

## Clinical diagnosis of pneumococcal, adenoviral, mycoplasmal and mixed pneumonias in young men

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**ABSTRACT:** Clinical characteristics and course of disease of 19 pneumococcal, 11 adenoviral, 15 mycoplasmal and 10 mixed pneumonias, diagnosed in 55 military conscripts, were compared. Controls consisted of 104 conscripts with upper respiratory infections (URI). The triad: productive cough, blood stained sputum, and chest pain aggravated by breathing (pneumococcal score) distinguished pneumococcal and mixed pneumonias but not adenoviral and mycoplasmal pneumonias from URI. Higher C-reactive protein (CRP) and white blood cell (WBC) count distinguished the pneumococcal pneumonias, but not the other pneumonias, from URI. The pneumococcal scores and simple laboratory tests on admission were compared. The score effectively separated pneumococcal from adenoviral and mycoplasmal pneumonias, and patients with mixed infections from mycoplasmal infections. Higher CRP values and WBC counts distinguished pneumococcal pneumonia from other pneumonias. Auscultation revealed crackles in 27% of adenoviral and in 60-70% of mycoplasmal, pneumococcal and mixed pneumonias. Maxillary sinusitis was more common in pneumococcal (56%) than in mycoplasmal (7%) or mixed pneumonia (10%) or URI (14%). Pneumococcal pneumonias differed in most respects from the other groups. It is difficult to distinguish between adenoviral, mycoplasmal and mixed pneumonia and also URI.

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By the combined use of several microbiological methods, an aetiological diagnosis can be achieved in 97% of pneumonia patients [9]. New methods, which allow rapid detection of pneumococcal antigens from sputum, and adenovirus antigens from nasopharyngeal aspirates and sputum, have proved useful [3, 7, 9, 15]. However, sophisticated tests may not always be available in clinical practice. Moreover, detection of one agent is not necessarily sufficient for adequate treatment, as 35% of the patients in an earlier study [10] and 30% of the patients in this material (K. Lehtomäki, M. Leinonen, A. Takala, T. Hovi, E. Herva, M. Koskela, unpublished observations) had a mixed infection with at least two agents.

In a recent study carried out at the Central Military Hospital in Helsinki an aetiological diagnosis was obtained in 86% of 106 pneumonia patients (K. Lehtomäki, M. Leinonen, A. Takala, T. Hovi, E. Herva, M. Koskela, unpublished observations). The results were further analysed 1) to find those patients with uncomplicated upper respiratory disease (URI) and those with pneumococcal, adenoviral, mycoplasmal and mixed pneumonias who could be distinguished on the basis of clinical symptoms and signs, and 2) to evaluate the changes in auscultation findings and simple laboratory parameters such as C-reactive protein (CRP), white blood cell count (WBC) and

erythrocyte sedimentation rate (ESR) during the two weeks from admission to hospital.

### Patients and methods

#### Patients

The patients consisted of 55 previously healthy military conscripts (mean age 21,  $SE \pm 0.2$  yr) selected from a series of 106 pneumonia patients on the basis of microbiological classification.

Pneumococcal, adenoviral and mycoplasmal infections were clearly the three most common aetiological agents of pneumonia in this material, as detected in 81% of pneumonia patients; mixed infections were encountered in 30% of the patients. The patients with definite or very probable evidence of aetiology of pneumonia were selected and divided into the following four groups:

- I. *Streptococcus pneumoniae* group (n=19). Pneumococcus was considered to be the aetiological agent if the blood culture was positive, if an equal or greater than 3-fold change in pneumococcal antibody titre occurred between paired sera analysed by the enzyme immunoassay (EIA) method [4], or if pneumococci could be cultured and pneumococcal antigens detected from sputum [3].
- II. *Adenoviral pneumonia* group (n=11). Adenovirus

pneumonia was diagnosed if the complement fixing (CF) or EIA methods showed a significant difference in antibody titre between paired sera [2].

III. *Mycoplasmal pneumonia group* (n=15). Mycoplasma was diagnosed if the CF method showed at least 4-fold antibody change in paired sera.

IV. *Mixed pneumonia group* (n=10). The mixed infection group comprised six patients with a combined infection of pneumococcus and adenovirus or mycoplasma, and four patients with a combined adenovirus or mycoplasma and bacterial infection, i.e. adenovirus and *B. pertussis*, adenovirus and *H. influenzae*, mycoplasma and *Chlamydia sp.*, mycoplasma and *N. meningitidis* (one patient having each combination). *Chlamydia sp.*, *N. meningitidis* and *B. pertussis* were determined on the basis of antibody response in paired sera [8, 13]. Antibodies to *B. pertussis* were measured by bacterial agglutination. *H. influenzae* was isolated from sputum.

Thus, the groups I–IV presented above consisted of 55 patients and will be called the 'pneumonia groups'. In the pneumonia groups the patients had a respiratory infection diagnosed clinically and a pneumonic infiltrate demonstrated in chest X-rays evaluated by two radiologists. Axillary temperature was measured with a mercury thermometer. The patients were treated at the Central Military Hospital, Helsinki, Finland between March 1983 and February 1984.

The control group consisted of 104 conscripts with febrile (axillary temperature > 37.0 °C) upper respiratory infection and a normal chest X-ray. Controls were selected by picking every alternate patient following the patient admitted for pneumonia, and checked so as to fulfill the criteria set for controls.

#### *Questionnaires, pneumococcal score and follow up*

On admission the patients, assisted by a nurse, filled out a questionnaire for background medical information, such as earlier diseases and smoking (duration and amount). The patients also completed, on admission and every day during hospital treatment, a form concerning symptoms: cough, type of cough (productive, nonproductive, blood-stained), chest pain aggravated by breathing, dyspnoea, coryza, headache, sore throat, eye irritation. The day after admission was taken as being the first hospital day.

Typical symptoms of pneumococcal pneumonia are: productive cough, blood stained sputum and chest pain aggravated by breathing [5]. The four pneumonia groups were compared for the presence of these symptoms by denoting the presence of each by a score of one point. Maximum symptomatology thus yielded a total of three points. A form on daily objective status was filled out and stethoscopic auscultation was performed by the author. The pneumonic crackles recorded consisted of coarse or fine crackles in inspiration and/or expiration [6]. Auscultation was performed daily both at the site of X-ray consolidation and at the site representing other lobes.

#### *Laboratory analysis*

Blood samples for WBC, CRP, ESR and haemoglobin measurement were taken from all patients on admission, and on days 4, 7, and 14 of hospitalization. CRP was quantitated immunonephelometrically [12].

#### *Chest X-ray analysis*

Maxillary sinus and chest radiographs were taken from every patient on admission. In pneumonia patients chest X-rays were taken again 7 and 14 days later, and then every 7 days until the findings normalized.

#### *Statistical methods*

The significance of differences between the groups was analysed by means of the t-test, the  $X^2$  test and Fisher's exact test. One-way analysis of variance was selected when more than two groups were compared simultaneously.

## Results

#### *Prevalence and duration of symptoms and signs*

Analysis of medical history showed that in the pneumonia groups (four aetiological groups together) fever had lasted longer and cough, productive sputum and chest pain had been more common than in the URI group on admission (table 1).

The four aetiological pneumonia groups were compared on admission regarding the presence of typical symptoms for pneumococcal pneumonia: productive cough, blood stained sputum and chest pain aggravated by breathing. By using the pneumococcal score, this combination separated reliably the pneumococcal from the mycoplasmal and adenoviral groups ( $p < 0.001$  and  $p < 0.01$  respectively) but not from the mixed group (table 1).

The history of the pneumococcal group revealed higher rates of maxillary sinusitis (33%) than that of the adenoviral (0%), mycoplasmal (27%), mixed (20%) or URI (11%) groups.

#### *Laboratory findings*

The pneumonia groups had statistically higher CRP, WBC, and ESR values but lower haemoglobin values than the URI group on admission (table 1). Higher CRP and WBC counts distinguished the pneumococcal group, but not the adenoviral, mycoplasma or mixed groups, from URI patients ( $p < 0.001$  in both).

In the comparison of the four aetiological groups on admission, the pneumococcal group showed statistically higher CRP and WBC values than the adenovirus, mycoplasma and mixed groups (table 1). These last three groups could not be separated from each other by the above parameters.

The CRP and WBC values decreased markedly in

Table 1. - Symptoms, signs and laboratory findings (mean values) in 55 pneumonia and 104 upper respiratory infection (URI) patients on admission

Symptom/finding	Pneumonia groups				URI n=104	p <sup>1</sup>
	Pneumo- coccal n=19	Adeno- viral n=11	Myco- plasma n=15	Mixed infect n=10		
Fever °C	39.2 <sup>2</sup>	38.4	38.8	38.5	38.9	ns,t
Duration of fever days	2.5 <sup>3</sup>	3.6	3.3	4.0	2.0	<0.001,t
Cough %	100	80	93	100	58	<0.001,X <sup>2</sup>
Duration of cough days	7.9 <sup>4</sup>	5.1	4.6	5.0	5.1	ns,t
Productive cough %	84 <sup>5</sup>	50	40	70	44	0.05,X <sup>2</sup>
Blood stained cough %	22	10	-	10	5	ns,F
Chest pain %	44 <sup>6,7</sup>	-	-	30	7	<0.05,X <sup>2</sup>
Pneumococcal score points	1.6 <sup>8,9</sup>	0.5	0.4	1.1 <sup>4</sup>	0.4	<0.001,t
Sore throat %	28	50	27	50	66	<0.001,X <sup>2</sup>
Eye irritation %	11	10	7	10	27	<0.05,X <sup>2</sup>
CRP mg/l	158 <sup>10</sup>	50	59	70	44	<0.001,t
WBC x10 <sup>9</sup> /l	16.4 <sup>10</sup>	6.9	6.5	8.5	7.4	<0.01,t
ESR mm/h	45 <sup>4</sup>	38	30	54 <sup>4</sup>	20	<0.001,t
Haemoglobin g/l	147	142	154 <sup>9</sup>	148	154	<0.01,t

1. Significance of difference between pneumonia groups (4 etiologic groups together) and URI group; t: t-test; X<sup>2</sup>: X<sup>2</sup>-test; F: Fisher's test 2. Significantly different from adenovirus group (p<0.05,t) 3. Significantly different from mixed group (p<0.05,t) 4. Significantly different from mycoplasma group (p<0.05,t) 5. Significantly different from adenovirus and mycoplasma groups (p<0.05,X<sup>2</sup>) 6. Significantly different from adenovirus group (p<0.05,F) 7. Significantly different from mycoplasma group (p<0.01,F) 8. Significantly different from mycoplasma group (p<0.001,t) 9. Significantly different from adenovirus group (p<0.01,t) 10. Significantly different from adenovirus, mycoplasma and mixed groups (p<0.001,t)

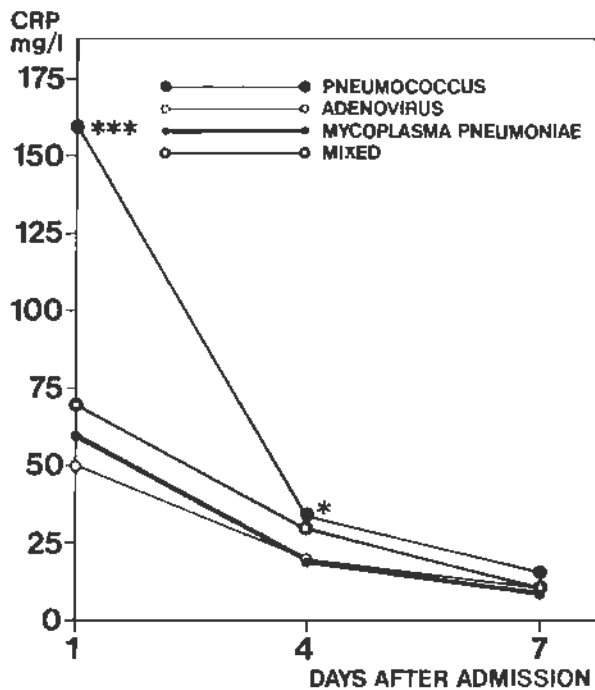


Fig. 1. Mean C-reactive protein (CRP) levels in four pneumonia groups during 7 days, from admission. \*\*\* = p<0.001 in comparison with all other groups at day 1 (t-test), \* = p<0.05 in comparison with mycoplasma group at day 4 (t-test).

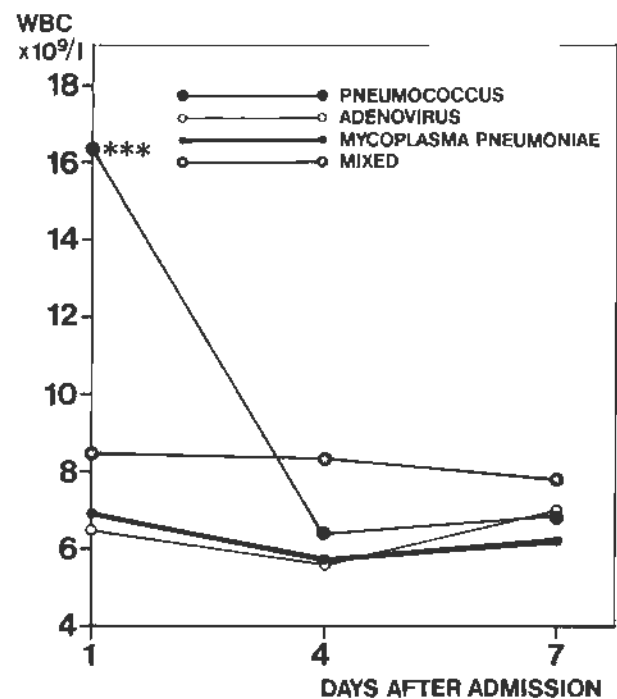


Fig. 2. Mean white blood cell (WBC) count in four pneumonia groups during 7 days, after admission. \*\*\* = p<0.001 in comparison with all other groups at day 1 (t-test).

the pneumococcal group during the four day follow up (figs 1 and 2). In the pneumococcal group the CRP values, on admission, were above reference limits (10mg/l) in 100%, and the WBC values ( $10 \times 10^9/l$ ) in 72% of the patients.

Nineteen URI patients had definite or probable bacterial involvement (nine beta haemolytic Gp A tonsillitis, nine sinusitis maxillaris and one otitis media). Their mean CRP was 49 mg/l and it did not differ significantly from that of the other URI patients. In URI patients without serological response to adenovirus or bacterial involvement (n=42) mean CRP (38 mg/l) was lower than that of adenoviral URI patients (n=42, 52 mg/l,  $p < 0.001$ ).

#### Auscultation

Stethoscopic auscultation on admission revealed crackles in 63% of pneumococcal, 27% of adenoviral, 60% of mycoplasmal and 70% of mixed pneumonias (fig. 3). The frequency of positive auscultation findings increased in the adenovirus and the mycoplasma groups during the first four follow-up days, being positive in 63 and 73% of the patients, respectively, at day 4, whereas it decreased in the pneumococcal and mixed groups (fig. 3).

#### X-ray examinations

Normalization of X-ray findings occurred in the pneumococcal group in  $16 \pm 1$  (mean  $\pm$  SE) days, in the adenovirus group in  $21 \pm 4$  days, in the mycoplasma group in  $16 \pm 2$  days, and in the mixed group in  $17 \pm 2$  days. The pneumonia groups had higher rates of maxillary sinusitis on admission (27%) than the URI group (14%,  $p < 0.05$ ). Sinusitis was diagnosed in the pneumococcal group in 56% of patients, compared to

7% in the mycoplasmal ( $p < 0.01$ ), 10% in the mixed ( $p < 0.05$ ) and 30% in the adenoviral group. Pneumococci were isolated from maxillary sinus aspirates in 4/5 pneumococcal patients treated with maxillary puncture and *H. influenzae* was isolated from one patient.

#### Smoking

Reported smoking habits showed that smokers had a 1.6 times greater risk of pneumonia than nonsmokers. Patients in the pneumococcal group smoked the most (mean 11.3 cigarettes/day) and the URI patients the least (5.6 cigarettes/day,  $p < 0.01$ ).

#### Discussion

Respiratory infections account for most visits to general practitioners. Firstly, it must be clarified whether the patient has an uncomplicated upper respiratory infection, or whether there is evidence of a more serious involvement of the disease, like pneumonia? Productive cough, blood stained sputum and chest pain aggravated by breathing (pneumococcal score) are symptoms indicative of bacterial pneumonia. The symptoms in adenoviral or mycoplasmal pneumonias and URI are very similar and are of no clinical help when pneumonia is suspected. High CRP (over 80 mg/l) and WBC (over  $10 \times 10^9/l$ ) can distinguish pneumococcal, but not adenoviral, mycoplasmal or mixed pneumonias, from URI. Elevated ESR values (over 35 mm/h) can however be of help in the separation of pneumococcal, mycoplasmal and mixed pneumonias from URI.

If auscultation reveals pneumonic crackles, lower respiratory infection is revealed. However, in two thirds of adenoviral pneumonias and in one third of pneumococcal, mycoplasmal and mixed pneumonias crackles may not be heard.

After radiographic confirmation of the pneumonia, the most probable causative agent(s) must be estimated. Firstly, the bacterial or viral involvement of the pneumonia must be clarified. Here the type of X-ray consolidation is of no help [16].

Pneumococcal pneumonia is easiest to distinguish from other groups. A heavily smoking patient with a history of earlier sinusitis maxillaris is in special risk of pneumococcal pneumonia.

The symptoms in the pneumococcal score are typical; this is in concordance with earlier studies [5]. The presence of these symptoms is indicative of bacterial involvement, and the absence of all of these symptoms seems to point to non-pneumococcal aetiology, as only one (6%) pneumococcal patient lacked all three symptoms. The CRP and WBC values are remarkably elevated and axillary temperature is high.

It is much more difficult to separate mixed pneumonias than pneumococcal infections, from adenoviral and mycoplasmal pneumonias. The symptoms typical for pneumococcal pneumonia (pneumo-

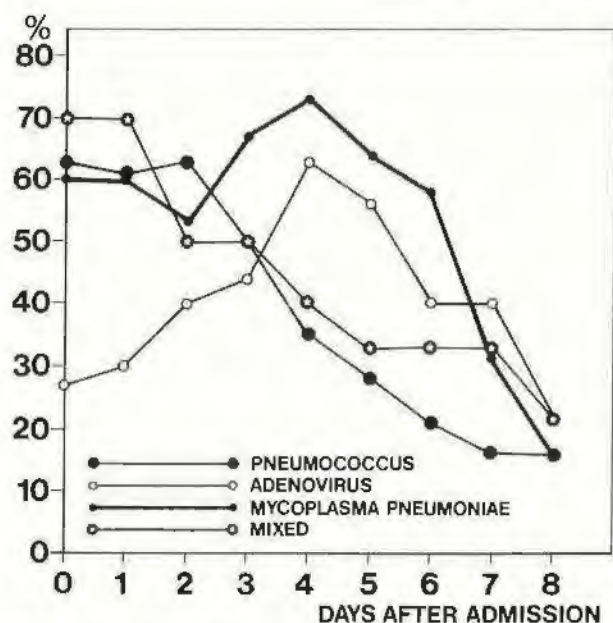


Fig. 3. Proportion (%) of patients exhibiting crackles on stethoscopic auscultation in four pneumonia groups on admission and during the following 8 days.

coccal score) and higher ESR values can give some evidence of bacterial involvement.

Adenoviral and mycoplasmal pneumonias resemble each other so closely in signs and symptoms, laboratory parameters and clinical course that their separation is not possible with these methods.

CRP has been reported to be lower than 20 mg/l in viral infections [12]. Elevated values (mean 58 mg/l) have been recently observed in adenoviral infections, but only slightly elevated values (mean 17 mg/l) in influenza, parainfluenza and respiratory syncytial virus infections [14]. In this study, the mean CRP level of adenoviral URI was more elevated than in other URI, but it was also clearly elevated in the latter group (mean 38 mg/l) on admission. 76% of the URI patients had CRP values higher than 20 mg/l. It is obvious on the basis of the present results as well as those reported earlier [14] that CRP levels almost invariably exceed this limit in upper and lower respiratory viral infections.

It is noteworthy that in 28% of pneumococcal pneumonias, on admission WBC was in the normal range, while CRP was elevated in 100% of the pneumococcal and mixed groups, with a minimum of 40 and 26 mg/l respectively. Thus, in distinguishing between viral and bacterial aetiology, low CRP values, e.g. below 20 mg/l, are strongly, whereas low WBC values are only weakly indicative of non-bacterial infection.

On day four CRP and WBC are only of limited value in separating the pneumonia groups from each other, as the pneumococcal group could be separated from the mycoplasmal group only by CRP not by WBC (fig. 1). High CRP or WBC values at day four could mean a complicated disease or a failure in treatment, as shown in children [1, 11, 12]. The patients in this study were treated with appropriate antibiotics.

The subjects in this study were young men and were thus likely to present a more clearcut clinical picture than elderly patients with underlying (pulmonary) diseases.

Maxillary sinusitis complicated over 50% of the pneumococcal pneumonias; the sinusitis was mostly caused by pneumococcus. It is therefore conceivable that the maxillary cavity is the primary pneumococcal focus from which the infection may have spread to the lower airways.

In conclusion, pneumococcal pneumonias can be reliably separated by these methods both from URI patients and other pneumonia groups. Adenoviral pneumonias are the most difficult to distinguish from URI. Adenoviral, mycoplasmal and mixed pneumonias resemble each other closely in signs and symptoms, laboratory parameters and clinical course. The recognition of mixed pneumonia presents a clinical problem. The use of microbiological methods seems particularly warranted in the diagnostics of mixed pneumonias.

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**RÉSUMÉ:** Nous avons comparé, chez 55 conscrits de l'armée, les caractéristiques cliniques et le décours de la maladie dans 19 pneumonies pneumococciques, 11 adénovirales, 15 mycoplasmiques et 10 mixtes. Les contrôles ont été représentés par 104 conscrits atteints d'infections des voies respiratoires supérieures. Il a été possible de distinguer les pneumonies pneumococciques ( $p < 0.001$ ) et mixtes ( $p < 0.05$ ), mais non les pneumonies adénovirales et mycoplasmiques, d'avec les infections des voies respiratoires supérieures, par une combinaison de symptômes: le score pneumococcique comportant une expectoration mêlée de sang et des douleurs thoraciques aggravées par la respiration. On distingue la pneumonie pneumococcique des infections des voies respiratoires supérieures par un taux plus élevé de C reactive protein et par

une leucocytose plus marquée. Ces caractères différentiels ne sont pas valables pour les pneumonies adénovirales, mycoplasmiques ou mixtes. Les scores pneumococciques, ainsi que des tests de laboratoire simples à l'admission ont été comparés dans les quatre groupes de pneumonie. Le score permettait effectivement de distinguer les pneumonies pneumococciques des adénovirales ( $p < 0.01$ ) et des mycoplasmiques ( $p < 0.001$ ), ainsi que les patients atteints d'infections mixtes d'avec les infections mycoplasmiques ( $p < 0.05$ ). Des valeurs plus élevées de CRP et de leucocytose à l'admission distinguent les pneumonies pneumococciques des autres pneumonies ( $p < 0.01$ ). L'auscultation au stéthoscope lors de

l'admission montre des crépitements respectivement dans 27% des pneumonies adénovirales, dans 60% des mycoplasmiques, 63% des pneumococciques et 70% des mixtes. La sinusite maxillaire s'avère plus fréquente dans la pneumonie pneumococcique (56%) que dans la mycoplasmique (7%,  $p < 0.01$ ), ou dans la pneumonie mixte (10%,  $p < 0.05$ ), ou dans les infections des voies respiratoires supérieures (14%,  $p < 0.001$ ). Les pneumonies pneumococciques diffèrent des autres sous la plupart des aspects. Il est très difficile de distinguer entre elles les pneumonies adénovirales, mycoplasmiques et mixtes, aussi bien que les infections des voies respiratoires supérieures.