Clinical picture of community-acquired *Chlamydia pneumoniae* pneumonia requiring hospital treatment: a comparison between chlamydial and pneumococcal pneumonia

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Abstract

Background – The importance of *Chlamydia pneumoniae* as a cause of pneumonia has remained controversial. The clinical picture of *C pneumoniae* and *Streptococcus pneumoniae* in patients admitted to hospital with community-acquired pneumonia was compared during a *C pneumoniae* epidemic in Finland. **Methods** – Group I consisted of 24 patients in whom serological testing and bacterial culture indicated an association with *C pneumoniae* only, group II comprised nine patients with both *C pneumoniae* and *S pneumoniae*, and group III consisted of 13 patients with *S pneumoniae* only.

Results – The patients with *C pneumoniae* suffered from headache more frequently than the other patients (group I, 46%; group II, 11%; and group III, 15%) and had received antimicrobial treatment more often before admission to hospital (group I, 54%; groups II and III, 0%). The patients with *C pneumoniae* produced few good sputum samples and had suffered from respiratory symptoms longer than those with *S pneumoniae* (group I, 10 days; groups II and III, 4 days). C reactive protein values on admission were lowest in group I and highest in group II. The antimicrobial treatment provided in hospital covered *C pneumoniae* in 36% of cases in group I and 0% in group II, while *S pneumoniae* was covered in all patients. *C pneumoniae* and *S pneumoniae* together were associated with more severe disease and a longer stay in hospital.

Conclusions – Pneumonia caused by *C pneumoniae* was milder but clinically resembled that caused by *S pneumoniae*, and required hospital treatment even among young patients. Mixed infections were common and should be taken into account when planning antimicrobial treatment for community-acquired pneumonia. Further studies with more patients are needed to evaluate the severity of *C pneumoniae* pneumonia.

(Thorax 1996;51:185-189)

Keywords: *Chlamydia pneumoniae*, community-acquired pneumonia, clinical signs.

Chlamydia pneumoniae, the third member of the genus *Chlamydia*, causes both upper respiratory

tract infections such as sinusitis, pharyngitis, and otitis media, and lower respiratory tract infections, bronchitis and pneumonia.^{1,2} It is the cause of at least 10% of all cases of community-acquired pneumonia treated either in out-patient clinics or in hospitals.³⁻⁵ In previous reports on the clinical picture of pneumonia caused by *C pneumoniae*, patients have usually been young – for example, teenagers at vocational schools, university students, or military recruits – and the onset of pneumonia has been slow, starting with upper respiratory symptoms such as pharyngitis with hoarseness followed by cough and other lower respiratory symptoms.^{4,6-10} During epidemics among military recruits in Finland, only about 10% of *C pneumoniae* infections manifested themselves as pneumonia.⁸ Since most *C pneumoniae* infections are mild or even asymptomatic, its importance as a respiratory pathogen has been neglected.^{11,12}

In Finland *C pneumoniae* caused a widespread epidemic in 1986-7 which was verified both serologically and by the presence of *C pneumoniae* in respiratory samples in culture and by the polymerase chain reaction.^{10,13,14} At the same time a prospective study of the aetiology of community-acquired pneumonia requiring hospital treatment was carried out at Oulu University Hospital in northern Finland. During this period *C pneumoniae* closely followed *Streptococcus pneumoniae* in frequency as an aetiological agent for pneumonia, and this provided us with a unique opportunity to investigate the clinical picture of patients with *C pneumoniae* pneumonia and to compare it with that of pneumococcal pneumonia.

Methods

PATIENTS AND SPECIMENS

During the period between May 1986 and May 1987, 125 adults with radiologically confirmed community-acquired pneumonia were admitted to the ward for infectious diseases at Oulu University Hospital, and paired serum samples were obtained for serological examination on admission and on discharge approximately one week later. A third serum sample was obtained from 72% of the 125 patients during a follow up visit approximately one month later. The patients who fulfilled the diagnostic criteria for pneumonia caused by *C pneumoniae* and/or *S pneumoniae* (see below)

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Received 1 February 1995
Returned to authors
1 June 1995
Revised version received
27 July 1995
Accepted for publication
3 October 1995

without any evidence of other causative agents formed the groups for comparison of the clinical picture.

BACTERIOLOGICAL METHODS

Two aerobic and anaerobic blood cultures (Hemobact, Orion Diagnostic, Finland) were obtained from all 125 patients on admission, before antimicrobial chemotherapy was started. One hundred and fifteen patients were able to produce a sputum sample for culture. The specimens were treated with N-acetyl-L-cysteine and cultured semiquantitatively on blood, chocolate, and *Legionella* selective agar (BCYE) plates.¹⁵ *Mycobacterium* cultures were made on Löwenstein-Jensen medium with and without pyruvic acid. The quality of the sputum sample was assessed by the method of Bartlett *et al* and graded as good, moderate or poor.¹⁶ The culture results were accepted as aetiologically indicative if the growth from a good or moderate quality sputum sample was heavy or moderate.^{16,17} Such growth of *Haemophilus influenzae*, *Moraxella* (*Branhamella*) *catarrhalis*, *Staphylococcus aureus*, or Gram negative bacilli in cases of pneumococcal or chlamydial pneumonia was considered to indicate mixed infection. No culture result from a poor quality sputum sample was accepted.

Pneumococcal capsular antigens were sought from 109 of 115 sputum samples utilising a latex agglutination reagent prepared from polyvalent pneumococcal Omniserum (Staten's Serum Institute, Copenhagen, Denmark).¹⁸

SEROLOGICAL METHODS

Chlamydial antibodies were measured by the microimmunofluorescence method using the following elementary bodies as antigens: *C pneumoniae* AR 39 and/or Kajaani 6 (epidemic) strains, *C trachomatis* pools of immunotypes CHIJ, GFK, BDE, and *C psittaci* OA and 6BC strains.^{10,19} All IgM positive serum samples indicating primary infection were retested after treatment with Gullisorb (Gull Laboratories, USA) to avoid false positive IgM findings due to rheumatoid factor.^{3,10} The complement fixation method was used to measure antibodies to *Mycoplasma pneumoniae*, influenza A and B, parainfluenza 1, 2, and 3, respiratory syncytial virus, adenovirus, measles, herpes simplex, varicella zoster, cytomegalovirus, parotitis, and coxsackie (B5) virus. Antibodies to *Legionella* were measured by indirect immunofluorescence and those to *S pneumoniae*, *H influenzae*, and *M catarrhalis* by enzyme immunoassay.^{15,17,20} The serological criterion used in enzyme immunoassay testing was a threefold increase in antibodies.

DIAGNOSTIC CRITERIA FOR PNEUMONIA CAUSED BY *C PNEUMONIAE*

A fourfold or greater rise in titre in any Ig class of antibodies to *C pneumoniae* between paired serum samples or an IgG titre of ≥ 512 , an IgA titre of ≥ 512 , or the presence of IgM (≥ 16) antibodies in any serum sample were

considered diagnostic for pneumonia caused by *C pneumoniae*.¹⁹ Only clearcut even fluorescence of elementary bodies specific for *C pneumoniae* was accepted, and any case with evidence of cross reactivity was excluded.²¹ The presence of IgM class antibodies on admission was considered to be a mark of primary infection. Other positive findings were considered reinfections.

DIAGNOSTIC CRITERIA FOR PNEUMONIA CAUSED BY *S PNEUMONIAE*

S pneumoniae was considered a pathogen when isolated from blood culture or verified both bacteriologically and serologically. The bacteriological criterion was isolation from a sputum specimen of good or moderate quality (see methods) showing Gram positive diplococci in a Gram stained smear and/or a positive pneumococcal capsular antigen, and the serological criteria were either a twofold or greater increase in antibodies to pneumolysin or the presence of pneumolysin-specific immune complexes in any serum sample.^{22,23}

CLINICAL SYMPTOMS AND LABORATORY PARAMETERS

The following clinical data were analysed: symptoms, pre-existing chronic conditions, physical examination, clinical laboratory findings, responses to antimicrobial treatment, duration of hospital stay, and outcome. The laboratory parameters included white blood cell count (WBC, $\times 10^9/l$) with differential counts, erythrocyte sedimentation rate (ESR, mm/h), plasma sodium, potassium, albumin, creatinine, calcium, aspartate transaminase (ASAT), alanine transaminase (ALAT), bilirubin, alkaline phosphatase, creatine kinase, and cholesterol. C reactive protein (CRP, mg/l) was analysed by an immunoturbidometric method.²⁴

DATA ANALYSIS

Continuous variables were analysed statistically by one way analysis of variance (ANOVA) and the Student's *t* test and non-continuous variables by the χ^2 test using SPSS for Windows.²⁵ If the number of findings was less than five, Fisher's exact test was used.

Results

Forty six of the 125 patients were classified on the strict criteria as belonging to one of the three groups. In 24 cases the pneumonia was caused by *C pneumoniae* alone (group I), five of whom had an IgM positive primary infection and 19 had a reinfection; in nine cases the pneumonia was caused by *S pneumoniae* and *C pneumoniae* together (group II), two of whom had an IgM positive *C pneumoniae* primary infection and seven a reinfection, and two had pneumococcal bacteraemia; and in 13 cases the pneumonia was caused by *S pneumoniae* alone (group III) including eight who had pneumococcal bacteraemia.

Table 1 Characteristics and major symptoms of the patients in the three aetiological groups of pneumonia

Features	Group I <i>C pneumoniae</i> (n = 24)	Group II Both agents (n = 9)	Group III <i>S pneumoniae</i> (n = 13)
Male	14	4	7
Smoking	10	4	3
Alcoholism	1	1	2
Any underlying condition	9	6	9
Antibiotic treatment before admission*	13	0	0
Fever at home	22	8	13
Respiratory symptoms:			
Cough	19	8	10
Sputum production	17	9	12
Haemoptysis	3	1	2
Shortness of breath	8	6	7
Chest pain	6	1	6
Sinusitis or otitis	4	0	1
CNS symptoms†	13	1	2
Headache	11	1	2
Confusion	2	0	0
Diarrhoea	2	2	2

* p<0.001; † p<0.05.

Figure 1 Sputum production and purulence of the specimen. Group I = *C pneumoniae* only; group II = double aetiology; group III = *S pneumoniae* only.

COMPARISON OF CLINICAL DATA

Table 1 shows that the three aetiological groups did not differ significantly in terms of sex, smoking, alcohol abuse, or underlying clinical diseases (asthma, chronic obstructive pulmonary disease, diabetes mellitus, chronic coronary heart disease, heart failure, hypertension, dementia, immunosuppression, haematological malignancy or other tumour). The patients in group I were about 15 years older

on average than those in group II, but the difference did not reach statistical significance (62.2 (95% CI 52.2 to 72.2) versus 53.2 (95% CI 44.3 to 61.1)). The prevalence of respiratory symptoms was similar in the three groups (table 1). Almost half of the patients in group I complained of a headache, whereas the corresponding figures for groups II and III were 15.4% and 11.1%, respectively ($p = \text{NS}$). The patients in group I produced sputum less frequently and the quality of the specimen was poor compared with the other groups, and only a few purulent sputum samples were obtained ($p < 0.01$, fig 1). Interestingly, 52% of the patients in group I had received antibiotic treatment before entering hospital, compared with none in the other two groups ($p < 0.0005$). However, this did not influence the sputum purulence results in group I. Of the 13 patients who received antibiotic treatment prior to admission, two could not produce any sputum and nine had sputum of poor quality, while the corresponding figures for patients who did not receive antibiotics were five and four, respectively.

As shown in table 2, the patients in group I had a longer duration of respiratory symptoms than the other two groups ($p < 0.01$), whereas the duration of fever varied only from three to four days between the groups. Physical examination conducted on admission did not reveal any differences between the three groups. Both the patients in group I and those with pneumococcal pneumonia showed a clear correlation between pulse rate and body temperature ($r = 0.48$, $p < 0.05$ and $r = 0.52$, $p = 0.01$, respectively). Chest auscultation revealed pneumonic rales in 100% of the cases in the patients in group III, and in 78–80% of the two other groups ($p = \text{NS}$). The most profound difference in the laboratory tests was seen in CRP values on admission, where patients in group II had the highest values and those in group I the lowest ($p < 0.005$). The kinetics of CRP are shown in fig 2. Both WBC ($p = \text{NS}$) and CRP ($p < 0.01$) were highest in patients in group II on admission, while the CRP concentration was much higher on admission in patients in group III than in those in group I without any overlap in the 95% confidence

Table 2 Mean (95% confidence interval) major physical and laboratory findings of the patients in the three aetiological groups of pneumonia on admission

Features	Group I <i>C pneumoniae</i> (n = 24)	Group II Both agents (n = 9)	Group III <i>S pneumoniae</i> (n = 13)
Duration of symptoms (days)*	10.5 (6.8 to 14.1)	4.0 (1.7 to 6.3)	3.5 (2.1 to 4.8)
Duration of fever (days)	4.1 (2.7 to 5.4)	4.0 (0.9 to 7.0)	3.0 (1.6 to 4.3)
Physical findings:			
Blood pressure (mm Hg)			
Systolic	133 (125 to 141)	128 (107 to 148)	127 (112 to 142)
Diastolic	75 (70 to 80)	69 (59 to 78)	70 (65 to 75)
Heart rate (/min)	88 (80 to 96)	102 (89 to 115)	101 (91 to 112)
Temperature (°C)	38.2 (37.7 to 38.6)	38.2 (37.1 to 39.2)	38.5 (37.9 to 39.0)
Laboratory findings:			
ESR (mm/h)	63 (48 to 78)	92 (75 to 108)	64 (41 to 87)
C-reactive protein (mg/l)*	107 (78 to 135)	193 (98 to 287)	179 (143 to 215)
Creatinine (μmol/l)	117 (52 to 182)	89 (79 to 99)	106 (93 to 119)
Albumin (g/l)	35 (33 to 37)	31 (26 to 36)	34 (30 to 38)
WBC ($\times 10^9/\text{l}$)	11.6 (8.8 to 14.6)	17.6 (10.3 to 24.9)	15.6 (11.5 to 19.6)
Granulocytes	65.3 (59.7 to 71.0)	66.9 (51.6 to 82.2)	72.1 (61.6 to 82.5)
Lymphocytes	23.0 (18.3 to 27.7)	17.2 (8.8 to 25.6)	16.6 (8.9 to 24.4)
Band forms	3.5 (1.3 to 5.8)	8.6 (1.4 to 15.7)	6.6 (2.8 to 10.4)

* $p < 0.001$.

Figure 2 Kinetics of C reactive protein (CRP) in the three aetiological groups during the first week of admission to hospital (mean, 95% confidence interval).

Table 3 Antibiotic treatment in the three aetiological groups of pneumonia

Antibiotics	Group I <i>C pneumoniae</i> (n=25)	Group II Both agents (n=9)	Group III <i>S pneumoniae</i> (n=13)
First antibiotic			
Penicillin	14 (56)	3 (33)	9 (69)
Cefuroxime	10 (40)	6 (67)	4 (31)
Penicillin only	5 (20)	3 (33)	8 (62)
Appropriate treatment*	9 (36)	0†	13 (100)
No of antibiotics used‡			
1	8 (32)	5 (56)	8 (62)
2	14 (56)	2 (22)	4 (31)
3	2 (8)	1 (11)	1 (8)
4	1 (4)	0	0
>4	0	1 (11)	0

Values in parentheses are percentages.

* Group I: doxycycline or erythromycin; group II: penicillin or erythromycin or cefuroxime; group III: penicillin/cefuroxime and erythromycin/doxycycline.

† The change from penicillin G to penicillin V from cefuroxime to oral cephalaxine was considered as one course.

‡ All patients received appropriate treatment against *S pneumoniae* but none against *C pneumoniae*.

intervals. During the admission period the differences in parameters between the groups fell. White blood cells, their differential counts, and ESR did not differ between the groups, although the patients in group I had the lowest counts. The same was true for serum electrolytes, bilirubin, calcium, creatine kinase, cholesterol, and the liver function tests (data not shown). Increased alkaline phosphate levels (>250 U/l) were seen in five cases in group I and two cases in group III.

ANTIBIOTIC TREATMENT DURING HOSPITAL STAY

Only 36% of the patients in group I received either doxycycline hydrochloride or erythromycin treatment (table 3), whereas all the patients in group III received penicillin G, cefuroxime, or erythromycin – that is, antibiotics that are active against *S pneumoniae*. All the patients in the group II also received antibiotics active against *S pneumoniae*, but none of them was treated with either doxycycline hydrochloride or erythromycin. The patients in group II received more courses of antibiotics than those in the other two groups.

The first antibiotic given was penicillin G in more than half the cases in groups I and III, whereas in group II treatment was more often started with cefuroxime. When all the patients infected with *C pneumoniae* were analysed together (groups I and II), nine of the 36 had received appropriate antimicrobial treatment, whereas all 13 patients with *S pneumoniae* infection (group III) and nine of the patients infected with both organisms (group II) were treated with appropriate antibiotics against pneumococcus ($p < 0.001$). The importance of appropriate antimicrobial treatment was reflected by the faster decrease in CRP values observed in group III than in the other groups ($p = \text{NS}$, fig 2).

OUTCOME FOR PATIENTS WITH PNEUMONIA

The mean duration of hospital treatment differed significantly between the three groups ($p = 0.001$) being 8.4 days (95% CI 6.7 to 10.2) in patients in group I, 21.9 days (95% CI 4.2 to 39.5) in group II, and 10.5 days (95% CI 6.8 to 14.3 days) in group III. Two patients with pneumococcal bacteraemia and alcohol abuse had major complications. A 60 year old man in group III died on the eleventh day despite receiving mechanical respiratory support and a 36 year old woman in group II recovered from adult respiratory distress syndrome and was discharged from hospital after 70 days having received seven courses of antibiotic during her hospital stay. In addition, one patient without bacteraemia in group II had a pulmonary embolism.

Discussion

C pneumoniae pneumonia has been described previously as a mild atypical pneumonia which can be treated on an outpatient basis.^{7,11} Our results indicate that *C pneumoniae* as a single aetiological agent is capable of causing pneumonia severe enough to require admission to hospital even in relatively young patients. The clinical picture, although milder, resembles that of pneumococcal pneumonia. Furthermore, *C pneumoniae* and *S pneumoniae* as a dual infection results in more severe illness with higher CRP values requiring longer hospital treatment than either *C pneumoniae* or *S pneumoniae* infection alone.

Among the clinical symptoms, headache was more common in the patients with *C pneumoniae* pneumonia (46%). The frequency of headache in earlier reports has varied from 17% to 60%.^{2,4,5,13,26} Central nervous system symptoms including headache seem to be common in *C pneumoniae* pneumonia, which has also been seen with other atypical pneumonias.^{4,26,27}

The physical examination did not reveal any outstanding differences between the groups, as has been reported earlier.^{2,27,28} Increased alkaline phosphate levels have been reported in association with *C pneumoniae* pneumonia, but this was not evident in our patients.⁵ The relatively slow pulse rate in relation to the fever reported in association with other intracellular

infections such as brucellosis, typhoid fever, legionellosis, and psittacosis was not seen in our patients with *C pneumoniae* pneumonia.

C pneumoniae was not recognised as a pathogen for pneumonia during the period of our study, and the ongoing *C pneumoniae* epidemic was only demonstrated later. In the group of patients with *C pneumoniae* infection six had received doxycycline and one erythromycin for a median of three days before admission to hospital. These treatments were changed to either penicillin G or cefuroxime on admission. All the patients in the *C pneumoniae* group recovered, however, although only 36% had received the appropriate antimicrobial treatment (that is, erythromycin or tetracycline). Reports from North America have also mentioned that patients with *C pneumoniae* pneumonia recovered without adequate antibiotic treatment.^{28,29} Current guidelines for community-acquired pneumonia stress the importance of *C pneumoniae* as an aetiological agent and of prescribing macrolides which are also effective against other pathogens that cause community-acquired pneumonia such as *S pneumoniae*, *M pneumoniae*, and *L pneumophila*.³⁰

Patients with *C trachomatis* or *C psittaci* infections also respond to treatment with β lactam antibiotics.^{31,32} The duration of fever in psittacosis has nevertheless been longer during treatment with β lactams than with tetracycline or erythromycin.³¹

The patients with both *C pneumoniae* and *S pneumoniae* infections received the appropriate treatment for *S pneumoniae* but not for *C pneumoniae*, which may account for their longer period in hospital. The severe clinical picture associated with simultaneous pneumococcal and *C pneumoniae* infections emphasises the importance of rapid diagnostic methods such as the polymerase chain reaction for the identification of pathogens.^{33,34} Furthermore, these rapid diagnostic methods should be used together as the demonstration of one aetiological agent does not exclude others, for which different antibiotic treatments may be needed.

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