Lower respiratory tract infections in adults : a clinical diagnostic study in general practice

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Chapter V

Prediction rules fail prediction: Validation of prediction rules for pneumonia in adult patients in general practice

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5.1 Abstract

Background: Prediction rules based on clinical information have been developed to support general practitioners to diagnose pneumonia. However, prediction rules need to be validated in other populations. We investigated the value of clinical information in the prediction of pneumonia. In addition to that we validated prediction rules from published literature.
Methods: Adult patients who met our definition of Lower Respiratory Tract Infection were included between November 15, 1998 and June 1, 2001 in the Leiden region (The Netherlands). Clinical information was collected and chest radiography was performed. The models we designed were based on logistic regression, on textbooks and on the opinion of general physicians. A literature search was done to detect prediction rules for pneumonia. Receiver operating characteristics (ROC) curves with areas under the curves, positive predictive values and negative predictive values were calculated.
Results: In the present study 129 patients, 26 with pneumonia and 103 without pneumonia were included. In total ten prediction rules were applied to our data set. Two models ('prediction II' and 'Hopstaken II') had a significant area under the curve of ROC, 0.67 (95% confidence interval 0.55 to 0.80) and 0.69 (95% confidence interval 0.58 to 0.80) respectively. These two models showed positive predictive values of 57% (95% confidence interval 18% to 90%) and 47% (95% confidence interval 23% to 71%). The negative predictive values of these models were 82% (95% confidence interval 75% to 89%) and 84% (95% confidence interval 77% to 91%), respectively. The pre-test probabilities for the presence of pneumonia and non-pneumonia were 20% and 80%, respectively.
Conclusions: Models that are only based on clinical information, do not reliably predict the presence of pneumonia. The addition of an elevated CRP seems of some value. However, the predictive value remains limited.

5.2 Introduction

Lower respiratory tract infections (LRTIs) are very common in general practice. Only a minority of the patients suffering from LRTI actually has a diagnosis of pneumonia on the chest X-ray. Studies in general practice settings show radiographically confirmed pneumonia in 6% to 39% of the patients, depending on the inclusion criteria of the patients.[1,2,3,4,5] Pneumonia is a serious disease and in every day practice antibiotic therapy has become the standard of care for all patients who are suspected to have pneumonia. Usually, general practitioners

(GPs) diagnose pneumonia based on information from medical history taking and physical examination, without the support of further investigations.
Several investigators made prediction rules for pneumonia using information from the clinical history, physical examination and simple laboratory tests.[6,7,8,9,10,11] Although the variables in these prediction rules vary considerably, fever, dyspnoea and any abnormality on auscultation are recurring criteria for the prediction of pneumonia.
Validation of the prediction rules is necessary to create reliable tools for clinicians to make a diagnosis of pneumonia more or less likely. Only Heckering's rule[9] had already been validated in other populations.
The present study was conducted to validate prediction rules for the presence of pneumonia from existing literature in a general practice setting in our group of patients with LRTI. Furthermore, we have developed our own prediction rules using clinical information and prediction rules based on textbooks and the opinion of GPs, and we have checked these rules as to their predictive values.

5.3 Methods

Patients
Adult patients aged 18 and over who met our definition for LRTI (See definitions), and who consulted their GP for symptoms and signs of LRTI in the Leiden region (The Netherlands) between November 15, 1998 and June 1, 2001 (with a summer break in June, July and August 2000) were included, with the assistance of 23 GPs, serving a total population of 27000 people. Patients who were younger than 18 and patients who were pregnant or had diseases that could have obstructed completion of follow-up, for instance the final period of a malignant disease were excluded. A standard medical history taking and physical examination were performed. Sputum samples, throat swabs and blood samples were collected for microbiological analysis. Furthermore, blood was taken for an erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). Information on patients, microbiological assays and criteria for microbiological diagnosis are given in detail elsewhere.[12]

Chest radiographs
In accordance with the study protocol the chest radiographs (posteroanterior and lateral) were made 5 to 7 days after inclusion of the patients with LRTI into the study, in one of the four hospitals (two in Leiden, one in Zoetermeer and one in Leiderdorp), close to where the patients lived. Local radiologists made the first assessment during routine daily practice. The radiologist was asked to assess the existence of a consolidation on the radiographs. Our radiologist (FEJAW), who was aware of the clinical details but not informed about the results of the first assessment, reviewed the radiographs systematically. In case of a discrepancy

between the two assessments, a third radiologist (HMZ) was asked to judge. The aim was to reach consensus. If previous X-rays were available, they were used for comparison.
The finding of a consolidation was regarded as evidence of pneumonia and served as the reference standard for pneumonia. All other radiological features were considered to represent 'non-pneumonia'. A total of 145 patients with LRTI were included in the study. In 137 of these patients a chest radiograph was taken. From these chest radiographs 129 could be reviewed by two radiologists, eight were lost after the first assessment.

Definitions
Definition of LRTI:
(1) Any abnormality on pulmonary auscultation and
(2) at least two of the following three signs and symptoms;
(a) fever >38°C, or fever in the past 48 hours;
(b) dyspnoea or cough (productive or non-productive);
(c) tachypnoea, malaise or confusion.[12]
The variable 'viral symptoms' was regarded as positive if three or more of the following symptoms were present: hoarse voice, sore throat, headache or myalgia.
The term 'temperature' was used for the actual temperature measured on examination of the patient by the investigator.
The term 'fever' was used for fever reported by the patient.
The variable 'pulmonary diseases' was defined as: asthma or chronic obstructive pulmonary disease (COPD).

Literature search for prediction rules
Prediction models for pneumonia from the literature were identified by a search of MEDLINE from 1966 to June 2003 using the following search terms: lower respiratory tract infections and pneumonia in combination with medical history, physical examination, diagnosis, prediction, sensitivity and specificity. The search was supplemented by reference checking. The search was limited to adult persons.
Prediction models from studies meeting the following criteria were selected:
(a) The studies had to be original prospective studies into the accuracy or precision of the medical history and physical examination in populations of patients in a general practice or ambulant setting with inclusion criteria comparable to our definition of LRTI.
(b) The prediction models given in the studies ought to be developed with the use of multivariate techniques.
(c) Articles that focused on prediction rules for hospital admission, hospital-acquired pneumonia, pediatric pneumonia, specific pneumonia

(e.g. tuberculosis) or acquired immunodeficiency syndrome related pneumonia were excluded.

Models for the diagnosis of pneumonia derived from our data

We developed four prediction models to diagnose pneumonia. Two models were based on significant predictors in our dataset, one model was based on predictive variables mentioned in textbooks and one model was based on variables considered important by GPs.

In the first model ('prediction I') the parameters of medical history and physical examination that differed significantly between patients with pneumonia and patients with non-pneumonia were entered into a logistic regression model. In the second model ('prediction II') two laboratory variables (ESR and CPR), which had an additional significant influence, were added to the variables of model Prediction I.

A third model ('textbook') considered the predictive value of variables indicated in textbooks. Two textbooks were examined[13,14] and the predictive variables for pneumonia mentioned in both textbooks were entered into a logistic regression model.

The fourth model ('GP') used variables that general physicians indicated as predictive factors for pneumonia. Nine GPs affiliated with the Department of General Practice and Nursing Home Medicine of the LUMC were asked to list the most important criteria for the diagnosis of pneumonia. Variables that were indicated by at least 6 GPs, were entered into the 'GP' model.

Statistical analysis

We analysed the data with SPSS version 11.0 for Windows. Sensitivities, specificities, positive and negative predictive values and crude Odds Ratios (ORs) with 95% confidence intervals (CIs) were calculated from 2x2 tables, comparing the outcomes of discrete variables with the reference standard ('pneumonia' or 'non-pneumonia').

Logistic regression was used to develop multivariate models. For the development of the models 'prediction I' and 'prediction II' a P-value smaller than 0.10 (likelihood ratio test) was considered significant.

The models 'prediction I', 'prediction II', the 'textbook', 'GP' and the models from the literature were validated on our data set. For this purpose the regression scores corresponding

to the different models for each patient were computed. The regression scores were used to calculate Receiver Operating Characteristic (ROC) curves with areas under the curve. For the models 'prediction I', 'prediction II', 'textbook' and 'GP' cross-validated ROC curves were calculated.[15] Positive and negative predictive values of the models were calculated, where a predicted probability larger than 0.5 (i.e. score ≥ 0) was taken as cut-off point.

The Medical Ethics Committee of the Leiden University Medical Center approved the study.

5.4 Results

From the 129 patients studied in detail the mean age was 50 (range 18-83 years) and 63 patients (49%) had co-morbidity. Pneumonia on the chest X-ray was present in 26 (20%) of the patients. The frequencies, Crude Odds Ratios and predictive values of the symptoms, signs, co-morbidity, clinical diagnosis and laboratory investigations for patients with pneumonia and non-pneumonia are shown in Table 5.1.

The variables retro-sternal pain, temperature ≥38°C and pulmonary diseases had significant Odds Ratios ($p<0.10$) and these variables were used to develop model 'prediction I' (Table 5.2). Among the laboratory variables CRP proved to be the most significant additional contribution and thus was added to derive model 'prediction II' (Table 5.2).

Table 5.2 also shows the results of our 'textbook' and 'GP' models. Temperature ≥38°C, severe illness, chest pain, sputum production, dyspnoea, focal dullness on percussion and focal bronchial breath sounds were mentioned as predictive for pneumonia in both textbooks and were entered into the 'textbook' model. Abnormality on auscultation, fever or temperature ≥38°C, severe illness and absence of viral symptoms were mentioned by at least six of the nine GPs who were asked to list symptoms for pneumonia. These variables were entered into the model 'GP'. The variable 'abnormality on auscultation' was not used since all patients had abnormality on auscultation.

The literature search for prediction models of pneumonia resulted in five papers, which met our criteria and from which we obtained six prediction rules: model 'Singal'[7], model 'Heckerling'[9], model 'Melbye'[10], model 'González Ortiz'[11] and the models 'Hopstaken I' and 'Hopstaken II'[5]. The regression equations of these rules are also given in Table 5.2. The model by Diehr et al.[6] was not applied, as the inclusion criteria (patients with cough) did not fit our definition for selected studies. The study by Gennis et al.[8] only showed a univariate analysis of variables in the prediction of pneumonia.

Table 5.1 Diagnostic value of information from medical history, physical examination, clinical diagnosis and laboratory investigation in 129 patients with a Lower Respiratory Tract Infection, using chest radiograph confirmed pneumonia (n=26) as reference standard. Univariate analysis.

	Pneumonia N (%)	Non-pneumonia N (%)	Crude Odds Ratio (95% CI)	PPV (%)	NPV (%)
Symptoms					
Fever	22 (85)	87 (84)	1.0 (0.3-3.3)	20	80
Rhinitis	16 (62)	60 (58)	1.1 (0.5-2.8)	21	81
Sore throat	7 (27)	43 (42)	0.5 (0.2-1.3)	14	76
Myalgia	13 (50)	63 (61)	0.6 (0.3-1.5)	17	76
Dyspnoea	18 (69)	80 (78)	0.6 (0.2-1.7)	18	74
Diarrhoea	8 (31)	23 (22)	1.5 (0.6-4.0)	26	82
Retrosternal pain	10 (39)	19 (18)	2.8 (1.1-7.0)[a]	35	84
Chest pain	14 (54)	43 (42)	1.6 (0.7-3.9)	25	83
Sputum production	19 (73)	83 (81)	0.7 (0.2-1.8)	19	74
No viral symptoms	13 (50)	44 (43)	1.3 (0.6-3.2)	23	82
Physical examination					
Severe illness	5 (19)	19 (18)	1.1 (0.4-3.1)	21	80
Temperature ≥38°C	14 (54)	35 (34)	2.3 (0.9-5.4)[a]	29	85
Pulse >100/min	1 (4)	4 (4)	1.2 (0.1-11.0)	20	82
Breath>20/min	7 (27)	43 (42)	0.5 (0.2-1.3)	14	76
Dullness on percussion	7 (27)	21 (20)	1.4 (0.5-3.9)	25	81
Dullness on percussion, focal	7 (27)	20 (19)	1.5 (0.7-4.1)	26	81
Crepitations	19 (73)	58 (56)	2.1 (0.8-5.4)	25	87
Crepitations, focal	15 (58)	50 (49)	1.4 (0.6-3.4)	23	83
Decreased breath sounds	3 (12)	13 (13)	0.9 (0.2-3.4)	19	80
Co-morbidity					
Absence of asthma	26 (100)	95 (92)	∞ (0.14-∞)[d]	22	100
Pulmonary diseases	1 (4)	23 (22)	0.1 (0.02-1.1)[a]	4	76
Diagnosis of pneumonia by GP	11 (42)	40 (39)	1.2 (0.5-2.8)	22	81
Use of Paracetamol	7 (27)	18 (17)	1.7 (0.6-4.8)	28	82
Laboratory investigation					
CRP≥20 mg/l[b]	23 (92)	66 (67)	5.6 (1.2-25.1)[a]	26	94
CRP≥50 mg/l[b]	18 (72)	44 (45)	3.2 (1.2-8.2)[a]	29	89
ESR[c]	19 (73)	53 (54)	2.3 (0.9-6.0)[a]	26	87

[a] *P-value <0.10, selected for logistic regression.*
[b] *CRP Number of patients above cut-off value. N=123.*
[c] *ESR Number of patients with ESR above reference value (adjusted for age and sex). N=124.*
[d] *Exact confidence interval.*
PPV = Positive Predictive Value, NPV = Negative Predictive Value.

Table 5.2 Summary of the regression equations of the different models used in the present study	
Model	Regression equation
Model 'prediction I'	Y= - 1.857 + 0.921* Temp≥38°C + 1.137 * Retro-sternal chest pain – 2.141 * Pulmonary diseases
Model 'prediction II'	Y= - 3.082 + 0.683 * Temp≥38°C + 1.049* Retro-sternal chest pain – 2.102 * Pulmonary diseases + 1.677 * CRP≥20mg/l
Model 'textbook'	Y= - 1.243 + 1.174 * Temp≥38°C – 0.758 * Severe illness + 0.895 * Chest pain – 0.791 * Sputum – 0.626 *Dyspnoea + 0.450 * Focal dullness on percussion + 1.153 * bronchial breath sounds
Model 'GP'	Y= - 1.939 + 1.022 * Temp≥38°C – 0.460 * Severe illness + 0.437 Absence of viral symptoms
Model 'Singal'[7]	Y = -3.539 + 0.884 * cough + 0.681 * fever+ 0.464 * crackles + 0.030* 20.16.©
Model 'Heckerling'[9]	Y = -1.705 + 0.494 * Temperature>37.7C + 0.428 * Pulse >100 beats/min + 0.658 * rales + 0.638 * decreased breath sounds + 0.691 * absence of asthma.
Model 'Melbye'[10]	Y = + 4.7*fever (reported by patient) with duration of illness of one week or more – 4.5*coryza - 2.1*sore throat + 5.0*dyspnoea + 8.2*chest pain, lateral + 0.9*crackles
Model 'González Ortiz'[11]	Y = -1.87 + 1.3 * pathologic auscultation + 1.70 * neutrophilia + 1.70 *pleural pain + 1.21 * dyspnoea
Model 'Hopstaken I'[5]	Y = - 2.74 + 1.02 *dry cough + 1.78 * diarrhoea + 1.13 * temperature ≥38°C
Model 'Hopstaken II'[5]	Y = -4.15 +0.91 *dry cough + 1.01 * diarrhoea + 0.64 * temperature ≥38°C + 2.78 * CRP≥20mg/l
©For the pre-test probability of pneumonia the frequency (20.16%) of patients with pneumonia found in our data set was used.	

We applied the models to our data set; the results are shown in Table 5.3. Model 'prediction II', based on logistic regression with the addition of CRP≥20mg/l, showed a significant area under the curve of ROC after cross-validation. Model 'Hopstaken II'[5], which also included CRP≥20mg/l, was the only model from the existing literature with a significant area under the curve of ROC. Looking at the distribution of the scores on the regression equations of the models 'prediction II' and 'Hopstaken II', it was observed that patients with non-pneumonia more often had a low score. For example for the model 'prediction II', 33% of the patients with non-pneumonia had a score below -3, versus 8% of the patients with pneumonia. Four percent of the patient with non-pneumonia and 16% of the patients with pneumonia had a score above 0. (Data not shown)
The models 'prediction II' and 'Hopstaken II' showed positive predictive values of 50% and 47%, respectively, with large confidence intervals (Table 5.3). The pre-test probabilities for the presence of pneumonia were 20% and 80%, respectively. These percentages are based on the results of the chest radiographs in our data set.

Table 5.3 The 'Receiver Operating Characteristic' (ROC) curves and the predictive values of the models applied. The pre-test probability for the presence of pneumonia was 20% and the pre-test probability for the absence pneumonia was 80% in the present study

	ROC area (95% CI)	ROC area (95% CI) Cross-validated	ROC area (95% CI) as given in selected articles	Post-test probability	
Model				PPV (95% CI)	NPV (95% CI)
'prediction I'	0.71 (0.60, 0.82)[a]	0.58 (0.45, 0.72)		44% (14% -79%)	82% (75% - 89%)
'prediction II'	0.77 (0.67, 0.87)[a]	0.67 (0.55, 0.80)[a]		50% (16% - 84%)	82% (75% - 89%)
'textbook'	0.72 (0.62, 0.82)[a]	0.53 (0.41, 0.66)		20% (13% -27%)	79% (72% - 86%)
'GP'	0.65 (0.53, 0.77)[a]	0.52 (0.39, 0.65)		[b]	80% (73% - 87%)
'Singal'[7]	0.58 (0.45, 0.70)		0.75 (0.71, 0.79)	[b]	80% (73% - 87%)
'Heckerling'[9]	0.63 (0.50, 0.75)		0.82 (0.78, 0.86)	24% (11%-38%)	85% (77%-93%)
'Melbye'[10]	0.49 (0.37, 0.62)[c]		[d]	17% (6%-36%)	79% (70%-86%)
'González Ortiz'[11]	0.57 (0.45, 0.68)		0.84[e]	23% (15%-31%)	88% (74%-100%)
'Hopstaken I'[5]	0.62 (0.50, 0.75)		0.76[e]	43% (17%-69%)	83% (76%-90%)
'Hopstaken II'[5]	0.69 (0.58, 0.80)[a]		0.80[e]	47% (23%-71%)	84% (77%-91%)

PPV = Positive Predictive Value, NPV = Negative Predictive Value. CI = confidence interval.
[a] *P-value <0.05.*
[b] *No patients had a value above the cut-off point for the regression equation of 0.*
[c] *The cut-off point was set at 9.7. At this point 20.2% of the patients had pneumonia.*
[d] *ROC not given.*
[e] *95% CI not given.*

5.5 Discussion

The results of this study show that models that only use information from medical history taking and physical examination do not reliably predict the presence of pneumonia, i.e. a consolidation on the chest X-ray. Models, which use an elevated CRP level in the blood as parameter in addition to the aforementioned information, do better. However, the predictive value for the presence of pneumonia remains limited. Given a pre-test chance of 20%, the post-test chance is 50% (Model 'prediction II', derived from our data set) and

47% (Model 'Hopstaken II'[5]). The negative predictive value is 82% (Model 'prediction II') and 84% (Model 'Hopstaken II'), with a pre-test chance of non-pneumonia of 80%.
The two models ('prediction II' and "Hopstaken II'), each with a total of four variables, had two common parameters, i.e. temperature ≥38°C and CRP ≥20mg/l. The presence of the parameter temperature ≥38°C was not surprising. In all the models shown here it was an important predictor of pneumonia or an inclusion criterion (model 'González Ortiz'[11]). Addition of CRP improved the positive predictive value from 44% (model 'prediction I') to 50% (model 'prediction II') and from 43% (model 'Hopstaken I') to 47% (model 'Hopstaken II'). Several investigators[16,17,18,19,20,21] confirmed the value of CRP-measurement in the diagnosis of infectious diseases.
Chest radiography was used as the standard reference to confirm the diagnosis of pneumonia, because of its low cost and general accessibility. However, the reliability of this test is debated. In the present study the chest X-rays were reviewed to increase the reliability of the diagnosis. The chest X-rays were taken about five to seven days after inclusion in the study and on average two weeks after the onset of the symptoms. A study by Macfarlane et al.[22] showed that abnormalities generally persist for a quite long time, one week after the diagnosis of pneumonia only 5% to 10% of the abnormalities had resolved. Nevertheless, we may have missed the diagnosis of pneumonia in a few patients.
Our study was conducted in a general practice setting in the Netherlands just as the study by Hopstaken et al.[5] was. The studies by Singal et al.[7] , Heckering et al.[9] and González Ortiz et al.[11] concerned patients from emergency departments in the USA and Spain. In these countries the organisation of medical care is different from the Netherlands. As a prerequisite for the inclusion of patients we applied abnormality on auscultation, which had not been the case in the other studies. González Ortiz et al.[11] had fever >38°C and Hopstaken et al.[5] had cough as a prerequisite for inclusion. Singal et al.[7] and Heckering et al.[9] included patients in whom a chest X-ray had been done. This could have introduced some selection bias in the studies by Singal et al.[7] and Heckering et al.[9]. Although there were different inclusion criteria all the patients were suspected of having a lower respiratory tract infection. Thus, the validation of the models in our data set seems to be justified.
In the present study we assessed the value of several models to predict the presence of pneumonia in patients suffering from lower respiratory tract infections and in whom abnormalities on auscultation were found. None of the models came up to our expectations. Even the addition of elevated CRP levels was of limited value. This is in line with two review papers on the use of medical history taking and physical examination in diagnosing pneumonia in general practice by Metlay et al. in 1997[23] and in 1998 by Zaat et al.[24].

In another paper based on the same patient population[25] we found significant more bacterial infections in patients who had a radiographic confirmed pneumonia. However, the majority of the patients with a bacterial infection did not show changes due to pneumonia on the chest X-ray. Therefore, recommendation of the chest X-ray is no solution. In the view of this limited prediction of pneumonia it could be better to bring into focus the choice of the prediction of the aetiology, i.e. the prediction of a bacterial infection, based on information from medical history and physical examination.

5.6 References

1. Macfarlane J, Holmes W, Gard P, Macfarlane R, Rose D, Weston V, Leinonen M, Saikku P, Myint S. Prospective study of the incidence, aetiology and outcome of adult lower respiratory tract illness in the community. Thorax 2001;56:109-114.
2. Macfarlane JT, Colville A, Guion A, Macfarlane RM, Rose DH. Prospective study of aetiology and outcome of adult lower-respiratory-tract infections in the community. Lancet 1993;341:511-514.
3. Lieberman D, Lieberman D, Korsonsky I, Ben-Yaakov M, Lazarovich Z, Friedman MG, Dvoskin B, Leinonen M, Ohana B, Boldur I. A comparative study of the etiology of adult upper and lower respiratory tract infections in the community. Diagn Microbiol Infect Dis 2002;42:21-28.
4. Woodhead MA, Macfarlane JT, McCracken JS, Rose DH, Finch RG. Prospective study of aetiology and outcome of pneumonia in the community. Lancet 1987;1(8534):671-674.
5. Hopstaken RM, Muris JWM, Knottnerus JA, Kester ADM, Rinkens PELM, Dinant GJ. Contributions of symptoms, signs, erythrocyte sedimentation rate, and C-reactive protein to a diagnosis of pneumonia in acute lower respiratory tract infection. Br J Gen Pract 2003;53:358-364.
6. Diehr P, Wood RW, Bushyhead J, Krueger L, Wolcott B, Tompkins RK. Prediction of pneumonia in outpatients with acute cough- a statistical approach. J Chron Dis 1984;37:215-225.
7. Singal BM, Hedges JR, Radack KL. Decision rules and clinical prediction of pneumonia: evaluation of low-yield criteria. Ann Emerg Med 1989;18:37-44.
8. Gennis P, Gallagher J, Falvo C, Baker S, Than W. Clinical criteria for the detection of pneumonia in adults: guidelines for ordering chest roentgenograms in the emergency department. J Emerg Med 1989;7:263-268.
9. Heckerling PS, Tape TG, Wigton RS, Hissong KK, Leikin JB, Ornato JP, Cameron JL, Racht EM. Clinical prediction rule for pulmonary infiltrates. Ann Intern Med 1990;113:664-670.
10. Melbye H, Straume B, Aasebo 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;10:226-233.
11. González Ortiz MA, Carnicero Bujarrabal M, Verela Entrecanales M. Prediction of existence of pneumonia in adults with fever. Med Clin (Barc) 1995;105:521-524.

12. Graffelman AW, Knuistingh Neven A, Le Cessie S, Kroes ACM, Springer MP, Van den Broek PJ. Pathogens involved in lower respiratory tract infections in general practice. Br J Gen Pract 2004;54:15-19.
13. Koëter GH, Postma DS, Groen HJM, Van MinnenCA. Longziekten. In: Van Der Meer J, Stehouwer CDA, eds. Interne Geneeskunde. 12th ed. Houten, Bohn Stafleu Van Loghum, 2001:449-523.
14. Levison ME. Pneumonia, including necrotizing pulmonary infections (Lung abscess). In: Braunwald E, Fauci AS, Kasper DL, Hauser SL, Longo DL, Jameson JL, eds. Harrison's Principles of Internal Medicine 15th ed. New York, The McGraw-Hill Companies, 2001:1475-1485.
15. Van Houwelingen JC, Le Cessie S. Predictive value of Statistical Models. Stat Med 1990;9:1303-1326.
16. Melbye H, Straume B, Aasebo U, Brox J. The diagnosis of adult pneumonia in general practice. The diagnostic value of history, physical examination and some blood tests. Scand J Prim Health Care 1988;6:111-117.
17. Lindback S, Hellgren U, Julander I, Hansson LO. The value of C-reactive protein as a marker of bacterial infections in patients with septicaemia, endocarditis and influenza. Scand J Infect Dis 1989;21:543-549.
18. Hjortdahl P, Landaas S, Urdal P, Steinbakk M, Fuglerud P, Nygaard B. C-reactive protein: a new rapid assay for managing infectious disease in primary health care. Scand J Prim Health Care 1991;9:3-10.
19. Dahler Eriksen BS, Lauritzen T, Lassen JF, Lund ED, Brandslund I. Near patient test for C-reactive protein in general practice: assessment of clinical, organizational and economic outcomes. Clin Chem 1999;45:478-485.
20. Melbye H**,** Straume B. The spectrum of patients strongly influences the usefulness of diagnostic tests for pneumonia. Scand J Prim Health Care 1993;11:241-246.
21. Melbye H, Straume B, Brax J. Laboratory tests for pneumonia in general practice: the diagnostic values depend on the duration of illness. Scand J Prim Health Care 1992;10:234-240.
22. Macfarlane JT, Miller AC, Roderick Smith WH, Morris AH, Rose DH. Comparative radiographic features of community acquired legionnaires' disease, pneumococcal pneumonia, mycoplasma pneumonia, and psittacosis. Thorax 1984;39:28-33.
23. Metlay JP, Kapoor WN, Fine MJ. Does this patient have community-acquired pneumonia? Diagnosing pneumonia by history and physical examination. JAMA 1997;278:1440-1445.
24. Zaat JOM, Stalman WAB, Assendelft WJJ. Groaning, moaning and percussion. A systematic literature review on the diagnostic value of history and physical examination in patients with a suspicion of pneumonia. Huisarts Wet 1998;41:461-469.
25. Graffelman AW, Knuistingh Neven A, Le Cessie S, Kroes ACM, Springer MP, Van den Broek PJ. A diagnostic rule for the aetiology of lower respiratory tract infections as guidance for antimicrobial treatment. Br J Gen Pract 2004;54:20-24.