

Contributions of symptoms, signs, erythrocyte sedimentation rate, and C-reactive protein to a diagnosis of pneumonia in acute lower respiratory tract infection

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SUMMARY

Background: Diagnostic tests enabling general practitioners (GPs) to differentiate rapidly between pneumonia and other lower respiratory tract infections (LRTIs) are needed to prevent increase of bacterial resistance by unjustified antibiotic prescribing.

Aims: To assess the diagnostic value of symptoms, signs, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) for pneumonia; to derive a prediction rule for the presence of pneumonia; and to identify a low-risk group of patients who do not require antibiotic treatment.

Design of study: Cross-sectional.

Setting: Fifteen GP surgeries in the southern part of The Netherlands.

Method: Twenty-five GPs recorded clinical information and diagnosis in 246 adult patients presenting with LRTI. Venous blood samples for CRP and ESR were taken and chest radiographs (reference standard) were made. Odds ratios, describing the relationships between discrete diagnostic variables and reference standard (pneumonia or no pneumonia) were calculated. Receiver operating characteristic analysis of ESR, CRP, and final models for pneumonia was performed. Prediction rules for pneumonia were derived from multiple logistic regression analysis.

Results: Dry cough, diarrhoea, and a recorded temperature of $\geq 38^{\circ}\text{C}$ were independent and statistically significant predictors of pneumonia, whereas abnormal pulmonary auscultation and clinical diagnosis of pneumonia by the GPs were not. ESR and CRP had higher diagnostic odds ratios than any of the symptoms and signs. Adding CRP to the final 'symptoms and signs' model significantly increased the probability of correct diagnosis. Applying a prediction rule for low-risk patients, including a CRP of <20 , 80 of the 193 antibiotic prescriptions could have been prevented with a maximum risk of 2.5% of missing a pneumonia case.

Conclusion: Most symptoms and signs traditionally associated with pneumonia are not predictive of pneumonia in general practice. The prediction rule for low-risk patients presented here, including a CRP of <20 , can considerably reduce unjustified antibiotic prescribing.

Keywords: respiratory tract infections; pneumonia; diagnosis; diagnostic tests, routine; predictive value of tests.

Introduction

THE main diagnostic challenge of general practitioners (GPs) facing patients with acute community-acquired lower respiratory tract infections (LRTIs) is selecting the right patients for antibiotic treatment. In contrast with acute bronchitis, where antibiotics are rarely indicated because the infection is mostly self-limiting,^{1,2} in pneumonia it is considered bad practice to withhold antibiotic treatment from a patient. GPs have the difficult task of balancing the fear of missing the diagnosis of pneumonia against their duty not to contribute to the growing problem of bacterial resistance by routine prescription of antibiotics.³⁻¹⁰ Therefore, it would be useful to have diagnostic tools in general practice that enabled GPs to differentiate between pneumonia and other LRTIs rapidly, i.e. during one consultation, without the need to refer a patient for chest X-rays or laboratory tests.¹¹ However, to the best of our knowledge there have not been any diagnostic studies on the full scope of LRTIs in general practice. Classical symptoms and signs of pneumonia, derived from hospital studies, are of limited value in everyday general practice, because of the lower incidence and smaller extent of disease found there. Owing to this lower pre-test probability of pneumonia, the predictive value of a positive symptom or sign (for example, crackles on auscultation) for pneumonia will automatically be lower, assuming equal diagnostic skills of the doctors involved.¹²⁻¹⁴ Additional use of erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) tests might be helpful.¹⁵⁻¹⁷

Despite the diagnostic uncertainties, the incidence of acute bronchitis has been estimated at 24 to 46 per 1000 patients per year.¹⁸⁻²¹ The annual incidence of community-acquired pneumonia is approximately five to 11 per 1000 patients.¹⁸⁻²¹ The present study evaluated the diagnostic value of symptoms, signs, ESR, and CRP for pneumonia in adult patients presenting to a GP with an LRTI. A rule to predict the probability of pneumonia was derived to identify a group of patients with a low risk of pneumonia.

Method

Patients and procedures

Consecutive patients in the southern part of The Netherlands, who presented to their GP with symptoms and signs of LRTI (defined as a new or increasing cough, combined with other clinical characteristics), were eligible to enter the study. Inclusion criteria are listed in Box 1. Exclusion criteria were: pregnancy and lactation; history of

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HOW THIS FITS IN*What do we know?*

There have not been any diagnostic studies on the prediction of pneumonia in the full scope of LRTIs in general practice.

*What does this paper add?*

Most symptoms and signs traditionally associated with pneumonia, including abnormal pulmonary auscultation, did not contribute to the diagnosis of pneumonia in the present study. Dry cough, diarrhoea, a temperature of $\geq 38^{\circ}\text{C}$, and elevated ESR and CRP values were independent and statistically significant predictors of pneumonia. The identified prediction rule for low-risk patients, including a CRP value of < 20 , can considerably reduce antibiotic prescriptions, with a low risk of missing a pneumonia case.

hypersensitivity to penicillin or macrolide antibiotics, concomitant treatment with ergot alkaloids and/or terfenadine during the study period; other severe clinical disease; treatment with antibiotics within the preceding 14 days; and a hospital stay for a respiratory complaint during the previous four weeks. Some of the exclusion criteria were relevant to a randomised clinical trial, which was running in parallel to the diagnostic study.²²

The GPs performed and recorded an extensive standardised medical history and physical examination, and stated a clinical diagnosis of either pneumonia or other LRTI, summarised for the purpose of the present study as acute bronchitis. The GPs applied and interpreted the diagnostic tests (symptoms and signs) in their usual way, and were not trained in any sense. This was done to increase the generalisability of the study results to everyday general practice. In addition, venous blood samples for CRP and ESR analysis were taken and submitted to the Haematology and Clinical Chemistry laboratories of Maastricht University Hospital on the same day, and were analysed using standard procedures.²³

Reference standard

Chest radiographs (lateral and postero-anterior) were made of every patient on the third day after inclusion, the third day

being chosen to ensure that possible infiltrates were detectable on the chest radiograph.²⁴ The radiologist was asked to rate infiltrates or other abnormalities. The radiographs were then re-assessed for the presence or absence of infiltrates by an independent senior radiologist at Maastricht University Hospital, blinded to the first radiologist's results for conclusions. If the first and second radiologists disagreed, a third senior radiologist of the Maastricht University Hospital conducted an independent, decisive assessment. The radiologists were blinded to the clinical status of the patient. The conclusive finding of an infiltrate was regarded as evidence of pneumonia and served as the reference standard for the diagnostic analysis. All other outcomes were considered to represent 'no pneumonia'. The GPs were only informed by the radiologist about the results of the radiographs after the study had been completed.

Statistical analysis

The data were analysed in several steps, using SPSS 9.0 and Stata 7 software. Sensitivities, specificities, positive and negative predictive values (PV+, PV-) and diagnostic odds ratios (ORs) with 95% confidence intervals (95% CIs) were calculated from 2×2 tables, comparing the outcomes of all discrete diagnostic variables with the reference standard ('pneumonia' or 'no pneumonia'). Receiver operating characteristic (ROC) analysis was used to describe the association between sensitivity and specificity of the blood tests (ESR and CRP) at different cut-off values. To compare the overall diagnostic power of ESR and CRP, the respective areas under the curve (AUC) were calculated. Differences between the AUCs were tested for significance by the DeLong equality test.²⁵

The independent diagnostic contributions of symptoms and signs to the prediction of pneumonia were assessed using multiple logistic regression analysis. However the number of available variables was too large to have ten cases per variable.²⁶ Therefore, three criteria had to be met for a variable to enter the model. First, each variable had to be positive in at least ten patients. Secondly, each variable had to be positive in at least five patients with pneumonia. Thirdly, the association of the variables with the presence or absence of

Criterion A		Age 18 years and over
	AND	
Criterion B		New (i.e. less than 29 days) or increasing cough
	AND	
Criterion C: at least one of the following four:		Shortness of breath Wheezing Chest pain Auscultation abnormalities
	AND	
Criterion D: at least one of the following four:		Reported fever ($\geq 38^{\circ}\text{C}$) Perspiring Headache Myalgia
	AND	
Criterion E		Diagnosis of LRTI according to GP

Box 1. Inclusion criteria for the study.

pneumonia (2×2 tables) had to have a P -value ≤ 0.1 (χ^2 or Fisher's exact test). Multiple logistic regression analysis (backward elimination with $P > 0.05$ for exclusion) was performed with the selected variables from history taking and physical examination, resulting in the final 'symptoms and signs' model. Several potentially relevant interaction terms were included in the model and removed again if they did not contribute to the diagnostic accuracy. This allowed a rule to be derived predicting the probability of pneumonia in each individual case. In accordance with everyday practice, where additional blood tests are performed after information has been acquired from history taking and physical examination, logistic regression analysis was repeated for the 'symptoms and signs' model, adding ESR or CRP at different cut-off points and as numerical variables. ROC curves were constructed to visualise the diagnostic performance of the final models. The AUCs of these models were calculated and tested mutually for significance.²⁵

Ethical approval

The Medical Ethics Committee of Maastricht University and the Maastricht University Hospital approved the protocol. After being informed by the GP of the purpose and content of the study, and having read the information for patients, all patients gave written informed consent.

Results

Patients and univariate analysis of symptoms and signs

Between January 1998 and April 1999, 25 GPs from 15 prac-

tices included 246 patients in the study, with a mean age of 52 years (range = 18 to 89 years). Radiographic pneumonia was present in 32 (13%) patients. Chest radiographs were missing in three patients. The frequencies of the symptoms and signs presented and the GPs' diagnostic conclusions are shown in Table 1. The corresponding ORs show that the presence of nausea and diarrhoea at least doubled the probability of pneumonia. 'Recent cough for two days or less' and mental confusion, present in only 11 and eight patients respectively, were highly specific, their presence almost tripling the probability of pneumonia. The lower limit of the confidence interval of the OR of mental confusion, however, equalled 1.0.

The classical symptoms and signs of pneumonia, i.e. dyspnoea, thoracic pain, fever (as recalled by the patient), a respiratory rate greater than 20 per minute, percussion dullness, and crackles, were not discriminative for pneumonia. A clinical diagnosis of pneumonia by the GPs was associated with a very modest, non-significant increase in the probability of pneumonia, from 13% (prior probability) to 19% (PV+, posterior probability). The GPs could not exclude pneumonia with more certainty (PV- 87%) than before their clinical judgment, since the prior probability of not having pneumonia was 87%.

ROC analysis of ESR and CRP

ESR and CRP at various cut-off points were compared with the reference standard and ROC curves were constructed (Figure 1). The figure shows ORs, with confidence intervals, for three clinically relevant cut-off values per blood test. In general, ESR and CRP were elevated (≥ 10) in 97% of the

Table 1. Diagnostic value of symptoms, signs, and clinical diagnosis in pneumonia. Univariate analysis ($n = 243$).

	Pneumonia (prior probability = 13.2%)				
	<i>n</i>	%	OR (95% CI)	PV+ (%)	PV- (%)
Symptoms					
Age 65 years or older	70	28.8	1.3 (0.6–3.0)	15.7	87.9
Recent cough ≤ 2 days	11	5.1	3.8 (1.0–13.8) ^d	36.4	86.9
Dry cough ^a	58	23.9	2.2 (1.0–4.7) ^b	20.7	89.2
Sputum purulence	133	54.7	1.2 (0.6–2.6)	14.3	88.2
Dyspnoea	188	77.4	0.7 (0.3–1.6)	12.2	83.6
Thoracic pain	145	59.7	1.3 (0.6–2.9)	14.5	88.8
Fever ^c	85	35.0	1.8 (0.8–3.8)	17.6	89.2
Chills ^a	122	50.2	2.4 (1.1–5.4) ^d	18.0	91.7
Confusion	8	3.3	4.3 (1.0–18.8) ^b	37.5	87.7
Nausea ^a	39	16.0	2.9 (1.2–6.6) ^d	25.6	89.2
Diarrhoea ^a	19	7.8	3.5 (1.2–10.0) ^d	31.6	88.4
Smoking	81	33.3	0.8 (0.3–1.7)	11.1	85.8
Smoking in the past	150	61.7	1.0 (0.5–2.2)	13.3	87.1
Co-morbidity					
Asthma	47	19.3	1.2 (0.5–3.0)	14.9	87.2
COPD	32	13.2	1.3 (0.4–3.6)	15.6	87.2
Physical signs					
General impression: moderate/severe illness ^a	65	26.7	2.8 (1.3–6.1) ^d	23.1	90.4
Respiration rate > 20 /min.	9	3.7	0.8 (0.1–6.8)	11.1	86.8
Percussion dullness	11	4.5	–	–	100
Auscultation abnormality	204	84.0	2.0 (0.6–6.9)	14.2	92.3
Bronchial breathing	64	26.3	1.4 (0.7–3.4)	17.2	87.8
Crackles	50	20.6	1.5 (0.7–3.7)	18.0	87.6
Temperature $\geq 38^\circ\text{C}$ ^a	58	23.9	2.5 (1.2–5.5) ^d	22.4	89.7
Clinical diagnosis of pneumonia	21	8.6	1.6 (0.5–5.2)	19.0	87.4

^aVariable selected for multiple logistic regression analysis. ^bNumber rounded to 1.0, but in reality less than 1.0. ^cRectal temperature $\geq 38.0^\circ\text{C}$ or axillary temperature $\geq 38.5^\circ\text{C}$ and measured less than 24 hours previously. ^dStatistically significant ($P < 0.05$).

The predicted probability of pneumonia for each individual patient can be calculated from the equation:

$$P = 1/(1 + e^{-y})$$

in which

$$y = a + b_1x_1 + b_2x_2 + b_3x_3$$

where a is the coefficient of the constant in the model and b_1 , b_2 and b_3 are the regression coefficients of the variables in the model. Calculations for the final 'symptoms and signs' model and one of the final 'symptoms and signs + ESR/CRP' models are given below:

'Symptoms and signs' model

$$y = -2.74$$

+ 1.02 when dry cough was present; + 1.78 when diarrhoea was present; + 1.13 when temperature $\geq 38^\circ\text{C}$.

Examples

A patient with dry cough, diarrhoea and temperature $\geq 38^\circ\text{C}$ has a prediction score of $-2.74 + 1.02 + 1.78 + 1.13 = 1.19$, resulting in a probability of 76% (95% CI = 42–93%) of having pneumonia. Similarly, a patient with dry cough and temperature $\geq 38^\circ\text{C}$, but no diarrhoea, has a probability of 36% (95% CI = 19–56%) of having pneumonia. A patient without any of these three items has a probability of 6% (95% CI = 3–11%) of having pneumonia.

'Symptoms and signs + CRP cut-off value of 20' model

$$y = -4.15$$

+ 0.91 when dry cough was present; + 1.01 when diarrhoea was present; + 0.64 when temperature $\geq 38^\circ\text{C}$; + 2.87 when CRP ≥ 20 .

Examples

A patient with dry cough, diarrhoea and temperature $\geq 38^\circ\text{C}$ and CRP ≥ 20 has a probability of 78% (95% CI = 44–94%) of having pneumonia. Similarly, a patient with the maximum of one positive score on the three items dry cough, diarrhoea and temperature $\geq 38^\circ\text{C}$, and with CRP < 20 (the low-risk group), has a probability of 3% (95% CI = 1–8%) of having pneumonia. A patient without any of these items has a probability of 2% (95% CI = 0–5%) of having pneumonia.

The 95% confidence interval can be calculated from the interval:

$$y \pm [1.96 \times \text{SE}(y)]$$

of the predicted log odds.

Box 2. Derivation of probability test for pneumonia.

patients with radiographic pneumonia. Both tests had much higher ORs than variables from history and physical examination. The overall diagnostic performance of CRP was significantly better than that of ESR ($P = 0.02$).

Multivariable analysis of symptoms and signs

Logistic regression analysis was performed with six selected variables from history taking and physical examination, adding the variable age (as a numerical variable). This was the 'symptoms and signs' model. The variables dry cough, diarrhoea and temperature $\geq 38^\circ\text{C}$ had statistically significant ORs (final 'symptoms and signs' model, Table 2). This allowed the predicted probability of pneumonia for individual patients to be calculated.

Multivariable analysis 'symptoms and signs + ESR/CRP value'

The diagnostic value of the variables in the final 'symptoms and signs' model with added ESR or CRP value is also shown in Table 2. The AUCs of the 'symptoms and signs + ESR/CRP' models were higher than those of the 'symptoms and signs' model, and rose further at higher cut-off values of ESR and CRP. A CRP cut-off value of 50 led to the highest OR (18) upon addition of CRP to the final 'symptoms and signs' model, leading to non-significant ORs for all other variables.

ROC analysis of final models

The diagnostic performances of the final models with ESR

and CRP as numerical values were visualised in ROC curves (Figure 2). Both the 'symptoms and signs + ESR' model and the 'symptoms and signs + CRP' model predicted the probability of pneumonia significantly better than the 'symptoms and signs' model ($P = 0.004$ and $P < 0.001$, respectively). In addition, the 'symptoms and signs + CRP' model was also significantly better than the 'symptoms and signs + ESR' model ($P = 0.012$).

Low-risk groups

A review of the equations (Box 2), resulting in diagnostic trees with all possible predicted (posterior) probabilities of pneumonia, allowed a group of patients to be identified with a low risk of having pneumonia after history taking, physical examination and measurement of CRP, compared with the (prior) probability of pneumonia at the start of the consultation (13%). This low-risk group ($n = 107$) consisted of patients with a maximum of one positive score on the three items diarrhoea, dry cough, and temperature $\geq 38^\circ\text{C}$, and with CRP < 20 . The combined PV in this low-risk group of not having pneumonia was 97% (95% CI = 92% to 99%). When an ESR value of < 20 was used instead of CRP < 20 , the combined PV in this group ($n = 121$) of not having pneumonia was 95% (95% CI = 89% to 98%). If the prediction rule for low-risk patients, including CRP < 20 , was applied to the patients who received antibiotic treatment, 80 prescriptions (41%) could have been avoided, with a risk of 2.5% (i.e. the risk of missing two patients with pneumonia). Applying

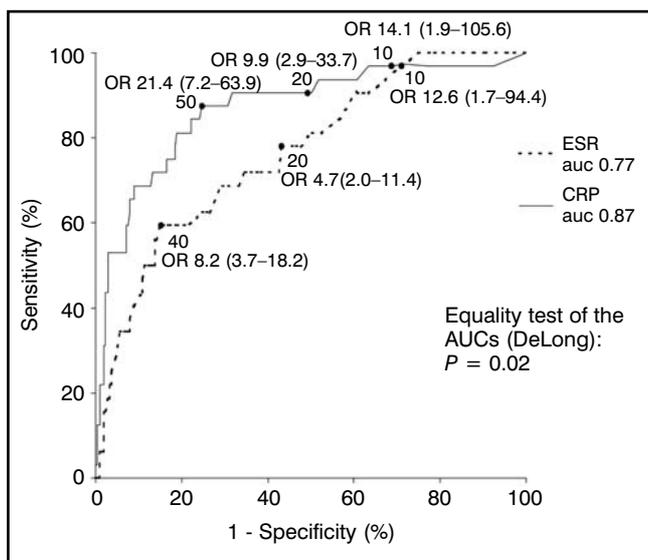


Figure 1. ROC curves of erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) for pneumonia (n = 243), with various cut-off points and corresponding diagnostic odds ratios (ORs).

the rule to the patients who did not receive antibiotic treatment (n = 50), 27 patients would not receive an antibiotic with a risk of 4% (i.e. the risk of missing one patient with pneumonia). According to the reference standard, five of the 50 patients who did not receive antibiotic treatment had pneumonia. Thus, the GPs' decision not to prescribe antibiotics comprised a risk of 10% of missing pneumonia.

Discussion

The need for better diagnostic tools enabling GPs to differentiate between pneumonia and other LRTIs was obvious from the GPs' clinical assessment: there was no relation between their assessment that pneumonia was present and pneumonia actually being found subsequently. However, this finding needs to be treated with caution, because it assumes that the widely acknowledged reference standard used (the finding of an infiltrate on chest radiographs by two radiologists) is 100% accurate, which is not the case. To gain more insight into the acceptability of chest X-rays as a reference standard, the outcomes of the chest X-rays were compared with the microbiological test results, assuming — although both acute bronchitis and pneumonia are infectious diseases — a higher probability of pathogens in pneumonia than in other LRTIs: pathogens were found in 77% of the 'infiltrate' group, compared with 44% of the 'no infiltrate' group (OR = 4.2, 95% CI = 1.7 to 10.3), which was in accordance with our expectations.

Diagnostic studies on LRTIs have rarely been performed, and especially not with a population of LRTI in general practice, so it was considered too early to start the present study with promising variables from other studies alone. The drawback is a potential introduction of paradoxical associations, when the number of diagnostic variables is high. As a result of the applied restrictions for entering the logistic regression analysis a satisfactory strong reduction in variables was acquired, although, statistically, an even stronger reduction of variables would have been preferable.

Table 2. Diagnostic value of 'symptoms and signs' (SS), 'symptoms and signs + erythrocyte sedimentation rate (SS + ESR) and 'symptoms and signs + C-reactive protein' (SS + CRP) at different cut-off points in the reduced logistic regression models.

Clinical items	OR (95% CI)						
	SS	SS + ESR 10	SS + ESR 20	SS + ESR 40	SS + CRP 10	SS + CRP 20	SS + CRP 50
History							
Dry cough	2.77 (1.19-6.44)	2.64 (1.12-6.21)	2.65 (1.11-6.31)	2.46 ^a (1.00-6.08)	2.84 (1.20-6.73)	2.88 (1.19-6.94)	2.48 ^a (0.97-6.37)
Chills	-	-	-	-	-	-	-
Nausea	-	-	-	-	-	-	-
Diarrhoea	5.90 (1.89-8.49)	5.57 (1.71-18.09)	5.25 (1.58-17.39)	3.92 (1.12-13.66)	4.97 (1.55-15.95)	4.35 (1.33-14.29)	2.74 ^a (0.78-9.64)
Physical examination							
General impression: moderate/severe illness	-	-	-	-	-	-	-
Temperature $\geq 38^{\circ}\text{C}$	3.08 (1.35-7.02)	2.53 (1.09-5.85)	2.86 (1.22-6.70)	2.71 (1.12-6.56)	2.38 (1.03-5.53)	2.21 ^a (0.93-5.21)	1.90 ^a (0.76-4.74)
Blood test							
ESR 10/20/40	-	10.52 (1.39-79.73)	4.29 (1.74-10.59)	6.81 (2.96-15.65)	-	-	-
CRP 10/20/50	-	-	-	-	11.70 (1.55-88.61)	8.48 (2.45-29.39)	17.62 (5.77-53.85)
Constant	-2.74	-4.73	-3.58	-3.29	-4.79	-4.18	-4.15
Area under curve	0.70	0.76	0.78	0.80	0.77	0.80	0.87

^aNon-significant test result.

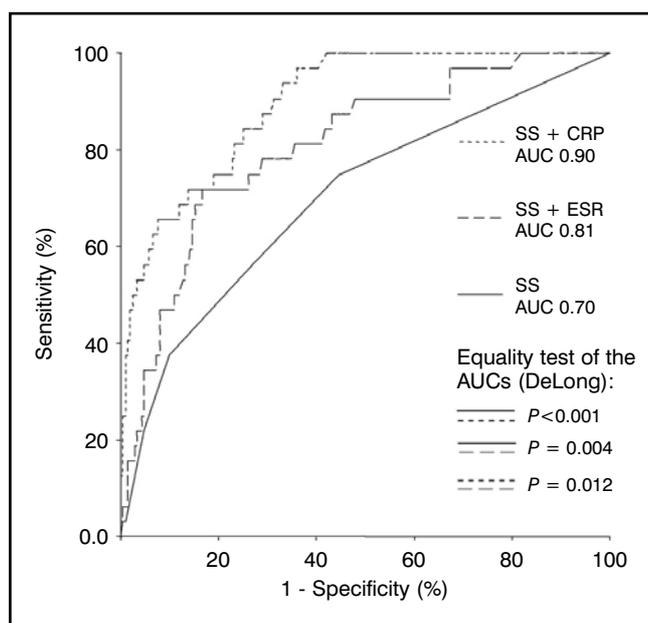


Figure 2. Multiple logistic regression analysis. ROC curves of the three final models: 'symptoms and signs' model (SS), 'symptoms and signs + ESR' model (SS+ESR), and 'symptoms and signs + CRP' model (SS+CRP). The AUCs of the models were calculated and tested mutually for significance by DeLong equality tests.

In this practice-based study we have tried to remain as close as possible to daily practice: different GPs diagnosing illnesses with their own interpretations of history taking and physical examination, who were not trained in any sense but who followed strict study criteria to define the study population and to facilitate comparisons with other studies performed, and future studies. The chosen approach increases the generalisability of the study results. For the same reason, additional blood tests were added to the logistic regression model after analysis with symptoms and signs only.

Significant predictors of pneumonia in multivariable logistic regression analysis were dry cough, diarrhoea, and a temperature of $\geq 38^{\circ}\text{C}$. In the present study population, all patients coughed (inclusion criterion). One of the main characteristics of patients with acute bronchitis is that they have productive cough. In pneumonia, productive cough may well be present, but not necessarily so, and it is often not an early symptom. So it is not obvious to look for primarily inflamed bronchi with subsequent high sputum production in pneumonia patients, unlike that seen in acute bronchitis. Dry cough was a predictor of pneumonia in one other study known to us.²⁸ Diarrhoea is probably a para-infectious symptom of pneumonia, caused by the release of cytokines and other inflammation mediators, which lead to malabsorption in the intestines, combined with an adrenergic stress reaction.²⁹ It is present in 10% to 30% of patients with community-acquired pneumonia.³⁰ Originally described as a common symptom in pneumonia caused by *Legionella pneumophila*, *Chlamydia pneumoniae*, and *Mycoplasma pneumoniae*, it later became clear that diarrhoea occurs in both types of pneumonia. Moreover, the specific clinical pictures of these so-called atypical pneumonias are less common than previously thought.^{31,32} Therefore, it is now

accepted to consider instead the atypical pathogens as bacteria. A recorded temperature of $\geq 38^{\circ}\text{C}$ was identified as an independent predictor in all the published diagnostic studies on community-acquired pneumonia that were consulted.^{28,33-38} However, fever, as recalled by the patient, was not a good substitute for the actual recording of rectal temperature in this study. Mental confusion seemed highly specific for pneumonia, but the small number of cases in the present study presumably was not enough to achieve statistical significance.

Most symptoms and signs traditionally associated with pneumonia, including abnormal pulmonary auscultation, did not contribute to the diagnosis of pneumonia in the present study. Other studies have also found that crackles, in particular, are not discriminative,^{33,34,38,39} or not sufficient to rule in or rule out pneumonia.^{35,37}

Antibiotics were prescribed to 196 of the 246 patients, while a clinical diagnosis of pneumonia was made in only 21 patients. Leaving out these 21 patients with presumed pneumonia, this means that antibiotics were prescribed in 175/225 patients (78%) with presumed acute bronchitis, which is in accordance with earlier studies.⁴⁰⁻⁴² The high percentage of antibiotic prescriptions is probably owing to a strong belief in the efficacy of antibiotics for acute bronchitis, as well as by the negative consequences of missing a diagnosis of pneumonia, in terms of the patient's morbidity, and possible damage to the doctor-patient relationship, in addition to various other doctor- and patient-related factors.⁴³

The identified prediction rule for low-risk patients, including a CRP < 20, can help GPs reduce their fear of missing pneumonia, and can serve as a supportive argument in negotiations with patients about whether or not to prescribe antibiotics. In addition to the identification of a low-risk patient, a scheduled reattendance at the surgery the next day, for example, may be timely enough to recognise potential dangers for the patient, using time as a diagnostic tool. However, the final prediction models and the rule for low-risk patients may be too optimistic for clinical use, since they were derived from this study population. They should therefore be tested in a new, similar set of patients in general practice, to obtain external validation of the results.⁴⁴ Internal validation procedures, such as split-half or bootstrap methods, are both inferior to validation in a new study population and statistically not advisable, because of the relatively small sample size. As the exclusion criteria, which were not needed for this diagnostic study, mainly consisted of pregnant or breastfeeding women and patients with rare conditions, there is no indication that they have hampered the generalisability of the study results.

Dutch GPs generally have the opportunity to measure ESR in their surgeries, but it is hardly used for LRTIs. The need for a venous blood sample, and the time delay of one hour before the test result is obtained, may contribute to the choice of prescribing antibiotics instead of selecting the right patients for antibiotic treatment. A CRP rapid test, which requires only a finger prick and a few minutes, may prevent this course of action, and thus potentially reduce antibiotic prescriptions in general practice. Introduction in routine practice seems to be justified, since the test has been proved to be accurate, robust, and cost effective.^{15,17,45,46}

To the best of our knowledge, the present study is the first diagnostic study on the full scope of LRTIs in general practice. Dry cough, diarrhoea, a temperature of $\geq 38^{\circ}\text{C}$ and elevated ESR and CRP values were significant predictors of pneumonia. Safely withholding LRTI patients from antibiotic treatment was possible, if the patient satisfied the criteria of the prediction rule for low-risk patients, including a CRP value of < 20 . A new primary care study is necessary to accept or reject our findings and to validate this prediction rule.

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