ISM skriftserie Nr. 24

DIAGNOSIS OF PNEUMONIA IN ADULTS IN GENERAL PRACTICE

by
Hasse Melbye

Institute of Community Medicine
University of Tromsø

ISM skriftserie
blir utgitt av Institutt for samfunnsmedisin
Universitetet i Tromsø.

Forfatterne er selv ansvarlige for sine funn og konklusjoner. Innholdet er derfor ikke uttrykk for ISM´s syn.

ISBN 82 - 90262 - 28 - 0
1992

Diagnosis of pneumonia in adults in general practice.

A clinical epidemiologic study of the diagnostic efficacy of symptoms, signs and laboratory tests in the differentiation of pneumonia from other respiratory tract infections.

Hasse Melbye
Institute of Community Medicine
University of Tromsø
Norway

Contents

PREFACE

In 1984, after five years in general practice, Bjørn Straume, who later became my main counceler, asked me to give lectures for medical students on lung diseases and respiratory infection as seen from the point of view of a general practitioner. When preparing the lecture I read a paper in the journal "Practitioner" (Everett MT. Major chest infection managed at home. Practitioner 1983;227:1743-54). The author described his pneumonia patients through seven years in general practice. He concluded that most pneumonias patients presented with influenza-like illness or with pyrexia following a prodromal phase of cold and/or cough. I felt that his description was close to my own reality, but different from what I was taught in medical school, and a new interest in the diagnosis of pneumonia was awakened. During the autumn 1985 I got a half-time appointment as a lecturer in general practice at the Institute of Community Medicine (ISM), University of Tromsø, and thus got the opportunity to study "pneumonia in general practice". Having finished a small-scale study, the "pilot study", my research was helped further by a lucky coincidence. In 1986 a research program for general practice was established by the Norwegian Research Council for Science and the Humanities (NAVF). I applied for one of the fellowships, and thus became a research fellow for the years 1988-90 with the project "Lower respiratory tract infection in general practice". The main investigation was carried out at the Municipal Emergency Ward in Tromsø, in collaboration with Department of Radiology, Department of Microbiology, Chest Clinic, Department of Medicine, University Hospital of Tromsø, and Department of Clinical Chemistry, Hospital of Hammerfest. Six papers on the diagnosis of pneumonia

based on this investigation constitute the core of this thesis.

ACKNOWLEDGEMENTS

In this work I have drawn on the resources and help of several people, and I wish to express my gratitude to the following:

The general practitioners of Tromsø, who willingly have participated both in the pilot study and in the main investigation.

The nurses at the Municipal Emergency ward of Tromsø, in particular the seven who were employed in the investigation: Elsa Nordgård Simonsen, Hagny Staff Eidesen, Grete Konglevoll, Rigmor Jacobsen, Mary Iversen, Kirsten Fagernes, and Ragnhild Busk Johnsen. They performed their task with enthusiasm, accuracy and inventive spirit.

Coworkers at the University Hospital of Tromsø:

Chest Clinic, Department of Medicine: Vigdis Næss, Helen Schei, Ragna Andreassen and in particular my colleague and friend Ulf Aasebø, who gave support from the birth of the project and all the way through.

Department of Radiology: The radiological nurses and assistents who prepared the reading sessions, my colleagues Edly Grape and Stein Aage Gyltnes and in particular professor Knut Dale.

Department of Microbiology: Sissel Andreassen and the laboratory technicians, the doctors, in particular Lars Vorland and professor Bjørn P Berdal.

Coworkers at Department of Clinical Chemistry, Hospital of Hammerfest: Roger Johansen and in particular Jan Brox, who first introduced me to the CRP-test.

Norwegian Defence Microbiological Laboratory, Oslo: Valeria Gacek, who did the serological analyses for Legionella.

Dr. Harold Russell at CDC (Centers for Disease Control), USA for performing the serological investigations for Pneumococci.

The medical students Anne-Grethe Karlson, Guri Greiff and Tove Skjelbakken for accuracy in punching of the data.

Coworkers at the Institute of Community Medicine, University of Tromsø:

The researchers and the secretaries have all been very helpful and encouraging through these years, and good advice have been given by many of them. In particular I wish to thank the professors Anders Forsdahl and Olav Helge Førde, Ivar Aaraas, Roar Johnsen and my other colleagues at the Department of General Practice for support, inspiration, and help with manuscripts. Most of all I will thank Bjørn Straume, my main counceler and supporter from the beginning, who has taught me statistical methods and has given invaluable critical comments, both in the planning of the studies and in the writing of papers.

My family, who always reminded me of the real things in life.

I wish to express my gratitude to NAVF and the leader of the program for research in general practice, Dag Bruusgaard. I thank for financial support from LHL, Gerd and Lars Volder's legacy, Nycomed A/S, Conrad Holmboe's legacy, University of Tromsø Medical School, and the University Hospital of Tromsø.

CONCEPTS AND ABBREVIATIONS

Sensitivity:

The sensitivity of a clinical finding (or positive test result) for a certain disease is the proportion (frequency) of subjects with the finding in a population with the disease.

Specificity:

The specificity of a clinical finding for a certain disease is the proportion (frequency) of subjects without the finding in a population without the disease.

LR (Likelihood ratio):

The LR of a clinical finding for a certain disease is the proportion (frequency) of subjects with the finding in patients with the disease, divided by the proportion (frequency) of subjects with the finding in patients without the disease.

LR = Sensitivity / 1 - Specificity.

PPV (Positive predictive value):

The PPV of a clinical finding for a certain disease is the proportion (frequency) of subjects with the disease in a population with the clinical finding.

LIST OF PAPERS

I. Melbye H, Straume B, Aasebø U and Dale K. Diagnosis of pneumonia in adults in general practice. The relative importance of typical symptoms and abnormal chest signs, evaluated against a radiographic reference standard. Scand J Prim Health Care 1992;10:226-33.

II. Melbye H, Straume B, Brox J. Laboratory tests for pneumonia in general practice. The diagnostic values depend on the duration of illness. Scand J Prim Health Care 1992;10:234-40.

III. Melbye H, Berdal BP, Straume B, Russell H, Vorland L, Thacker WL. Pneumonia - a clinical or radiographic diagnosis. Etiology and clinical features of lower respiratory tract infections in adults in general practice. Scand J Infect Dis 1992;24:647-55.

IV. Melbye H, Straume B. The spectrum of patients strongly influences the usefulness of diagnostic tests for pneumonia. Scand J Prim Health Care. Accepted for publication.

V. Melbye H, Dale K. Interobserver variability in the radiographic diagnosis of adult outpatients pneumonia. Acta Radiol 1992;33:79-81.

VI. Melbye H. Radiographic pneumonia: validity as reference standard of pneumonia in a clinical epidemiologic study. Submitted for publication.

LRTI = Lower respiratory tract infection:

LRTI, as used in this thesis, comprise all infections of the respiratory tree below the Trachea: bronchitis, bronchiolitis and pneumonia, as well as infectious aggrevations of chronic diseases of the lungs and bronchi, as asthma, COPD, chronic bronchitis and bronchiectasis.

COPD = Chronic obstructive pulmonary disease:

COPD is defined by chronic bronchial airflow limitation which can only be moderately reversed by bronchodilators. Many patients with chronic bronchitis, defined by chronic productive cough, also have chronic airflow limitation, and these patients, as well as patients with emphysema are classified as having COPD. Adults with chronic airflow limitation, but with considerable variability of airflow, being strongly influenced by antasthmatic treatment are usually diagnosed as having asthma. However, many patients belong to a grey zone and may be diagnosed as having either asthma or COPD.

References

Sensitivity, specificity, LR and PPV are thoroughly described in:

Sacket DL, Haynes RB, Tugwell P. Clinical epidemiology. A basic science for clinical medicine. Boston: Little, Brown and co. 1985.

The definition of COPD is discussed in:

Editorial. Definition of emphysema, chronic bronchitis, asthma, and airflow obstruction: 25 years on from the Ciba symposium. Thorax 1984;339:81-85.

GENERAL INTRODUCTION

Pneumonia - the disease

Pneumonia is inflammation of the lung tissues with exudate in the alveolar spaces (1). The bronchi/bronchioli, interstitial tissues and pleura may be involved. The disease may be caused by inhalation of infectious agents into the alveoli. An alternative route of infection is spreading from an ongoing bronchitis. The infection may pass the basal membran of the bronchial epithelium and extend into the surrounding peribronchiolar alveoli (bronchopneumonia). When the inflammation is caused by inhalation of toxic chemical substances or by toxic drugs (i.e. Methotrexat), the disease is usually called pneumonitis (2).

Depending upon both etiologic agent and host defence the severity of the disease shows great variation. When a great part of the lung tissue is involved, as in lobar pneumonia, severe and fatal hypoxaemia may develop, particularly when the ventilatory capasity of the unaffected regions of the lungs is reduced. The most serious pneumonias are caused by bacteria: pneumococci, staphylococci, legionella species and gram-negative bacteria (3,4,5). Such infections are associated with a considerable mortality, particularly among the elderly, and early treatment with antibiotics may be of great importance (6). Less severe are the so called "atypical pneumonias" (7), caused by the small bacteria Mycoplasma Pneumoniae and the Chlamydia species, and the viral pneumonias, also called viral pneumonitis (8). Viral pneumonias, most frequently caused by the respira

tory viruses: Influenza-, Parainfluenza-, Adeno- and Respiratory Syncytial virus, are anatomically characterized by interstitial exudate (1), as are the atypical pneumonias.

Non-productive cough is a typical clinical feature (7). The viral pneumonias usually show a benign clinical course, but may be severe when infants, old people and deterioriated adults have been attacked (8). Secondary bacterial infection may develop. Influenza-pneumonia complicated with Stafylococcus aureus infection is particularly feared, and has a high mortality (6).

The epidemiology of pneumonia

In the Nordic countries 3-5% of deaths are caused by pneumonia (9). The death rates of pneumonia is low in the western societies compared to the developing world (10). Old people and infants have the highest death rates. The reduced mortality from pneumonia during the last 150 years may probably be ascribed to better nutrition, hygiene and housing condi- tions, and possibly also reduced pathogenicity of the most common bacterial agents (11). Introduction of antibiotics resulted in a further reduction in mortality. In the United States a considerable reduction in mortality from pneumonia and influenza has also taken place during the last two decades in people younger than 75 years (10).

The mortality from community-acquired pneumonia as registered in hospitals varies between 5 and 15% (3,4,5,6), being much higher in elderly than in younger people. Most cases of pneumonia are treated outside hospital (12), and a favourable outcome is the rule in developed countries. In a British study from general practice 4.7 pr 1000 adults were diagnosed as having pneumonia per year (12). Among the 236 cases included in that study the mortality was 3% (seven cases). More than three-quarters of the patients were managed at home and of these only one (0.5%) died. Although the clinical diagnosis of pneumonia was confirmed radiographically in less the half of the patients, the study illustrated that pneumonia is usually not a severe disease in today's western societies.

Most studies on the etiology of pneumonia have been carried out in hospitals. MacFarlane has summarized the distribution of etiological agents for adult

community-acquired pneumonia, based on studies in developed countries (13), as follows:

Bacterial:	Streptococcus pneumoniae (pneumococci)	60-75 %
	Hemophilus influenzae	4-5 %
	Legionella species	2-5 %
	Staphylococcus aureus	1-5 %
Atypicals:	Mycoplasma pneumoniae	5-18 %
	Chlamydia Psittaci	2-3 %
	Coxiela burneti	1 %
Viruses:	Influenza	8 %
	Other viruses	2-8 %

In a recent large study Chlamydia pneumoniae was a frequent agent, found in 6.1 % of the patients (4), and a contemporary study indicate that a large part of pneumonias previously ascribed to Chlamydia psitacci actually have been caused by Chlamydia pneumoniae (14). Legionella was one of the most frequent causes (6-15 % of pneumonias) in three large studies (4,5,15). In children viral etiology is more frequent than in adults (10).

The diagnosis of pneumonia in historical perspective

The hippocratic era

Pneumonia was referred to as a disease by Hippocrates in the 5th century BC (16). A later Greek, Aretaeus, from the fourth century AC described the clinical features of pneumonia as: cough, expectoration, dyspnea, fever and chest pain (16). Until the beginning of the 19th century the physical examination was restricted to the observation of the pulse, and inspection of the tongue and expectorated sputum. Boerhave (1668-1738) stated that the disease was present "if a fiery, persistent fever, a firm pulse, a burning, sharp inflammatory pain, aggravated by inspiration" was experienced (16). Although adventitious lung sounds had been described by Hippocrates, auscultation of the chest was not used in the diagnosis until early in the 19th century. Percussion of the chest was first described by Auerbrugger (1722-1809) in 1761, but it was hardly applied in clinical practice before his death (16).

Théophile R. M. H. Laennec

The development of pathology led to interest in comparing clinical manifestations and abnormalities seen at autopsy. The French physician Laennec (1781-1826) took up auscultation of the chest and invented the stethoscope in 1816. He described the normal and adventitious lung sounds and, based on clinico-pathological comparisons, their diagnostic usefulness (17).

Laennec realized the difficulties in diagnosing pneumonia on the basis of symptoms alone. "Symptoms . . . usually are an obtuse and deep-seated pain, dyspnea, quick respiration, cough, and expectoration of a peculiar kind . . . each of them may be wanting, and even, in particular cases, all of them may be so at the same time. Moreover, they may all co-exist in many other diseases as well as pneumonia; and each of them exhibits many varieties". About acute bronchitis or "pulmonary catharr" he wrote: "The pulmonary catharr, unquestionally one of the most frequent of diseases . . . is usually preceded by coryza, . . . When the inflammation extends to the bronchi, there is sometimes a slight pain, more commonly a sense of dryness and roughness, behind the sternum or at its lower extremity. When the disease is very severe, there is greater, sometimes indeed very sharp, though transient pain extending over the whole chest, particularly after the fits of coughing . . . If the diseases is more severe, there is fever constantly present, usually accompanied by sweating, and also dyspnea".

Laennec meant to be able to distinguish pneumonia from acute bronchitis. In pneumonia crepitant rales were present, at least at certain stages of the disease, while in "pulmonary catarrh" sibilous or sonorous rhonci were heard. Not all contemporaries of Laennec agreed with his statements, and Andral stated that crepitant rales also could be heard in bronchitis (17). However, crepitant rales were at that time thought to be caused by bubbles of air in alveolar fluid and thus to be pathognomonic of pneumonia and pulmonary edema. In the second half of the nineteenth century the stethoscope came into extensive use, based on Laennecs description and interpretation of adventitious lung sounds.

Radiography

Based on the discoveries of Röntgen, the first X-ray-films were made in 1897 (16). Chest radiography soon became widely employed, and giving a fairly accurate picture of structural abnormalities in the lung, substituted more and more the elaborous physical examination. By radiographic appearance lobar pneumonias could be differentiated from bronchopneumonia. A third category, so-called atypical pneumonia, was first described in the nineteen-twenties (18). This was characterized by sparse auscultatory findings and dry cough, and (after the introduction of antibiotics) no response to sulphonamids and penicillin.

Radiography more and more replaced auscultation in the diagnosis of pneumonia, and the obligate occurence of crepitant rales as stated by Laennec became questionned. After the introduction of antibiotics the course of the disease was modified, and accordingly also the physical chest findings. In a study by Osmer and Cole in 1965 (19), rales were heard in only 50% of hospitalized patients with radiographic pneumonia, in spite of several examinations in the course of the disease. Only in 25% of the patients rales were heard over an area with a radiographic density.

The chest radiograph has been regarded to be sensitive for "true" pneumonia (20,21), and in most literature on pneumonia no doubt is raised about the validity of the radiographic diagnosis. However, a delay of one or two days between the first symptoms of the disease and the appearance of a radiographic counterpart has been reported (22). Studies have also revealed a considerable interobserver variability in the interpretation of chest radiographs (23).

Paul Forgacs

After chest radiography came into general use, declining attention has been paid to the detailed description of adventitious lung sounds. Confusion on the flowerish terminology which had been elaborated when patients with pneumonia and tuberculosis overflowed the hospitals, led Robertson and Coope to propose a new and simple classification: The adventitious sounds were divided into two groups: continous sounds or wheezes, and interrupted sounds or crackles (24).

This classification was supported and carried on by Paul Forgacs. His interest in lung sounds resulted in a new understanding of the meaning of crackles. He stated that the airflow when reaching the alveoli were to weak to generate bubling in alveolar fluid. Crackles could be explained as explosive sounds caused by sudden openings of deflated alveoli (25). Accordingly, crackles may be caused by several diseases compromising the airflow between bronchi and alveoli (26). The specificity of crackles for pneumonia in patients with respiratory infections may thus be questionned, as the sign may also be present in bronchitis.

The new description and interpretation of adventitious lung sounds was soon adopted by new textbooks on clinical examination (27,28). In internal medicine textbooks, such as Cecil's, Harrison's, and Davidson's, the new explanation of crackles was not introduced during the nineteen-eighties. One may ask whether the old explanation still is being credited in Harrison's textbook from 1988 in the following description of pneumonia: "Among the earliest auscultatory findings is the presence of high-pitched end-inspiratory crackles, originating from fluid-filled alveoli, that are often increased by, or heard only after, coughing" (29). In the

issue of 1991 this passage has been omitted.

Clinical epidemiology

The frequency with which a symptom or sign is present in a disesase, or in other words, the sensitivity of clinical cues, has usually been indicated in descriptions of diseases in medical textbooks, as examplified by this passage in Harrisons textbook: "In some patients, inspite impressive roentgenographic abnormalities, physical examination of the chest is entirely normal" (29). However, considerations on the specificity of cues are usually lacking. In the last two decades, epidemiologists and medical statisticians have been concerned about certain shortcomings of hospital-based medical knowledge, as reflected in medical textbooks:

1. Selection of patients towards the most serious cases influences the sensitivity of clinical cues. Symptoms and signs may be more sensitive in hospital patients with abundant symptoms than in general practice where all stages of a disease are represented.
2. To be able to assess the probability of a disease from symptoms and signs, their specificity need to be studied, and the prevalence of the disease in the clinical context must be known.

Textbooks presenting these new outlines for clinical research have been written by Weinstein and Fineberg and by Sacket and coworkers (30,31). During the last

15 years several studies on pneumonia have been published with the objective to evaluate the sensitivity and specificity of clinical cues, both in children (32) and adults. At Brooke Army Medical Center in USA during 1976 to 79 clinical information and chest radiographs were gathered from 1819 unselected adults presenting with acute cough. Several papers were grounded on this investigation (33-38). A substantial discrepancy was demonstrated between the doctors' probability estimates of pneumonia and the radiographic diagnosis of pneumonic infiltrate. The sensitivities of abnormal chest findings for pneumonia were found to be low, crackles were heard in only 19 % of the patients with radiographic infiltrate (33). Higher sensitivities of chest signs were found by Heckerling (39), in emergency room patients who had been evaluated by chest radiography, a population of patients with a higher prevalence of pneumonia, 27.8%, compared to 2.6% in the study by Diehr et al (33).

Diagnosis of pneumonia in recent medical literature

Although some studies have been aiming at the differentiation of pneumonia from other acute respiratory diseases, as just mentioned, the majority of papers on the diagnosis of pneumonia from the last 10-15 years have been concerned with etiological diagnosis in established pneumonia. The epidemiology of causal agents in community-acquired (as well as in hospital-acquired) pneumonias has been determined, in order to yield an empiric basis for antimicrobial treatment (3-6,14,15). Methods for early differentiation of the etiological types of pneumonia have been evaluated, such as radiographic pattern recognition (40) and different methods of antigen identification (41). Prediction of etiology based on clinical and laboratory features has also been studied (42-44). Almost all these studies have been hospital-based.

As identification of etiology strongly influences the antibacterial treatment, a classification of pneumonias based on causative agent has replaced the older anatomical classification. The classical lobar pneumonia is moreover less frequently seen in the western societies after the second world war, which partly may be ascribed to the widespread use of antibiotics (1).

The pilot study

As mentioned in the preface, a first study (45) was carried out during the winter 1986. General practitioners in Tromsø were asked to recruit adult patients treated with antibiotics suspected to have a possible pneumonia. The aim was to assess the diagnostic value of symptoms, signs and some blood tests for pneumonia, using a radiographic "gold standard". 71 patients were included, and radiographic pneumonia was diagnosed in 11 of them. Diagnostic values for symptoms, signs and blood tests were evaluated, guided by "Clinical epidemiological rounds" by David Sacket and coauthors, later published in the textbook "Clinical epidemiology" (31). As found by Diehr et al (33), no chest symptom or sign turned out to be of great predictive value for pneumonia. The blood tests, however, in particular C-reactive protein analysis, had both high sensitivity and specificity for pneumonia.

The sensitivity of crackles for pneumonia was 0.64, considerably higher than the corresponding value, 0.19, found by Diehr et al (33), while the specificity was low, 0.48. Of all the included patients, crackles were heard in 51 %, compared to 8 % of the unselected patients with acute cough in the study by Diehr et al. This discrepancy indicated that crackles had been strongly emphasized by the doctors in the pilot study, leading to a selection in favour of patients with crackles, both with and without pneumonia.

Fifty of the patients attended a follow-up consultation after 4 to 5 weeks, and auscultation and spirometry was then carried out. In ten patients crackles were

still heard, and the ratio between forced expiratory volume in one second and the forced vital capacity (FEV_1/FVC) was significantly lower in the ten patients with crackles compared with the 40 patients without crackles (2-tailed t-test, $p < 0.05$). This finding indicated that crackles heard in patients with respiratory tract infection frequently may represent bronchial obstruction.

An obvious weakness of the pilot study could be ascribed to the selection of patients. When only patients judged to have a possible pneumonia were included, the overlooked pneumonia patients were excluded. In the study by Diehr et al the doctors had ordered radiography in less than half of the patients who turned out to have radiographic pneumonia (33).

THE MAIN INVESTIGATION

Aims

1. Diagnostic value of symptoms and chest signs for pneumonia

To avoid the selection bias of the pilot study and also include overlooked pneumonias, our study population was to consist of unselected adults with respiratory tract infection in general practice.

Diehr et al found presence of myalgia and absence of upper respiratory symptoms to be of greater value in the diagnosis of pneumonia compared with the typical symptoms, cough, dyspnea, and chest pain (33). I wondered whether the dichotomizing of the lower respiratory tract symtoms as present/not present could be misleading. Information of pronounced discomfort from the symptoms might prove to be of greater diagnostic value than their sole presence. I wanted to reevaluate the diagnostic efficacy of the typical symptoms, by asking the patient to report the degree of discomfort associated with the symptoms.

Marked differences in sensitivity and specificity of symptoms and signs were found when the pilot study was compared with study by Diehr et al. These difference could partly be explained by the spectrum of patients. In our pilot study the patients were selected by general practitioners, while in the study by Diehr et al the patients were unselected adults with acute cough. In the main investigation I wanted to determine the effect of patient spectrum by comparing

diagnostic values obtained in unselected patients with respiratory tract infection with the values obtained in subgroups of the patients assumed to have a higher probability of pneumonia: patients undergoing physical chest examination, patients being classified as having LRTI, and patients of whom a chest radiograph is ordered, because pneumonia is thought to be a diagnostic possibility.

2. Diagnostic value of C-reactive protein for pneumonia

The main finding of the pilot study was a promisingly high diagnostic value of C-reactive protein (CRP). The concentration in serum of this acute-phase protein shows a manifold rise few hours after tissue damage or inflammation, particularly in bacterial infection (46). A rapid CRP-test might show to be of great benefit in the diagnosis of serious infections as pneumonia (42,47,48), and to guide the doctor in the decision on antibacterial treatment.

3. The etiology of pneumonia and other lower respiratory tract infections

Knowledge of the epidemiology of infectious agents is of importance for the decision on antibacterial treatment and for the choice of antibiotic. The etiology of pneumonia has been determined in hospitalized patients, except in a few studies. Etiology of other lower respiratory tracts infection in adults has been indicated by some studies (15,49-53), but investigations covering a wide range of potential agents in unselected adults in general practice are wanting.

Study design

Two main concerns determined the design of the study:

1. The patients should be representative of adults consulting general practitioners for a possible respiratory tract infection.
2. The radiographic reference standard* should be as reliable as possible.

Recruitment of patients

Owing to difficult access at the general practice offices in Tromsø, many adults with respiratory tract infections consult the Municipal Emergency Ward. The doctors at this ward are very busy, and could not be expected to systematically recruit patients for a study. We chose to employ nurses for the recruitment and examination of the patients, leaving only a small form to be filled in by the doctor. Patients aged 18 years or more presenting a complaint or reason for encounter suggesting a respiratory tract infection or a throat infection,(as listed in table II, paper I), were asked to enter the study. Patients attending the ward between 16 and 21 p.m. were chosen. At this time of the day the patients usually wait one to three hours in the waiting room before the consultation, and since the patients were called in before turn, participation in the study did not necessarily result in additional time spent at the ward.

* Reference standard is used in stead of the more apassionate expression "gold standard".

Eligible patients were called into the examination room, and was then asked to enter the study. The examination by the nurse, comprising blood tests, spirometry and questionnaires (see Appendix) took about 30 minutes. On some busy days there was not sufficient time to include all the eligible patients. Then, the patient with the longest waiting time was always asked first.

All the doctors working at the ward consented to the research scheme. They were asked to examine the patients according to their usual practice, and record findings and diagnosis on a form (see Appendix).

Out of 626 patients asked to participate, 581 accepted, and the doctors carried out chest examination in 402. These 402 were regarded as a relevant subgroup for the evaluation of diagnostic tests for pneumonia.

The reference standard

Being aware of the limitations of radiographic diagnosis mentioned earlier, an acute density on chest radiograph was used as reference standard, as in all other studies evaluating diagnostic tests for pneumonia. Ideally all participating patients should be radiographed, but this was not done out of practical and ethical reasons. We had to avoid a too huge workload for the Department of Radiology at the University Hospital in Tromsø and wanted to minimize unnecessary X-ray exposure in patients with a low probability of pneumonia. A great part of the patients presented a with sore throat, ear pain or a mild cold or flu, and we found it more acceptable only to radiograph a 25% random sample of

these patients.

In addition, we wanted to set up a "net" for collecting pneumonia cases missed by our selection for radiography. Patients with persistent discomfort from cough or dyspnea were invited to attend the Chest Clinic at the University Hospital in Tromsø when the illness had lasted 10 days or after three days if the illness had already lasted a week or more. A chest radiograph was taken if not obtained at entry.

Follow-up radiographs are useful when acute findings are equivocal, but has not been obtained systematically in previous studies, except our own pilot study. However, for the same practical and ethical reasons as mentioned above, we did not take follow-up radiographs of the randomised patients. Details about the radiographic diagnosis is presented in paper V.

Statistical methods

Standard statistical methods, chisquare-test, t-test, and Wilcoxon rank sum test, were used in the comparison of groups according to the characteristics of the variables (cathego- rical or continous) and the distribution of measurement variables (normal or not). Sensitivity and specificity of clinical cues were calculated at various cut-off points, and likelihood ratio (LR) was calculated (sensitivity/1-specificity) (31,54). The combined sensitivities and specificities for various cut-off point of temperature and blood test results were presented as receiver operating characteristics (ROC)-curves (55). Confidence limits (CL) for LR were calculated as for CL of proportions recommended by Morris and

Gardner (56). Logistic regression was also used (57-59). The chi-square value of an independent variable in this analysis reflects the statistical strength of the adjusted association between this variable and the dependent variable. In the presentation of the results the chi-square value of the diagnostic cues has been referred to as the weight obtained by the cue as a predictor of pneumonia.

Kappa-statistics (60) and proportion of agreement between observers (61) was used in the evaluation of inter-observer variability in radiographic diagnosis. 95% confidence limits was calculated for both measures (61).

SUMMARY AND MAIN CONCLUSIONS OF THE PAPERS

Paper I:

The aim of the study was to evaluate the diagnostic usefulness of typical symptoms and physical chest signs for radiographic pneumonia and their value as perceived by doctors. A main result was the limited diagnostic value of abnormal chest findings for pneumonia, which was in contrast with the great emphasis laid on these signs by the doctors. The grading of dyspnea and chest pain enabled us to demonstrate high diagnostic values of these symptoms. Strong lateral chest pain and very annoying dyspnea had likelihood ratios of similar size as crackles, 4.8, 4.0 and 3.7, respectively. Logistic regression indicated that abnormal chest signs was of minor diagnostic value when added to the variables elicited through a thorough history.

Paper II

The diagnostic efficacy of temperature measurement, WBC-count, ESR, and CRP-test for radiographic pneumonia were evaluated, and the impact of the duration of illness on diagnostic values was studied. The four tests, and in particular ESR and CRP showed to be useful in the diagnosis of pneumonia. The greatest discriminative power of ESR and CRP was found when the illness

had lasted one week or more. Accordingly, the duration of illness should be taken into account when the result of the tests are interpreted. The diagnostic usefulness of ESR and CRP showed to be highly significant when added to symptoms and signs in logistic regression analysis. The study confirmed that a CRP value > 50 mg/l strongly support a clinical diagnosis of pneumonia. When the duration of illness exceeded one week CRP values between 20 and 50 mg/l were also of diagnostic value. If both ESR and CRP values are within the normal range, pneumonia is unlikely.

Paper III

Serological investigations revealed that bacterial infection, mycoplasma and chlamydia included, occurred as often in the 22 patients whose clinical diagnosis of pneumonia was not evident radiologically, as in the 20 patients with radiographic pneumonia. However, in the patients with radiographic pneumonia significantly higher ESR and CRP values was demonstrated, and cough, dyspnea, and chest pain were more frequently reported. Although WBC-count had a low sensitivity for radiographic pneumonia, as shown i paper II, probably due to the high frequency of viral, mycoplasmal and chlamydial pneumonias, this test seemed to be of great value in distinguishing the pneumococcal pneumonias from mycoplasmal and chlamydial pneumonias. The study supports the common view that patients with a positive chest radiograph usually present more serious manifestations of lower respiratory pathology than patients with a normal

radiograph. However, radiography alone did not seem to offer sufficient information for selecting patients for antibacterial therapy. The results indicated that some early pneumonias were radiographically invisible.

Paper IV

In this study the impact of patient selection on the diagnostic value of some clinical cues, ESR and CRP was studied. By following a standard diagnostic pathway, subgroups with increasing prevalence of pneumonia were defined. A tendency of lower specificity of symptoms and signs in selected patients with a high prevalence of pneumonia compared to unselected patients with a lower prevalence of the disease, was demonstrated. This decline in specificity resulted in great change in likelihood ratio. The LR of very annoying dyspnea, for instance, dropped from 5.7 in all the 581 patients included in the study, to 2.0 in the 79 patients who were referred to chest radiography by the doctors. Decline in specificity may reflect the diagnostic process. The use of a clinical cue in the selection, increasing the prevalence of the cue in the selected patients, may explain the decrease in specificity. The impact of prevalence on positive predictive values, according to the rule of Bayes', was strongly modified by the changes in diagnostic properties.

Paper V

A considerable interobserver variability was demonstrated between a radiology panel and routine reports from the Department of Radiology. Twenty-seven patients were diagnosed as having pneumonia by either the panel or routine interpretation, and there was agreement on pneumonia in 15, yielding a kappa-value of 0.71. While the panel interpreted both acute and follow-up radiographs, the routine reports were only based on acute radiographs (and old films in a few cases), and this difference may have contributed to the discrepancy of interpretation. Still lower kappa-agreements (0.50) were found between the panel and two residents in radiology who independently interpreted both acute and follow-up radiographs. The study thus underlined the importance of experience in the interpretation of chest radiographs.

Paper VI

In this study a compound reference standard was constructed, based on both radiographic, serological and laboratory results. When typical symptoms and chest signs were evaluated against this new reference standard, the LR values did not significantly differ from the LRs presented in paper I. It was concluded that bias due to insufficiency of the radiographic reference standard probably only had a moderate influence on the evaluation of diagnostic tests.

GENERAL DISCUSSION

Methodological considerations

Evaluations of diagnostic tests will always be biased due to methodological limitations (62). The possibilities of bias will here be reviewed and the impact of bias on the results will be discussed.

Sources of bias:

A. The reference standard

The radiographic reference standard has been discussed in all the six papers, from different viewpoints. Bias from the reference standard may be summarized as follows.

1. Bias due to incomplete specificity of the reference standard.

The interobserver variability described in paper V implies that both over and underdiagnosis of pneumonia probably has occurred. However, since the interpretations were based on both acute and follow-up radiographs the risk of overdiagnosis was probably small. Non-infectious pulmonary infiltrates radiographically mimicking pneumonia are rare disorders (2), and could probably not be expected to occur in our material. The fact that all the radiographic pneumonias were included in the compound reference standard presented in

paper VI, also weigh against overdiagnosis.

2. Bias due to incomplete sensitivity of the reference standard

We know that early pneumonia may lack a radiographic counterpart (20,22), but the quantitative role of this phenomenon has not been determined. Some few patients with true pneumonia may have been falsely classified as having non-pneumonia by our radiographic reference standard, as discussed in paper III and VI.

3. Bias due to the randomization for radiography

Since none of the patients in our random sample was diagnosed as having radiographic pneumonia, and most clinical data had been registered in all the patients subjected to randomization, we could choose between two alternative approaches when calculating specificities: We could either four-fold the findings of the random sample (the only alternative if only the randomized patients had been enrolled in the study as a control group), or we could make the assumption that there really was no pneumonia among the patients subjected to randomization and include all of them in the calculation. We chose the last approach, and by doing so the calculation of sensitivities and specificities in subgroups of the participating patients also became straight forward.

Among the patients subjected to randomization, but not radiographed at entry, a chest radiograph was obtained in 49 patients with persistent symptoms at the

Chest Clinic few days later. The fact that no pneumonias were diagnosed in these patients support our assumption of no pneumonias among the patients subjected to randomization.

(As mentioned in paper I, radiographic pneumonia was diagnosed in one patient who were first radiographed at the chest clinic. This patient was diagnosed as having LRTI and had an ESR of 30 mm/h at entry, and should, according to instruction, have been radiographed in the first place. Since the illness of this patient had worsened clinically and biochemically after entry, he was not regarded as a pneumonia case in the analyses.)

In retrospect I see problems with the randomization for radiography not foreseen when the investigation was planned. If there had been pneumonias in the random sample the analyses would have been much more complicated.

Consequencies of misclassifying patients into the pneumonia (PN) and non-pneumonia (NPN) groups

Misclassification will in general lead to a thinning out of the differences between the PN and NPN groups, lowering the sensitivity and specificity of the actual clinical finding. In our investigation the sensitivities are more fragile compared to the specificities, beeing calculated from only 20 patients. Let us suppose that one patient without true pneumonia was misclassified into the PN group and five patients with true pneumonia were misclassified into the NPN group. If the initial sensitivity of a certain finding was calculated to be 0.5, and this finding was absent in the false positive pneumonia and present in the five false negative

pneumonias an increase in sensitivity from 0.50 to 14/24 = 0.58 would result. If the initial sensitivity was zero, the revised sensitivity would be 5/24 or 0.21, which is the maximal error in sensitivity. If the initial sensitivity was 0.50 the error would be less than 0.08.

Let us calculate the maximal error in specificity in our material of 402, 382 without pneumonia, supposing the same misclassification: If the initial specificity was 0.90 (344/382) the revised specificity would be 345/378 or 0.91. If the initial specificity was 0.99 (377/382) the revised value would be 378/378 = 1.0. Greater changes would occur with low initial specificities, but not exceeding 0.02. When the specificity is high, a change of 0.01 may be substantial. A drop in specifity from 0.99 to 0.98 leads to a halving of the likelihood ratio.

B. Study population

Great differences in diagnostic properties were demonstrated when the same symptoms and signs were evaluated in different subgroups of patients (paper IV). This fact calls for caution as regards generalization from the study.

Characteristics of the patients at the Emergency Ward have probably influenced the results, especially the underrepresentation of elderly people and patients with chronic diseases. The most seriously ill patients were not included, as they usually are visited by the doctors at home. This selection bias may, as discussed in paper I and II, have resulted in too low sensitivities for some symptoms, signs and laboratory tests. The underrepresentation of elderly people with chronic bronchial or pulmonary disease but without pneumonia, may have resulted in too

high specificities of chest signs. However, it would be difficult to find a separate health care setting with a more representative material of otherwise healthy adults consulting general practitioners with respiratory complaints than the Municipal Emergency Ward in Tromsø.

The main evaluation of symtoms, signs and laboratory results were done in the 402 patients who underwent physical chest examination. The implications of this choice are indicated in paper IV. Although the doctors were asked to examine the patients as usual, the participation in the study may have influenced their practice, and physical chest examination has probably been carried out more frequently than usual. According to the results of paper IV, this bias may have increased the specificities of symptoms and signs, since additional patients without chest symptoms probably were included.

C. Other sources of bias

A considerable inter-doctor variation in recording of chest findings have been demonstrated (62,63). However if the participating doctors are representative of general practitioners, the average diagnostic values of the findings in medical practice may be determined. All the doctors working at the ward were willing to participate. Although they were not all general practitioners, they were working regularly at the ward. Auscultation of the chest is moreover a frequent examination in other specialities as well.

Symptoms and duration of illness was reprorted by the patients in retrospect. Since the duration of illness seldom exceeded two weeks, recall bias has probably

been of little significance. The use of self-administered questionnaire is not quite comparable to real life history-taking. Doctor's recording of patient history is frequently coloured by inference (31), for instance when pleuritic pain and expectoration is registered. Important questions may be forgotten during a busy interview, and some of the patients complaints may be ignored. However, details concerning symptoms and clinical course appreciated through history-taking may be missed in a questionnaire. After all, the registration by questionnaire represents a standardization of the recording of symptoms. The recording of chest signs, on the other hand, was dependent on the average examinatory skills of the doctors.

D: Summary of bias

The most important source of bias is probably connected to the selection of patients to the study, as indicated in paper IV. Misclassification of patients due to insufficiency of the reference standard may also have influenced the results, but to a smaller degree.

Implications for bayesian reasoning

The probability of a disease after a diagnostic test has been performed may be estimated, when the prevalence of the disease and the sensitivity and specificity of the test is known, by applying Bayes' theorem (30,31,64). In a clinical setting the prevalence is to be understood as the pre-test probability. However, the pre-test probability of a disease in a certain patient is difficult to assess, and is to be based both on the prevalence of the disease in the clinical setting and on clinical features of the patient appearent to the doctor (31).

The problem of determining pre-test probability (65) is not the only objection raised against the application of Bayes' rule in clinical medicine. Instability of sensitivity and specificity due to variation in spectrum of patients has been demonstrated by some studies (58,63,66,67), and caution in transferring the diagnostic value of a test from one clinical setting to another has been advocated. The importance of selection bias in the evaluation of diagnostic tests has been strongly underlined by this study. A strong tendency of lower specificity of typical symptoms and signs of pneumonia in subpopulations with high prevalence of pneumonia compared to case-mixes with lower prevalence was demonstrated, even within our frame of general practice. Selection of patients with increased probability of pneumonia may lead to accumulation of false positive as well as true positive test results. The influence of the duration of illness on sensitivy and specificity of ESR and CRP, as shown in paper II, revealed another possible source of selection bias. Since the diagnostic properties of one test may show

such dependency on other clinical cues, (in this case the duration of illness) the calculation of post-test probability of a disease based on an assumed pre-test probability and a fixed likelihood ratio, using Bayes' theorem, may be questionable, even when the LR has been determined in a similar case-mix.

Selection of patients is in clinical practice usually based on the presence of symptoms or signs. The diagnostic value of clinical cues on which the selection depends are strongly affected when these cues are evaluated in the selected patient population. The high diagnostic value of lateral chest pain and dyspnea found in this investigation contrasts the insignificance of these findings in a recent study by Heckerling et al (68). Not only the grading of the symptoms, but also the selection of patients in the two studies may explain this difference (paper IV).

Limitations of univariate analysis

The diagnostic values' dependency on selection and case-mix, reflects not only the use of the clinical cues in the selection of patients, but also associations between cues. Cough and dyspnea, for instance, do not coexist in a patients with pneumonia by chance. One finding may be useless when added to another. For instance, temperature measurement may be useless when the CRP value is known. On the other hand, a finding may be useless when not combined with a certain other finding. The diagnostic efficacy of raised body temperature is dependent on the duration of illness, as shown in paper III. In recent studies

evaluating diagnostic tests, multivariate analysis has frequently been used (44,68,69,), In our investigation logistic regression was applied primarily to confirm the results of the univariate analysis, but the significance of adding laboratory tests to history and physical examination could not have been demonstrated by univariate analysis alone. A disadvantage of multivariate analysis is the complexity of the method. Being difficult to see through and comprehend, one may find it hard to really trust in the results. Sensitivity and specificity, on the other hand, is easy math.

A case history

To further extend this discussion I will refer to a patient who recently consulted me at the emergency ward. A 53 year old man, non-smoker and previously healthy, had felt a slight pain in the middle of the chest, when he woke up in the morning the day before. He felt feverish, and on arising he startet to cough. The chest pain was strongly aggravated by coughing. This was Sunday, and he stayed at home the whole day. He felt fatigue, but had no coryza, no soreness of the throat, and no myalgia. In the afternoon he felt some tightness in the chest and wheezing could be heard. He coughed up considerable amounts of greenish and bloody sputum, and then the wheezing disappeared. The next morning he felt well enough to go to work. However, he soon realized that the chest pain on cough and the fatigue persisted. In the evening he got a shaking chill and decided to consult a doctor.

At the consultation he appeared to be at good health, the chins were maybe

somewhat reddish. The respiration seemed untroubled and he denied dyspnea. He had not measured the temperature, but counted the pulse to be 90 per minute. Physical chest examination did not reveal any adventitious lung sounds, and there was no dullness to percussion. After chest examination he coughed carefully, while holding his hand over the chest, and he spitted a big purulent clot on a paper. A CRP-test was carried out, and a value of 50 mg/l was measured. Chest radiography was not ordered.

When reflecting on the diagnosis, I tried to apply the results of paper I and II. He did not present lateral chest pain or very annoying dyspnea. His chest was clear. He had chills, very annoying cough and purulent sputum, but none of these cues has a high likelihood ratio, according to paper I. A CRP of 50 mg/l also is of little use during the first week of illness, as determined in paper II. I returned to the classic descriptions of diseases. "Pneumococcal pneumonia", I site from Harrisons' textbook (29), "begins abruptly with a single shaking chill, fever, pleuritic chest pain, and a cough productive of purulent, often bloody sputum". This description lists a combination of symptoms, contrasting the univariate test evaluation of this thesis. Could it be crucial that certain combinations of symptoms have a high specificity, while the single symptoms are unspecific ?
In previously healthy adults influenza may frequently be a differential diagnosis to pneumonia. Purulent sputum may occur in influenza as well as in pneumococcal pneumonia, but is usually scanty the first day of illness (70), and expectoration is usually preceeded by coryza and/or myalgia. In my patient the diagnostic dilemma was to decide whether the chest infection he obviously

suffered from was influenza or a bacterial bronchitis/pneumonia. The combination of fever, purulent expectoration, absence of upper respiratory tract symptoms, and above all, a short duration of illness was the reason why I thought early pneumonia or a acute bacterial bronchitis was more likely than influenza, and treated the patient with penicillin.

This case illustrated that, until the complexity of the clinical course of illness has been sensibly acted on in the evaluation of symptoms and signs, we also have to look to classical descriptions of diseases. Particular combinations of physical chest findings certainly also have a much higher specificity compared to the single signs. Crackles combined with diminished breath sounds and an obvious dullness to percussion over the same part of the lung would probably show to have a high LR. Because classical combinations are seldom met in walk-in patients in general practice, evaluation of such combinations needs to be based on a larger population of patients than enrolled in our investigation, or on a selection of patients also including house calls.

Clinical implications

Adjustment of diagnostic approach

1. Decreased emphasis on crackles.

Paper I showed that the doctors' overestimation of crackles and other abnormal chest signs is an important source of misdiagnosis. Awareness of the fact that abnormal chest signs only can be found in about half of the patients with pneumonia may lead to a greater emphasis on history taking. The low specificity of crackles also implies that other possibilities than pneumonia should be considered when crackles are heard, and that a diagnosis of pneumonia should be supported by a typical history and/or laboratory tests. This adjustment implies a changed pathophysiological reasoning, affecting not only the diagnosis of pneumonia, but also acute bronchitis and aggravation of asthma and COPD. Forgacs theory about the origin of crackles (71) yields a rationale for this change.

One may question whether the value of chest findings would improve if doctors were better trained in the examination of the chest. As far as we know, no investigation has indicated an answer to this question. A recent study (72) demonstrated improved sensitivity of crackles when the patient was examined in the lateral decubitus position. By following this advice, the specificity might be reduced, and the LR would possibly be unchanged.

After all, abnormal chest signs remain to be manifestations of disorders of the

lungs and bronchi. The relative depreciation of chest signs showed by this thesis may only represent a step into a renewed upgrading of chest auscultation, facilitated by future studies on lung sounds and their pathophysiological correlates. The doctors interpretation of lung sounds may in turn both be adjusted and become more uniform, and a more efficient diagnosis of pneumonia, bronchial obstruction and other pathological changes of the lung may come forth.

2. Upgrading of history taking.

History taking is still a very important part of the clinical examination (31,73,74). Too low attention payed to the history has also been demonstrated in other clinical settings (59). The symptoms emphasized in hippocratic medicine, chest pain, dyspnea and fever are still of substantial diagnostic value, even in the moderately ill patients of our investigation. Why do doctors overestimate the value of chest signs at the expence of chest symptoms ? Both a survival of Laennecs optimistic view regarding the diagnostic properties of auscultation and the doctors weakness for technology and "objective" signs, may be reasons for this.

The doctors should not only record the presence and abscence of symptoms, the degree of discomfort from the symptoms should also be explored. Knowledge about the duration of illness showed to be of great importance when temperature and blood tests are interpreted. Illness duration should also be kept in mind when symptoms are considered. A rapid clinical course is probably more frequent in bacterial pneumonia compared to bronchitis and upper respiratory tract infection, and chest pain and dyspnea may develop within few days. In the

pilot study duration of illness less than 24 hours was the clinical cue from history of greatest diagnostic value (46). Patients were enrolled at home calls in addition to general practice offices and the Emergency Ward, and two out of the three pneumonia patients with duration of illness less than 24 hours were visited at home. The diagnostic value of such short duration of illness was not confirmed by this study, as none of the pneumonia patients had been ill less than 24 hours.

3. Temperature measurement and laboratory tests are useful.

The importance of inflammatory markers: temperature, WBC-count, ESR and CRP in the diagnosis of pneumonia was confirmed by our investigation (paper II). Pneumonia may be ruled out if both CRP and ESR show normal values. Raised values of these tests may strongly support a clinical diagnosis of pneumonia, but the duration of illness should be considered when test results are interpreted. Paper IV indicates that ESR may be useful in rather unselected patients with respiratory infection, while CRP is most useful when the patient is classified as having lower respiratory tract infection. The implementation of these tests in general practice depends mostly on practical aspects: financial costs, the consumption of time by performing the test, and how many minutes to wait for the result. A new semiquantitative CRP-test (Nycocard-CRP, Nycomed, Oslo, Norway) yielding result in five minutes seems to be an attractive alternative in general practice.

Pneumonia as diagnostic cathegory

One may question whether it is worthwhile to differentiate pneumonias from other lower respiratory tract infections. A correct diagnosis should not be an objective in itself, only a means for an optimal treatment (75). Owing to the difficulty in distinguishing pneumonia from bronchitis, and the similarity in therapeutic approach observed in the two diseases, Fry and co-authors have argued for the use of the term "chest infection" in a textbook for general practitioners (76). A subclassification into "chest infection with crackles" and "chest infection with wheezes" was also suggested, and the authors emphasized the possibility of obstructive pulmonary disease in the latter group. Although the objective of this differentiation is rational (77,78), such weight on chest findings was not supported by this investigation. The term "chest infection" may thus obscure the important difference between pneumonias and obstructive pulmonary disease (although they may coexist), diseases with many similarities in clinical presentation but with quite different treatments. As discussed in paper III, both blood tests and spirometry may be valuable adjuvants to history and physical examination in the differentiation of these diseases. Besides, a differentiation between pneumonia and acute bronchitis may contribute to a more rational treatment of the latter disease. The current treatment consisting mainly of antibiotics (79-81), is probably not optimal. Antibiotics are probably useless in the majority of cases diagnosed as acute bronchitis (82), as is also indicated in paper III, and sole expectance or symptomatic treatment with an antitussivum or a bronchodilator (77) is probably preferable in most cases. Moreover, the mortality

of pneumonia referred to in the introduction, tells us that the concept of pneumonia should survive as a clinical entity.

Directions for future research.

Diagnosis of pneumonia will remain an important field for research in the years to come. Tests identifying specific infectious agents will be sought for, and the trend of dividing pneumonias into etiological subgroups will be strengthened. Laboratory investigations will play a greater role in the diagnostic work-up of lower respiratory tract infection in "avant garde" general practice, but practical and economical limitations will still call for simple clinical tests, which can be performed without advanced technology. Symptoms and signs will be evaluated in the light of the advances in etiological diagnosis.

Rough diagnostic classification of respiratory infection for use in general practice, as examplified by this thesis, will be brought further. Such studies have also been carried out in the third world and has, for instance, documented a considerable diagnostic value of counting the respiratory rate for childhood pneumonia (83,84). More attention will probably be paid to the diagnosis of pneumonia in the elderly in future studies. The differentiation of patients according to need of antibiotics will probably be clarified, both in patients with acute bronchitis and COPD, in order to reduce unnecessary antibacterial treatments. Patients diagnosed as having pneumonia will probably be treated

with antibiotics, until bacterial infection can be excluded with nearly 100 % certainty, due to the possibility of a severe clinical course.

Conclusive remarks

Many problems connected to the evaluation of diagnostic test have been demonstrated by this investigation. Interobserver variability in the interpretation of chest radiographs has been confirmed to add uncertainty to the reference standard. The selection of study population has been shown to be of great importance for the results, indicating that caution should be shown when generalizing diagnostic properties of clinical cues and diagnostic tests. These are valuable experiences worthy of being shared with other researchers. Some knowledge of importance for the clinician has although emerged from the investigation. The myth of crackles as almost pathognomonic of pneumonia has been challenged with greater strength than previously, and the study make allowances for doctors to pay more attention to the patients' symptoms. The utility of laboratory tests for pneumonia in a primary care setting has been elucidated, and the efficacy of ESR and CRP-test have been confirmed. The serological study of the patients with lower respiratory tract infection showed that these tests and white blood cell count may be useful in the differentiation of viral and bacterial infection. Although viral infection was more frequently established than bacterial infection, pneumococcal and mycoplasmal infections were not uncommon. As bacterial infection were established in many patients without radiographic pneumonia, radiography alone did not seem to offer sufficient information for selecting patients for antibacterial treatment.

References

1. Anderson JR (ed.). Muir's textbook of pathology, 11th ed. London: Edward Arnold Ltd. 1980: 466-74.
2. Gross TJ, Chavis AD, Lynch JP. Noninfectious pulmonary diseases masquerading as community-acquired pneumonia. Clin Chest Med 1991;12:363-93.
3. MacFarlane J. Community-acquired pneumonia. Br J Dis Chest 1987;81:116-27.
4. Fang GD, Fine M, Orloff J, Arisumi D, Yu VL, Kapoor W et al. New and emerging etiologies for community-acquired pneumonia with implications for therapy. Medicine 1990;69:307-16.
5. Blanquer J, Blanquer R, Borrás R, Nauffal D, Morales P, Menéndez R et al. Aetiology of community acquired pneumonia in Valencia, Spain: a multicentre prospective study. Thorax 1991;46:508-11.
6. The 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;62:195-220.
7. Atmar RL, Greenberg SB. Pneumonia caused by Mycoplasma pneumoniae and the TWAR agent. Semin Respir Infect 1989;4:19-31.
8. Ruben FL, Nguyen MLT. Viral pneumonitis. Clin Chest Med 1991; 12:223-35.

9. Nordic Statistical Secretariat. Yearbook of Nordic statistics 1984. Stockholm: Nordic Council, 1985:64-5.

10. Graham NMH. The epidemiology of acute respiratory infections in children and adults: a global perspective. Epidemiol Rev 1990;12:149-78.

11. McKeown T. The role of medicine. Oxford:Basil Blackwell 1989:45-65.

12. Woodhead MA, MacFarlane JT, McCracken JS, Rose DH, Finch RG. Prospective study of the aetiology and outcome of pneumonia in the society. Lancet 1987;i:671-4.

13. MacFarlane JT. Treatment of lower respiratory infections. Lancet 1987;ii:1446-9.

14. Bruu AL, Haukenes G, Aasen S, Grayston JT, Wang SP, Klausen OG et al. Chlamydia pneumoniae infections in Norway 1981-87 earlier diagnosed as ornithosis. Scan J Infect Dis 1991;23:299-304.

15. MacFarlane JT, Finch RG, Ward MJ, MacRae. Hospital study of adult community acquired pneumonia. Lancet 1982;ii,255-8.

16. Gsell O. Geschichte der pneumonie [History of pneumonia]. Sudhoffs Arch 1984;68:182-216.

17. Laennec RTH. Treatise on the diseases of the chest. 4th ed. London: Longman 1834.

18. Levin S. The atypical pneumonia syndrome. JAMA 1984;251:945-8.

19. Osmer JC, Cole BK. The stethoscope and roentgenogram in acute pneumonia. South Med J 1966;59:75-7.

20. Conte P, Heitzman ER, Markarian B. Viral pneumonia. Roentgen pathological correlations. Radiology 1970;95:267-72.

21. Goodman LR, Goren RA, Teplick SK. The radiographic evaluation of pulmonary infection. Med Clin North Am 1980;64:553-74.

22. Stein MT. Delayed roentgenographic signs associated with acute pneumonia in children. J Fam Pract 1981;12:639-44.

23. Herman PG, Gerson DE, Hessel SJ, Mayer BS, Watnick M, Blesser B, et al. Disagreements in chest roentgen interpretation. Chest 1975;68:278-82.

24. Robertsen AJ, Coope R. Rales rhonchi and Laennec. Lancet 1957; ii,417-23

25. Forgacs P. Crackles and wheezes. Lancet 1967;ii:203-5.

26. Piirilä P, Sovijärvi ARA, Kaisla T, Rajala HM, Katila T. Crackles in patients with fibrosing alveolitis, bronchiectasis, COPD, and heart failure. Chest 1991;99:1076-83.

27. Macleod J, Munro J. Clinical examination. 7th ed. Edinburgh: Churchill Livingstone, 1986:182-3.

28. Swash M. Hutchison's clinical methods. 9th ed. London: Baillière Tindall 1989:199.

29. Hirschman JV, Murray JF. In: Harrison's principles of internal medicine 11 ed. New York 1987:1076.

30. Weinstein MC, Fineberg HV. Clinical decision analysis. Philadelphia: WB Saunders Co. 1980.

31. Sacket DL, Haynes RB, Tugwell P. Clinical epidemiology. A basic science for clinical medicine. Boston: Little, Brown and co. 1985.

32. Leventhal JM. Clinical predictors of pneumonia as a guide to ordering chest roentgenogram. Clin Pediatr 1982;21:730-4.

33. Diehr P, Wood RW, Bushyhead J, Krueger L, Wolcott B, Tompkins RK. Prediction of pneumonia in outpatients with acute cough: a statistical approach. J Chronic Dis 1984;37:215-25.

34. Bushyhead JB, Christensen-Szalanski JJJ. Feedback and the illusion of validity in a medical clinic. Med Decis Making 1981;1:115-23.

35. Christensen-Szalanski JJJ, Bushyhead JB. Physicians use of probabilistic information in a real clinical setting. J Exp Psychol 1981;7:928-35.

36. Bushyhead J, Wood RW, Tompkins RK, Wolcott BW, Diehr P. The effect of chest radiographs on the management and clinical course of patients with acute cough. Med Care 1983;21:661-73.

37. Christensen-Szalanski JJJ, Diehr PH, Bushyhead J, Wood RW. Two studies of good clinical judgment. Med Decis Making 1982;2:275-83.

38. Christensen-Szalanski JJJ, Bushyhead J. Physicians misunderstanding of normal findings. Med Decis Making 1983;3:169-75.

39. Heckerling PS. The need for chest roentgenograms in adults with acute respiratory illness. Clinical predictors. Arch Intern Med 1986;146:1321-4.

40. Wollschlager CM, Khan FA, Khan A. Utility of radiography and clinical features in the diagnosis of community-acquired pneumonia. Clin Chest Med 1987;8:393-404.

41. Tobin MJ. Diagnosis of pneumonia: Techniques and problems. Clin Chest Med 1987;8:513-27.42. Lehtomäki K. Clinical diagnosis of pneumococcal, adenoviral, mycoplasmal and mixed pneumonias in young men. Eur Respir J 1988;1:324-9.

43. Farr BM, Kaiser DL, Harrison BDW, Connolly CK. Prediction of aetiology at admission to hospital for pneumonia from the presenting clinical features. Thorax 1989;44:1031-5.

44. Holmberg H, Bodin L, Jönsson I, Krook A. Rapid aetiological diagnosis of pneumonia based on routine laboratory features. Scand J Infect Dis 1990;22:537-45.

45. Melbye H, Straume B, Aasebø U, Brox J. The diagnosis of adult pneumonia in general practice. Scand J Prim Health Care 1988;6:111-7.

46. Morley JJ, Kushner I. Serum C.reactive protein levels in disease. Ann N Y Acad Sci 1982;389:406-17.

47. McCarthy PL, Frank AL, Ablow RC, Masters SJ, Dolan TF. Value of the C-reactive protein test in the differentiation of bacterial and viral pneumonia. J Pediatr 1978;92:454-6.

48. Hanson LA, Wadsworth Ch. C-reactive protein and its diagnostic usefulness - especially in infections. Med Lab 1980;8:34-44.49. Fransen H, Wolontis S. Infections with viruses, Mycoplasma pneumoniae and bacteria in acute respiratory illness. Scand J Infect Dis 1969;1:31-7.

50. Monto AS, Cavallaro JJ. The Tecumseh study of respiratory illness. II. Patterns of occurrence of infection with respiratory pathogens, 1965-1969.

Am J Epidemiol 1971;94:280-9.

51. Mardh PA, Hovelius B, Nordenfelt E, Rosenberg R, Soltesz LV. The incidence and aetiology of respiratory tract infections in general practice -- with emphasis on Mycoplasma pneumoniae. Infection 1976;4 suppl. 1:40-8.

52. Sundsfjord A, Vorland L, Melbye H. Serologi ved nedre luftveisinfeksjoner. [Diagnostic serology in lower respiratory tract infections. Abstract in English.] Tidsskr Nor Lægeforen 1988;108:2719-20, 2750.

53. Boldy DAR, Skidmore SJ, Ayres JG. Acute bronchitis in the community: clinical features, infective factors, changes in pulmonary function and bronchial reactivity to histamine. Respir Med 1990;84:377-85.

54. Radack KL, Rouan G, Hedges J. The likelihood ratio. Arch Patol Lab Med 1986;110:689-93.

55. Beck JR, Shultz EK. The use of Relative Operating Characteristic (ROC) curves in test performance evaluation. Arch Patol Lab Med 1986; 110:13-20.

56. Morris JA, Gardner MJ. Calculating confidence intervals for relative risks, odds ratios, and standardised ratios and rates. In: Gardner MJ, Altman DG, eds. Statistics with confidence: Confidence Intervals and Statistical Guide-lines. London, England: British Medical Association 1989:50-63.

57. Wigton RS. Use of linear models to analyze physicians' decisions. Med Decis Making 1988;8:241-52.

58. Hlatky MA, Pryor DB, Harrell FE jr, Califf RM, Mark DB, Rosati RA. Factors affecting the sensitivity and specificity of the exercise electrocardiogram: A multivariable analysis. Am J Med 1984;77:64-71.

59. Centor RM, Witherspoon JM, Dalton HP, Brody CE, Link K. The diagnosis of strep throat in adults in the emergency room. Med Decis Making 1981;1:239-46.

60. Fleiss JL. Statistical methods for rates and proportions. New York: John Wiley & Sons 1981:212-36.

61. Grant JM. The fetal heart rate is normal, isn't it? Observer agreement of categorical assessments. Lancet 1991;337:215-18.

62. Begg CB. Biases in the assessment of diagnostic tests. Statistics in medicine 1987;6:411-23.

63. Smylie HC, Blendis LM, Armitage P. Observer disagreement in physical signs of the respiratory system. Lancet 1965;2:412-3.

64. O'Connor GT, Sox HC. Bayesian reasoning in medicine: the contributions of Lee B. Lusted, MD. Med Decis Making 1991;11:107-11.

65. Dolan JG, Bordley DR, Mushlin AI: An evaluation of clinicians' subjective prior probability estimates. Med Decis Making 1986;6:216-23.66. Ransohoff DF, Feinstein AR. Problems of spectrum and bias in evaluating the efficacy of diagnostic tests. N Eng J Med 1978;299:926-30.

67. Harris JM, The hazards of bedside Bayes. JAMA 1981;246:2602-5.

68. Heckerling PS, Tape TG, Wigton RS, Hissong KK, Leikin JB, Ornato JP et al. Clinical prediction rule for pulmonary infiltrates. Ann Int Med 1990;113:664-70.

69. Tape TG, Heckerling PS, Ornato JP, Wigton RS. Use of clinical judgement analysis to explain regional variations in physicians' accuracies in diagnosing pneumonia. Med Decis Making 1991;11:189-97.

70. Douglas RG jr. Influenza in man. In: Kilbourne ED (ed.). The influenza virus and influenza. New York: Academic press 1975:395-447.

71. Forgacs P. Lung sounds. London: Baillière Tindall, 1978.

72. Gilbert VE. Detection of pneumonia by auscultation of the lungs in the lateral decubitus position. Am Rev Respir Dis 1989;149:1012-16.

73. Hampton JR, Harrison MJG, Mitchell JRA, Prichard JS, Seymour C. Realative contributions of history-taking, physical examination, and laboratoty investigation to diagnosisis and management of medical outpatients. Br Med J 1975;ii:486-9.

74. Rich EC, Crowson TW, Harris IB. The diagnostic value of the medical history. Perceptions of internal medicine physicians. Arch Intern Med 1987;147:1957-60.

75. Wulff HR. Rationel klinik 3. utg. Copenhagen: Munksgård, 1987:107-8.

76. Fry J, White R, Whitfield M. Respiratory disorders. Library of general practice. Edinburgh: Churchill Livingstone 1984: 94-105.

77. Melbye H, Straume B, Aasebø U. Symptomatic effect of fenoterol in acute bronchitis. A placebo-controlled double-blind study. Family Practice 1991;8:216-22.

78. Delay in diagnosing asthma, is the nature of general practice to blame? J R Coll Gen Pract 1986;36:52-3.

79. Howie JGR. Clinical judgement and antibiotic use in general practice. Br Med J 1976;ii:1061-4.

80. Melbye H. Forskrivning av antibiotika ved luftveisinfeksjoner. Hvilken rolle spiller pasientens ønske? In Førde OH, Straume B, Westlund K (eds.) Til Anders Forsdahls 60-års dag. Tromsø: ISM's skriftserie, Universitetet i Tromsø 1990: 113-23.

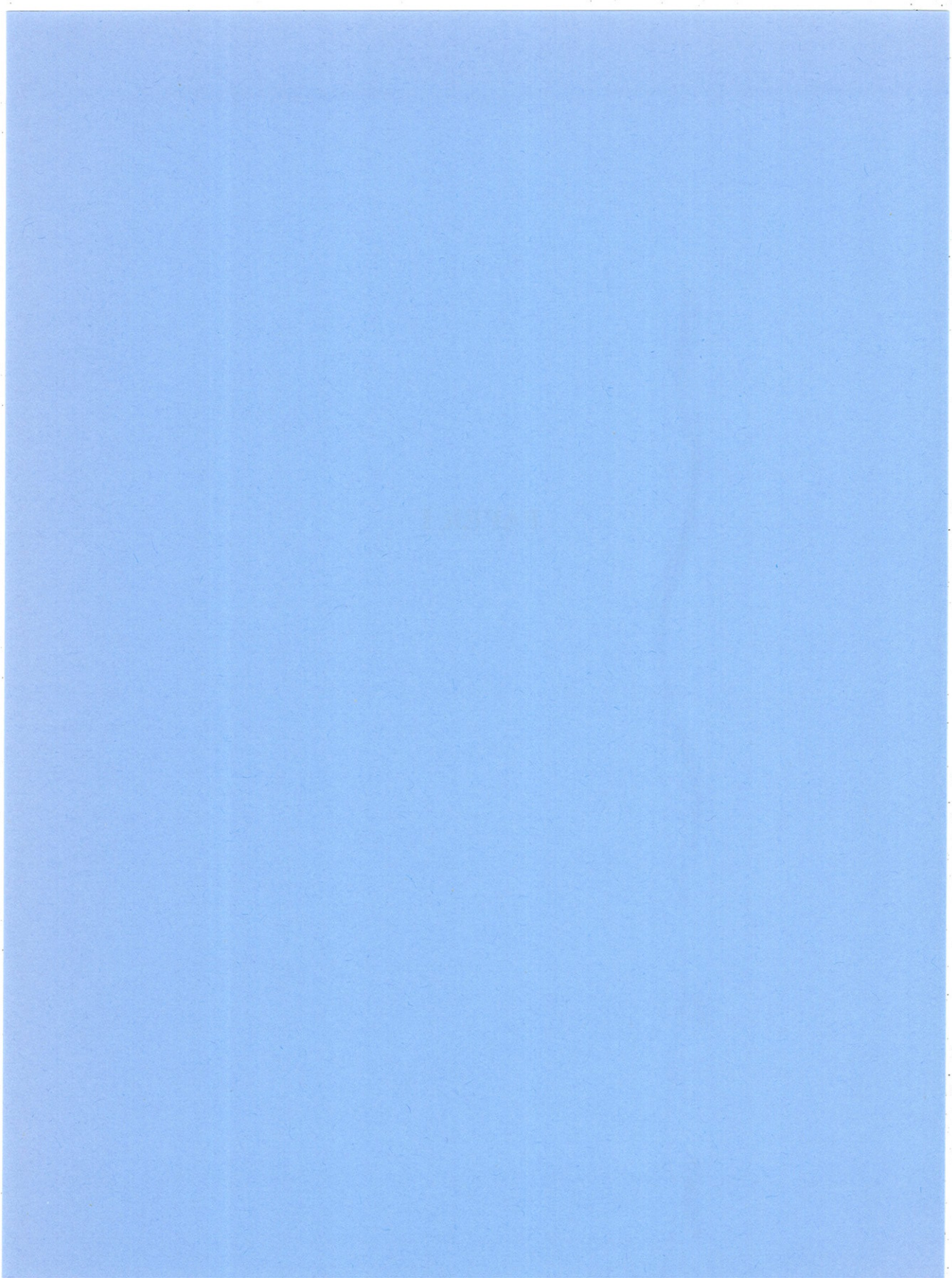
81. Dunlay J, Reinhardt R. Clinical features and treatment in acute bronchitis. J Fam Pract 1984;18:719-22.

82. Verheij TMJ, Kaptein AA, Mulder JD. Acute bronchitis: aetiology, symptoms, and treatment. Family Practice 1989;6:66-9.

83. Cherian T, John TJ, Simoes E, Steinhoff MC, John M. Evaluation of simple clinical signs for the diagnosis of acute lower respiratory tract infection. Lancet 1988;ii:125-28.

84. Harari M, Shann F, Spooner V, Meisner S, Carney M, De Campo J. Clinical signs of pneumonia in children. Lancet 1991;338:928-30.

PAPER I



Scand J Prim Health Care 1992, 10: 226–233

Diagnosis of Pneumonia in Adults in General Practice

Relative Importance of Typical Symptoms and Abnormal Chest Signs Evaluated Against a Radiographic Reference Standard

HASSE MELBYE[1], BJØRN STRAUME[1], ULF AASEBØ[2] and KNUT DALE[3]

[1]Institute of Community Medicine, University of Tromsø, [2]Chest Clinic, Department of Medicine, University Hospital of Tromsø, [3]Department of Radiology, University Hospital of Tromsø, 9000 Tromsø, Norway

Melbye H, Straume B, Aasebø U, Dale K. Diagnosis of pneumonia in adults in general practice. Relative importance of typical symptoms and abnormal chest signs evaluated against a radiographic reference standard. Scand J Prim Health Care 1992; 10: 226–33.

The diagnostic value of typical symptoms and abnormal chest signs for pneumonia have been evaluated against a radiographic reference standard in 402 adult patients with respiratory tract infection in general practice. Pneumonia was diagnosed in 20 patients by a positive chest radiograph. The doctors diagnosed pneumonia in seven of these on the basis of history and physical examination alone, and in addition in 22 patients with normal radiographs. The diagnostic value of the typical symptoms cough, chest pain, and dyspnoea, reported by the patients on a questionnaire, increased with increasing intensity of the symptoms, and both "very annoying lateral chest pain" and "very annoying dyspnoea" had likelihood ratios (LR) between 4 and 5. The LR of crackles was 3.7. When evaluated against the doctor's clinical diagnosis of pneumonia as reference standard, crackles achieved an LR of 14.8, while the typical symptoms achieved lower LRs than when evaluated against the radiographic reference standard. These discrepancies, which were confirmed by logistic regression, indicate that crackles and other abnormal chest findings are intepreted too frequently as features of pneumonia and that the importance of typical symptoms is underestimated in the diagnosis of pneumonia.

Key words: pneumonia, clinical examination, diagnosis, medical judgement.

Hasse Melbye, MD, Institute of Community Medicine, University of Tromsø, Breivika, 9000 Tromsø, Norway.

The diagnosis of pneumonia in general practice is frequently based on history and physical examination alone. The difficulties in differentiating pneumonias from other respiratory tract infections in unselected patients have been clearly demonstrated by Diehr et al. (1). The diagnostic values of chest pain and dyspnoea, symptoms often referred to as typical of pneumonia, were low in that study. Crackles (rales), the cardinal auscultatory finding, were heard in only 19% of the patients with pneumonia. A higher sensitivity of abnormal chest signs has been found in selected patients judged to have a possible pneumonia (2, 3), and in hospitalized patients with radiographic pneumonia (4).

In previous studies, the typical symptoms have usually been recorded as present or not present. In this study we wanted to assess the usefulness of these symptoms for pneumonia in adults in primary care, taking the associated degree of discomfort into account. In addition, we wanted to describe the diagnostic value of the symptoms and signs as seen by doctors. An overestimation of crackles has previously been indicated (2, 5), and we wanted further to elucidate whether the emphasis laid on symptoms and chest signs could be better balanced.

MATERIAL AND METHODS

The investigation took place between 17 October 1988 and 31 May 1989 at the Municipal Emergency Clinic in Tromsø. This clinic is organized in cooperation with general practitioners (GPs) in Tromsø for

the management of out-of-hours calls. 40 doctors, mainly GPs, participated in the examination of the patients.

Patients

Consecutive walk-in patients aged 18 years or more, who attended the ward between 1600 and 2100 hrs., presenting with symptoms suggestive of a respiratory tract or throat infection, were asked to participate. Pregnant women and patients with dyspnoea severe enough to need urgent treatment were excluded. The participants gave informed consent, and the study was approved by the Regional Committee of Medical Research Ethics.

Examinations

The patients were interviewed and examined by specially trained nurses. Using a self-administered questionnaire, the patients reported duration of illness, respiratory symptoms, and general symptoms of infectious disease during the present illness. Graded discomfort from cough, chest pain, and dyspnoea was also reported, and the site of the chest pain. Blood was taken for erythrocyte sedimentation rate (ESR) (Seditainer, Becton Dickenson Co., France) and a semiquantitative test for C-reactive protein (Nycocard-CRP, Nycomed, Norway). The doctors were told to examine and treat the patients as usual. They recorded on a form whether auscultation and percussion of the chest were carried out, and whether crackles, wheezes, pleural rubs, diminished breath sounds or dullness to percussion were heard. The patients were classified as having upper respiratory tract infection, URTI, (including throat infection), or lower respiratory tract infection (LRTI), or both, and one main diagnosis based on history and physical examination alone was reported, referred to as the clinical diagnosis.

Radiography

For practical and ethical reasons we found it inappropriate to performe x-ray examination in all the patients, and decided to order a chest radiograph in only a random sample of those with the lowest probability of pneumonia. The guidelines for radiography, to be performed the same evening or the following day (three patients), were as follows:

1. When the doctors thought that pneumonia was a diagnostic possibility, a radiograph was to be ordered.
2. Because pneumonias are frequently associated with elevated ESR and CRP levels (2, 6), radiography was ordered by the nurse if the ESR exceeded 50 mm/h or CRP exceeded 60 mg/l. If the doctor reported LRTI, the thresholds for ordering were 20 mm/h and 20 mg/l, respectively.
3. A chest film was ordered in a 25% random sample of the remaining patients.

To disclose pneumonias not diagnosed because of the randomization, patients were invited to attend the Chest Clinic at the University Hospital of Tromsø if pronounced cough or dyspnoea persisted when the illness had lasted ten days, or after three days if the illness had already lasted a week. A chest film was taken, if it had not been obtained at entry. All the acute-phase radiographs were read by the Department of Radiology at the University Hospital.

The patients were asked to return 4–5 weeks later. A follow-up radiograph was taken if the doctors had reported an LRTI, or if the Department of Radiology had interpreted the acute-phase radiograph as indicative of pneumonia.

Table I. *Age and male/female ratio in 626 adult patients with respiratory infection, according to subgroups referred to in the text.*

	n	Age (mean)	Male/female ratio
Patients			
asked to participate	626	31.9	0.73
refused	45	29.0	0.96
included	581	32.1	0.71
Chest radiography			
ordered by the doctor	79	38.2	0.68
ordered because of pathological blood tests	101	30.8	0.63
ordered after randomization	90	32.2	0.76
taken at the Chest Clinic	49	37.3	0.75
not done	262	29.8	0.74
Chest examination			
auscultation performed	402	33.2	0.70
percussion also done	214	34.0	0.70
Follow-up			
came for follow-up	438	33.1	0.67
follow-up radiograph done	138	38.1	0.73

Table II. *Reasons for consultation and associated frequencies of physical chest examination. The suggested diseases and symptoms were used as criteria for asking 626 patients to participate. The frequencies of chest examination are based on the 581 patients who participated.*

Reason for consultation	No. of patients	Frequency of chest examination (%)
Disease suggested by the patient		
1. Common cold	32	83
2. "Flu"	85	90
3. Sinusitis	97	38
4. Exacerbation of asthma	5	100
5. Bronchitis, acute or chronic	30	100
6. Pneumonia	46	100
Symptom presented by the patient		
7. Cough	68	97
8. Fatigue, with no probable cause outside the respiratory tract	2	100
9. Fever without urogenital symptoms or other obvious cause outside the respiratory tract	3	100
10. Sore throat	188	45
11. Earache, combined with common cold, sore throat or fever	30	56
12. Dyspnoea, when myocardial infarction is not suspected or urgent treatment is not needed	6	100
13. Chest pain, non-traumatic, made worse by deep inspiration, movements, or coughing, when myocardial infarction is not suspected	20	100
14. Acute hoarseness	4	100
No reason recorded	10	80

The reference standard

A density on chest film, showing signs of resolution on a follow-up radiograph, was used as the reference standard of pneumonia. The interpretation of the films, described in detail elsewhere (7), may be summarized as follows. When the investigation was completed, the chest films were interpreted independently by two radiologists (residents) and one senior chest physician. If an obvious or possible pneumonia was diagnosed by at least one interpreter, or if the Department of Radiology reported the same conclusion, the films were judged by a radiology panel. Only one final diagnosis of pneumonia was based on the acute-phase radiograph alone.

Statistical analysis

The diagnostic value of symptoms and signs was evaluated in the patients who underwent physical chest examination. The data were analysed in three ways. First, sensitivities, specificities, and likelihood ratios (LR) (8) were calculated against the radiographic reference standard of pneumonia, as well as 95% confidence intervals for the LRs (9). LR is the frequency of a finding in patients with the disease (sensitivity) divided by the frequency of the finding in patients without the disease (1-specificity) (10).

Second, to estimate the diagnostic usefulness of the clinical variables perceived by the doctors, the same calculations were made using the doctors' clinical diagnosis of pneumonia as reference standard. If this LR was outside the 95% confidence limits of the LR based on the radiographic diagnosis, the difference was regarded as significant.

Third, logistic regression (11) was performed for two separate models. To compare "actual" and perceived weight of the clinical variables, radiographic and clinical diagnoses were used as dichotomous outcomes. Independent variables were selected as follows: sex, age, and variables significantly associated with either radiographic or clinical pneumonia in contingency tables or in stepwise linear regression ($p < 0.05$). Missing values were interpreted as absence of the variables. The adjusted diagnostic weight obtained by the variables are presented as

Table III. *Diagnostic value of typical symptoms for pneumonia in 402 patients with respiratory infection in general practice, using radiographic pneumonia (n = 20) as reference standard, and corresponding diagnostic values perceived by the doctors, using the doctors' clinical diagnosis of pneumonia (n = 29) as reference standard. LR = likelihood ratio, CL = 95% confidence limits.*

Typical symptoms	Diagnostic values for radiographic pneumonia			Perceived diagnostic values		
	Sensitivity	Specificity	LR (CL)	Sensitivity	Specificity	LR
Cough during illness						
more annoying than normal	0.95	0.22	1.2(1.0–1.5)	0.86	0.22	1.1
very annoying	0.65	0.65	1.8(1.2–2.9)	0.52	0.64	1.4
dry cough	0.40	0.81	2.2(1.1–4.1)	0.24	0.81	1.3
purulent sputum	0.35	0.65	1.0(0.5–1.8)	0.38	0.35	1.1
Dyspnoea during illness						
more annoying than normal	0.85	0.37	1.4(1.0–1.8)	0.76	0.37	1.2
very annoying	0.35	0.91	4.0(2.0–8.2)	0.31	0.92	3.7
Chest pain during illness						
medial only	0.20	0.67	0.6(0.3–1.4)	0.24	0.67	0.8
strong, medial only	0.10	0.92	1.2(0.3–4.8)	0.03	0.91	0.4
lateral	0.40	0.79	1.9(1.0–3.6)	0.31	0.79	1.5
strong lateral	0.25	0.95	4.8(2.0–11.4)	0.17	0.95	3.2
Fever, day of consultation reported by patient as measured or assumed	0.65	0.51	1.3(0.9–2.0)	0.59	0.52	1.2
combined with duration of illness exceeding 6 days	0.40	0.86	2.8(1.5–5.4)	0.21	0.85	1.4*
Chills during illness	0.80	0.67	1.9(1.2–3.1)	0.61	0.68	1.9

* The perceived LR is below the 95% confidence limits of the LR for radiographic pneumonia.

chi-square values (12, 13), with minus sign if beta was negative.

SAS software was used in all the statistical analyses.

RESULTS

Of 626 patients who were asked to participate, 581 entered the study, 339 women (mean age 32.5 years, range 18–78) and 242 men (mean age 31.8 years, range 18–76). Mean age and male/female ratio of the entire material and in relevant subgroups are listed in Table I. A reluctance to bloodsampling was the reason most frequently stated by the 45 patients who refused. Mean duration of illness at entry to the study was nine days. 85 participants had previously consulted a doctor for the present illness, and antibiotics had been prescribed for 43 of them. Chest examination was carried out in 402 patients. The frequency of chest examination according to reason for consultation is shown in Table II.

The chest films of 51 patients were selected for a final judgement by the radiology panel. Radiographic pneumonia was diagnosed in 21 patients: 12 were among the 79 whose chest films were ordered by the doctor, eight among the 102 who were referred to x-ray examination because of pathological blood tests, and one was radiographed at the Chest Clinic, a few days after entry to the study. The illness of this patient, clinically diagnosed as bronchitis, had become worse after the first consultation, both clinically and biochemically, and in the further analysis he has not been classified among the pneumonias. No pneumonias were diagnosed in the 25% random sample (seven of the 97 who were randomized refused). We have made the assumption in the analysis that there was no radiographic pneumonia among the 401 patients, who were randomized.

Two of the patients with radiographic pneumonia were later diagnosed as having lung cancer. They were classified as pneumonia in the analysis. Accordingly, the group referred to as having radio-

Table IV. *Diagnostic values of symptoms, not regarded as typical of pneumonia, for pneumonia in 402 patients with respiratory infection in general practice, using radiographic pneumonia (n = 20) as reference standard, and corresponding diagnostic values perceived by the doctors, using the doctors' clinical diagnosis of pneumonia (n = 29) as reference standard. LR = likelihood ratio, CL = 95% confidence limits.*

Not typical symptoms	Diagnostic values for radiographic pneumonia			Perceived diagnostic values		
	Sensitivity	Specificity	LR (CL)	Sensitivity	Specificity	LR
Sweating and clamminess	0.80	0.16	0.9 (0.8–1.2)	0.76	0.15	0.9
Fatigue	1.00	0.11	1.1 (1.0–1.3)	0.93	0.10	1.0
Headache	0.75	0.23	1.0 (0.8–1.3)	0.76	0.23	1.0
Myalgia/arthralgia	0.55	0.45	1.0 (0.7–1.5)	0.64	0.45	1.2
Coryza	0.65	0.18	0.8 (0.6–1.1)	0.76	0.18	0.9
Sore throat	0.45	0.25	0.6 (0.4–1.0)	0.50	0.25	0.7
Earache	0.15	0.61	0.4 (0.1–1.1)	0.32	0.62	0.8
Fascial pain	0.37	0.65	1.0 (0.6–1.9)	0.32	0.64	0.9

graphic pneumonia consisted of 20 patients, nine men and 11 women. Physical chest examination had been carried out in all. The mean age was 38 years (range 18–71), and mean duration of illness at entry was 10 days (range 2–30). None had been treated with an antibiotic in advance. The reason for the consultation was influenza in three, sinusitis in one, bronchitis in five, pneumonia in three, cough in six, fatigue in one, and dyspnoea in one.

The doctors diagnosed pneumonia clinically in 29 patients, referred to as the perceived pneumonias. The diagnosis was confirmed radiographically in seven of these.

Univariate analysis

The LR of the typical symptoms for radiographic pneumonia increased with increasing degree of discomfort (Table III). This was most evident for dyspnoea and lateral chest pain, reaching LRs of 4.0 and 4.8, respectively. Dry cough was a more specific

Table V. *Diagnostic value of abnormal chest findings for pneumonia in 402 patients with respiratory infection in general practice, using radiographic pneumonia (n = 20) as reference standard, and corresponding diagnostic values perceived by the doctors, using the doctors' clinical diagnosis of pneumonia (n = 29) as reference standard. LR = likelihood ratio, CL = 95% confidence limits.*

Abnormal chest findings	Diagnostic values for radiographic pneumonia			Perceived diagnostic values		
	Sensitivity	Specificity	LR (CL)	Sensitivity	Specificity	LR
Auscultation (n = 402)						
Wheezes, no crackles	0.15	0.85	1.0 (0.3–2.8)	0.03	0.84	0.2*
Wheezes and crackles	0.15	0.97	3.3 (1.3–8.7)	0.28	0.98	12.9**
Crackles no wheezes	0.20	0.94	4.4 (1.4–13.6)	0.52	0.97	16.1**
Crackles with or without wheezes	0.35	0.91	3.7 (1.8–7.6)	0.79	0.95	14.8**
Pleural rubs	0.10	0.98	6.4 (1.6–25.3)	0.17	0.99	21.4
Decreased breath sounds	0.15	0.95	3.2 (1.0–10.0)	0.41	0.98	17.1**
Percussion (n = 211, 14 "true" pneumonias)						
Dullness to percussion	0.14	0.96	4.0 (1.0–16.7)	0.36	1.00#	72.0**
"Pneumonic" chest findings (crackles, pleural rubs diminished breath sounds or dullness to percussion)	0.40	0.88	3.3 (1.8–5.9)	0.86	0.92	10.7**

* The perceived LR is below the 95% confidence limits of the LR for radiographic pneumonia.
** The perceived LR is above the 95% confidence limits of the LR for radiographic pneumonia.
\# When calculating the LR, the specificity is corrected to 0.995.

Table VI. *Weight of clinical variables as predictors of radiographic and perceived pneumonia analysed by logistic regression, in 402 patients with respiratory infection.*

Symptom or sign	Actual weight	Perceived weight
Fever combined with duration of illness of one week or more	+4.7*	−3.1
Coryza	−4.5*	+0.8
Sore throat	−2.1	−4.1*
Dyspnoea, very annoying	+5.0*	+3.2
Chest pain, strong, lateral	+8.2**	+0.9
Crackles	+0.9	+32.0***

* $p < 0.05$, ** $p < 0.005$, *** $p < 0.0001$.

cue than coloured sputum for radiographic pneumonia, and it had a higher LR. This difference was not perceived by the doctors. The LR of fever at the time of consultation, as reported by the patient, combined with a duration of illness exceeding six days, was significantly higher than perceived by the doctors.

Among the symptoms not regarded as typical of pneumonia, no statistically significant association with pneumonia was found, neither when dichotomized as present/not present, as shown in Table IV, nor as much discomfort/not much discomfort (data not shown).

The most sensitive chest finding, crackles, had an LR of 3.7 (Table V). The LR ascribed to crackles by the doctors, 14.8, was far above the 95% confidence limits of this value, (1.8–7.6). The perceived LRs of dullness to percussion and pleural rubs were also much higher than the corresponding LRs for radiographic pneumonia.

Logistic regression

The following independent variables were entered in the two models: age, sex, patient report of fever combined with a duration of illness of one week or more, sweating/clamminess, sore throat, coryza, earache, cough, dyspnoea, lateral chest pain, crackles, diminished breath sounds, and dullness to percussion. The variables significantly associated with either radiographic or perceived pneumonia are presented in Table VI. Strong lateral chest pain and very annoying dyspnoea got the highest weights for radiographic pneumonia, but they were both insignificant independent predictors of perceived pneumonia. Crackles got a high weight for perceived pneumonia, while the corresponding weight against radiographic pneumonia was insignificant.

DISCUSSION

Grading of the typical symptoms enabled us to demonstrate their importance in the diagnosis of pneumonia. When the symptoms were dichotomized as present/not present, the diagnostic usefulness was far less, in accordance with previous studies (2, 3). A considerable discrepancy between actual and perceived diagnostic values of crackles and other chest signs was strongly confirmed (5), particularly by logistic regression. In contrast to the study by Diehr et al, the presence of myalgia did not achieve significant diagnostic value (1), while absence of coryza was confirmed as important by logistic regression.

The credibility of the results depends on the validity of the reference standard. A density on an acute-phase radiograph is generally accepted as a diagnostic criterion of pneumonia in hospital practice and medical literature (14, 15), but it is not a perfect gold standard. The consistency of different radiologists' interpretation of the same chest radiographs is far from perfect (16, 17). This was also demonstrated when the interpretations by our radiological panel were compared with the reports of the acute-phase radiographs by the Department of Radiology (7). Since the panel based their judgement on both acute-phase and follow-up radiographs, the bias from this inconsistency, as well as the risk of overdiagnosis, was probably minimized. We know that early pneumonic changes may lack a radiographic counterpart (15, 18). The possibility of misclassifying a true pneumonia as non-pneumonia was also somewhat increased by the assumption that there was no pneumonia in the patients who were randomized for radiography. However, any patient with pneumonia not radiographed at entry would be likely to attend the chest clinic and undergo radiography a few days later. Accordingly, bias due to the randomization for radiography probably had little impact on the results.

Interobserver variation in the recording of abnormal chest findings is a well-known source of bias (19, 20). However, the average diagnostic usefulness of findings in medical practice may be demonstrated in studies like ours, with a large number of doctors, all willing to participate.

In our study the sensitivity of crackles for radiographic pneumonia was higher than found by

Diehr et al. (1), 0.35 and 0.19, respectively. Few cases of pneumonia in both studies may partly explain this difference, but a more valid reference standard in our study, being based on both acute-phase and follow-up radiographs, may also have contributed. A higher sensitivity of crackles, exceeding 0.50, has been found in hospital-based studies (4, 6, 21), and this may be explained in two ways. Pneumonia patients with crackles may on average be more seriously ill than those without, and thus be admitted more frequently. The lower sensitivity of crackles found in atypical pneumonia as opposed to pneumococcal pneumonia (6, 22) lends support to this mechanism. A second explanation, supported by our study, implies that the diagnosis of pneumonia may frequently be missed when crackles are not heard, decreasing the probability of admission. A more thorough auscultation in hospitalized patients supposed to have pneumonia probably also contributes to the difference in sensitivity.

As regards generalization from this study, we will make some reservations. At the Emergency Clinic in Tromsø, young and otherwise healthy adults are overrepresented. Patients with heart insufficiency, chronic obstructive pulmonary disease or known asthma were accordingly less frequent in this study than expected in an ordinary general practice population. This selection bias has probably tended to increase the specificity of crackles and other abnormal chest findings (2). We found, however, about the same specificity of crackles as Diehr et al. (1).

The pneumonias were all minor or moderate and all cases were managed outside hospital. If the study had also covered house calls, more severe pneumonias would probably have occurred. The lack of severe pneumonias may explain why our study did not confirm the high diagnostic value of a duration of illness shorter than 24 hours, found in a previous study from Tromsø (2). None of our pneumonia patients had such a short duration of illness.

Elderly patients were sparsely represented. Cough and probably also chest pain are less frequently present in pneumonias of geriatric patients, and history-taking is more often troubled by mental confusion (21).

Conclusion

The typical symptoms, dyspnoea, chest pain, and fever are of considerable value in the diagnosis of pneumonia in young and middle-aged adults with respiratory tract infection in primary care, and normal chest findings should not overrule a typical history. More attention must be paid by general practitioners to the typical symptoms, if their performance in diagnosing pneumonia is to be improved.

ACKNOWLEDGEMENT

We wish to thank the Norwegian Research Council for Science and the Humanities, of which Hasse Melbye was a research fellow. We also thank the Norwegian Heart and Lung Association for financial support.

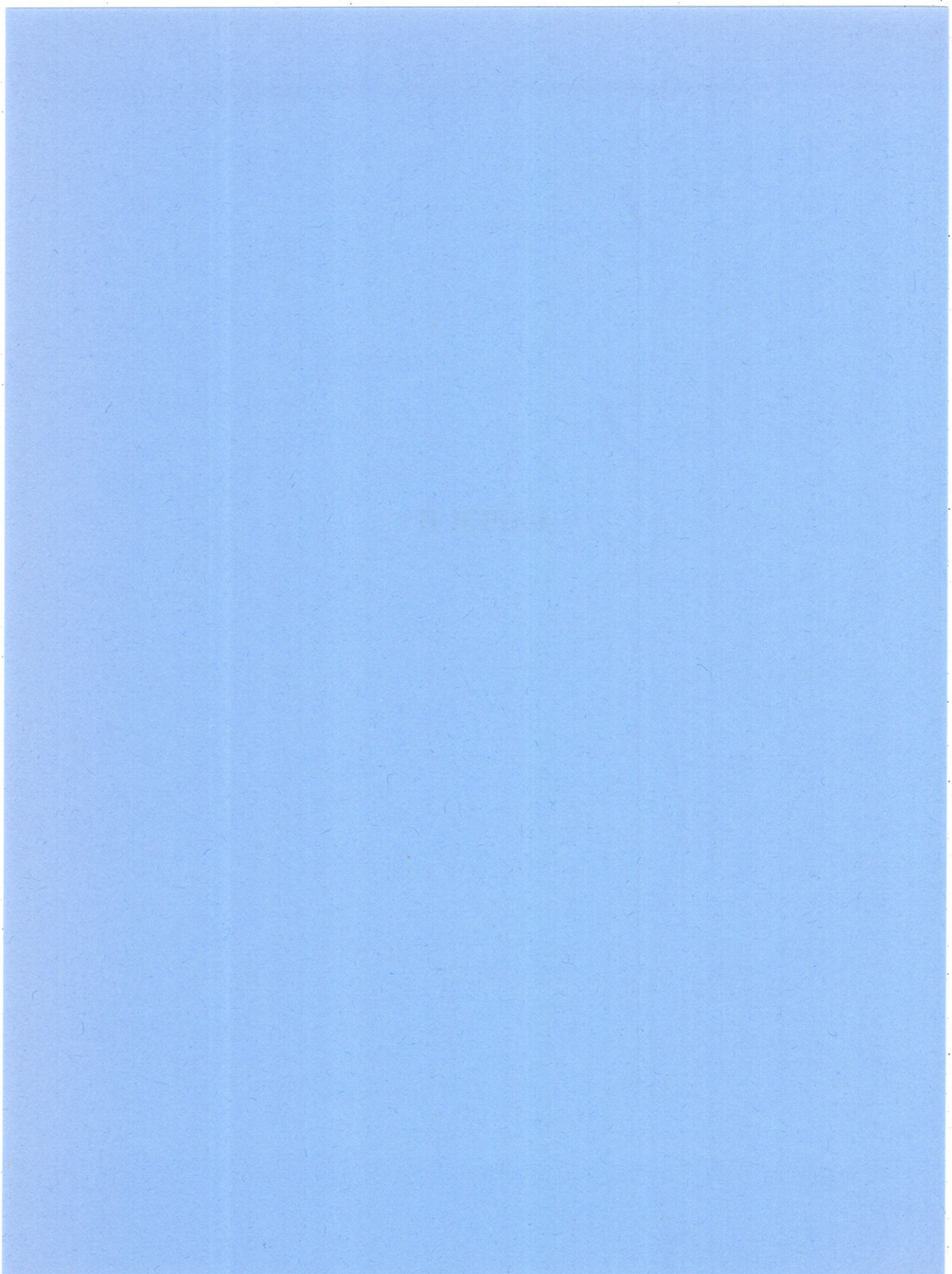
REFERENCES

1. Diehr P, Wood RW, Bushyhead J, Krueger L, Wolcott B, Tompkins RK. Prediction of pneumonia in outpatients with acute cough: a statistical approach. J Chronic Dis 1984; 37: 215–25.
2. Melbye H, Straume B, Aasebø U, Brox J. The diagnosis of adult pneumonia in general practice. Scand J Prim Health Care 1988; 6: 111–7.
3. Heckerling PS. The need for chest roentgenograms in adults with acute respiratory illness. Arch Intern Med 1986; 146: 1321–4.
4. Osmer JC, Cole BK. The stethoscope and roentgenogram in acute pneumonia. South Med J 1966; 59: 75–7.
5. Bushyhead JB, Christensen-Szalanski JJJ. Feedback and the illusion of validity in a medical clinic. Med Decis Making 1981; 1: 115–23.
6. Lehtomaki K. Clinical diagnosis of pneumococcal, adenoviral, mycoplasmal and mixed pneumonias in young men. Eur Respir J 1988; 1: 324–9.
7. Melbye H, Dale K. Interobserver variability in the radiographic diagnosis of adult outpatient pneumonia. Acta Radiol 1992; 33: 79–81.
8. Radack KL, Rouan G, Hedges J. The likelihood ratio. Arch Pathol Lab Med 1986; 110: 689–93.
9. Morris JA, Gardner MJ. Calculating confidence intervals for relative risks, odds ratios, and standardised ratios and rates. In: Gardner MJ, Altman DG, eds. Statistics with confidence: Confidence intervals and statistical guide-lines. London, England: British Medical Association; 1989: 50–63.
10. Sacket DL, Haynes RB, Tugwell P. Clinical epidemiology. A basic science for clinical medicine. Boston: Little, Brown and Co. 1985: 71.
11. Wigton RS. Use of linear models to analyze physicians' decisions. Med Decis Making 1988; 8: 241–52.
12. Centor RM, Witherspoon, Dalton HP, Brody CE, Link K. The diagnosis of strep throat in adults in the emergency room. Med Decis Making 1981; 1: 239–46.
13. Hlatky MA, Pryor DB, Harrell FE jr, Califf RM, Mark DB, Rosati RA. Factors affecting the sensitivity and specificity of the exercise electrocardiogram: A multivariable analysis. Am J Med 1984; 77: 64–71.
14. Goodman LR, Goren RA, Teplick SK. The radiographic evaluation of pulmonary infection. Med Clin North Am 1980; 64: 553–74.

15. Conte P, Heitzman ER, Markarian B. Viral pneumonia. Roentgen pathological correlations. Radiology 1970; 95: 267–72.
16. Stein MT. Delayed roentgenographic signs associated with acute pneumonia in children. J Fam Pract 1981; 12: 639–44.
17. Herman PG, Gerson DE, Hessel SJ, et al. Disagreements in chest roentgen interpretation. Chest 1975; 68: 278–82.
18. Stickler GB, Hoffman AD, Taylor WF. Problems in the clinical and roentgenographic diagnosis of pneumonia in young children. Clin Pediatr 1984; 23: 398–9.
19. Smylie HC, Blendis LM, Armitage P. Observer disagreement in physical signs of the respiratory system. Lancet 1965; ii: 412–3.
20. Begg CB. Biases in the assessment of diagnostic tests. Statistics in medicine 1987; 6: 411–23.
21. Marrie TJ, Durant H, Kwan C. Nursing home-acquired pneumonia. A case-control study. J Am Geriatr Soc 1986; 34: 697–702.
22. Atmar RL, Greenberg SB. Pneumonia caused by Mycoplasma pneumoniae and the TWAR agent. Semin Respir Infect 1989; 4: 19–31.

Received October 1991
Accepted February 1992

PAPER II



Scand J Prim Health Care 1992; 10: 234–240

Laboratory Tests for Pneumonia in General Practice: The Diagnostic Values Depend on the Duration of Illness

HASSE MELBYE[1], BJØRN STRAUME[1] and JAN BROX[2]

[1]Institute of Community Medicine, [2]Department of Clinical Chemistry, Hospital of Hammerfest, University of Tromsø, 9000 Tromsø, Norway

Melbye H, Straume B, Brox J. Laboratory tests for pneumonia in general practice. The diagnostic values depend on the duration of illness. Scand J Prim Health Care 1992; 10: 234–40.

The usefulness in the diagnosis of pneumonia of temperature and the laboratory tests: erythrocyte sedimentation rate (ESR), leucocyte count, and C-reactive protein (CRP) was evaluated against a radiographic reference standard in 402 adult patients with respiratory tract infection in general practice. Radiographic pneumonia was diagnosed in 20 patients. CRP and ESR were the most useful tests. CRP > 50 mg/l had lower sensitivity and likelihood ratio (LR), 0.50 and 4.8, respectively, compared with previous studies of selected patient populations. Among patients whose duration of illness exceeded six days the corresponding LR was 11.3, due to a higher specificity in this subgroup of patients. ESR and oral temperature were also more useful in this subgroup than in patients with a shorter duration of illness. A highly significant diagnostic contribution of adding ESR and CRP to history and physical examination, particularly when the illness had lasted one week or more, was demonstrated by logistic regression.

Key words: pneumonia, diagnosis, temperature, ESR, leucocyte count, C-reactive protein.

Hasse Melbye, MD, Institute of Community Medicine, University of Tromsø, Breivika, 9000 Tromsø, Norway.

Differentiating pneumonias from other respiratory tract infections, on the basis of history and physical examination alone, is a difficult task, as demonstrated by several studies (1–5). The erythrocyte sedimentation rate (ESR), white blood cell count (WBC), and C-reactive protein analysis (CRP), which are general indicators of infectious disease, are of value in this differentiation (2, 6–8). Most pneumonias in adults are of bacterial origin (9), tending to cause a greater rise in WBC, ESR, and especially CRP level than occurs in pneumonias caused by mycoplasmal or viral agents (10, 11).

Temperature, WBC count, and CRP rise quickly in serious bacterial infections, often reaching a peak in one or two days, returning to normal within a few days when adequate treatment is given (12). ESR rises more slowly, and may remain raised for two or three weeks, despite a favourable clinical course (13). The diagnostic usefulness of the CRP-test was promisingly high in previous studies (2, 7, 8). However, those studies were either hospital-based, or based on patient populations with a high probability of pneumonia. In the present evaluation of blood tests and body temperature, the study population comprised unselected adults with respiratory tract infection in general practice. Apart from determining test usefulness in a primary care setting, we also wanted to study the impact of the duration of illness on the diagnostic properties.

Taking the diagnostic values of symptoms and signs into account, as evaluated in the same population of patients (5), we also wanted to assess the usefulness of adding the laboratory tests to history and physical examination.

MATERIAL AND METHODS

Patients

The investigation took place at the Municipal Emergency Clinic in Tromsø, between 17 October 1988

and 31 May 1989. Consecutive patients aged 18 years or more, presenting with symptoms suggestive of a respiratory or throat infection were asked to enter the study. Patients with dyspnoea, severe enough to need urgent treatment, and pregnant women were excluded. 40 doctors participated in the examination of the patients.

The doctors were told to examine and treat the patients as usual. Physical chest examination was carried out in 402 of the 581 patients enrolled, and our analyses concern this subgroup of patients. The mean age of 33.2 years, male/female ratio of 0.7, and mean duration of illness of 10.2 days did not differ significantly from the total material (5).

The study was approved by the Regional Committee of Medical Research Ethics.

Temperature measurement and blood tests

Before consulting the doctor the patients were examined by a specially trained nurse. Blood samples were taken, and the patients completed a questionnaire concerning symptoms and duration of illness. Oral temperature was measured by a digital thermometer (Citizen Watch Co, China). ESR was examined using closed vacuum tubes (Seditainer, Becton Dickinson Co, France). An automatic cell counter, Linson CX 320 (Sweden) was used in WBC-counting. CRP was analysed by an immunoassay method in RA1000 autoanalyser with reagents from Orion (Finland).

The reference standard

A radiology panel diagnosed pneumonia in 20 patients, based on the acute-phase and follow-up chest films. The diagnostic procedures, described in detail elsewhere (5, 14), may be summarized as follows:

The doctors at the Emergency Clinic, who were not informed about the laboratory results until after the consultation, reported on a form whether the patient had upper or lower respiratory tract infection (LRTI), or both. X-ray examination was to be ordered when pneumonia was considered a diagnostic possibility. Not to overlook pneumonias, a radiograph was also ordered by the nurse when a patient had an ESR of 50 mm/h or more, or CRP 60 mg/l or more, judged by a semiquantitative test (Nycocard CRP, Nycomed, Norway). When the doctor reported LRTI, the thresholds for ordering were 20 mm/h and 20 mg/l, respectively. X-ray examination was performed in a 25% random sample of the rest of the patients, who were anticipated to have a low probability of pneumonia. The radiographs were taken the same evening, or the following day (three cases). Patients with persistent cough or dyspnoea after 10 days of illness were invited to attend the Chest Clinic at the University Hospital of Tromsø for further examinations, and a chest radiograph was taken if not obtained at entry. A follow up chest film after 4–5 weeks was obtained in most of the patients except those radiographed after randomization.

The 20 radiographic pneumonias were all diagnosed among the 402 patients who underwent physical chest examination. Twelve were based on the 79 radiographs ordered by a doctor and 8 on the 102 radiographs ordered because of raised ESR and CRP values. No radiographic pneumonias were found among the 97 patients randomly selected for radiography, and in the analysis we made the assumption that there were no pneumonias among the 402 patients who were randomized.

Statistical analysis

Univariate analysis

Mean temperature and blood test values were calculated according to duration of illness in patients with and without pneumonia. Mean values when the duration was more or less than a week were compared, and differences were statistically assessed by Student's t-test and the Wilcoxon rank sum test. For the presented differences the same p-values were obtained by both tests.

Sensitivity, specificity, and likelihood ratio (LR) (15) were calculated for various thresholds of the tests, as well as 95% confidence intervals for the LRs (16). LR is the frequency of a finding in patients with the disease (sensitivity) divided by the frequency of the finding in patients without the diseases (1-specificity). Receiver Operating Characteristic (ROC) curves (17) were used in the presentation of the results. In order to obtain a clear picture of the LR from the figures, we have plotted the function: sensitivity = LR × (1−specificity), as straight dashed lines, radiating from the lower left corner (Fig. 2), for integer values of LR from 1 to 5.

Logistic regression

In order to evaluate the significance of applying the tests as part of a full clinical evaluation, the following six clinical variables, found to be most strongly associated with pneumonia in our previous study (5), were entered as independent variables in a model with radiographic diagnosis as dependent variable:

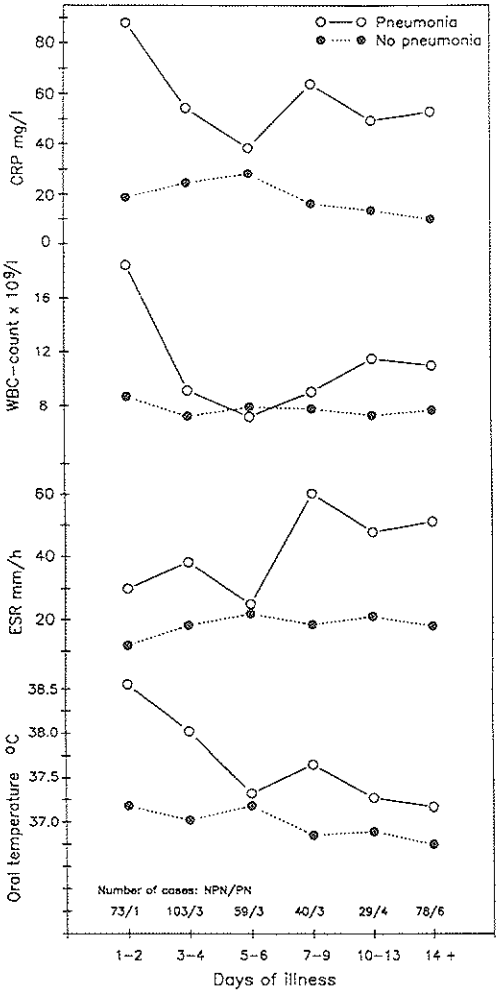


Fig. 1. Oral temperature, erythrocyte sedimentation rate (ESR), white blood cell count (WBC), and C-reactive protein (CRP) according to duration of illness in 402 patients with respiratory tract infection. 20 with radiographic pneumonia (PN) and 382 without (NPN).

strong lateral chest pain, very annoying dyspnoea, patient report of fever combined with a duration of illness of 7 days or more, coryza, sore throat, and crackles (rales). The significance was assessed of each of the laboratory tests added one by one as well as in combinations by a stepwise procedure.

The analyses were carried out in all 402 patients and in the two complementary subgroups with duration of illness either more or less than a week. The chi-square values achieved by the laboratory tests are presented.

SAS software was used in all the statistical analyses.

RESULTS

Among the 402 patients included in the analyses, valid measurements of temperature were obtained in 399, WBC count in 400, ESR in 401, and CRP in all. These differing numbers of observations are not specified in the tables and figures.

Test results according to duration of illness

For all the tests, higher mean values were found in the pneumonia patients than in those without radiographic pneumonia, irrespective of the duration of illness, with one exception (Fig. 1).

In patients without radiographic pneumonia, there were significantly higher temperature and CRP-values (Fig. 1) when the illness had lasted less than seven days, p-values < 0.0001. Due to the low number of patients with pneumonia, the impact of duration of illness on the test results was not statistically assessed in this group of patients. There was a tendency for the temperature and WBC-count to decrease as the duration of illness increased, while

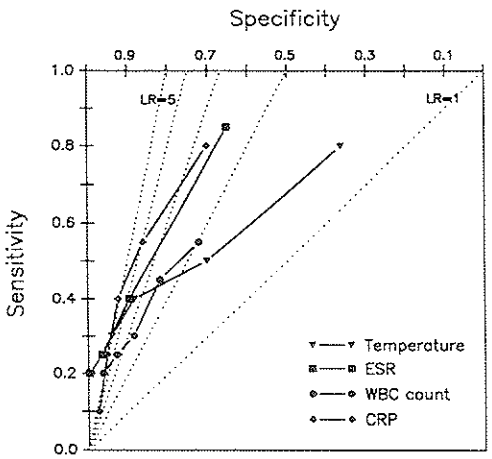


Fig. 2. ROC curves showing the diagnostic properties of oral temperature, erythrocyte sedimentation rate (ESR), white blood cell count (WBC), and C-reactive protein (CRP) for radiographic pneumonia in 402 adult patients with respiratory tract infection in general practice.
Footnote: The following thresholds are used:
Oral temperature: 37.0, 37.5, 38.0 and 38.5°C, ESR: 20, 40, 60 and 80 mm/h, WBC-count: 9, 10, 11, 12 and 14×10^9/l, and CRP: 20, 40, 60, 80 and 100 mg/l.

Table I. *Sensitivity, specificity, and likelihood ratio (LR) of temperature and blood tests for radiographic pneumonia in 402 adult patients with respiratory infection, 20 with radiographic pneumonia.*

	Sensitivity	Specificity	LR (95% confidence interval)
Temperature ≥ 37.5°C	0.50	0.70	1.7 (1.0–2.9)
ESR ≥ 35 mm/h	0.50	0.89	4.3 (2.4–7.8)
WBC count ≥ 10.4	0.53	0.85	3.1 (1.7–5.7)
CRP ≥ 50 mg/l	0.50	0.90	4.8 (2.7–8.6)

Thresholds were chosen that corresponded to a sensitivity of about 0.50.

the opposite tendency was found for ESR (Fig. 1). No impact of duration on the CRP values could be inferred in the pneumonia group.

Diagnostic value of the tests

CRP and ESR were the most useful tests, shown by the fact that their ROC-curves are positioned over and to the left of the ROC-curves of the other two tests (Fig. 2). At thresholds with a sensitivity of 0.50, the LR of CRP and ESR was between 4 and 5 (Table I). When higher thresholds of the tests were evaluated, with sensitivities between 0.20 and 0.30, ESR had the best LR. ESR above 80 mm/h had a sensitivity of 0.20 and an LR of 77. All patients with radiographic pneumonia had either CRP > 20 mg/l or ESR > 20 mm/h.

The diagnostic usefulness of ESR and CRP improved when the duration of illness exceeded six days (Table II). A shift to the left of the ROC-curves of these tests is shown in Fig. 3. The diagnostic value of an oral temperature > 38.0°C also improved after one week's illness, and a temperature above 38.5°C had an LR of 3.3 at a duration of less than one week and 22.1 when the duration was more than one week.

Logistic regression

Each of the four tests contributed significantly in the discrimination of patients with and without pneumonia (Table III). When the patients had been ill for less than one week, the weights obtained by the tests hardly achieved significant values, but with a longer duration of illness ESR and CRP in particular had high weights. In a stepwise analysis, combinations of tests in all the patients were modelled with the same independent clinical variables. WBC count and temperature did not reach significance when added to CRP or ESR. CRP contributed significantly only when added to WBC count and temperature, while ESR did so when added to any of the three other tests.

DISCUSSION

ESR and CRP contributed with high significance in the diagnosis of pneumonia only when the patients had been ill for one week or more. Although the high sensitivity of the CRP-test was confirmed in the early phase of illness, a substantial increase in specificity after one week was the reason why the LR of

Table II. *Sensitivity and likelihood ratio (LR) of temperature and blood tests for radiographic pneumonia according to duration of illness. CI = 95% confidence internal.*

	Days of illness: < 7				Days of illness: 7 or more			
	n = 242*				n = 160**			
	Sensitivity	Specificity	LR	(CI)	Sensitivity	Specificity	LR	(CI)
Temperature ≥ 37.5°C	0.71	0.63	1.9	(0.9–3.8)	0.38	0.83	2.2	(1.0– 5.2)
ESR ≥ 35 mm/h	0.29	0.89	2.6	(0.7–9.6)	0.69	0.85	4.6	(2.4– 8.7)
WBC count ≥ 10.4 × 10⁹/l	0.57	0.83	3.3	(1.4–7.9)	0.42	0.88	3.6	(1.5– 8.5)
CRP ≥ 50 mg/l	0.43	0.86	3.1	(1.1–8.6)	0.54	0.95	11.3	(5.1–25.0)

Thresholds were chosen that corresponded to a sensitivity of about 0.50 in the total material.
* 7 with radiographic pneumonia.
** 13 with radiographic pneumonia.

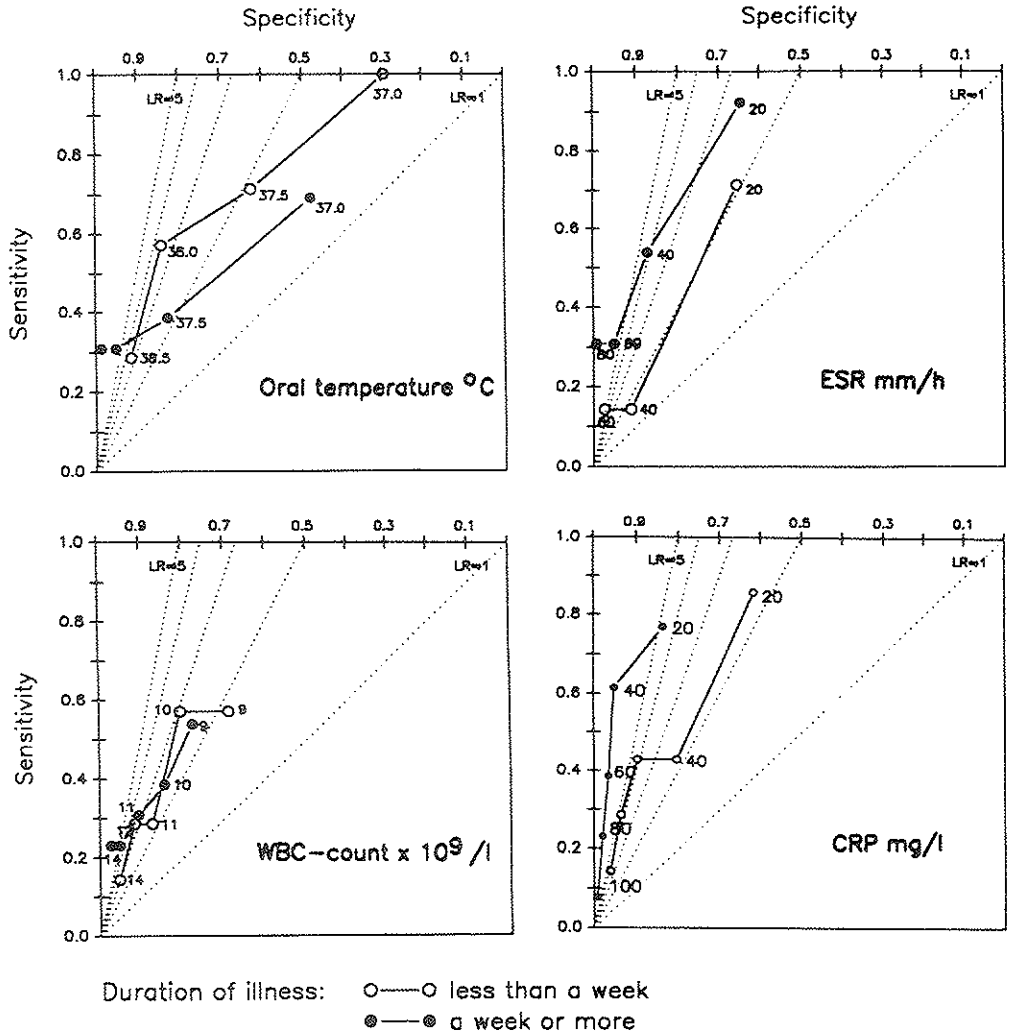


Fig. 3. ROC curves showing the diagnostic properties of oral temperature, erythrocyte sedimentation rate (ESR), white blood cell count (WBC), and C-reactive protein (CRP) for radiographic pneumonia in 402 adult patients with respiratory infection. The results in patients with a duration of illness less than seven days (n = 242), and one week or more (n = 160), are compared.

CRP improved. Moderate elevation of CRP in uncomplicated viral respiratory infection has previously been demonstrated (18), diseases usually subsiding within one week, and peak values of CRP have been found after three days of illness in experimentally induced influenza (19). The improvement in the diagnostic usefulness of the ESR was due to higher sensitivity of high ESR values after one week.

The sensitivity of CRP > 50 mg/l of only 0.50 was low, compared with previous reports (2, 7, 8, 10). Home visits were not included in the present study, and none of the patients with pneumonia was so ill that hospital admission was necessary. There was obviously a selection bias towards mild and moderate pneumonias, while severe pneumonias have probably been overrepresented in other studies (8, 11). The low sensitivity of WBC counts above 10×10^9 may have been caused by a relatively high

Table III. *The significance by logistic regression of adding a laboratory test to clinical information obtained by history and physical examination in predicting radiographic pneumonia. Chi-square values are presented.*

Laboratory test	Duration of illness		
	Ill < 7 days n = 242	Ill 7 days or more n = 154	All n = 402
Oral temperature	6.0 *	4.5 *	5.1 *
ESR	4.4 *	22.1 ***	29.0 ***
WBC count	1.2 (NS)	5.8 *	3.2 (NS)
CRP	7.4 **	21.0 ***	21.4 ***

NS: Not statistically significant at 0.05 level
* $p < 0.05$
** $p < 0.01$
*** $p < 0.0001$

frequency of viral, mycoplasmal, and chlamydial aetiology (10, 20).

Our radiographic reference standard is not perfect (5, 14), and misclassification of patients into the pneumonia and non-pneumonia groups may have influenced the results. Because the radiographic diagnosis was based on both acute-phase and follow-up radiographs, the risk of overdiagnosis was probably minimized. Early pneumonias may be invisible (21), and the risk of misclassifying a true pneumonia as non-pneumonia was in addition somewhat increased by the assumption that there was no pneumonia among the patients who were randomized. However, if only few patients were misclassified into the non-pneumonia group, the specificities computed from 382 patients would only be slightly influenced.

It may be argued that the use of ESR and CRP in the selection for chest radiography leads to circular argumentation. The random sample was intended to compensate for this, but if there was indeed a pneumonia case among the patients not radiographed, a selection bias in favour of increased value of these two tests, by raising their sensitivity, would be brought about.

Clinical implications

ESR and the CRP-test are valuable supplementary tools in the diagnosis of pneumonia in general practice. Our study indicates that pneumonia may be ruled out if both CRP and ESR show normal values, a message supported by previous studies (6–8). The study also confirmed that a value of CRP > 50 mg/l strongly supports a clinical diagnosis of pneumonia (2, 6–8). The comparable predictive value of ESR > 35 mm in our study was probably dependent on the otherwise good health of the population consulting the Emergency Clinic, securing a high specificity. Our study shows that moderately raised CRP-values should be interpreted in the light of illness duration. CRP-values between 20 and 50 mg/l in the first week of illness may frequently be found in respiratory infections without pneumonia, as has also previously been demonstrated in uncomplicated viral infections (18, 19). With a duration of illness exceeding one week, however, such CRP values may support a diagnosis of pneumonia.

Temperature measurement is still indicated, at least when the laboratory tests are not practicable. Significant weight was obtained from oral temperature in the logistic regression, even when added to a report of fever by the patient. Even better diagnostic value might probably be achieved if rectal temperature had been measured, due to a higher reliability (21).

ACKNOWLEDGEMENTS

We wish to thank the Norwegian Research Council for Science and the Humanities, of which Hasse Melbye was a research fellow, for financial support.

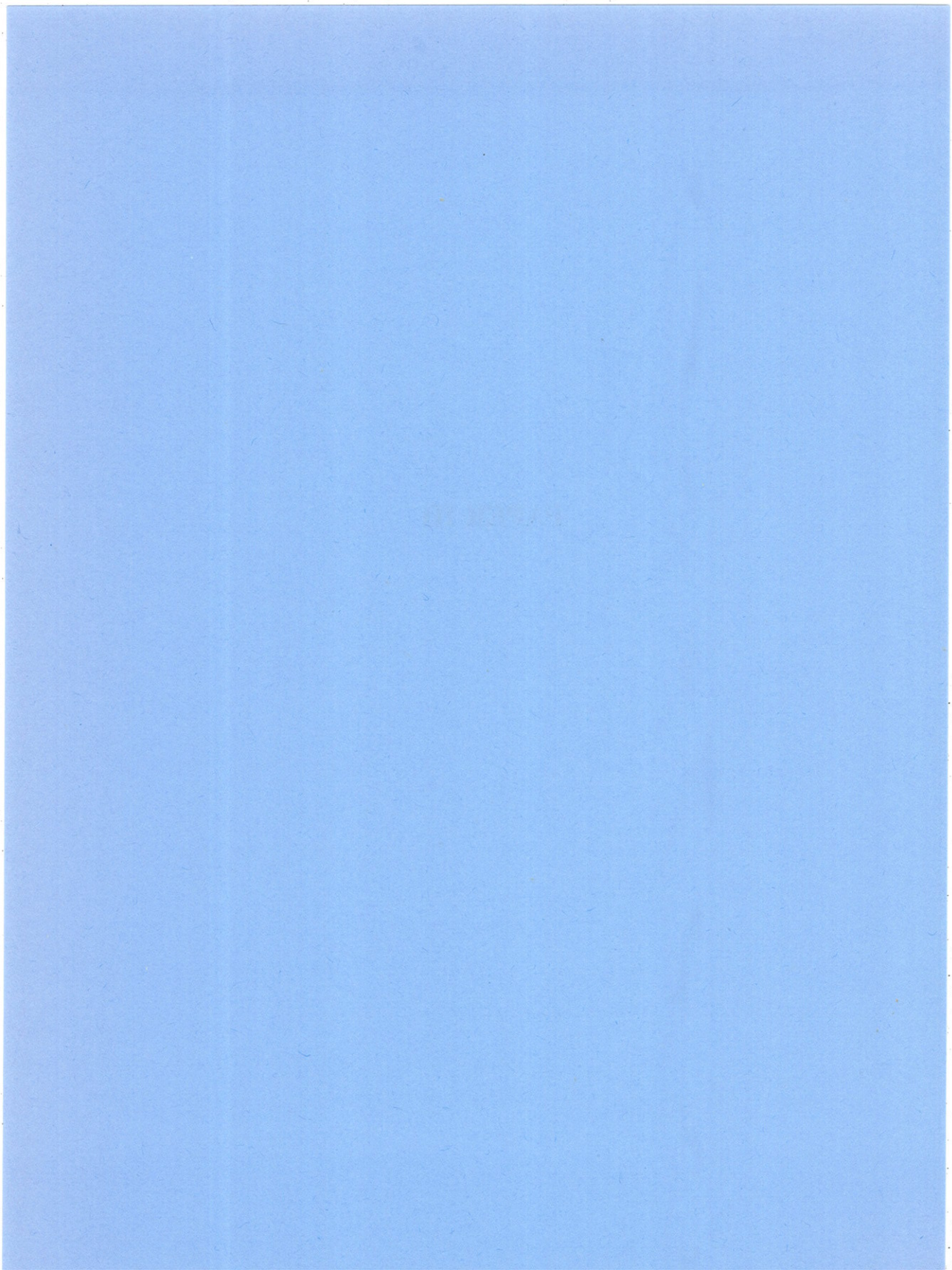
REFERENCES

1. Diehr P, Wood RW, Bushyhead J, Krueger L, Wolcott B, Tompkins RK. Prediction of pneumonia in outpatients with acute cough: A statistical approach. J Chronic Dis 1984; 37: 215–25.
2. Melbye H, Straume B, Aasebø U, Brox J. The diagnosis of adult pneumonia in general practice. Scand J Prim Health Care 1988; 6: 111–7.
3. Leventhal JM. Clinical predictors of pneumonia as a guide to ordering chest roentgenograms. Clin Pediatr 1982; 21: 730–4.

4. Heckerling PS. The need for chest roentgenograms in adults with acute respiratory illness. Arch Intern Med 1986; 146: 1321–4.
5. Melbye H, Straume B, Aasebø U, Dale K. Diagnosis of pneumonia in adults in general practice. The relative importance of typical symptoms and abnormal chest signs evaluated against a radiographic reference standard. Scand J Prim Health Care 1992; 10: 226–33.
6. Morley JJ, Kushner I. Serum C-reactive protein levels in disease. Ann N Y Acad Sci 1982; 389: 406–17.
7. Babu G, Ganguly NK, Singhi S, Walia BNS. Value of C-reactive protein concentration in diagnosis and management of acute lower respiratory infections. Trop Geogr Med 1989; 41: 309–15.
8. Ritland N, Melbye H. C-reaktivt protein, SR og hvite blodlegemer ved akutte nedre luftveislidelser. Nytten av blodprøver i diagnostisering av pneumoni [The usefulness of blood tests in distinguishing pneumonia from asthma and bronchitis. "Summary in English"]. Tidsskr Nor Laegeforen 1991; 111: 2249–52.
9. McFarlane JT. Treatment of lower respiratory infections. Lancet 1987; ii: 1446–9.
10. McCarthy PL, Frank AL, Ablow RC, Masters SJ, Dolan TF. Value of the C-reactive protein test in the differentiation of bacterial and viral pneumonia. J Pediatr 1978; 92: 454–6.
11. Lehtomaki K. Clinical diagnosis of pneumococcal, adenoviral, mycoplasmal and mixed pneumonias in young men. Eur Respir J 1988; 1: 324–9.
12. Hanson LA, Wadsworth CH. C-reactive protein and its diagnostic usefulness – especially in infections. Med Lab 1980; 8: 34–44.
13. Sox HC, Liang MH. The erythrocyte sedimentation rate. Guidelines for rational use. Ann Intern Med 1986; 104: 515–23.
14. Melbye H, Dale K. Interobserver variability in the radiographic diagnosis of adult outpatient pneumonia. Acta Radiol 1992; in press.
15. Radack KL, Rouan G, Hedges J. The likelihood ratio. Arch Pathol Lab Med 1986; 110: 689–93.
16. Morris JA, Gardner MJ. Calculating confidence intervals for relative risks, odds ratios, and standardised ratios and rates. In: Gardner MJ, Altman DG, eds. Statistics with confidence: Confidence intervals and statistical guide-lines. London, England: British Medical Association; 1989: 50–63.
17. Beck JR, Shultz EK. The use of Receiver Operating Characteristic (ROC) curves in test performance evaluation. Arch Pathol Lab Med 1986; 110: 13–20.
18. Ruuskanen O, Putto A, Sarkkinen H, Meurman O, Irjala K. C-reactive protein in respiratory virus infections. J Pediatr 1985; 107: 97–100.
19. Whicher JT, Chambers RE, Higginson J, Nashef L, Higgins PG. Acute phase response of serum amyloid protein and C-reactive protein to the common cold and influenza. J Clin Pathol 1985; 38: 312–6.
20. Atmar RL, Greenberg SB. Pneumonia caused by Mycoplasma pneumoniae and the TWAR agent. Semin Respir Infect 1989; 4: 19–31.
21. Stein MT. Delayed roentgenographic signs associated with acute pneumonia in children. J Fam Pract 1981; 12: 639–44.
22. Tandberg D, Sklar D. Effect of tachypnea on the estimation of body temperature by an oral thermometer. N Eng J Med 1983; 308: 945–6.

Received October 1991
Accepted February 1992

PAPER III



Scand J Infect Dis 24: 647–655, 1992

Pneumonia – a Clinical or Radiographic Diagnosis?

Etiology and Clinical Features of Lower Respiratory Tract Infection in Adults in General Practice

HASSE MELBYE[1], BJØRN P. BERDAL[2], BJØRN STRAUME[1], HAROLD RUSSELL[3], LARS VORLAND[4] and W. LANIER THACKER[3]

From the Institutes of [1]Community Medicine, and [2]Medical Biology, University of Tromsø, Norway, the [3]National Center for Infectious Diseases, CDC, Atlanta, GA, USA, and the [4]Department of Medical Microbiology, University Hospital, Tromsø, Norway

Etiology and clinical manifestations have been studied in 153 adult patients with lower respiratory tract infection, and the results are presented according to clinical and radiographic diagnosis. Laboratory investigations revealed that bacterial infection, mycoplasma and chlamydia included, occurred as often in 22 patients whose clinical diagnoses of pneumonia were not evident radiographically, as in 20 patients with radiographic pneumonia. In the latter group significantly higher values of erythrocyte sedimentation rate and C-reactive protein were demonstrated. The most common pathogen was influenzavirus A, followed by respiratory syncytial virus, Streptococcus pneumoniae, and Mycoplasma pneumoniae. Chlamydia pneumoniae infection was found in 3 patients with radiographic pneumonia. The study supports the traditional view that patients with a positive chest radiograph as a rule present more serious manifestations of lower respiratory tract pathology than patients with a normal radiograph. However, as only 1/9 patients with pneumococcal infection and 2/7 with mycoplasmal infection had radiographic evidence of pneumonia, radiography alone did not seem to offer sufficient information for selecting patients for antibacterial therapy.

H. Melbye, MD, Institute of Community Medicine, University of Tromsø, Breivika, N-9037 Tromsø, Norway

INTRODUCTION

When diagnosing patients with a possible lower respiratory tract infection, the following two questions are of crucial interest: which parts of the respiratory tract are involved, and what is the etiological agent? Most general practitioners have experienced the discrepancy between their own clinical diagnosis of pneumonia, based on history and physical examination, and the radiographic diagnosis. This discrepancy has been clearly demonstrated in previous studies (1,2). A similar experience is underdiagnosis of asthma in the evaluation of respiratory infection in children (3): this feature may be an important problem in adults as well. Adult community-acquired pneumonia has been found to be caused by bacteria in at least half of the cases, Pneumococcus species being the most frequent agent (4). In the ill-defined clinical entity "acute bronchitis", many investigators consider viral etiology to be more frequent than bacterial etiology, and a number of placebo-controlled clinical trials evaluating treatment with antibiotics in acute bronchitis have not demonstrated any effect (5). Acute airway infection may bring about aggravation of asthma and chronic obstructive pulmonary disease (COPD) (6). A considerable part of these aggravations has been shown to be caused by respiratory viruses (7).

The aim of this study from general practice was to describe clinical features and etiology in unselected adult patients with a lower respiratory tract infection, and to relate the findings both to the clinical diagnosis based on history and physical examination alone, and to the radiographic diagnosis of pneumonia. In particular we wanted to shed light on the etiology and clinical features of the patients diagnosed by doctors to have pneumonia, but who had a

normal chest radiograph, by comparing these patients with the patients diagnosed as having pneumonia radiographically but not clinically and with the acute bronchitis patients.

MATERIALS and METHODS

Patients

Among 581 patients aged 18 years or more attending the emergency ward in Tromsø because of a respiratory tract infection, 147 patients were diagnosed as having an infection of the lower respiratory tract: pneumonia, acute bronchitis, or aggravation of asthma or COPD. Six of the other patients had radiographic evidence of pneumonia. Accordingly, 153 patients could be regarded as having a lower respiratory tract infection, and these constitute the patient population of this study. The investigation, which took place between October 1988 and June 1989, and had 40 physicians participating in the examination of the patients, has also been described elsewhere (8).

Examinations

The patients reported the symptoms associated with the present illness on a self-administered questionnaire. Oral temperature was measured and blood samples were drawn for serological analyses, and for the analysis of erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and white blood cell (WBC) count. Valid measurements of oral temperature were obtained in 150 patients, ESR in 151, WBC count in 149, and CRP in all of the 153 patients. Additional details about these non-specific laboratory tests, as well as the distribution of the test results with reference to patients with and without radiographic signs of pneumonia, have been presented elsewhere (9).

Spirometry was carried out with the patient standing upright. Vitalograph Alpha (Vitalograph Ltd., UK), an electronic spirometer with a pneumotachograph-type flowhead, was used, with recalibration carried out daily. The best result of FEV_1 (forced expiratory volume in 1 second) after 3 attempts was registered, and percent value of predicted FEV_1 was calculated. Reference values from a Norwegian urban population were used (10). Only one patient, presenting violent chest pain, were unable to perform spirometry.

The participating physicians, who were not informed about the results of the tests, were asked to examine and treat the patients following their usual practice. Physical chest examination was carried out in all the 153 patients, and the findings were recorded. The main clinical diagnosis, based on history and physical examination alone, was noted.

A chest radiograph was to be ordered by the physicians when pneumonia was considered likely. Radiography was also ordered for patients presenting raised levels of ESR or CRP, and of a 25% random sample of the remaining patients. Patients with pronounced discomfort from cough or dyspnea after 10 days of illness were asked to attend the Chest Clinic of the University Hospital of Tromsø, and a chest radiograph was taken. Thus, an acute-phase radiograph was obtained in 133/153 patients. At a follow-up consultation after 4–5 weeks, control radiographs were obtained. The acute and control radiographs were judged by a radiology panel blinded for all clinical information about the patients. Additional information about the interpretation of the radiographs has been presented in a previous publication (11).

Patients who attended the Chest Clinic were tested with "reversibility tests" and bronchial challenges in order to diagnose asthma and COPD. If bronchial hyperresponsiveness was found, the patients were followed up for a period of 1 year.

The study was approved by the Regional Committee of Medical Research Ethics.

Classification into diagnostic groups

According to both the clinical and the radiographic diagnosis the patients were classified into 5 diagnostic groups, as follows:

1. **XPO** Radiographic pneumonia only: patients with a diagnosis of pneumonia according to the radiology panel, but not diagnosed by the physicians as having pneumonia.
2. **CXP** Clinical and radiographic pneumonia: patients diagnosed as having pneumonia, both by the physicians, based on history and physical examination, and by the radiology panel.
3. **CPO** Clinical pneumonia only: patients diagnosed clinically as having pneumonia, but who had a normal chest radiograph.
4. **AB** Acute bronchitis: patients diagnosed as having acute bronchitis, and with no radiographic signs of pneumonia.

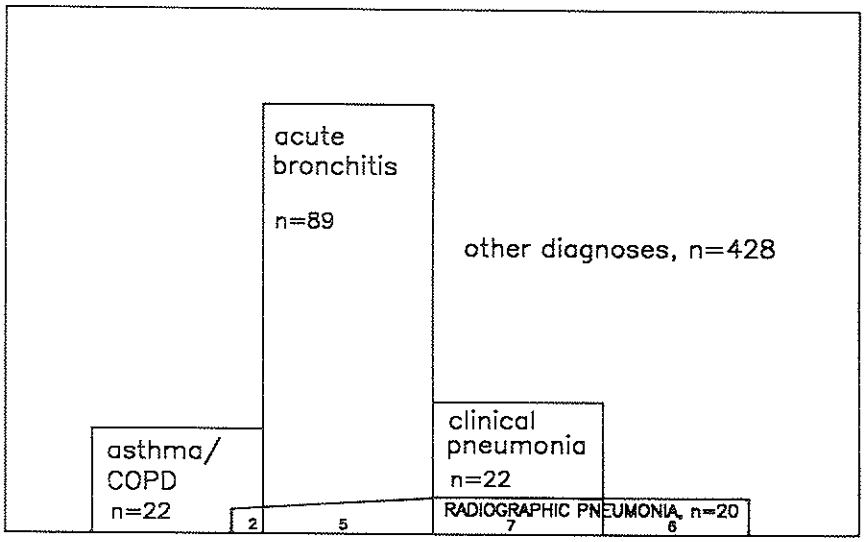


Fig. 1. Clinical diagnosis of the patients in the study, based on history and physical examination alone, and the concordance with radiographic diagnosis. COPD = chronic obstructive pulmonary disease.

5. **ACOPD** Asthma or COPD: patients diagnosed as having an aggravation of asthma, COPD or chronic bronchitis, and with no radiographic signs of pneumonia.

Microbiological analyses

At the return consultation blood samples for convalescence serology were obtained in 117/153 patients. The serum specimens were frozen at −45°C for later paired-sera analyses, confined to these 117 patients. The sera were assayed for IgG antibodies against the following agents: Streptococcus pneumoniae, Chlamydia species, Mycoplasma pneumoniae, Legionella species, influenzavirus A and B, parainfluenzavirus 1 and 3, adenovirus, Epstein Barr (EB)-virus and respiratory syncytial (RS)-virus. The pneumococcal antibodies, against a 37 kD protein (12), were determined by ELISA at Division of Bacterial and Mycotic Diseases, National Center for Infectious Diseases, CDC, Atlanta, GA, USA. Antibodies against legionella, 14 different serotypes (L.pneumophila serogroups 1–6, L. longbeachae serogr. 1–2, L. bozemanii serogr. Wiga and serogr. Mi-15, L. dumoffi, L. gormanii, L. micdadei and L. jordanis) were analysed at the Norwegian Defence Microbiological Laboratory, Oslo, Norway, using a microagglutination method and their own reagents (13). With this procedure, a 4-fold rise in antibody titer or a single titer of ≥ 256 is considered as evidence of infection. The serological analyses for complement-fixing (CF) antibodies against chlamydia, mycoplasma and the respiratory viruses were performed at the Department of Microbiology, University Hospital of Tromsø. The mycoplasma serology results were confirmed at the Division of Bacterial and Mycotic Diseases, CDC, Atlanta. The chlamydia CF-test was carried out with reagents from Behring (Behringwerke AG, Marburg, Germany). If a 4-fold rise in antibody titer or a single titer ≥ 80 was found, a species-specific microimmunofluorescence test for Chlamydia pneumoniae was done (14). The CF reagents for mycoplasma and the respiratory viruses were provided by the Department of Virology, National Institute of Public Health, Oslo, and a 4-fold rise in antibody titer or a single IgG-titer of ≥ 80 was considered as evidence of actual infection. The serological diagnosis of EB-virus infection was based on Monosticon (Organon, NC, USA) and IgM-test (DuPont Ltd), in acute and convalescence sera, respectively.

Statistical analyses

According to the distribution of results, mean or median values were calculated for the different groups. The statistical significance of differences between groups was tested with student's *t*-test, Wilcoxon rank sum test or chi-square test. A significance level of 5% was chosen. SAS software package (SAS Institute Inc., NC, USA) was used in all the statistical analyses.

Table I. *Age, sex, current smoking habits and duration of illness in 153 adult patients with lower respiratory tract infection, divided into 5 diagnostic groups*

XPO = radiographic pneumonia only, CXP = clinical and radiographic pneumonia, CPO = clinical pneumonia only, AB = acute bronchitis, ACOPD = asthma or chronic obstructive pulmonary disease

Background	XPO (n=13)	CXP (n=7)	CPO (n=22)	AB (n=89)	ACOPD (n=22)
Age (median)	38	39	27.5	31	41.5
Male (%)	46	43	55	34	50
Smokers (%)	46	100	50	60	48
Duration (days) of illness at entry (median)	9	10	5	5	7

RESULTS

The distribution of diagnoses among the 153 respiratory disease patients is shown in Fig. 1, together with the concordance between clinical and radiographic diagnoses. A clinical diagnosis of pneumonia was confirmed radiographically in 7/29 patients, the CXP-group, whereas the remaining 22 patients had no corresponding radiographic signs, and thus constituted the CPO-group. Among the 13 other patients with radiographic pneumonia, the XPO-group, 5 where clinically diagnosed as having acute bronchitis, 1 as aggravation of asthma, and 1 as COPD. Accordingly, the AB-group comprised 89/94 patients diagnosed as

Table II. *Reported symptoms, clinical findings, temperature, white blood cell count, erythrocyte sedimentation rate, and C-reactive protein in 153 adult patients with lower respiratory tract infection*

XPO = radiographic penumonia only, CXP = clinical and radiographic pneumonia, CPO = clinical pneumonia only, AB = acute bronchitis, ACOPD = asthma or chronic obstructive pulmonary disease

	XPO (n=13)	CXP (n=7)	CPO (n=22)	AB (n=89)	ACOPD (n=22)
Reported symptoms (%)					
Fatigue	100	100	91	90	91
Headache	85	57	82	79	59
Sore throat	31	71	43	75	55
Coryza	54	86	73	87	86
Chest pain: medial	38	29	33	47	36
lateral	31	57	24	26	23
Cough (more than normal)	92	100	82	92	73
Dyspnea (more than normal)	77	100	68	74	77
Chills	67	86	62	51	30
Findings					
Wheezes (%)	31	29	39	44	73
Crackles (%)	15***	71	86	11	14
Temperature, oral (mean)	37.8	37.6	37.6	37.2	37.0
WBC × 10^9 (median)	10.2	9.1	9.0	7.5	6.8
ESR mm/h (median)	45**	30	16	14	10
CRP mg/l (median)	50*	38	11	<11	<11

* $p<0.05$, ** $p<0.005$, *** $p<0.001$, indicate significant differences between the XPO- and CPO-groups

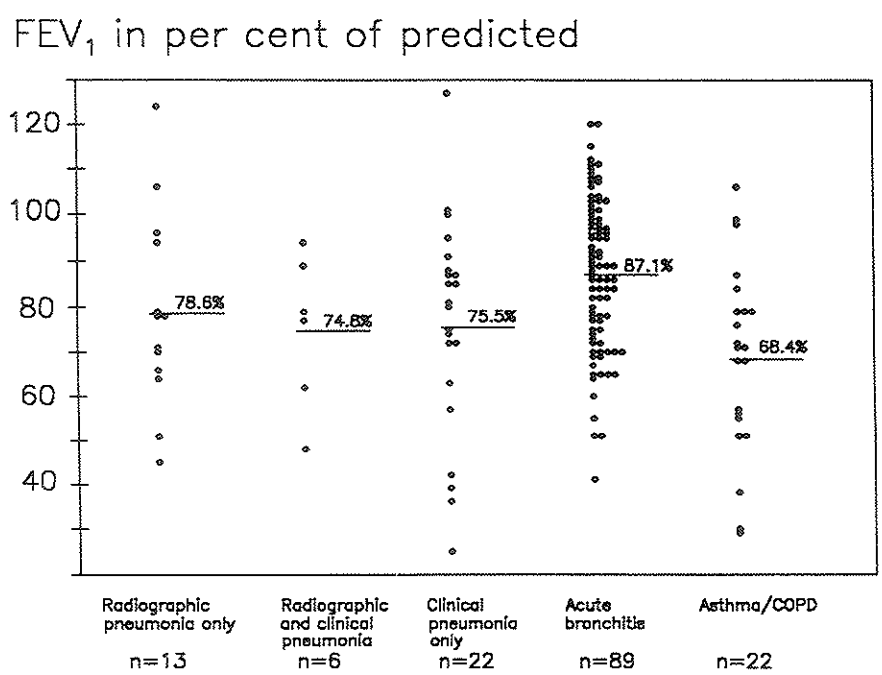


Fig 2. Forced expiratory volume in 1 second (FEV_1) as % of predicted in 153 adult patients with lower respiratory tract infection, according to diagnostic group. Mean values are indicated. COPD = chronic obstructive pulmonary disease.

Table III. *Causal pathogens established by serological investigations of paired sera in 117 adult patients with lower respiratory tract infection*

XPO = radiographic pneumonia only, CXP = clinical and radiographic pneumonia, CPO = clinical pneumonia only, AB = acute bronchitis, ACOPD = asthma or chronic obstructive pulmonary disease

Positive serology	XPO (n=13[a]) n (%)	CXP (n=6[a]) n	CPO (n=17) n (%)	AB (n=67) n (%)	ACOPD (n=14) n (%)
Chlamydia pneumoniae	2 (15)	1	0	0	0
Mycoplasma pneumoniae	2 (15)	0	3 (18)	2 (3)	0
Streptococcus pneumoniae	1 (8)	0	3 (18)	4 (6)	1 (7)
Influenzavirus (A+B)	5 (38)	0	2 (12)	7 (10)	2 (14)
Parainfluenzavirus	0	0	0	4 (6)	1 (7)
RS-virus	1 (8)	1	3 (18)	5 (7)	3 (21)
Adenovirus	0	0	0	1 (1)	0
EB virus	0	0	0	1 (1)	2 (14)
Total	11 (85)	2	11 (61)*	24 (36)	9 (64)

[a] One of the patients with negative serology in this diagnostic group turned out to have a pulmonary cancer.

* Significant difference between the CPO- and AB-groups, $p<0.05$.

Table IV. *Laboratory and spirometric results in 19 adults with lower respiratory tract infection due to bacterial agents. The patients have been divided into 5 diagnostic groups*

XPO = radiographic pneumonia only, CXP = clinical and radiographic pneumonia, CPO = clinical pneumonia only, AB = acute bronchitis, ACOPD = asthma or chronic obstructive pulmonary disease, F = female, M = male.

Pat. no.	Sex	Age (y.)	Diagnostic group	Duration of illness at entry (days)	Temp. C	ESR mm/h	CRP mg/l	WBC $\times 10^9$/l	FEV_1 % predicted
Pneumococcal infection									
1	M	41	XPO	3	37.8	10	39	12.8	51
2	F	22	CPO	15	37.7	8	<11	16.0	87
3	F	29[a]	CPO	6	38.2	30	65	10.9	87
4	M	28	CPO	1	38.3	2	<11	9.3	81
5	F	44	AB	6	39.2	50	82	20.3	79
6	M	21	AB	1	39.0	10	19	13.3	84
7	F	60	AB	14	38.0	70	92	12.5	108
8	M	24	AB	10	36.8	40	32	11.2	84
9	F	30	ACOPD	11	37.1	19	11	10.1	55
Mycoplasmal infection									
10	F	19	XPO	7	37.5	45	52	6.4	71
11	F	21	XPO	5	37.4	30	33	5.4	70
12	M	19	CPO	5	37.2	.	<11	9.6	57
13	F	21	CPO	13	37.8	70	31	8.0	36
14	M	37	CPO	4	37.1	70	112	7.8	72
15	M	33	AB	5	38.6	19	48	11.2	97
16	F	24	AB	5	37.0	20	<11	2.8	82
Chlamydia pneumoniae-infection									
17	F	39	CXP	14	36.5	38	34	9.1	94
18	F	18	XPO	10	37.2	55	17	7.3	94
19	M	25	XPO	14	37.0	17	24	7.8	96

[a] Evidence of recent RS-virus-infection was also found in this patient.

having acute bronchitis by the doctors, and 22 patients were classified into the ACOPD-group.

The CPO-patients tended to be younger than the XPO-patients and also had a shorter mean duration of illness at entry (Table I), but the differences were not statistically significant. Cough, dyspnea and chest pain were more frequent in the XPO-group compared with the CPO-group, while the opposite was the case for coryza and sore throat (Table II), but the differences did not reach statistical significance. Nor did the CPO-group differ significantly in symptoms from the AB-group.

Crackles were heard in 86% of the CPO-patients and in 15% of the XPO-group ($p < 0.001$). Significantly higher levels of CRP and ESR were found in the XPO-group compared to the CPO-group (Table II). The mean FEV_1 in % of predicted value was significantly lower in the CPO group, with 75.5%, compared to 87.1% in the AB-group, ($p < 0.05$) (Fig. 2).

85/153 patients attended the Chest Clinic a few days after entry due to persistent symptoms. Bronchial hyperresponsiveness was demonstrated in 4, who were not known to have asthma, but with a previous history and a later clinical course consistent with bronchial

asthma. Two of these patients belonged to the CPO-group, one to the XPO-group, and one to the AB-group.

Microbiology

Serological evidence of infection according to diagnostic group is shown in Table III. None of the patients had positive serology for legionella. Influenzavirus was the causal agent most frequently established, with influenza A in 14 patients and influenza B in 1 patient. RS-virus was next in frequency, followed by pneumococci and M. pneumoniae. The 3 patients with C. pneumoniae infection had all radiographic evidence of pneumonia. One patient classified in Table III as having pneumococcal infection, also presented serological evidence of recent RS-virus infection. Generally in the pneumonia groups (XPO, CPO, CXP), bacterial etiology was established with the same frequency as viral etiology.

In the AB-group, with infectious etiology established for 36%, viral infection was dominating with a frequency of 27%, whereas bacterial infection accounted for 9%. The corresponding frequencies in the ACOPD-group were 57% and 7%, respectively. As for the total material influenza- and RS-virus were the viral agents most frequently established, followed by parainfluenzavirus. Infection with EB-virus was established in 3 patients and adenovirus only in 1.

Pneumococcal, mycoplasmal and chlamydial infections were frequently associated with increased CRP and ESR values (Table IV). 8/9 patients with pneumococcal infection had a WBC count $> 10 \times 10^9$, whereas increased WBC count occurred in only 1/10 patients with mycoplasmal or chlamydial infection. This difference was statistically significant ($p < 0.001$). Oral temperature above normal was also often seen in the patients with pneumococcal infections. $FEV_1 < 80\%$ of predicted was most common in the mycoplasmal group, whereas normal FEV_1 was found in the 3 patients with C. pneumoniae infection.

DISCUSSION

A considerable discrepancy between the clinical diagnosis and the radiographic diagnosis of pneumonia was demonstrated. Our study lends some support to the validity of the radiographic diagnosis, because significantly higher levels of ESR and CRP was found in the XPO-group compared with the CPO-group. That serologic evidence of bacterial infection was demonstrated with equal frequency in the two groups may indicate that some of the CPO patients actually had lung infection, but at an early stage, not visible on a chest radiograph. A positive chest radiograph was found in only 1/9 patients with pneumococcal and 2/7 with mycoplasmal infection. Both these bacterial infections call for treatment with antibiotics. The absence of radiographic signs of infection indicates that a normal radiograph should not be strongly emphasized when a rational decision on antibacterial treatment is to be made. Diagnostic inaccuracies in lower respiratory tract infections, as shown in our study, make allowances for the high frequency of antibiotic prescription (5) encountered in such patients.

The CPO-group appeared to comprise 3 clinical entities:

1. Patients with a disease clinically indistinguishable from pneumonia, characterized by chest symptoms, impaired FEV_1, substantially raised levels of ESR, CRP or WBC count, and serological evidence of pneumococcal or mycoplasmal infection. These patients possibly did have a pneumonia, although not visible on a radiograph.
2. Another subgroup consisted of patients with obstructive pulmonary disease, presenting characteristic symptoms, physical findings, and spirometric results. Only 2 of the CPO-

patients could with certainty be categorized into this group, although other patients may prove to develop asthma in years to come (15). The patients of our study consisted predominantly of young adults. In an average general practice population, patients with aggravation of COPD are common. Since crackles may be heard in such patients (16), and since physicians put great emphasis on crackles as a sign of pneumonia (2,8), a special chance for misdiagnosing COPD as pneumonia may be present. Aggravation of asthma and COPD is usually associated with normal ESR, CRP and WBC count (17).

3. The greater part of the patients in the CPO-group probably had AB (acute bronchitis). Although wheezes is the typical abnormal auscultatory finding in AB, crackles may also be heard, and may represent an important source of diagnostic error. ESR, CRP, and WBC values are typically normal or slightly elevated in AB, and the spirometric performance usually within the normal range.

Among the patients diagnosed by the physicians to have AB, 5 had radiographic pneumonia. Another 6 patients had either pneumococcal or mycoplasmal infection. Diagnostic error and such occurrence of bacterial infection may be one of the reasons why both physicians and patients so often find antibiotics to be efficient against "acute bronchitis". However, according to our serological study, acute bronchitis was most frequently caused by virus, and as for the ACOPD-group influenza and RS-virus dominated the etiological picture.

Elsewhere, rhinovirus has been indicated as a common cause of acute bronchitis and aggravation of asthma and COPD (7). In the present study, however, rhinovirus was not included, due to the unavailability of suitable group-specific reagents.

The insignificant role of EB-virus in our patients was as expected. Adenovirus infection has more frequently been found associated with lower respiratory tract infection in previous studies (18–20).

If unnecessary prescription of antibiotics is to be reduced in lower respiratory tract infection, more diagnostic means for early diagnosis of viral as well as bacterial infections are needed. Our study indicates that ESR, CRP and WBC count may be useful in this respect. A possibility of early differentiation between pneumococcal as opposed to mycoplasmal or chlamydial infection by taking into account the WBC count (21) was also supported by this study.

Spirometry may represent a neglected technique in the diagnosis of acute respiratory infection. The C. pneumoniae patients as a group, all with positive radiography, had normal FEV_1 values, contrasting with distinctly lower values in both the mycoplasmal and pneumococcal patient groups. Normal spirometry is possibly not a characteristic feature of chlamydial pneumonias; an association between C. pneumoniae infection and bronchial obstruction was indicated by a recent study (22).

When airflow limitation is associated with normal ESR, CRP and WBC count, aggravation of asthma or COPD or a transient non-specific inflammation of the bronchi (bronchial hyperresponsiveness) may be the main reason for the patients' symptoms. With such findings a bronchodilator rather than an antibiotic may be the treatment to be tried first (23).

A previous study has indicated that chest radiography usually plays a minor role in the physicians decision to start antibacterial treatment (24). Our study seems to justify this practice, and we conclude that antibiotics should not be withheld because of a normal chest radiograph, if prescription otherwise seems reasonable.

ACKNOWLEDGMENTS

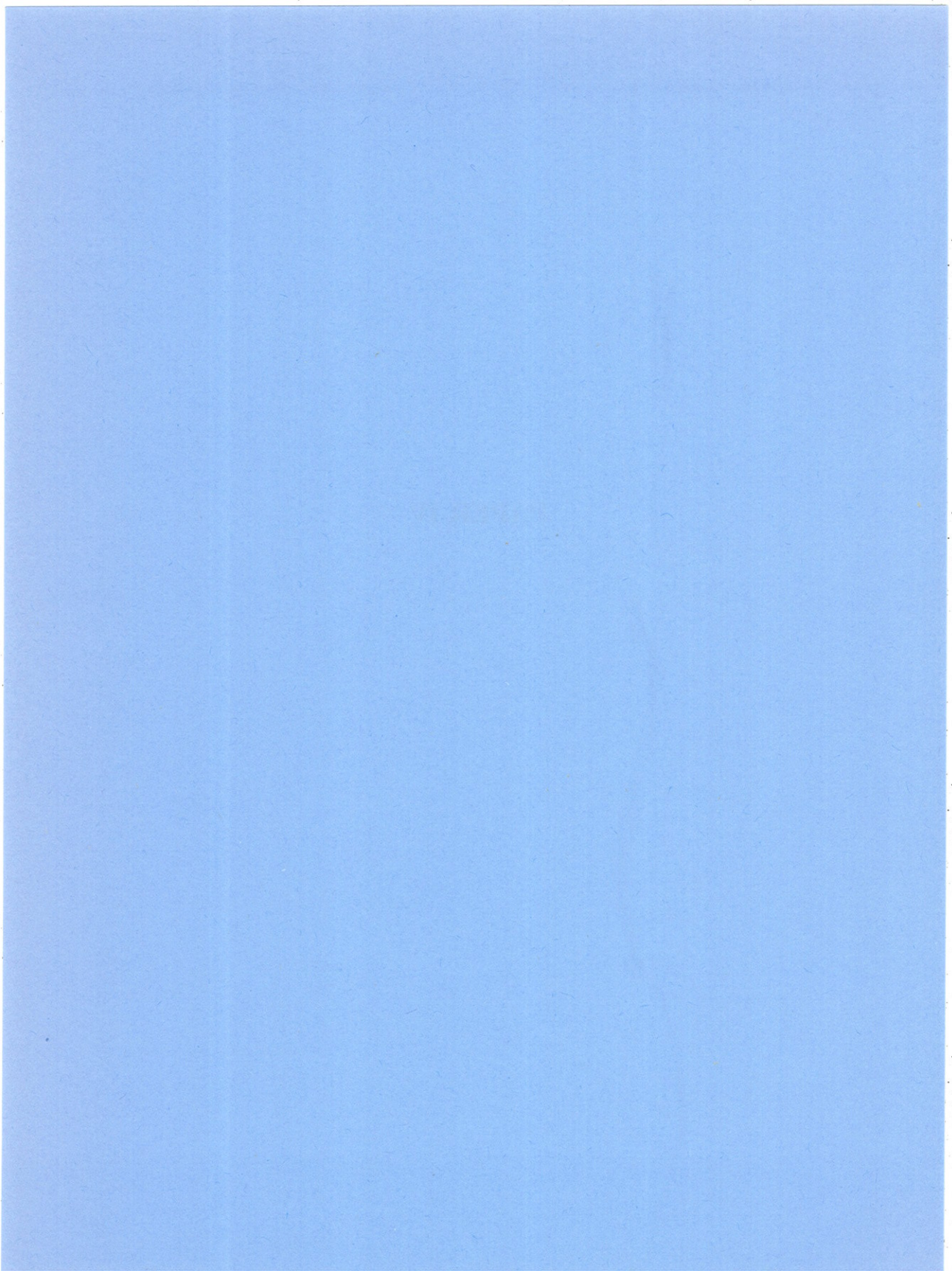
This research was supported by a grant from the Norwegian Research Council for Science and the Humanities, MRC, Program for Research in General Practice to H. Melbye. We thank for laboratory

assistance from Ms Valeria Gacek at the Norwegian Defence Microbiological Laboratory in Oslo and Ms Sissel Andreassen and the staff at the Virology Section, Department of Microbiology, University Hospital of Tromsø.

REFERENCES

1. Diehr P, Wood RW, Bushyhead J, Krueger L, Wolcott B, Tompkins RK. Prediction of pneumonia in outpatients with acute cough: a statistical approach. J Chronic Dis 37: 215–225, 1984.
2. Melbye H, Straume B, Aasebø U, Brox J. The diagnosis of adult pneumonia in general practice. Scand J Prim Health Care 6: 111–117, 1988.
3. Levy M. Delay in diagnosing asthma, is the nature of general practice to blame? J R Coll Gen Pract 36: 52–53, 1986.
4. McFarlane JT. Treatment of lower respiratory infections. Lancet 2: 1446–1449, 1987.
5. Verheij TMJ, Kaptein AA, Mulder JD. Acute bronchitis: Aetiology, symptoms and treatment. Fam Pract 6: 66–69, 1989.
6. Beasley R, Coleman ED, Hermon Y, Holst PE, O'Donnell TV, Tobias M. Viral respiratory tract infections and exacerbations of asthma in adult patients. Thorax 43: 679–683, 1988.
7. Minor TE, Dick EC, Baker JW, Ouellette JJ, Cohen M, Reed CE. Rhinovirus and influenza type A infections as precipitants of asthma. Am Rev Respir Dis 113: 149–153, 1976.
8. Melbye H, Straume B, Aasebø U, Dale K. Diagnosis of pneumonia in adults in general practice. Relative importance of typical symptoms and abnormal chest signs evaluated against a radiographic reference standard. Scand J Prim Health Care 10: 226–233, 1992.
9. Melbye H, Straume B, Brox J. Laboratory tests for pneumonia in general practice: The diagnostic values depend on the duration of illness. Scand J Prim Health Care 10: 234–240, 1992.
10. Gulsvik A. Obstructive lung disease in an urban population. Doctoral dissertation. Oslo: University of Oslo, 1979.
11. Melbye H, Dale K. Interobserver variability in the radiographic diagnosis of adult outpatient pneumonia. Acta Radiol 33: 79–81, 1992.
12. Russell H, Tharpe JE, Wells DE, White EH, Johnson JE. Monoclonal antibody recognizing a species-specific protein from Streptococcus pneumoniae. J Clin Microbiol 28: 2191–2195, 1990.
13. Phakkey A, Lindquist KL, Omland T, Berdal BP. Legionella antibodies in human and animal populations in Kenya. APMIS 98: 43–49, 1990.
14. Berdal BP, Fields PI, Melbye H. Chlamydia pneumoniae respiratory tract infection: The interpretation of high titres in the complement fixation test. Scand J Infect Dis 23: 305–307, 1991.
15. Hallett JS, Jacobs RL. Recurrent acute bronchitis: the association with undiagnosed bronchial asthma. Ann Allergy 55: 568–570, 1985.
16. Piirilä P, Sovijärvi ARA, Kaisla T, Rajala HM, Katila T. Crackles in patients with fibrosing alveolitis, bronchiectasis, COPD, and heart failure. Chest 99: 1076–1083, 1991.
17. Ritland N, Melbye H. C-reaktivt protein, SR og hvite blodlegemer ved akutte nedre luftveislidelser. Nytten av blodprøver i diagnostisering av pneumoni. [The usefulness of blood tests in distinguishing pneumonia from asthma and bronchitis. Summary in English] Tidsskr Nor Lægeforen 111: 2249–2252, 1991.
18. Woodhead MA, MacFarlane JT, McCracken JS, Rose DH, Finch RG. Prospective study of the aetiology and outcome of pneumonia in the society. Lancet 1: 671–674, 1987.
19. Lehtomäki K. Clinical diagnosis of pneumococcal, adenoviral, mycoplasmal and mixed pneumonias in young men. Eur Respir J 1: 324–329, 1988.
20. Sundsfjord A, Vorland L, Melbye H. Serologi ved nedre luftveisinfeksjoner. [Diagnostic serology in lower respiratory tract infections. Summary in English.] Tidsskr Nor Lægeforen 108: 2719–2720, 2750, 1988.
21. Holmberg H, Bodin L, Jönsson I, Krook A. Rapid aetiological diagnosis of pneumonia based on routine laboratory features. Scand J Infect Dis 22: 537–545, 1990.
22. Hahn DL, Dodge RW, Golubjatnikov. Association of Chlamydia pneumoniae (strain TWAR) infection with wheezing, asthmatic bronchitis and adult-onset asthma. JAMA 266: 225–230, 1991.
23. Melbye H, Aasebø U, Straume B. Symptomatic effect of inhaled fenoterol in acute bronchitis: a placebo-controlled double-blind study. Fam Pract 8: 216–222, 1991.
24. Bushyhead JB, Wood RW, Tompkins RK, Wolcott BW, Diehr P. The effect of chest radiographs on the management and clinical course of patients with acute cough. Med Care 21: 661–673, 1983.

PAPER IV



The Spectrum of Patients Strongly Influences the Usefulness of Diagnostic Tests for Pneumonia.

Hasse Melbye and Bjørn Straume,
Institute of Community Medicine, University of Tromsø,
Breivika, 9000 Tromsø, Norway. Telephone: 47 83 44816.
Telefax: 44 83 44831.

Correspondence: Hasse Melbye, Institute of Community Medicine, University of Tromsø, Breivika, 9000 Tromsø, Norway.

Running head: Pneumonia diagnosis and spectrum of patients

Key words: Pneumonia, diagnosis, selection bias, specificity.

The Spectrum of Patients Strongly Influences the Usefulness of Diagnostic Tests for Pneumonia.

ABSTRACT: The diagnostic values of five clinical cues for radiographic pneumonia were studied in 581 adult patients consulting a municipal emergency clinic for respiratory infection. Following a standard diagnostic pathway in the diagnosis of pneumonia, predictive values of the symptoms "very annoying dyspnea", "strong lateral chest pain", the sign crackles and the laboratory tests C-reactive protein (CRP) analysis and erythrocyte sedimentation rate (ESR) were evaluated at four levels of selection, associated with increasing prevalence of pneumonia: 1. in all the 581 patients included, 2. in 402 of these patients who underwent physical chest examination, 3. in 188 patients classified by the doctors as having a lower respiratory tract infection, and 4. in 79 patients referred to radiography by the doctors.

A tendency of decreasing specificity with increasing prevalence of pneumonia was demonstrated for all tests, except for CRP. This tendency may be explained either by the emphasis laid on the tests by the doctors in their selection of patients, or by an association between the evaluated tests and those emphasized by the doctors. As the diagnostic value of symptoms and signs are strongly influenced by selection, caution should be shown when transferring diagnostic values from one clinical setting to another.

The sensitivity and specificity of diagnostic tests evaluated in a clinical setting are subject to selection bias (1-3)· The impact of the spectrum of patients with and without the disease in issue has attained appreciable theoretical concern, but the significance in real life has been demonstrated in a few studies only (4-6)· When we evaluated clinical cues in the diagnosis of pneumonia in patients assumed to have a possible pneumonia (7), we were struck by the differences in sensitivities and specificities in our study compared with a study by Diehr et al (8), where unselected adults with acute cough were included. Selection bias was suggested as contributing to the difference.

In a recent investigation on pneumonia diagnosis, 581 adults were included, who consulted general practitioners for an acute respiratory infection. The diagnostic usefulness of symptoms, signs and laboratory tests evaluated againts a radiographic reference standard in 402 of these patients who underwent physical chest examination, have been presented elsewhere (9,10). In this paper we evaluate two symptoms, one physical chest finding and two laboratory tests which showed to be the most useful clinical variables. To determine the impact of selection, the diagnostic value of the variables have been assessed in all the 581 patients and, by following a standard diagnostic pathway, in subgroups associated with increasing prevalence of pneumonia.

MATERIAL AND METHODS.

Patients

The investigation took place at the Municipal Emergency Clinic in Tromsø between Oktober 1988 and May 1989. Consecutive patients aged 18 years or more, presenting complaints suggestive of a respiratory or throat infection were asked to enter the study. Pregnant women and patients with dyspnea, severe enough to need urgent treatment, were excluded. 581 patients were included, 339 women and 242 men. Mean age was 32.1 years. 40 doctors participated in the examination of the patients. The study was approved by the Regional Committee of Medical Research Ethics.

Examinations

The examinations carried out, described in detail elsewhere (9,10) may be summarized as follows: Before consulting the doctor the patients were examined by specially trained nurses. Blood samples were taken for the analysis of C-reactive protein analysis (CRP), and erythrocyte sedimentation rate (ESR), and on a questionnaire the patients reported symptoms associated with the present illness. Dyspnea was graded as follows: No dyspnea - as usual - more annoying than normal - very annoying. Medial and lateral chest pain was graded as light or strong pain. The doctors, who were not informed about the laboratory results before the end of the consultation, were asked to examine and treat the patients as usual. Auscultation of the chest was carried out and the

findings recorded in 402 patients. Of these 188 were classified as having lower (or combined upper and lower) respiratory tract infection (LRTI). A chest radiograph was ordered by the doctors because of a possible pneumonia in 79 patients. Among these 68 had been classified as having LRTI (Fig 1.). Age, sex, duration of illness and frequency of radiographic pneumonia in all the patients and the three subgroups is presented in Table 1.

The reference standard

Radiographic pneumonia was diagnosed in 20 patients, as judged by a radiology panel (9). A density on chest film, showing signs of resolution on a follow-up radiograph, was the diagnostic criterion. In addition to the radiographs ordered by the doctors, the nurses ordered chest films in 101 patients with raised values of ESR or CRP, and in a 25% random sample of the remaining patients, assumed to have a low probability of pneumonia. Patients with persistent cough or dyspnea after ten days of illness were invited to the Chest Clinic at the University Hospital of Tromsø for further examination, and a chest radiograph was thus obtained in 49 patients not radiographed at entry. Follow-up radiographs were taken 4 to 5 weeks after entry.

No pneumonias were diagnosed in the 25 % random sample or among the other randomized patients who were radiographed at the Chest Clinic. In the calculation of diagnostic values we made the assumption that there were no pneumonias among the patients who were randomized.

Statistical analyses

Sensitivity (proportion of pneumonia patients with the finding), specificity (proportion of non-pneumonia patients without the finding), likelihood ratio (LR) (sensitivity/ 1 - specificity) and positive predictive value (PPV) (the frequency of pneumonia among patients with the finding) were calculated (11). The following clinical variables and blood tests were evaluated, all dichotomized at boundaries previously shown to yield substantial diagnostic values (9,10): Very annoying dyspnea, strong lateral chest pain, crackles, CRP $\geq$ 60 mg/l and ESR $\geq$ 60 mm/h. The analyses were carried out at the four levels of selection shown in fig. 1. The diagnostic efficacy of ESR and CRP as continious variables have been presented as Receiver Operating Characteristic (ROC) curves (12). In order to obtain a clear picture of the LR from the figures, we have plotted the function:
sensitivity = LR x (1 - specificity), as straight dashed lines, radiating from the lower left corner (fig. 3), for integer values of LR from 1 to 5.

SAS software (SAS Institute Inc.,NC, USA) was used in the statistical analyses.

RESULTS

The diagnostic values of the clinical variables and blood tests at the different levels of selection are shown in Fig 2. The specificity of very annoying dyspnea decreased with increasing prevalence of pneumonia from 0.94 to 0.79. The LR dropped from 5.7 to 2.0, resulting in only a slight increase in PPV with increasing prevalence of radiographic pneumonia. For strong lateral chest pain the corresponding drop in specificity was smaller, from 0.93 to 0.90.

Crackles was the only finding with a marked increase in sensitivity through the levels of selection, from 0.35 to 0.58. The specificity dropped from 0.91 to 0.60, the LR from 3.7 to 1.4, and the PPV was nearly unchanged as the prevalence of radiographic pneumonia increased.

A marked drop in specificity, from 0.97 to 0.89, and in LR, from 9.2 to 2.3, was demonstrated for ESR. There was little change in the PPV. A different pattern of changes was found for CRP. The specificity was lower in the total material compared with the 402 auscultated patients and the 188 patients classified as having lower respiratory tract infection. A corresponding rise in LR from 3.7 to 6.7 was found. PPV increased from 0.12 to 0.43 through the four levels of selection.

The change in diagnostic value of ESR and CRP according to prevalence of pneumonia shown in Fig. 2, were not only confined to the selected thresholds. Similar changes in LR were also found for other thresholds of the tests, as shown by the ROC-curves of the tests (Fig. 3). ESR showed better

diagnostic properties in the unselected patients and the 402 patients who were auscultated compared to the two other selection groups, as shown by the positioning of the ROC-curves towards the upper left corner. The ROC-curve of CRP evaluated in the patients referred to radiography, followed an unexpected path, crossing the other curves. Low LRs at values below 60 mg/l and much higher LRs at values above 80 mg/l were found.

DISCUSSION

The study demonstrated a substantial impact of selection on diagnostic values. The sensitivity of the clinical cues, particularly crackles, and the laboratory tests tended to increase with increasing prevalence of pneumonia. A more important observation, however, was the changes in specificity due to altered spectrum of patients without pneumonia.

The changes in specificity reflect the diagnostic process. The first step in the diagnostic process consists of the evaluation of the presenting complaint and a short interview highlightening the patients main symptoms. The decision to carry out a physical chest examination in 402 patients, assumed here to be the second step in the diagnostic process, would depend on the symptoms presented by the patients. Most patients with strong lateral chest pain or very annoying dyspnea would be expected to undergo this examination, explaining the higher frequency of these symptoms in patients without pneumonia among the auscultated compared to all the patients, and why the specificity of the symptoms accordingly were lower.

Among the patients who were auscultated, abnormal chest findings were recorded in 113 patients. Of these 43 patients had crackles. A provisional classification of 188 patients into the LRTI-group, assumed to be a third diagnostic step, was done in 107 of the 113 patients with

abnormal auscultatory findings, and in 42 of the patients with crackles. The prevalence of crackles thus increased from 11 % in the 402 auscultated patients to 22 % in the LRTI patients. As the frequency of crackles did not only increase among pneumonia patients, but also in patients without pneumonia (NPN-patients), a substantial decrease in specificity could be observed. The doctors could be expected also to emphasize dyspnea and chest pain when classifying patients into the LRTI-group, and this may be the reason for a higher prevalence of these symptoms among NPN-patients in this group compared to NPN-patients in the 402 auscultated patients. Anyway, the increased prevalence explains the further decrease in specificity of the symptoms.

A similar explanation may be applied to the fourth step in the diagnostic process, the decision to order a chest radiograph. Radiography was ordered by the doctors in 79 patients, and in 34 of the 43 patients with crackles. Of 46 patients with wheezes but without crackles radiography was ordered in 16. Radiography was also ordered in 11 patients not classified as having LRTI (Fig. 1). Crackles was obviously a finding used by the doctors in their decision to order a radiograph, but clinical cues as chest symptoms, age and duration of illness (indicated in Table 1) certainly also contributed.

The ESR and CRP results were unknown to the doctors and accordingly not involved in the diagnostic process. Nevertheless, a similar drop in specificity was found for

ESR as for the clinical cues. This may reflect that elevated ESR and some of the findings guiding the doctor in their selection of patients are associated with each other. Dependency between clinical cues may also be an alternative explanation for the difference in specificity of lateral chest pain and dyspnea between the auscultated subgroup and the group refererred to radiography. These symptoms and crackles do not coexist in patients by chance alone, and as the doctors used crackles in the selection of patients through the diagnostic process, the accumulation of patients with dyspnea and chest pain could be secondary to this.

The change in the diagnostic value of CRP showed a pattern different from that of ESR. The difference may be explained as follows: Among the patients not selected for chest examination, about one third had either a streptococcal throat infection or otitis media, diseases more frequently associated with marked elevation of CRP than ESR. Among the patients who were auscultated, but classified as having an upper respiratory tract infection, influenza was frequently diagnosed by the doctors. Among the influenza patients moderately elevated CRP values were frequently found, in accordance with CRP levels previously demonstrated in influenza and adenoviral infection (13). Because a great part of the patients with elevated CRP values were not classified into the LRTI-group, the high specificity of CRP was preserved into this next step of selection.

Bias from insufficiency of the reference standard

Weakness of the reference standard, may also represent an important source of bias. We have reported a substantial interobserver variability in the interpretation of chest radiographs (14). Normal radiographic findings may be present in early pneumonia (15,16). In addition, pneumonia cases may in this study have been misclassified due to the assumption that there was no pneumonia among the patients subjected to randomization for radiography. However, because no pneumonias were discovered in the examination of patients with persistent cough or dyspnea at the Chest Clinic, bias from the randomization for radiography has probably played a minor role, if any at all.

Bias of the reference standard may have influenced the pattern of changes in diagnostic values according to selection. Patients with "true" pneumonia falsely diagnosed as not having pneumonia by the radiological interpretation, would have an increased probability of being auscultated, considered as having lower respiratory tract infection and being referred for radiographic examination. Through the stages of diagnosis false negative pneumonias might accumulate, resulting in lower specificity of findings associated with pneumonia.

Comparison with other studies

In two recent studies by Heckerling (17) et al and Singal et al (18) the symptoms dyspnea and chest pain were not found to be useful in the diagnosis of pneumonia in adult emergency room patients who had a chest radiograph to evaluate fever or respiratory complaints. Quite different results were found when symptoms and chest signs were evaluated in the 402 auscultated patients in our investigation[9]. Very annoying dyspnea and strong lateral chest pain were the clinical cues of greatest diagnostic value. Although this usefulness partly could be ascribed to the grading of the symptoms, ungraded dyspnea and lateral chest pain were also significantly associated with radiographic pneumonia. Heckerling et al (17) and Singal et al (18) suggested that the use of the symptoms in the selection of patients for radiography probably was the reason why the symptoms turned out to be insignificant predictors of pneumonia. Our study strongly supports this view.

This study demonstrates the difficulty of transferring diagnostic values from one clinical setting to another. According to Bayes' theorem the positive predictive value of clinical cues improve substantially (and predictably) with increasing prevalence of the disease. This may fail to occur due to instability in the diagnostic properties of the cues. In this study only the PPV of CRP changed corresponding to the rule of Bayes'. As stated by Feinstein (19), adjustment for prevalence, following this

rule, may often be misdirected.

Clinical implications

A study like this may indicate at which stages in the diagnostic work-up clinical cues or diagnostic tests should be emphasized. Our study underlines that dyspnea and lateral chest pain should not only be emphasized in the decision to carry out physical chest examination, but also later in the diagnostic considerations. ESR may be useful even in rather unselected patients, while CRP is most useful as predictor of pneumonia when the patient can be provisionally classified as having a lower respiratory tract infection.

References

1. Ransohoff DF, Feinstein AR. Problems of spectrum and bias in evaluating the efficacy of diagnostic tests. N Eng J Med 1978;299:926-30.
2. Begg CB. Biases in the assessment of diagnostic tests. Statistics in Medicine 1987;6:411-23.
3. Feinstein AR. Clinical epidemiology. The architecture of clinical research. Philadelphia, JB Saunders company, 1985:613-8.
4. Hlatky MA, Pryor DB, Harrell FE Jr et al. Factors affecting the sensitivity and specificity of the exercise electrocardiogram: A multivariable analysis. Am J Med 1984;77:64-71.
5. Rozanski A, Diamond GA, Berman D, Forrester JS, Morris D, Swan HJC. The declining specificity of exercise radionuclide ventriculography. N Eng J Med 1983;309:518-22.
6. Harris JM. The Hazards of bedside Bayes. JAMA 1981;246:2602-5.
7. Melbye H, Straume B, Aasebø U, Brox J. The diagnosis of adult pneumonia in general practice. Scand J Prim Health Care 1988;6:111-7.
8. Diehr P, Wood RW, Bushyhead J, Krueger L, Wolcott B, Tompkins RK. Prediction of pneumonia in out-patients with acute cough: A statistical approach. J Chronic Dis 1984;37:215-25.

9. Melbye H, Straume B, Aasebø U, Dale K. Diagnosis of adult pneumonia in adults in general practice. Relative importance of typical symptoms and abnormal chest signs evaluated against a radiographic reference standard. Scand J Prim Health Care 1992;10 In press.

10. Melbye H, Straume B, Brox J. Laboratory tests for pneumonia in general prctice: The diagnostic values depend on the duration of illness. Scand J Prim Health Care 1992;10 in press.

11. Sacket DL, Haynes RB, Tugwell P. Clinical epidemiology. A basic science for clinical medicine. Boston: Little, Brown and co. 1985.

12. Beck JR, Shultz EK. The use of Receiver Operating Characteristic (ROC) curves in test performance evaluation. Arch Patol Lab Med 1986;110:13-20.

13. Ruuskanen O, Putto A, Sarkkinen H, Meurman O. Irjala K. C-reactive protein in respiratory virus infection. J Pediatr 1985;107:97-100.

14. Melbye H, Dale K. Interobserver variability in the radiographic diagnosis of adult outpatient pneumonia. Acta Radiol 1992;33:79-81.

15. Stein MT. Delayed roentgenographic signs associated with acute pneumonia in children. J Fam Pract 1981;12:639-44.

16. Melbye H, Berdal BP, Straume B, Russell H, Vorland L, Thacker WL. Pneumonia, a clinical or radiographic diagnosis? Etiology and clinical features of lower respiratory tract infections in adults in general practice. Scand J Infect Dis 1992;24 in press.

17. Heckerling PS, Tape TG, Wigton RS, Hissong KK, Leikin JB, Ornato JP et al. Clinical prediction rule for pulmonary infiltrates. Ann Intern Med 1990;113:664-70.

18. Singal BM, Hedges JR, Radack KL. Decision rules and and clinical prediction of pneumonia: evaluation of low-yield criteria. Annals of Emergency Medicine 1989;18:13-20.

19. Feinstein AR. The inadequacy of binary models for the clinical reality of three-zone diagnostic decision. J Clin Epidemiol 1990;43:109-13.

Table 1

Mean age, sex, duration of illness and occurence of radiographic pneumonia in 581 adult patients with respiratory tract infection and in subpopulations of the patients selected according to a standard diagnostic pathway.

	N	Age (mean)	Male/female ratio	Duration of illness, days (mean)	Radiographic pneumonia n	%
All patients included	581	32.1	0.71	9.1	20	3.4
Patients who were auscultated	402	33.2	0.70	10.2	20	5.0
Patients classified as having LRTI*	188	35.4	0.68	10.7	15	8.0
Patients referred to chest radiography	79	38.6	0.72	13.3	12	15.2

* LRTI= Lower respiratory tract infection.

Legend to the figures.

Fig.1

Venn-diagram showing four levels of selection in 581 adult patients with respiratory infection, according to a standard diagnostic pathway.

Fig.2

Diagnostic values for radiographic pneumonia of three clinical variables and two laboratory tests according to four levels of selection of adult patients with respiratory infection in general practice.
(Footnote: LRTI= Lower respiratory tract infection.)

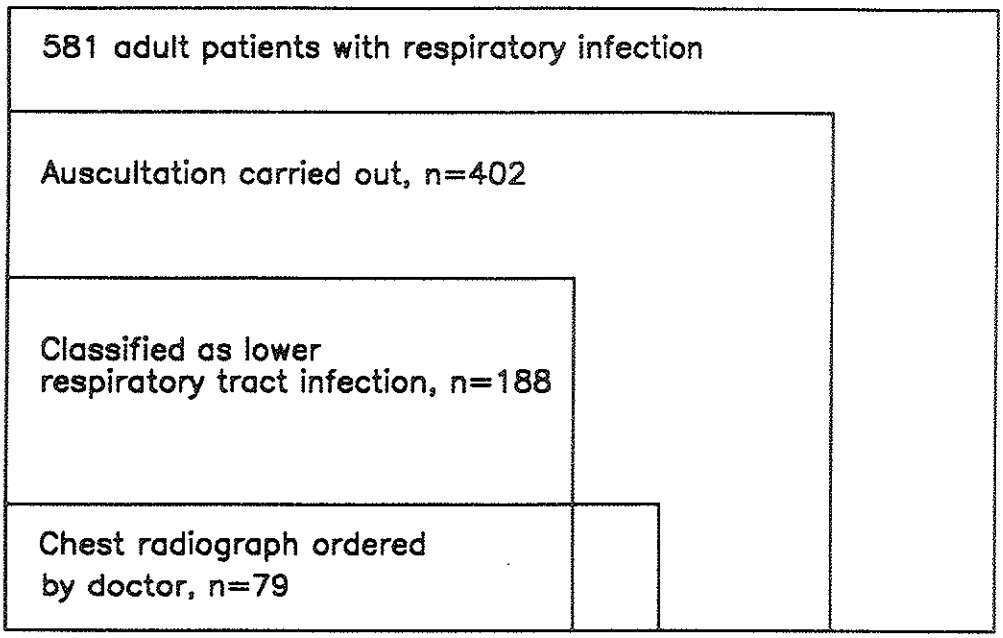
Fig. 3

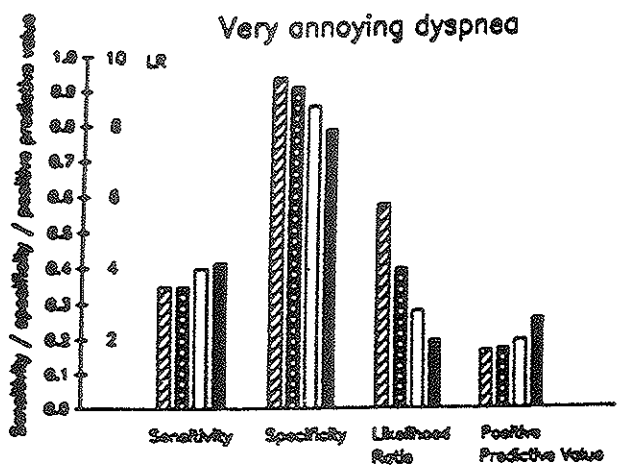
Receiver operating characteristic (ROC)-curves showing diagnostic value of ESR (erythrocyte sedimentation rate) and CRP (C-reactive protein) for pneumonia according to four levels of selection of adult patients with respiratory infection in general practice.

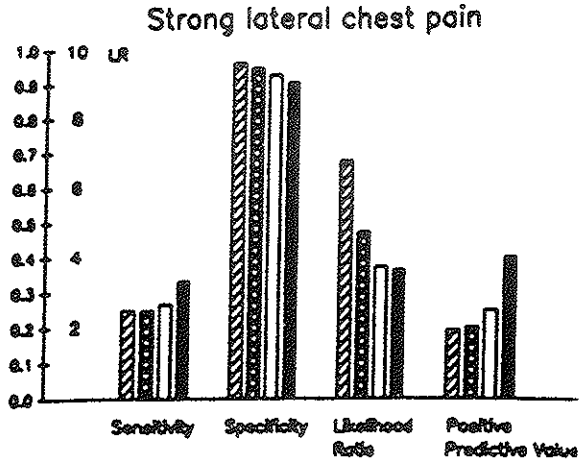
Footnote 1: The following thresholds of the tests have been used, marked from left to right in the curves: CRP: 20, 40, 60, 80, and 100 mg/ml, ESR: 20, 40, 60, and 80 mm/h.

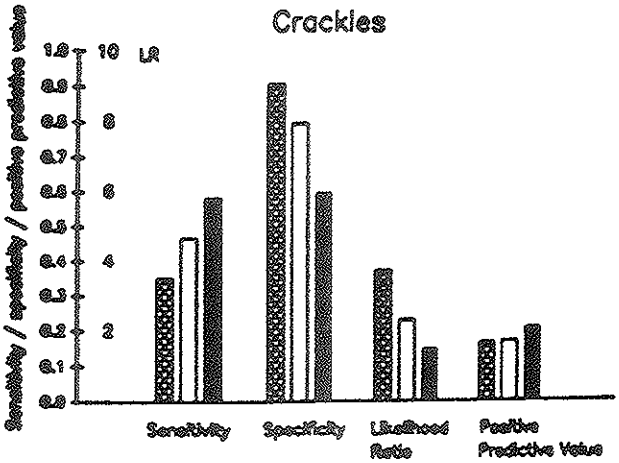
Footnote 2: LRTI= Lower respiratory tract infection.

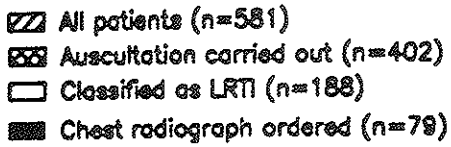
Figure 1

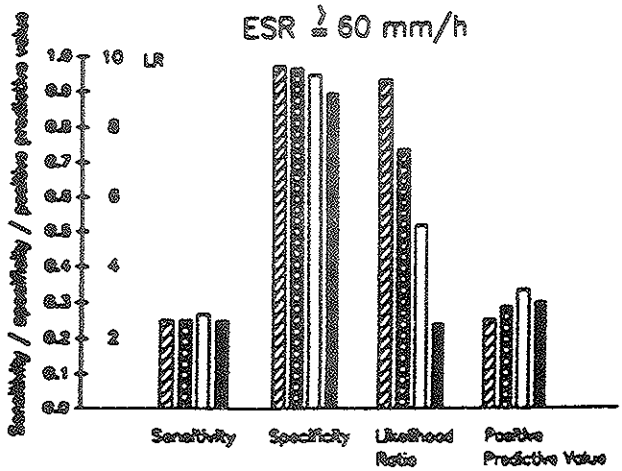

581 adult patients with respiratory infection
Auscultation carried out, n=402
Classified as lower respiratory tract infection, n=188
Chest radiograph ordered by doctor, n=79


Very annoying dyspnea
Sensitivity / specificity / positive predictive value
LR
Sensitivity
Specificity
Likelihood Ratio
Positive Predictive Value


Strong lateral chest pain
LR
Sensitivity
Specificity
Likelihood Ratio
Positive Predictive Value


Crackles
Sensitivity / specificity / positive predictive value
LR
Sensitivity
Specificity
Likelihood Ratio
Positive Predictive Value


All patients (n=581)
Auscultation carried out (n=402)
Classified as LRTI (n=188)
Chest radiograph ordered (n=79)


ESR ≥ 60 mm/h
Sensitivity / specificity / positive predictive value
LR
Sensitivity
Specificity
Likelihood Ratio
Positive Predictive Value

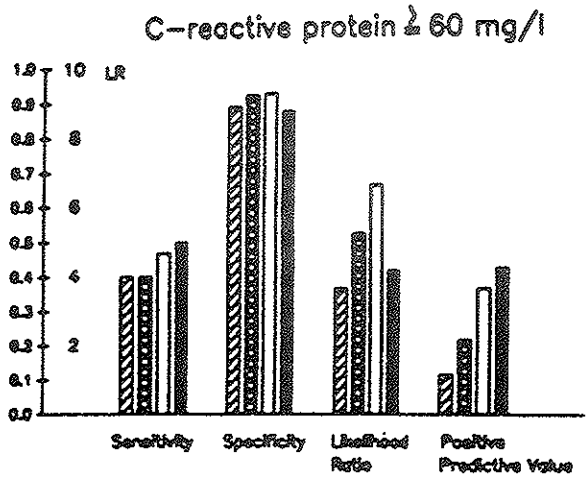
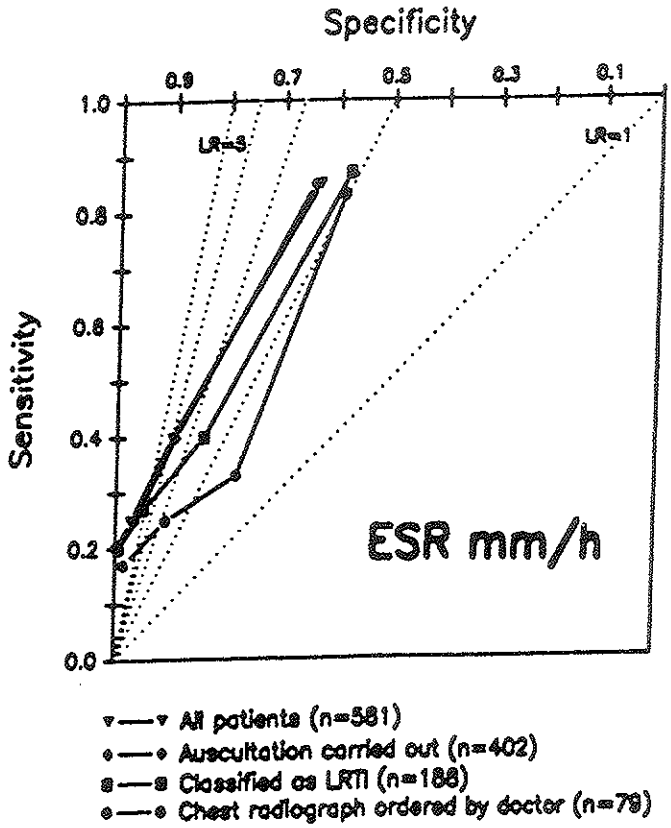
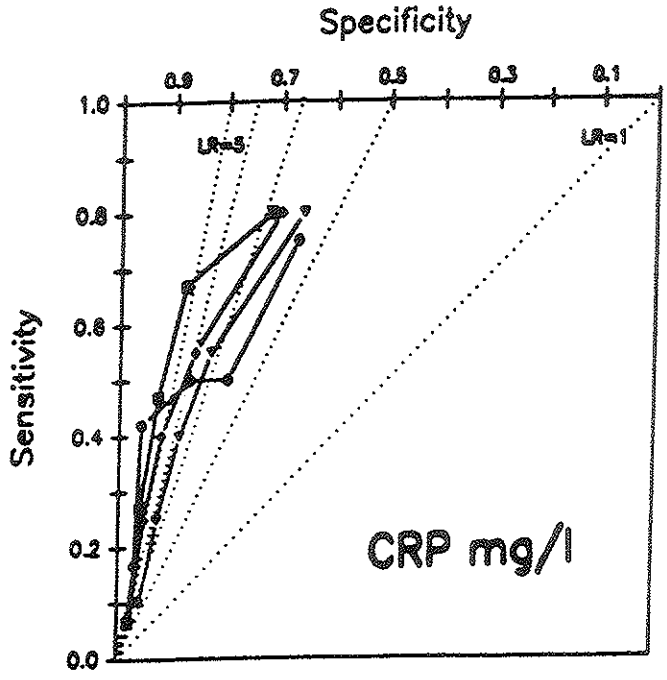
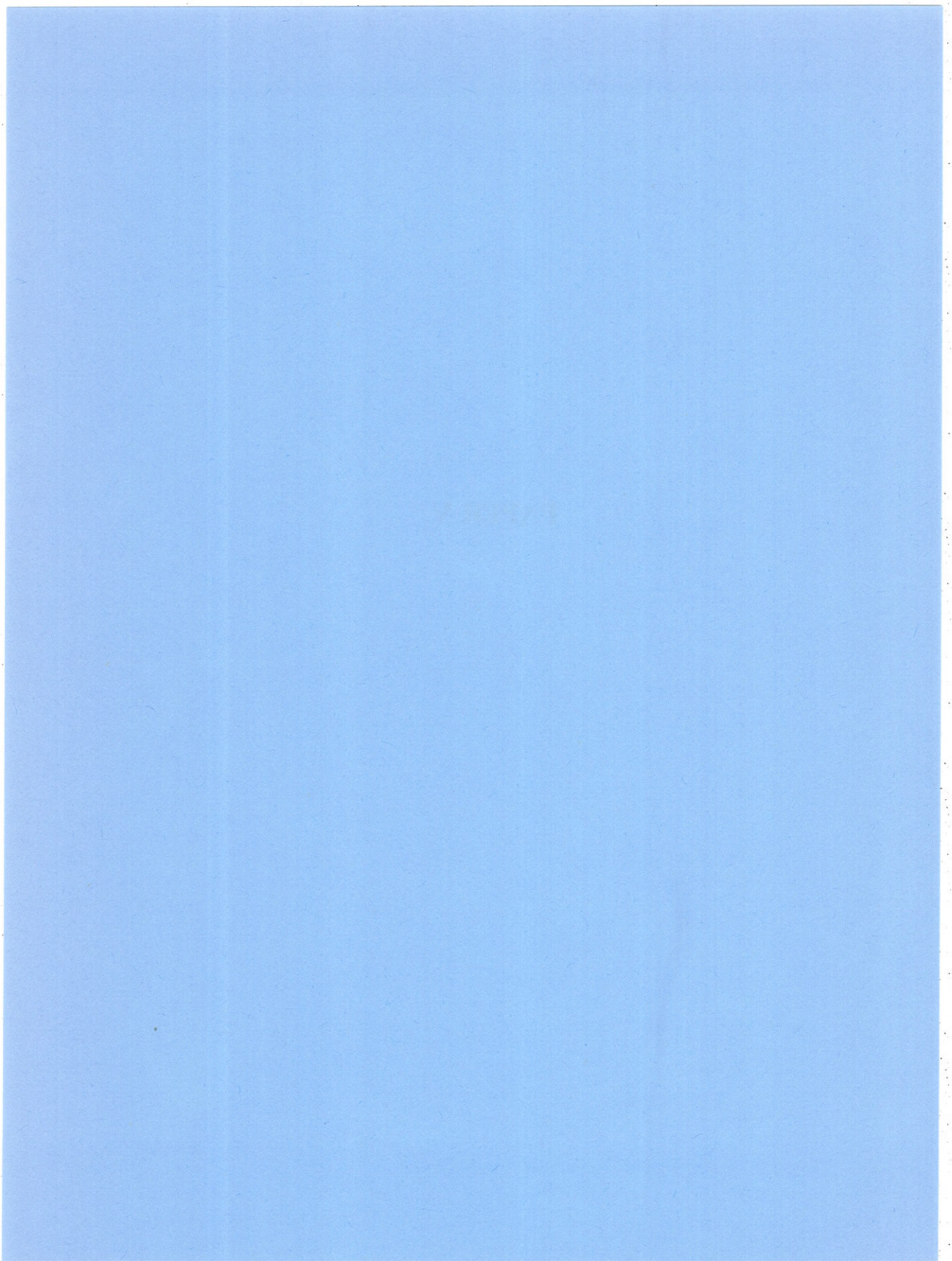

C-reactive protein ≥ 60 mg/l
LR
Sensitivity
Specificity
Likelihood Ratio
Positive Predictive Value

Figure 3


Specificity
0.9
0.7
0.5
0.3
0.1
1.0
0.8
0.6
0.4
0.2
0.0
Sensitivity
LR=5
LR=1
ESR mm/h
All patients (n=581)
Auscultation carried out (n=402)
Classified as LRTI (n=188)
Chest radiograph ordered by doctor (n=79)


Specificity
0.9
0.7
0.5
0.3
0.1
1.0
0.8
0.6
0.4
0.2
0.0
Sensitivity
LR=5
LR=1
CRP mg/l

PAPER V



Short Communication

INTEROBSERVER VARIABILITY IN THE RADIOGRAPHIC DIAGNOSIS OF ADULT OUTPATIENT PNEUMONIA

H. MELBYE and K. DALE

Institute of Community Medicine, and the Department of Radiology, University Hospital of Tromsø, Tromsø, Norway

Abstract

Acute chest radiographs were obtained from 319 adult patients with acute respiratory infections. Where a lower respiratory infection was diagnosed, follow-up chest radiographs were obtained in most patients. A radiologic panel diagnosed pneumonia in 21 patients. The agreements between the panel and 3 independent interpreters, 2 residents in radiology, and one senior chest physician, were assessed. Also the reports given by the specialist in radiology at the Department of Radiology were compared with the panel's evaluation. While the kappa-agreements between the panel's interpretations and those by the Department of Radiology and the consultant in chest medicine was 0.71 and 0.72, respectively, the corresponding kappa-values between the residents and the panel was only 0.50. The proportion of agreement when pneumonia was diagnosed was 0.56 between the panel and the Department of Radiology, and 0.59 between the panel and the chest consultant, compared to 0.36 between the panel and the residents. The study demonstrates the difficulty of diagnosing outpatient pneumonia and the importance of experience.

Key words: Lung, infection; —, radiographs; radiology and radiologists, observer performance.

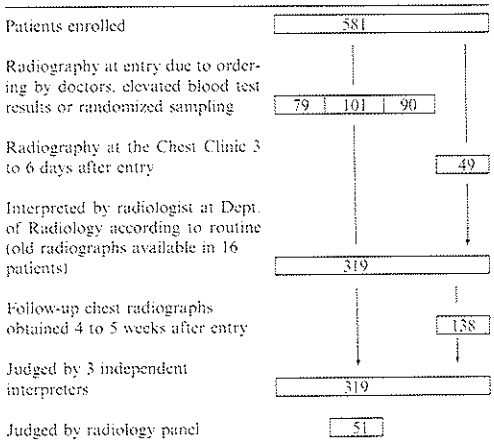
A noteworthy interobserver variability in the interpretation of chest radiographs (7), including the radiographic diagnosis of pneumonia in children (10), has been demonstrated. We assessed the diagnostic agreements on the diagnosis of pneumonia between the reports given by the specialist in radiology at the Department of Radiology, 3 independent interpreters, and a radiologic panel. Our aim was to throw light on the significance of interobserver variability in the radiographic diagnosis of adult outpatient pneumonia.

Material and Methods

Acute chest radiographs were obtained from 319 patients, aged 18 years or more, who consulted the Municipal Emergency Ward in Tromsø for a respiratory infection between October 1988 and May 1989. Radiographs were obtained from a total population of 581 patients (Table 1) using the following criterion: If pneumonia was considered possible by the physician, chest radiography was to be ordered. The patients were also selected for chest radiography if the erythrocyte sedimentation rate (ESR) exceeded 50 mm/h or if C-reactive protein (CRP) exceeded 60 mg/l. If the physician reported that the patient had a lower respiratory infection the thresholds for ordering a chest radiography were 20 mm/h (ESR) and 20 mg/l (CRP). Among the remaining patients, anticipated to have a low probability of pneumonia, chest radiography was performed in a 25% random sample. The patients were radiographed in p.a. and lateral projections the same evening or the following day (3 patients). The films were interpreted and reported by specialists in radiology at the Department of Radiology according to routine. The radiographs were also interpreted by the general practitioners at the Emergency Ward, except those taken after randomization.

Table 1

Flow chart showing the sequence of obtaining and interpreting chest radiographs in 581 adult patients with respiratory infection



The patients were asked to attend the Chest Clinic if they still had a cough or dyspnea after 10 days of illness. Chest radiography was then performed if not done at entry.

A return appointment was made for all patients 4 to 5 weeks after entry and 75% complied. Follow-up radiography was performed if the radiologists' report had revealed pneumonia (21 patients) or if the patient had been reported to have a lower respiratory infection (117 patients).

When the investigation was completed, the acute and follow-up chest radiographs (and old radiographs if available) were interpreted independently by 2 residents in radiology, who had been working 1 to 2 years at the department, and one consultant in chest medicine. The patients' participation in the study was known to the doctors, but no further information was given. The radiographs of 40 to 50 patients were interpreted at each reading session in a standard interpretation room at the Department of Radiology. If the conclusion of one or more of these doctors was an obvious or probable pneumonia, the chest radiographs were judged by a radiology panel consisting of the same 3 doctors who had made the independent interpretations and an experienced consultant in radiology (K. D.). If the routine radiology report of the acute radiograph had described a pneumonia or any other pathologic feature (8 patients), the films were also judged by the panel. After discussing the radiographs, each member of the panel gave a written vote: pneumonia or not. If 3 of the doctors voted for pneumonia, this became the final diagnosis. If the diagnosis of pneumonia was based only on an acute chest radiograph, a follow-up examination was performed and the diagnosis revised by the panel. Only one final diagnosis of pneumonia was based on the acute radiograph alone.

Statistics. The proportion of agreement between each interpreter

Table 2

Agreements on the radiographic diagnosis of pneumonia between a radiology panel and other interpreters in 319 adult patients with respiratory infection. 21 patients were judged by the panel to have a pneumonia

Interpreter	Judged as pneumonia n	Pneumonia-diagnosis in agreement with the panel n	Agreement when pneumonia was diagnosed p (CI)	Agreement when non-pneumonia was diagnosed p (CI)	k-agreement k (CI)
Radiologist, at Dept. of Radiology	21	15	0.56(0.37-0.74)	0.96(0.94-0.98)	0.71(0.59-0.83)
Resident in radiology A	9	8	0.36(0.16-0.56)	0.94(0.92-0.96)	0.50(0.40-0.60)
Resident in radiology B	17	10	0.36(0.18-0.53)	0.95(0.93-0.97)	0.50(0.40-0.60)
Consultant in chest medicine	25	17	0.59(0.41-0.76)	0.96(0.94-0.98)	0.72(0.60-0.84)

p = proportion of agreement, CI = 95% confidence interval, k = kappa

Table 3

Kappa-agreement on the radiographic diagnosis of pneumonia obtained between various interpreters in 319 adult patients with respiratory infection

	Radiology panel	Radiologist at Department of Radiology	Resident in radiology A	Resident in radiology B
Radiologist at Dept. of Radiology	0.71			
Resident in radiology A	0.50	0.44		
Resident in radiology B	0.50	0.43	0.51	
Consultant in chest medicine	0.72	0.49	0.39	0.34

and the panel and the 95% confidence interval of the proportions were calculated when a diagnosis of pneumonia was made by any of the 2 and when any of the 2 diagnosed non-pneumonia (5). Kappa-agreements were also calculated (3), between the panel and the individual interpreters, and between pairs of interpreters.

Results

Diagnoses made by the panel. The films of 51 of the patients were finally judged by the radiology panel. Pneumonia was diagnosed by the panel in 21 patients, 10 men and 11 women. Mean age was 39 years (range 18–71). The mean duration of illness at entry was 10 days (range 2–30). None had been treated with an antibiotic in advance. A radiographic diagnosis of pneumonia was made in 12 of the 79 patients who had chest radiography ordered by the doctor; in 8 of the 102 patients who were radiographed because of pathologic blood tests; and in one of the 49 patients who were radiographed at the Chest Clinic a few days after entry. No pneumonia was found among the 90 patients radiographed after randomization (7 of the 97 in the random sample refused).

Discrete densities were found in most of the pneumonias, and no patient had lobar consolidation. Two of the patients turned out to have a pulmonary cancer. In the analyses it was assumed that none of the radiographs considered to be normal by the 3 independent interpreters and the Department of Radiology, would have been diagnosed as pneumonia by the panel.

Diagnoses made by the other interpreters. Twenty-one of the acute radiographs were judged by the Department of Radiology to show pneumonia. The chest physician diagnosed pneumonia in 25 patients, and the residents in radiology in 9 and 17 patients, respectively. The doctors at the emergency ward who interpreted 157 acute chest radiographs, made a radiographic diagnosis of pneumonia in 30 patients.

Interobserver agreements. Agreements on the diagnosis of pneumonia are shown in Table 2. The radiologists at the Department of Radiology and the consultant in chest medicine obtained similar kappa-agreements with the panel, 0.71 and 0.72, respectively, while a lower kappa-value, 0.50, was found between the residents and the panel. Kappa-values obtained between pairs of the independent interpreters were generally lower than between the panel and the interpreters (Table 3). A low kappa-agreement, 0.35, was found between the general practitioners and the panel. There was an agreement on pneumonia in 11 patients only, and the proportion of agreement on a positive diagnosis was 0.27.

Discussion

The difficulty of diagnosing pneumonia is confirmed by the study. The proportion of agreement between the panel and the radiologists at Department of Radiology on a positive diagnosis was not satisfactory, although affected by the relatively low number of pneumonias. However, similar results were found in the study of STICKLER et al. (10). Better agreement would probably have been obtained if follow-up films had been available for both. Suggestive clinical information presented only to the radiologists at Department of Radiology, may also have contributed to the disagreement (2).

The agreements between the residents and the panel were still poorer. Low agreement with authorized judgment has previously been described in the first year of residency (8). The agreement between the general practitioner and the panel was lower than a corresponding agreement in a previous study (6), probably due to a greater experience in interpreting chest radiographs among American family physicians. The low agreement indicates that general practitioners should be very cautious when interpreting chest radiographs.

Pneumonias may be invisible on radiographs at an early stage of disease (9). Although supplementary information about the patient should be of concern in the overall clinical judgement, a reversible

density on chest radiographs is our best reference standard of pneumonia (1, 4). Discerning discrete densities from normality is obviously a difficult task, and should be strongly emphasized in the teaching of residents in radiology.

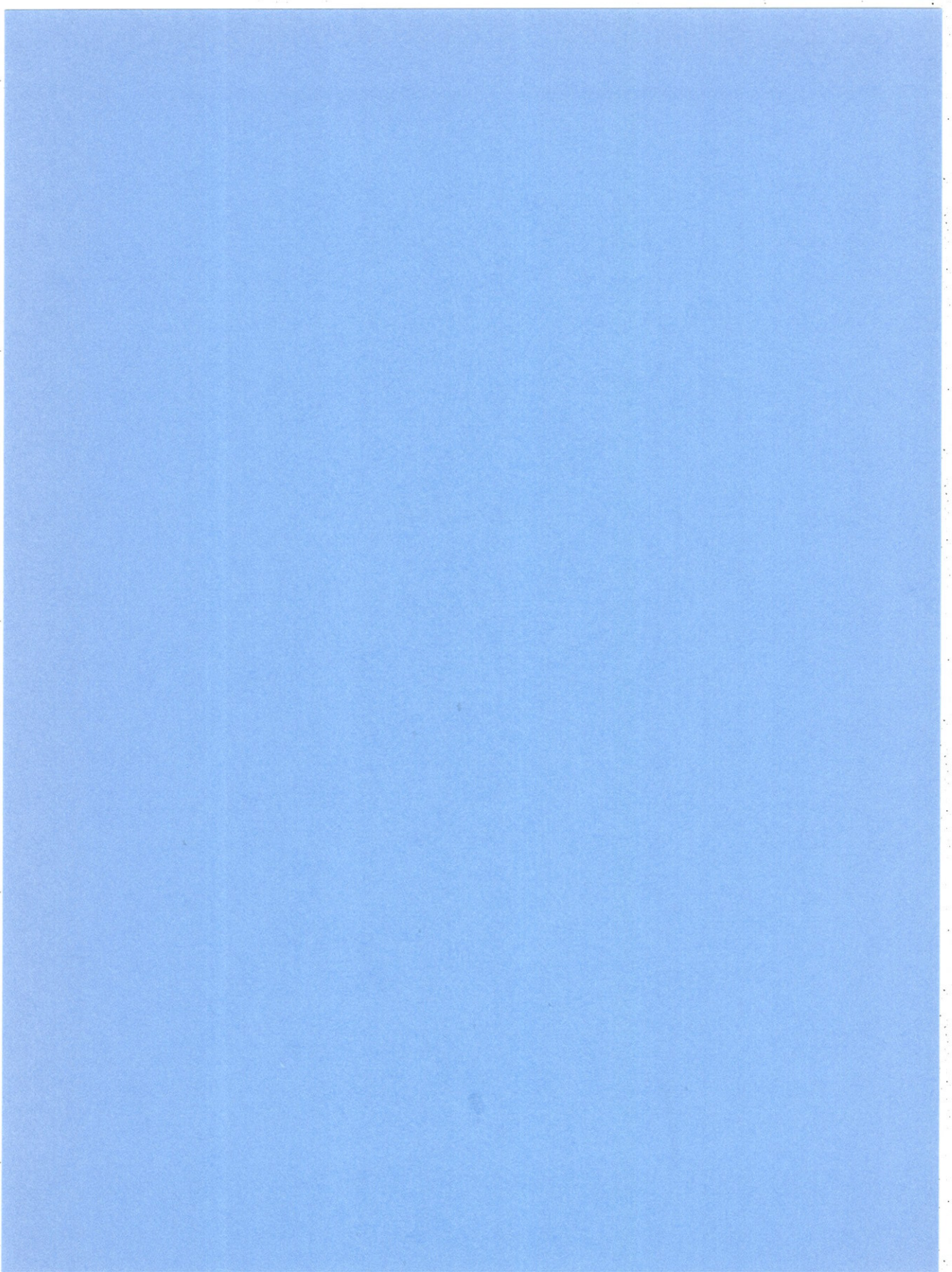
Request for reprints Dr. Hasse Melbye, Institute of Community Medicine, University of Tromsø, N-9000 Tromsø, Norway.

REFERENCES

1. Conte P., Heitzman E. R. & Markarian B.: Viral pneumonia. Roentgen pathological correlations. Radiology 95 (1970), 267.
2. Doubilet P. & Herman P. G.: Interpretation of radiographs. Effect of clinical history. AJR 137 (1981), 1055.
3. Fleiss J. L.: Statistical methods for rates and proportions. p. 212. John Wiley & Sons. New York 1981.
4. Goodman L. R., Goren R. A. & Teplick S. K.:The radiographic evaluation of pulmonary infection. Med. Clin. North Am. 64 (1980), 553.
5. Grant J. M.: The fetal heart rate is normal, isn't it? Observer agreement of categorical assessments. Lancet 337 (1991), 215.
6. Halvorsen J. G., Kunian A., Gjerdingen D. et al.: The interpretation of office radiographs by family physicians. J. Fam. Pract. 28 (1989), 426.
7. Herman P. G., Gerson D. E., Hessel S. J. et al.: Disagreements in chest roentgen interpretation. Chest 68 (1975), 278.
8. Herman P. G. & Hessel S. J.: Accuracy and its relation to experience in the interpreation of chest radiographs. Invest. Radiol. 10 (1975), 62.
9. Stein M. T.: Delayed roentgenographic signs associated with acute pneumonia in children. J. Fam. Pract. 12 (1981), 639.
10. Stickler G. B., Hoffman A. D. & Taylor W. F.: Problems in the clinical and roentgenographic diagnosis of pneumonia in young children. Clin. Pediatr. 23 (1984), 398.

Accepted for publication 11 August 1991.

PAPER VI



Radiographic Pneumonia: Validity as Reference Standard of Pneumonia in a Clinical Epidemiologic Study.

Hasse Melbye MD
Institute of Community Medicine, University of Tromsø.

Correspondence: Hasse Melbye, Institute of Community Medicine, University of Tromsø, Breivika, 9037 Tromsø, Norway.

Abstract:

Diagnostic values of symptoms and signs for pneumonia were evaluated against a compound referance standard, based on several indicators of pneumonia, and compared with the diagnostic values obtained when a traditional radiographic reference standard was used. Our objective was to estimate the magnitude of errors which could be expected, due to the use of a radiographic reference standard in a clinical epidemiologic study. Twenty-nine patients were classified as having pneumonia according to the compound reference standard, including all the 20 radiographic pneumonias. Four of the additional nine patients had been diagnosed, based on history and physical examination alone, as having pneumonia and five as acute bronchitis. Six had serological evidence of pneumococcal infection and three of mycoplasmal infection. When the LRs of clinical cues evaluated against the two different reference standards were compared, no significant difference was found. We conclude that the use of a radiographic reference standard of pneumonia in the evaluation of diagnostic tests probably does not represent an important source of error.

Key words: Reference standard, bias, pneumonia, diagnosis.

In most medical publications on pneumonia, an acute radiographic density is used as criterion of pneumonia (1). Single cases of early pneumonia without radiographic signs have been reported (2,3) but we do not know the frequency of such cases in medical practice. A roentgen pathological correlative study of viral pneumonia showed that all but the earliest pathological changes found by autopsy had a radiographic counterpart (4). The most obvious indication of unreliability of the radiographic diagnosis is probably the variability of interpretation between radiologists judging the same radiographs (5,6,7).

A radiographic reference standard was used in evaluating the diagnostic value of respiratory symptoms and chest signs for pneumonia in a recent study from general practice (8). Based on the same material clinical cues have been evaluated against an alternative reference standard in this study, based on combinations of indicative findings, a radiographic density being one of them. Diagnostic values against this new referance standard have been compared with those obtained when the traditional radiographic reference standard was used. Our objective was to estimate the magnitude of errors which could be expected, due to the use of a radiographic reference standard in a clinical epidemiologic study.

MATERIAL AND METHODS

Patients

The investigation took place at the Municipal Emergency Ward of Tromsø, between Oktober 1988 and May 1989. Forty doctors

participated. Consecutive patients aged 18 years or more, presenting an illness suggestive of a respiratory tract infection or throat infection were asked to enter the study. Patients with dyspnea, severe enough to need urgent help, and pregnant women were excluded. Among 581 patients who were included, the doctors carried out chest examination in 402, and our analyses are based on these patients. 70% were women, and mean age was 33.2 years. The study was approved by the Regional Committee of Medical Research Ethics.

Examinations

The examinations carried out, accounted for in detail elsewhere (8,9,10), may be summarized as follows: Before consulting the doctor the patients were examined by a specially trained nurse. Oral temperature was measured and blood samples were drawn for the analysis of eythrocyte sedimentation rate (ESR), C-reactive protein (CRP), white blood-cell (WBC) count, and microbiological serology. On a questionnaire the patients reported symptoms associated with the present illness. The doctors recorded physical chest findings and one main diagnosis was noted. 29 patients were diagnosed as having a pneumonia, based on history and physical examination alone. A chest radiograph was ordered in 79 patients, because the doctor regarded pneumonia to be possible, and 101 patients were in addition radiographed due to elevated CRP or ESR values. A chest radiograph was also ordered in a 25% random sample of the remaining patients, assumed to have a low probability of pneumonia.

Four to five weeks after entry 75% of the patients met for

a return consultation. Blood were drawn for convalescent serology, and follow-up radiographs were obtained.

The radiographic reference standard

Radiographic pneumonia was diagnosed in 20 patients, as judged by a radiology panel. The radiograph had been ordered by doctor in 12 of these patients and because of raised ESR and CRP values in eight. No pneumonias were diagnosed in the 25% random sample, and in the calculation of diagnostic values we made the assumption that there were no pneumonias among the patients subjected to randomization.

The compound reference standard

The radiographic pneumonias were included if:

1. pneumonia had also been diagnosed clinically or
2. if ESR > 25 mm/h, or CRP > 20 mg/l or WBC-count > $11x10^{1}9/l$, or positive serologi for respiratory pathogens (10) was established.

In addition were the following patients included:
Patients diagnosed as having a lower respiratory tract infection (pneumonia, acute bronchitis, aggravation of asthma or chronic obstructive pulmonary disease (COPD)) if positive serology for pneumococcal, mycoplasmal, chlamydial infection or legionellosis was established (10) and the value of ESR, CRP or WBC-count was above the reference limits listed above.

Twenty-nine patients were classified as having pneumonia

according to the compound reference standard. All the 20 radiographic pneumonias met the inclusion criteria, and nine of the other patients. Four of these had been clinically diagnosed as having pneumonia and five as having acute bronchitis. Six had serological evidence of pneumococcal infection and three of mycoplasmal infection (10).

Statistical analyses

Sensitivity, specificity, and likelihood ratio (LR) (11) were calculated against the compound reference standard for the symptoms and physical signs found be most significantly associated with radiographic pneumonia (8), and of oral temperature dichotomized at a threshold of 38°C. If LR was outside the 95% confidence (12) limits of the corresponding LR evaluated against the radiographic reference standard, the difference was regarded as significant. SAS statistical software package was used in the statistical analyses.

RESULTS

The diagnostic values of symptoms and signs obtained when using the coumpound reference standard are shown i table 1, together with the previously published results (8,9) from the evaluation against the radiographic reference standard. No significant difference in LR was found when the evaluations gainst the two different reference standards were compared. The largest

difference was found for the least prevalent finding: pleural rubs. The LRs of cough, temperature and crackles were a little higher when evaluated against the compound reference standard compared to the evaluation against the radiographic reference standard, while the opposite was found for lateral chest pain and dyspnea.

DISCUSSION

The compound reference standard may be subjected to criticism. Including patients with a normal chest radiograph only when pneumococcal, mycoplasmal or chlamydial infection was established, may be too restricted. However, the possible pneumonias calling for antibacterial treatment have probably been included. Moreover, the distinction of radiographically invisible viral pneumonias from viral acute bronchitis is probably not clinically significant.

The inclusion criteria of the compound reference standard may also be criticized of being to liberal. The patients with a normal chest radiograph who were included in the compound reference standard may have suffered solely from acute bronchitis, at least some of them. The greater diagnostic values of typical findings like crackles and pleural rubs when the compound reference standard was used compared with the evaluation against the radiographic reference standard, indicates that at least some of the additional pneumonias were real. The lower value of dyspnea and chest pain may be explained by a possible association between the size of infiltrate and the degree of dyspnea and chest pain, thus being

more frequent in pneumonias visible on radiographs.

The liberal criteria for including the radiographic pneumonias in the compound reference standard relies on the assumption that the risk of a false positive radiographic diagnosis is low. This is probably justified by the fact that the panels interpretations were based on both acute and follow-up radiographs, which may reduce the risk of false positives.

Error of the radiographic diagnosis has implications for the emphasis to be laid on the radiological report in the clinical evaluation of patients. One cannot always rely on a normal chest radiograph when a decision on antibacterial treatment is to be made (10). However, the use of a radiographic reference standard of pneumonia in the evaluation of diagnostic tests does not necessarily represent an important source of error.

References

1. Goodman LR, Goren RA, Teplick SK. The radiographic evaluation of pulmonary infection. Med Clin North Am 1980; 64:553-74.
2. Stein MT. Delayed roentgenographic signs associated with acute pneumonia in children. J Fam Pract 1981;12:639-44.
3. Aderka A, Sidi Y, Garfinkel D, Rothem A, Weinberger A, Pinkhas J. Roentgeologically invisible mucormycosis pneumonia. Respiration 1983;44:158-60.
4. Conte P, Heitzman ER, Markarian B. Viral pneumonia. Roentgen pathological correlations. Radiology 1970;95:267-72.
5. Herman PG, Gerson DE, Hessel SJ, Mayer BS, Watnick M, Blesser B, et al. Disagreements in chest roentgen interpretation. Chest 1975;68:278-82.
6. Stickler GB, Hoffmann AD, Taylor WF. Problems in the clinical and roentgenographic diagnosis of pneumonia in young children. Clin Pediatr 1984;23:398-9.
7. Melbye H, Dale K. Interobserver variability in the radiographic diagnosis of adult outpatients pneumonia. Acta Radiol 1992;33:79-81.
8. Melbye H, Straume B, Aasebø U and Dale K. Diagnosis of adult pneumonia in general practice. The relative importance of typical symptoms and physical signs, evaluated against a radiographic reference standard. Scand J Prim Health Care. Accepted for publication.

9. Melbye H, Straume B, Brox J. Laboratory tests for adult pneumonia in general practice. The diagnostic values depend on the duration of illness. Scand J Prim Health Care. Accepted for publication.Submitted for publi-
cation.

10. Melbye H, Berdal BP, Straume B, Russell H, Vorland L, Thacker WL. Pneumonia, a clinical or radiographic diagnosis. Etiology and clinical features of adult lower respiratory tract infections in general practice. Scand J Infect Dis. Accepted for publication.

11. Radack KL, Rouan G, Hedges J. The likelihood ratio. Arch Pathol Lab Med 1986;110:689-93.

12. Morris JA, Gardner MJ. Calculating confidence intervals for relative risks, odds ratios, and standardised ratios and rates. In: Gardner MJ, Altman DG, eds. Statistics with confidence: Confidence Intervals and Statistical Guidelines. London, England: British Medical Association 1989:50-63.

Table I

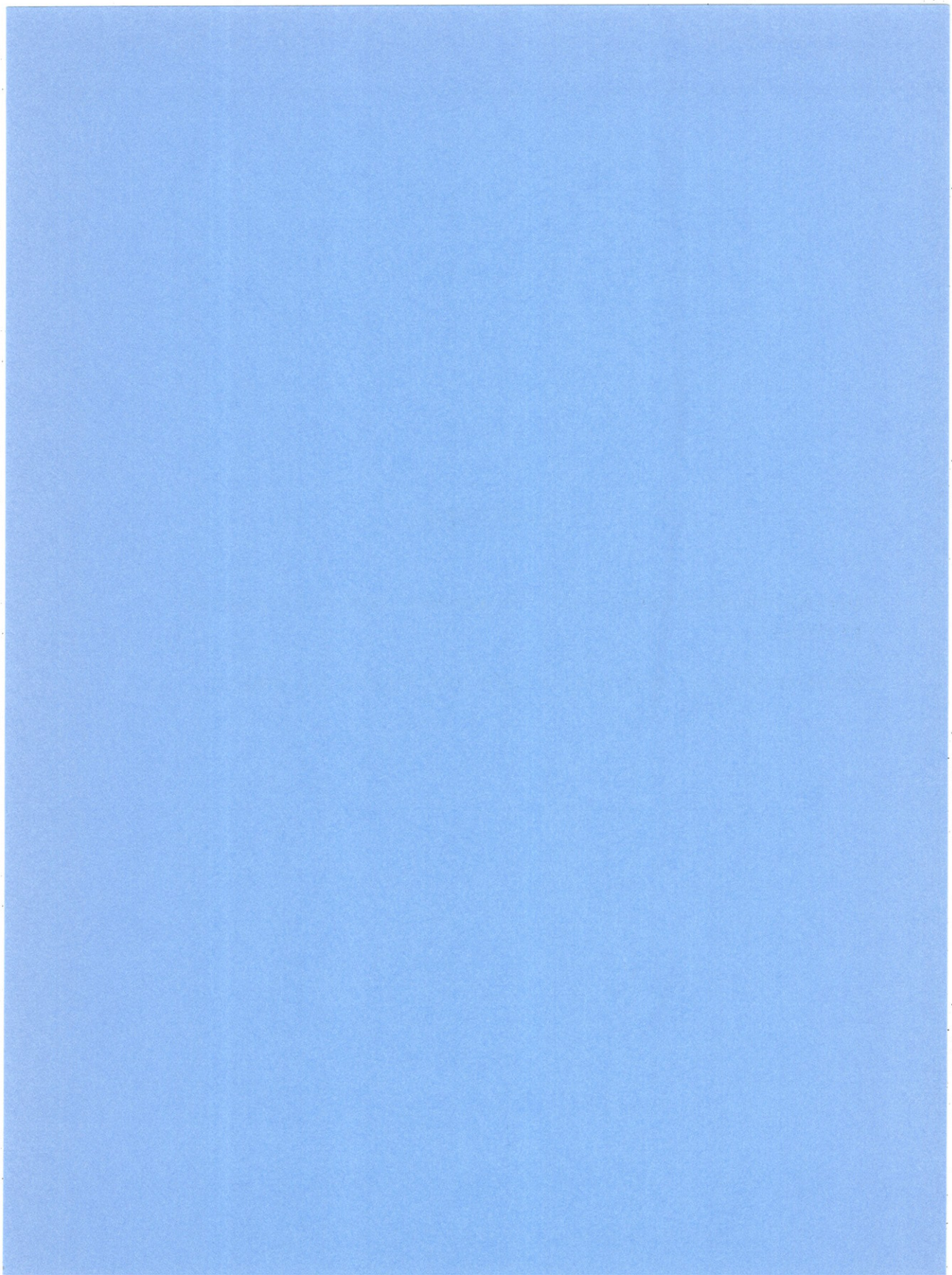
Diagnostic value of clinical cues for pneumonia evaluated against a radiographic (n=20) and a compound reference standard (n=29), in 402 adult patients with respiratory tract infection in general practice.

	Evaluated against radiographic pneumonia			Evaluated against the compound reference standard		
Findings	Sensitivity	Specificity	Likelihood ratio	Sensitivity	Specificity	Likelihood ratio
Very annoying cough	0.65	0.65	1.8 (1.2-2.9)	0.69	0.66	2.0
Very annoying dyspnea	0.35	0.91	4.0 (2.0-8.2)	0.31	0.92	3.7
Strong lateral chest pain	0.25	0.95	4.8 (2.0-11.4)	0.21	0.95	4.1
Temperature >= 38°C	0.40	0.88	3.5 (1.9-6.4)	0.45	0.90	4.3
Crackles	0.35	0.91	3.7 (1.8-7.6)	0.45	0.92	5.6
Wheezes, no crackles	0.15	0.85	1.0 (0.3-2.8)	0.14	0.84	0.9
Pleural rubs	0.10	0.98	6.4 (1.6-25.3)	0.14	0.99	12.9

APPENDIX

Self-administered questionnaire for patients´ report of symptoms (4 pages).

Form for doctors´ recording of signs and diagnosis (2 pages).



l.nr:	Nedre luftveisinfeksjoner i allmenn praksis	skjema 4

OBS!
Alle spørsmålene på dette spørreskjemaet gjelder den akutte sykdommen, som du oppsøker legevakta for i dag.

Dersom du kommer for en kronisk sykdom, gjelder spørsmålene bare den akutte forverrelsen av sykdommen, som har ført til at du nå oppsøker lege.

1. Hvor mange dager har den sykdommen som du nå oppsøker lege for, vedvart med daglige symptomer eller plager? .....dager

2. Har det vært slik ved denne sykdommen at du plutselig er blitt betydelig værre, etter at du har vært syk noen dager? Nei:I__I Ja:I__I

   Hvis ja, hvor mange dager er det siden? .....dager

3. Har du vært til legeundersøkelse før for denne sykdommen? Nei:I__I Ja:I__I
   Hvis nei hopp til spørsmål 7.
   Hvis ja, besvar også spørsmål 4-6.:

4. Har du fått penicillin eller annen antibiotika mot sykdommen? Nei:I__I Ja:I__I

   I så fall hvilken type? .....

5. Har du fått astmamedisin mot sykdommen? Nei:I__I Ja:I__I

6. Har du fått hostemedisin mot sykdommen? Nei:I__I Ja:I__I

7. Den viktigste grunnen eller de 2 viktigste grunner til at du oppsøker lege i dag ? (Sett ett eller to kryss).

a. trenger sykemelding.	I__I
b. ønsker å få vite hva jeg feiler.	I__I
c. for å få medisin, hvis det trengs.	I__I
d. jeg trenger penicillin eller annen antibiotika.	I__I
e. jeg trenger medisin mot hoste eller astma.	I__I
f. jeg vil utelukke at jeg har alvorlig sykdom.	I__I
g. annen grunn	I__I

8. Var det mindre enn en ukes opphold mellom forrige luftveisinfeksjon og den sykdommen du har nå? Nei:I__I Ja:I__I

9. Har du vært plaget med svette/klamhet? Nei:I__I litt:I__I mye:I__I

10. Har du vært plaget med slapphet? Nei:I__I litt:I__I mye:I__I

11. Har du vært plaget med hodepine? Nei:I__I litt:I__I mye:I__I

12. Har du hatt vondt i halsen ? Nei:I__I litt:I__I mye:I__I

    Hvis mye, blir det værst ved svelging av spytt:I__I eller mat:I__I

13. Har du hatt muskel eller leddsmerter? Nei:I__I litt:I__I mye:I__I

14. Har du hatt snue eller tett nese ? Nei:I__I litt:I__I mye:I__I

15. Har du hatt øresmerter ? Nei:I__I litt:I__I mye:I__I

16. Har du hatt ansiktssmerter(kinn/øyne)? Nei:I__I litt:I__I mye:I__I

17. Kommer det slim bak i halsen som du enten svelger ned eller hoster opp ? Nei:I__I litt:I__I mye:I__I

18. Har du hatt frysetokter med skjelving? Nei:I__I Ja:I__I

    Hvis ja, sett kryss der det passer (ett eller to):

    Det første døgnet:I__I

    Senere i sykdomsforløpet:I__I

HOSTE.

19. Har du hostet ved denne sykdommen? Nei: I__I
(sett bare ett kryss) Som normalt I__I
Mer plagsomt enn normalt I__I
Svært plagsomt I__I

Hvis "nei" eller "som normalt", hopp videre til spørsmål 23.
Hvis svaret er "mer plagsomt enn normalt" eller
"svært plagsomt", besvar også spørsmål 20 - 23.

20. Forverres hosten særlig, (sett kryss der det passer):

ved anstrengelser	I__I
når du trekker inn kald luft	I__I
når du kommer inn fra kulden (til et varmt rom.)	I__I
ved røyking eller røykfull luft	I__I
om natta	I__I
om morgenen	I__I
av andre årsaker	I__I
ikke av noe spesielt	I__I

21. Hvilket av de 3 utsagnene nedenfor passer best for deg?
(Sett bare ett kryss).

- Jeg kremter for det meste, hoster ikke så mye. I__I
- Jeg hoster p.g.a. slim eller irritasjon i halsen I__I
- jeg hoster p.g.a. slim eller irritasjon i brystet I__I

22. Når du hoster, kommer det oppspytt? Nei(tørrhoste):I__I ja:I__I

Hvis ja, hvordan ser oppspyttet ut?
(sett ett eller flere kryss):

bare hvitt,blankt	I__I
gult eller grønt	I__I
av og til blodig	I__I
vet ikke	I__I

23. Har du noen gang måttet brekke deg eller kaste
opp når du har hostet ved denne sykdommen ? Nei:I__I ja:I__I

Brystsmerter.

24. Har du hatt brystsmerter ved denne sykdommen? Nei:I__I ja:I__I

Hvis ja, sett kryss der det passer (ett eller flere):

Bare litt midt i brystet	I__I
Bare litt i brystkassa forøvrig	I__I
Sterke midt i brystet	I__I
Sterke i brystkassa forøvrig	I__I
Smertene sitter øverst i magen	I__I

25. Forverres brystsmertene i spesielle sitasjoner? Nei:I__I ja:I__I

Hvis ja, sett kryss der det passer (ett eller flere):

ved anstrengelser	I__I
når du hoster	I__I
når du puster dypt	I__I
når du ligger eller sitter i spesielle stillinger	I__I

Tung pust.

26. Har du vært tung i pusten ved denne sykdommen? Nei:I__I ja:I__I

Hvis ja, hvor tung i pusten har du vært?

Som normalt	I__I
Mer plagsomt enn normalt	I__I
Svært plagsomt	I__I

<u>Røykevaner.</u>

27. I hvor mange år har du røykt? ..... år

28. Hvor mange sigaretter røykte du pr. dag før du nå ble syk? ..... pr. dag

29. Hvor mange sigaretter har du røykt pr.dag mens du nå har vært syk? ..... pr. dag

l.nr:	Nedre luftveisinfeksjoner i allmenn praksis	skjema 5

Dette skjema skal inkluderte pasienter ha med seg til legevaktslegen, som skal fylle det ut. Pasienten tar det med seg tilbake til sykepleier etter undersøkelsen.

1. Perkusjon av thorax. Ikke utført:I__I Utført:I__I
   Hvis utført, finner du:

	Nei	h.lunge	v.lunge	begge lunger
2. Dempning ?	I__I	I__I	I__I	I__I
3. Hypersonor perk.lyd.?	I__I	I__I	I__I	I__I

4. Lungeauskultasjon. Ikke utført:I__I Utført:I__I
   Hvis utført, finner du:

	Nei	h.lunge	v.lunge	begge lunger
5. Knatrelyder (krepitasjoner/blærer)	I__I	I__I	I__I	I__I
6. Pipelyder (Rhonki/sibili)	I__I	I__I	I__I	I__I
7. Svekket respir.lyd	I__I	I__I	I__I	I__I
8. Pleural gnidningslyd	I__I	I__I	I__I	I__I

9. Vurdering av respirasjonen. Ikke utført:I__I Utført:I__I
   Hvis utført:
   10. Har pasienten en besværet respirasjon? Nei:I__I Ja:I__I
   11. Har pasienten forlenget expirium? Nei:I__I Ja:I__I

Luftveisinfeksjon, øvre eller nedre ?

12. Dersom pas. har en luftveisinfeksjon, er både øvre og nedre luftveier affisert? (nedre luftveier: bronkier, bronkioler og lunger.)

    Ikke luftveisinfeksjon:I__I

    Bare øvre:I__I Bare nedre:I__I Både øvre og nedre:I__I

Etiologisk diagnose.

13. Tror du pasienten har:
    a. virusinfeksjon I__I
    b. bakteriell infeksjon I__I
    c. Både virus- og bakteriell infeksjon I__I
    d. Ingen av delene I__I

Snu arket !

14. Har pasienten en infeksjon med influensavirus? Nei:I__I Ja:I__I
Merk av grad av sikkerhet på skalaen med et kryss.

Nei, sikkert ikke. Ja, helt sikkert.

I_____I

15. Har pasienten en streptokokkinfeksjon? Nei:I__I Ja:I__I
Merk av grad av sikkerhet på skalaen med et kryss.

Nei, sikkert ikke. Ja, helt sikkert.

I_____I

Svaret på strepokokktesten kan nå innhentes!

16. Har svaret på streptokokktesten betydd noe for din behandling av pasienten?
Nei:I__I Ja:I__I Prøvesvar ikke innhentet:I__I

17. **Hoveddiagnose**, (Organ/nivå-relatert, fylles ut på klinisk grunnlag uten rtg. bilde). Sett bare ett kryss:

a. Rhinitt	I__I	b. Faryngitt	I__I
c. Otitis media	I__I	d. Sinusitt	I__I
e. Tonsilitt	I__I	f. Laryngitt	I__I
g. Akutt bronkitt			I__I
h. Exacerbasjon av astma, kronisk bronkitt eller kronisk obstruktiv lungesykdom			I__I
i. Pneumoni			I__I
j. Ikke luftveisinfeksjon.			I__I

Hvis "j", diagnose?: .....

Pneumoni ?

18. Er det noen mulighet for at pasienten kan ha pneumoni, som er av klinisk betydning? Nei:I__I Ja:I__I

Hvis ja, send pasienten til rtg.u.s. med vedlagte remisse og vurder bildet før du fyller ut resten av skjemaet.

Hvis nei, hopp til spørsmål 20 og fyll ut resten av skjemaet.

Resultat av Rtg. Thorax.

19. Din vurdering av rtg.bildet: Ikke pneumoni:I__I Pneumoni:I__I

Medikamentell behandling som institueres nå.

20. Antibiotikabehandling? Nei:I__I Ja, rp. til evt. bruk:I__I
Ja, starter behandling i kveld:I__I
Hvis ja, hvilket medikament:.....

21. I__I Astmamedisin, hvilken?:.....

22. I__I Hostemedisin, hvilken?:.....

ISM SKRIFTSERIE - FØR UTGITT:

1. Bidrag til belysning av medisinske og sosiale forhold i Finnmark fylke, med særlig vekt på forholdene blant finskættede i Sør-Varanger kommune.
   Av Anders Forsdahl, 1976. (nytt opplag 1990)

2. Sunnhetstilstanden, hygieniske og sosiale forhold i Sør-Varanger kommune 1869-1975 belyst ved medisinal-beretningene.
   Av Anders Forsdahl, 1977.

3. Hjerte-karundersøkelsen i Finnmark - et eksempel på en populasjonsundersøkelse rettet mot cardiovasculære sykdommer. Beskrivelse og analyse av etterundersøkelsesgruppen.
   Av Jan-Ivar Kvamme og Trond Haider, 1979.

4. The Tromsø Heart Study: Population studies of coronary risk factors with special emphasis on high density lipoprotein and the family occurrence of myocardial infarction.
   Av Olav Helge Førde og Dag Steinar Thelle, 1979.

5. Reformer i distriktshelsetjenesten III: Hypertensjon i distriktshelsetjenesten.
   Av Jan-Ivar Kvamme, 1980.

6. Til professor Knut Westlund på hans 60-års dag, 1983.

7. Blodtrykksovervåkning og blodtrykksmåling.
   Av Jan-Ivar Kvamme, Bernt Nesje og Anders Forsdahl, 1983.

8. Merkesteiner i norsk medisin reist av allmennpraktikere - og enkelte utdrag av medisinalberetninger av kulturhistorisk verdi.
   Av Anders Forsdahl, 1984.

9. "Balsfjordsystemet." EDB-basert journal, arkiv og statistikksystem for primærhelsetjenesten.
   Av Toralf Hasvold, 1984.

10. Tvunget psykisk helsevern i Norge. Rettsikkerheten ved slikt helsevern med særlig vurdering av kontrollkommisjonsordningen.
    Av Georg Høyer, 1986.

11. The use of self-administered questionnaires about food habits. Relationships with risk factors for coronary heart disease and associations between coffee drinking and mortality and cancer incidence.
    Av Bjarne Koster Jacobsen, 1988.

12. Helse og ulikhet. Vi trenger et handlingsprogram for Finnmark.
    Av Anders Forsdahl, Atle Svendal, Aslak Syse og Dag Thelle, 1989.

interventions.
Av Anne Johanne Søgaard, 1989.

14. Helsekontroller i praksis. Erfaringer fra prosjektet helsekontroller i Troms 1983-1985.
Av Harald Siem og Arild Johansen, 1989.

15. Til Anders Forsdahls 60-års dag, 1990.

16. Diagnosis of cancer in general practice. A study of delay problems and warning signals of cancer, with implications for public cancer information and for cancer diagnostic strategies in general practice.
Av Knut Holtedahl, 1991.

17. The Tromsø Survey. The family intervention study. Feasibility of using a family approach to intervention on coronary heart disease. The effect of lifestyle intervention of coronary risk factors.
Av Synnøve Fønnebø Knutsen, 1991.

18. Helhetsforståelse og kommunikasjon. Filosofi for klinikere.
Av Åge Wifstad, 1991.

19. Factors affecting self-evaluated general health status - and the use of professional health care services.
Av Knut Fylkesnes, 1991.

20. Serum gamma-glutamyltransferase: Population determinants and diagnostic characteristics in relation to intervention on risk drinkers.
Av Odd Nilssen, 1992.

21. The Healthy Faith. Pregnancy outcome, risk of disease, cancer morbidity and mortality in Norwegian Seventh-Day-Adventists.
Av Vinjar Fønnebø, 1992.

22. Aspects of breast and cervical cancer screening.
Av Inger Torhild Gram, 1992.

23. Population studies on dyspepsia and peptic ulcer disease: Occurrence, aetiology, and diagnosis. From The Tromsø Heart Study and The Sørreisa Gastrointestinal Disorder Studie.
Av Roar Johnsen, 1992.