difference among the groups regarding laboratory results was recorded in the C-reactive protein (CRP) and aspartate aminotransferase (AST) levels. Patients with *C. pneumoniae* CAP had higher levels of CRP (178.3±129.81 mg/L), and AST (33.93±31.91 IU/L) than *M. pneumoniae*

(100.9±87.73 mg/L; 22.58±17.63 IU/L, respectively). The differences were statistically significant ($p<0.001$; $p<0.001$, respectively). More than one third of *C. pneumoniae* patients and one-fifth of *M. pneumoniae* patients had increased level of AST and ALT ($p=0.019$; $p=0.013$, respectively).

Radiological manifestations of pneumonia in the *C. pneumoniae* group were as follows: interstitial infiltrate in 79 (88.76 %), homogeneous segmental or lobar in five (5.62 %), and bronchopneumonia in five patients (5.62 %). Seven patients had multiple-lobe involvement (7.86 %), and only three patients had pleural effusion (3.36%). Out of 147 patients with *M. pneumoniae* CAP chest X-ray showed interstitial infiltrate in 133 (90.48%), alveolar infiltrate in 13 (8.84%), and bronchopneumonic infiltrate in one patient (0.68 %). Ten patients (6.80 %) had involvement more than one lobe, and pleural effusion had 13 patients (8.84 %). The two aetiological groups could not be differentiated by radiographic findings on admission.

DISCUSSION

One thousand two hundred and eighty five patients with CAP who had been hospitalized at the University Hospital for Infectious Diseases "Dr. Fran Mihaljević", Zagreb were included in a retrospective study conducted over a course of three years. They were residents of Zagreb or its surrounding area, including both genders and older than six years. *C. pneumoniae* and *M. pneumoniae* were common causes of pneumonia in our study (6.93% and 11.44%, respectively). The most prevalent concomitant aetiological agent was *S. pneumoniae* in both patient groups. The limitation of the study was its reliance on serological techniques alone for the diagnosis of *C. pneumoniae* and *M. pneumoniae* infection. The preferred diagnostic finding is documentation of a four-fold increase in titre from acute to convalescent specimen, with supporting evidence by PCR or culture [21, 22].

M. pneumoniae was the most commonly confirmed pathogen of CAP described in our previously published report [23]. *M. pneumoniae* causes a small percentage of cases of CAP requiring hospitalization [24]. The incidence of infection with *M. pneumoniae* among hospitalized adults with CAP ranges from 3 to 30 % [4, 6, 25], and it is much higher among young adults who are treated as outpatients [26]. Although the prevalence varies from year to year and between different geographic settings, *C. pneumoniae* causes approximately 5-15% of cases of CAP [2-4, 27, 28]. The majority of cases of pneumonia are relatively mild and associated with low mortality.

In the present study *C. pneumoniae* affected adults of all ages with the most frequent incidence in the 40-49 age group. *M. pneumoniae* infection was most common among older children and young adults. The mean age of patients with *C. pneumoniae* CAP was significantly higher than that of *M. pneumoniae* CAP. On the basis of serological criteria 11 (12.56%) patients with *C. pneumoniae* CAP had an acute primary infection (IgM antibody response), and 78 (87.44%) patients had a recurrent acute infection. Only three of our patients were heavy smokers

with chronic obstructive pulmonary disease (COPD). *C. pneumoniae* may lead to inhibition of ciliary motion and facilitate infection of the lower respiratory tract [13]. Five of our patients with serologically confirmed *C. pneumoniae* infection had a heart disease. Of those five, two patients had severe pneumonia with *S. pneumoniae* as co-pathogen. The patients were discharged as improved, but after prolonged hospital stay. However, clinical characteristics in these patients may reflected manifestations of *S. pneumoniae*, with *C. pneumoniae* aggravating the cardiac disease. Certainly, *C. pneumoniae* infection has been associated with cardiovascular diseases [12]. Our study has shown that elderly patients, and those with underlying diseases had an elevated risk of CAP caused by *C. pneumoniae*, and co-morbidities undoubtedly played a significant role in the clinical course.

Other studies described similar finding and reported that the highest incidence of *C. pneumoniae* pneumonia was among the elderly, and *M. pneumoniae* in adolescents and young adults [4, 7, 25-27]. Males were affected more often than females in both groups of patients which corresponds to findings of other researches [4-7, 25-27].

In our study, a higher incidence of *C. pneumoniae* CAP was recorded between June and October, but *M. pneumoniae* infection had the highest incidence in the fall. We noted a small outbreak of *C. pneumoniae* infection during the summer months in 1999. It was preceded by a great epidemic of *M. pneumoniae* pneumonia from August to December. Year 1999 was recorded as CAP epidemic caused by both *C. pneumoniae*, as well as *M. pneumoniae*. In the interepidemic period, we recorded no significant differences in the incidence of CAP in this two patient groups. Both CAP groups occurred throughout the observed period with somewhat lower incidence during the winter months.

Several publications have recorded no seasonal differences in the incidence of *C. pneumoniae* CAP [29,30] although one study described *C. pneumoniae* infection during all seasons with higher incidence in summer months [31]. *C. pneumoniae* epidemics are

characterised by an initial high incidence period which lasts a few months to two-three years followed by three-four years of lower incidence [32]. Some studies suggest that there is no seasonal variation in *M. pneumoniae* infection; however, other data suggest that its incidence is greatest during the autumn and winter months [33]. For less clear reasons, *M. pneumoniae* outbreaks occur every 3-6 years [22, 33, 34].

Several differences between the symptoms produced by *C. pneumoniae* and *M. pneumoniae* were recorded. The patients with *C. pneumoniae* were less likely to have a cough and upper respiratory tract symptoms (rhinitis, hoarseness and sore throat) than patients with *M. pneumoniae* CAP. Analysis of the laboratory findings in our study showed that CRP as well as AST were the most important laboratory findings in differentiating *C. pneumoniae* from *M. pneumoniae* CAP. The reason is that *C. pneumoniae* invades the blood and spreads into different organs, while *M. pneumoniae* remains on the respiratory tract epithelial causing a waeker inflammatory reaction with lower values of CRP and AST. The results suggest that CAP caused by *C. pneumoniae* is a more severe disease than pneumonia caused by *M. pneumoniae*. However, higher a proportion of *C. pneumoniae* patients had an increased aminotransferases level. There were no differences regarding radiological presentation of pneumonias, and most patients had intestitial infiltrates. Pleural effusion was more frequently recorded in *M. pneumoniae* patients. Numerous studies indicate that clinical symptoms, laboratory findings, and radiographic manifestations of *C. pneumoniae* pneumonia resemble those in patients with *M. pneumoniae* pneumonia [1, 8, 9, 25, 27]. Pneumonia caused by these pathogens is usually mild, but in some cases it can be severe even in normal healthy individuals [35, 36].

Electrocardiographic changes were found in nearly one-third of our patients. All ECG manifestations were transient and all patients completly recovered. Seedat et al. described ECG changes in 31% of patients of CAP [37]. Mechanisims of ECG changes in patients with

pneumonia may be multifactorial and may include hypoxia, electrolyte changes, adrenergic stimulation, and direct cardiac involvement [37].

In conclusion, there are no clinical signs or symptoms or routine, rapid laboratory tests that would differentiate *C. pneumoniae* CAP from *M. pneumoniae* CAP. However, some features of *C. pneumoniae* infection are indicative, such as older age of patients, cough and symptoms from the upper respiratory tract (rhinitis, hoarseness), and higher values of CRP and AST.

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Table 1. Baseline demographic and epidemiological details of patients with CAP caused by *C. pneumoniae* and *M. pneumoniae*

Characteristics	*C. pneumoniae* N = 89 (%)	*M. pneumoniae* N = 147	P-value
Males	73 (82.02%)	102 (69.39%)	0.022*
Females	16 (17.98%)	45 (30.61%)	
Age (year)	42.12 ± 17.92	24.64± 13.59	0.028**
Comorbidity[1]	14 (15.73%)	9 (6.12%)	0.016*
Current smoker	26 (29.21%)	46(31.29%)	0.426*
Outbreak[2]	12 (13.48%)	45 (30.61%)	0.002*
Duration of symptoms prior to admission	6.24±2.79	6.53±2.71	0.989**

CAP: community acquired pneumonia
[1]Comorbidity: liver disease, renal disease, congestive heart failure, cerebrovascular disease, neoplastic disease, chronic obstructive pulmonary disease
[2]Outbreaks in families, schools, military barracks, nursing homes
Statistical analysis: * Fisher`s exact one-tailed test; ** Student`s t-test

Table 2. Age-specific rates of infection in patients with CAP caused by *C. pneumoniae* and *M. pneumoniae*

Age group (Year)	*C. pneumoniae*		*M. pneumoniae*	
	No	%	No	%
7 – 14	3	3.37	27	28.36
15 – 19	7	7.87	34	23.13
20 – 29	18	20.22	44	29.93
30 – 39	9	10.11	23	15.64
40 – 49	21	23.60	8	5.45
50 – 59	14	15.73	8	5.45
60≥	17	19.10	3	2.04
Total	89	100.00	147	100.00

CAP: community acquired pneumonia

Table 3. Distribution of infection in patients with CAP caused by *C. pneumoniae* and *M. pneumoniae* by months of the year

Month	*C. pneumoniae*		*M. pneumoniae*	
	No.	%	No	%
January	4	4.49	2	1.36
February	5	5.62	0	0
March	3	3.37	1	0.68
April	4	4.49	7	4.76
May	4	4.49	7	4.76
June	16	17.98	2	1.36
July	14	15.73	11	7.48
August	6	6.74	16	10.89
September	10	11.24	26	17.69
October	7	7.87	34	23.13
November	8	8.99	34	23.13
December	8	8.99	7	4.76
Total	89	100.00	147	100.00

CAP: community acquired pneumonia

Table 4. Symptoms in patients with CAP caused by *C. pneumoniae* and *M. pneumoniae*

Symptoms	*C. pneumoniae*		*M. pneumoniae*		p-value
	No.	%	No	%	
Temperature (>37.5°C)	87	97.75	144	97.96	0.617
Cough	73	82.02	143	97.28	<0.001
Rhinitis	6	6.74	45	30.61	<0.001
Hoarseness	14	15.74	52	35.37	<0.001
Sore throat	8	8.99	22	14.87	0.127
Chest pain	8	8.99	22	14.87	0.127
Headache	53	59.55	78	53.06	0.201
Vomiting	17	19.10	14	9.52	0.029
Diarrhoea	10	11.24	7	4.70	0.056
Myalgias/arthralgias	36	40.45	48	32.65	0.142
Pleural effusion	3	3.33	13	8.84	0.101

CAP: community acquired pneumonia
Statistical analysis: Fisher`s exact one-tailed test

Table 5. Normal range and pathological laboratory findings in patients with CAP caused by *C. pneumoniae* and *M. pneumoniae*

Laboratory finding	Normal range	Pathological finding		P-value
		C. pneumoniae N = 89	*M. pneumoniae* N = 147	
ESR ↑	>20 mm/1.h	81	121	0.047
CRP ↑	10 mg/L	50/50	86/95	0.392
WBC ↑	4-10x10^9/L	38	61	0.481
AST ↑	11-38 IU/L	34	36	0.019
ALT ↑	12-48 IU/L	30	29	0.013
Alpha-2 globulin ↑	5.5-9.5 rel.%	62	91	0.142
Gamma globulin ↑	14.5-19.5 rel%	29	36	0.116
Sodium ↓	138-146 mmol/L	50	74	0.231
Abnormal ECG		32/76	42/125	0.248

Statistical analysis: Fisher`s exact one-tailed test
CAP: community acquired pneumonia
↑ - increased values
↓ - decreased values
ESR = Erythrocyte sedimentation rate
CRP = C-reactive protein
WBC = White blood cell
AST = Aspartate aminotransferase
ALT = Alanine aminotransferase
ECG = Electrocardiogram

Table 6. Laboratory findings in patients with CAP caused by *C. pneumoniae* and *M. pneumoniae*

Laboratory finding	*C. pneumoniae*		*M. pneumoniae*		p-value
	X±SD	Range	X±SD	Range	
ESR (mmHg/1.h)	58.82±24.46	8-130	47.64±24.79	6-112	0.900
CRP mg/L (N=95; N=50)	178.3±129.81	12-496	100.9±87.73	2-331	<0.001
WBC ($x10^9$/L)	10.32±4.30	4.6-29.0	9.87±3.91	3.8-35.8	0.310
AST (IU/L)	33.93±31.91	8-137	22.58±17.63	8-137	<0.001
ALT (IU/L)	41.22±43.77	11-212	27.52±37.13	7-383	0.079
Alpha-2 (rel.%)	11.26±2.43	6.9-17.1	10.14±2.20	5.4-16.5	0.271
Gamma (rel.%)	16.64±3.06	11.2-28.6	16.51±2.80	9.4-25.9	0.336
Sodium (mmol/L)	136.87±2.67	128-142	137.41±2.67	130-144	1.000

CAP: community acquired pneumonia
Statistical analysis: Student`s t-test
ESR = Erythrocyte sedimentation rate
CRP = C-reactive protein
WBC = White blood cell
AST = Aspartate aminotransferase
ALT = Alanine aminotransferase

Abbreviations

Alanine aminotransferase – ALT

Aspartate aminotransferase – AST

Chlamydia pneumoniae – C. pneumoniae

Chlamydia psittaci – C. psittaci

Community-acquired pneumonia – CAP

Coxiella burnetii – C. burnetii

C – reactive protein – CRP

Electrocardiogram – ECG

Erythrocyte sedimentation rate – ESR

International unit - IU

Mycoplasma pneumoniae – M. pneumoniae

Microimmunofluorescence –MIF

Legionella pneumophila – L. pneumophila

Polymerase chain reaction – PCR

Streptoccocus pneumoniae – S. pneumoniae

White blood cell – WBC