Procalcitonin versus C-reactive protein for predicting pneumonia in adults with lower respiratory tract infection in primary care

Anette Holm, Svend S Pedersen, Joergen Nexoe, Niels Obel, Lars P Nielsen, Ole Koldkjaer and Court Pedersen

ABSTRACT

Background

The role of procalcitonin in diagnosing bacterial infection has mainly been studied in patients with severe infections. There is no study on the value of procalcitonin measurements in adults with lower respiratory tract infection (LRTI) treated in primary care.

Aim

To evaluate the accuracy of plasma procalcitonin in predicting radiographic pneumonia, bacterial infection, and adverse outcome in a population of adults with LRTI treated in primary care.

Design of study

Prospective, observational study.

Setting

Forty-two general practices and an outpatient clinic at the Department of Infectious Diseases, Odense University Hospital, Denmark.

Method

A total of 364 patients with LRTI were prospectively enrolled from 42 general practices. Patients were examined with chest radiography, microbiological analyses, and measurements of C-reactive protein (CRP) and procalcitonin. The outcome measure was hospitalisation within 4 weeks of enrolment.

Results

Median procalcitonin was 0.05 ng/ml, which was below the functional sensitivity of the assay (0.06 ng/ml). In predicting radiographic pneumonia, bacterial infection, and hospitalisation, the sensitivities of procalcitonin >0.06 ng/ml were 0.70, 0.51, and 0.67, and of CRP ≥20 mg/l were 0.73, 0.56, and 0.74 respectively. Corresponding positive predictive values were between 0.09 and 0.28.

Conclusion

Both procalcitonin >0.06 ng/ml and CRP ≥20 mg/l were associated with radiographic pneumonia, bacterial infection, and subsequent hospitalisation, but positive predictive values were too low for any of the two inflammatory markers to be of use in clinical practice. To measure procalcitonin values accurately in the primary care setting, a more sensitive method is needed, but there was no indication that procalcitonin is superior to CRP in identifying patients with pneumonia, bacterial aetiology, or adverse outcome.

Keywords

C-reactive protein; diagnostic tests; pneumonia; primary health care; procalcitonin; respiratory tract infections; routine.

INTRODUCTION

Lower respiratory tract infection (LRTI) comprises acute bronchitis, pneumonia, and in some cases acute exacerbation of chronic obstructive pulmonary disease. More than 70% of patients with LRTI are treated with antibiotics in primary care,[1–3] most often without firm knowledge of the specific diagnosis or the aetiology. Although viral infections may cause radiographic pneumonia, it is generally believed that most cases of LRTI in adults are caused by bacteria and should be treated with antibiotics, that antibiotics are needed in some cases of acute exacerbation of chronic obstructive pulmonary disease, and that most cases of acute bronchitis are caused by viral infections with no benefit gained from antibiotic treatment.

Differentiation between pneumonia and acute bronchitis is important due to the therapeutic consequences. Making this distinction in primary care is difficult because of limited access to chest radiography, and the lack of a simple, rapid, and accurate marker of pneumonia. Common clinical signs lack sensitivity and specificity,[4] and standard

***A Holm**, PhD, specialist registrar in clinical microbiology; **SS Pedersen**, MD, consultant in infectious diseases; **N Obel**, MD, consultant in infectious diseases; **C Pedersen**, MD, professor of infectious diseases, Department of Infectious Diseases C; Odense University Hospital; **J Nexoe**, PhD, GP, Research Unit of General Practice, University of Southern Denmark; **LP Nielsen**, consultant in clinical microbiology, Department of Clinical Microbiology, Odense University Hospital; **O Koldkjaer**, consultant in clinical biochemistry, Department of Clinical Biochemistry, Soenderborg Hospital, Soenderborg, Denmark.*

Address for correspondence

Anette Holm, Department of Infectious Disease C, Odense University Hospital, Sdr. Boulevard 29, 5000 Odense C, Denmark. E-mail: anette.holm@ouh.regionsyddanmark.dk

Submitted: 22 August 2006; **Editor's response:** 12 December 2006; **final acceptance:** 23 February 2007.

How this fits in

Procalcitonin is an inflammatory marker which has been shown to identify bacterial infection and predicting adverse outcome in hospitalised patients with critical illness. In one study of patients hospitalised with LRTI, antibiotic prescribing was reduced when the antibiotic strategy was based on procalcitonin measurements. This is the first study on the value of procalcitonin in adults with LRTI treated in primary care. It can be concluded that both procalcitonin and CRP are unable to predict radiographic pneumonia, bacterial aetiology, or adverse outcome with sufficient accuracy.

microbiological examinations such as blood culture and sputum culture have low sensitivity,[5] and are not practical for use in primary care. Differing views are held on the role of C-reactive protein (CRP) measurement as a marker of pneumonia.[6–8] In a review, van der Meer *et al,* concluded that testing for CRP has neither sufficient sensitivity, nor sufficient specificity to be used as a test to guide antibiotic prescription.[8] This is concordant with the findings in a study of patients with LRTI in primary care.[9] An elevated level of CRP was significantly associated with having pneumonia, but the positive predictive value (PPV) of CRP was low.

Procalcitonin is the precursor of calcitonin, and is normally produced in the C-cells of the thyroid gland.[10] Under normal conditions, procalcitonin is not released in the blood stream, and the serum procalcitonin levels are therefore very low in healthy individuals. During systemic infections, procalcitonin is produced in other tissues, and the serum levels may be very high in severe, generalised bacterial or fungal infections. In a study of hospital patients with LRTI, Christ-Crain *et al* showed that a therapeutic strategy based on procalcitonin measurements significantly reduced antibiotic use without having a negative impact on clinical outcome.[11] The value of procalcitonin measurements in LRTI in primary care has not been previously studied in adults. This study prospectively evaluated procalcitonin and CRP in adults with LRTI treated in primary care. The aims of this study were to describe the range of procalcitonin values in this setting, to evaluate the accuracy of procalcitonin to detect patients with pneumonia, to discriminate between bacterial and viral infection, and to predict outcome.

METHOD

The study population consisted of 364 consecutive adults with LRTI treated in primary care as described elsewhere.[9] Patients aged ≥18 years old were enrolled if their GP made a clinical diagnosis of LRTI and the patients agreed to participate in the study. Exclusion criteria were: pregnancy, hospitalisation within the preceding 7 days, severity of illness requiring hospitalisation, and former participation in the study. Chest radiographs, microbiological analysis, and blood samples for procalcitonin and CRP were obtained on the day of diagnosis at the outpatient clinic, Department of Infectious Diseases, Odense University Hospital, Denmark. Chest radiographs were evaluated by an experienced specialist in infectious lung diseases, who was blinded to all other study information. Blood for procalcitonin was kept at 5°C for a maximum of 24 hours before being centrifuged, and plasma was thereafter kept at –80°C until analysed.

The Kryptor®-PCT assay (BRAHMS Diagnostica, Berlin, Germany) was used for measurements of procalcitonin according to the manufacturer's instructions. All measurements were performed in duplicate. The detection limit of the Kryptor®-PCT assay was reported by the manufacturer to be

Table 1. Procalcitonin and C-reactive protein (CRP) as predictors of radiographic pneumonia.

	All patients (*n* = 364) *n* %	Pneumonia (*n* = 48) *n* %	Non-pneumonic (*n* = 316) *n* %	*P*-value	Sensitivity	Specificity	PPV	NPV	Crude OR (95% CI)
Procalcitonin >0.06 ng/ml	139/357 (39)	33/47 (70)	106/310 (34)	<0.001	0.70	0.66	0.24	0.94	4.54 (2.33 to 8.84)
Procalcitonin >0.08 ng/ml	77/357 (22)	23/47 (49)	54/310 (17)	<0.001	0.49	0.83	0.30	0.91	4.54 (2.39 to 8.64)
Procalcitonin >0.10 ng/ml	41/357 (11)	17/47 (36)	24/310 (8)	<0.001	0.36	0.92	0.41	0.91	6.75 (3.27 to 13.96)
Procalcitonin >0.25 ng/ml	15/357 (4)	11/47 (23)	4/310 (1)	<0.001	0.23	0.99	0.73	0.89	23.38 (7.07 to 77.25)
Procalcitonin >0.50 ng/ml	8/357 (2)	8/47 (17)	0 (0)	<0.001	0.17	1.00	1.00	0.89	∞ (–)
CRP ≥20 mg/l	145/363 (40)	35 (73)	110/315 (35)	<0.001	0.73	0.65	0.24	0.94	5.02 (2.59 to 9.88)

CRP = C-reactive protein. LRTI = lower respiratory tract infection. PPV = positive predictive value. NPV = negative predictive value. OR = odds ratio.

0.02 ng/ml, and the functional sensitivity is 0.06 ng/ml (which is the lowest concentration at which the assay can report accurate results, when an interassay coefficient of variation of 20% is accepted).

The diagnostic value of the biochemical markers was assessed with regard to pneumonia (defined as the presence of a transient infiltrate on chest radiography), aetiology (determined by culture of blood and sputum and polymerase chain reaction on sputum for atypical bacteria and respiratory viruses), and failure of initial treatment in primary care (non-elective hospitalisation within 4 weeks).[9] Potentially clinical relevant cut-off points for procalcitonin were chosen at the level of the functional sensitivity of the test (0.06 ng/ml) and at the two levels for suspected bacterial infection as stated by the manufacturer (0.25 and 0.50 ng/ml). Additionally, two cut-off points of 0.08 and 0.1 ng/ml between the functional sensitivity and the expected level for bacterial infection were chosen. CRP was evaluated at a cut-off point of 20 mg/l as a low value appears to be optimal in the setting of primary care.[7]

Statistical methods

Data were analysed using STATA 8.0. To compare categorical variables, Fisher's exact test was used. Continuous variables were compared using the Mann–Whitney two-sample rank sum test. Sensitivities, specificities, positive predictive values (PPVs), and negative predictive values (NPVs) were calculated from 2×2 tables. Odds ratios (ORs) were calculated using a univariate logistic regression model. To compare the performance of procalcitonin and CRP in predicting pneumonia, receiver operating characteristic (ROC) curves were drawn, and the area under the curve (AUC) compared using χ^2 test. Levels of significance was set at $P<0.05$ for two-tailed tests.

RESULTS

Procalcitonin and C-reactive protein

Of the 364 patients, procalcitonin was measured in 357 patients (98%) and CRP in all but one.

In 35 patients (10%) procalcitonin values were below the detection limit of 0.02 ng/ml, and in 218 patients (61%) values were below the functional sensitivity of 0.06 ng/ml. Median procalcitonin was 0.05 ng/ml with an interquartile range of 0.04–0.08 ng/ml, and a total range from <0.02–42.92 ng/ml. Median CRP was 14 mg/l with an inter-quartile range of 10–35 mg/l and a total range from <10–600 mg/l.

Radiographic verified pneumonia

Forty-eight patients (13%) were diagnosed with radiographic pneumonia. A statistically significant difference between pneumonic and non–pneumonic patients was demonstrated for all cut-off points of procalcitonin (Table 1). PPV increased with increasing value of the cut-off point, but the sensitivity of the test concomitantly decreased. Sensitivity, specificity, PPV, and NPV for procalcitonin >0.06 ng/ml and CRP ≥20 mg/l were comparable. When the two biochemical markers were evaluated by a ROC curve in their ability to predict pneumonia (Figure 1), there was no significant difference in the AUC (0.79 for CRP and 0.73 for procalcitonin, $P = 0.187$). All eight patients with procalcitonin values higher than 0.5 ng/ml had pneumonia.

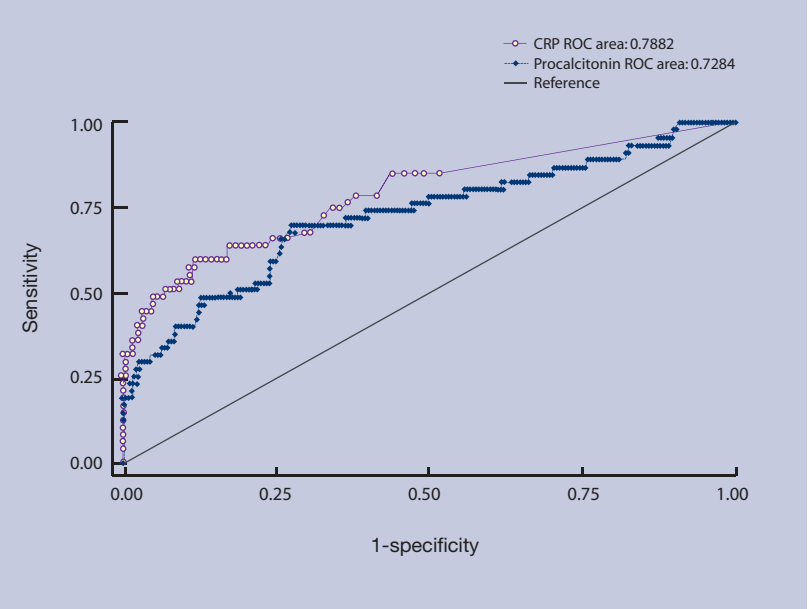


Figure 1. Receiver operating characteristic (ROC) curves of procalcitonin and C-reactive protein (CRP) predicting radiographic pneumonia.

Aetiology

In 69 patients (19%), bacterial infection was documented by the microbiological examinations.[9] Compared with patients without documented bacterial infection, a larger proportion of patients with bacterial infection had procalcitonin above 0.06 ng/ml or 0.08 ng/ml and CRP ≥20 mg/l (Supplementary Table 1). Patients with verified *Streptococcus pneumoniae* infection or *Mycoplasma pneumoniae* infection were looked at separately. Although numbers were small, it would appear that elevated CRP level (≥20 mg/l) is common in both infections, while elevated procalcitonin level (>0.06 ng/ml) is common in pneumococcal infection (74%) but unusual in mycoplasma infection (9%). The AUC of the ROC curves for procalcitonin and CRP in predicting bacterial infection were small for both markers (Figure 2). The four highest procalcitonin values (with a range of 5.76–42.92 ng/ml) and CRP values

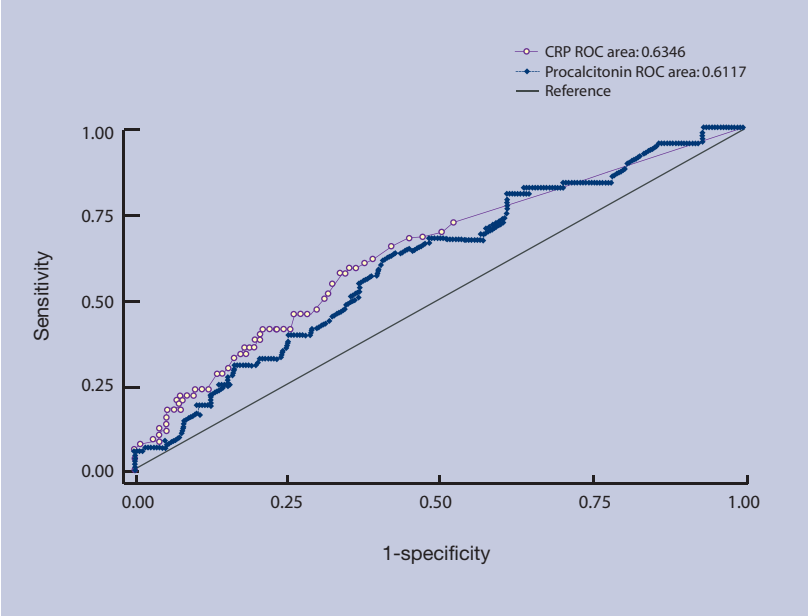


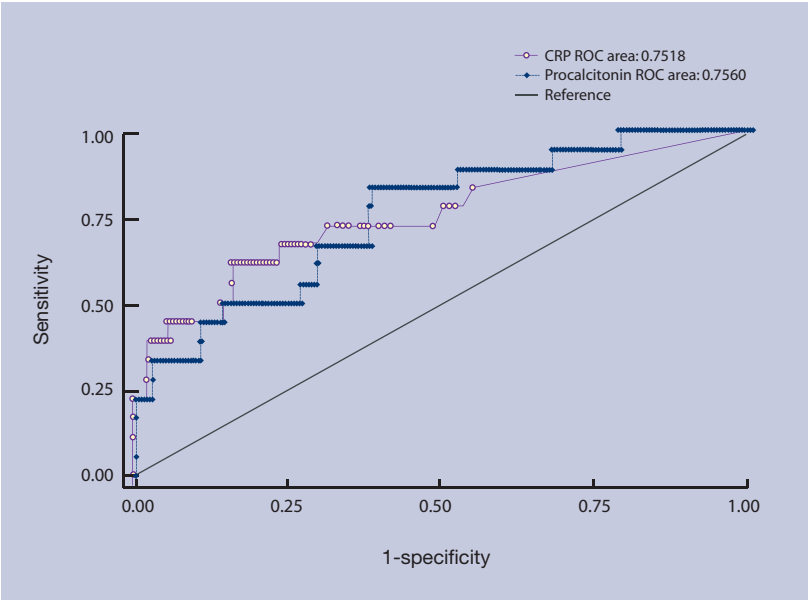
Figure 2. Receiver operating characteristic (ROC) curves of procalcitonin and C-reactive protein (CRP) predicting bacterial aetiology.

(with a range of 438–600 mg/l) were detected in four pneumonic patients with pneumococcal bacteraemia.

Outcome

All patients were initially treated in primary care. Nineteen patients (5%) were non-electively hospitalised within the 4-week follow-up period. Of the hospitalised patients, a larger proportion had procalcitonin and CRP values above the defined cut-off points compared with those who were not hospitalised. Procalcitonin >0.06 ng/ml and CRP ≥20 mg/l were comparable in all measures. AUC of the ROC curves were similar with values of 0.75 for CRP and 0.76 for procalcitonin (P = 0.944) in predicting hospitalisation (Figure 3).

Figure 3. Receiver operating characteristic (ROC) curves of procalcitonin and C-reactive protein (CRP) predicting hospitalisation.



DISCUSSION

Summary of main findings

Most adults diagnosed with LRTI in primary care had procalcitonin values below 0.06 ng/ml: 30% of pneumonic patients and 66% of patients with non-pneumonic LRTI. Both elevated procalcitonin and elevated CRP were significantly associated with pneumonia, bacterial infection of the lower respiratory tract, and the risk of hospitalisation within 4 weeks, but high PPVs were associated with unacceptably low sensitivities. There was no indication that procalcitonin has better accuracy as a predictor of pneumonia or bacterial infection than CRP, nor was there any finding to support the use of procalcitonin in LRTI in primary care. Procalcitonin may be a better marker than CRP to distinguish between mycoplasma and other bacterial infections, but this finding should be interpreted cautiously due to the low number of patients. The findings confirm that procalcitonin level is increased in patients with documented systemic infection (bacteraemia).

Strengths and limitations of the study

A strength of the study was a well-defined study population consisting of consecutive patients with LRTI. A limitation may be that few patients had pneumonia, and that an aetiological agent was not found in a large proportion of patients. However, both the proportion of patients found to have pneumonia, and the proportion of patients with a final aetiological diagnosis are similar to findings in other studies in primary care.

Most studies of procalcitonin have used an immunoluminometric assay (LUMItest®) which is unable to measure procalcitonin values below 0.3 ng/ml with sufficient accuracy. The strength of the newer, more sensitive Kryptor®-PCT assay is that it has become possible to evaluate procalcitonin levels in patients with less severe infection. According to the manufacturer, procalcitonin levels in healthy individuals are below 0.05 ng/ml, and bacterial infection should be suspected with levels above 0.25 ng/ml. In the present study, procalcitonin values were found to be below the reported functional sensitivity of 0.06 ng/ml in the majority of patients, even in 14 out of 47 (30%) pneumonic patients. A more sensitive method is required to evaluate fully the range of procalcitonin levels in patients with LRTI in primary care compared to healthy individuals. Using an ultra-sensitive research assay, Morgenthaler *et al* determined the optimal cut-off point at 0.05 ng/ml for discerning between healthy controls and patients with infection.[12] The findings of this study do not indicate that improved sensitivity of the assay will improve the accuracy of procalcitonin to identify pneumonia or clinical

relevant bacterial infection in the setting of adults with LRTI in primary care.

Comparison with existing literature

Since the association of procalcitonin with severe bacterial infection was reported,[13] studies have primarily assessed the value of procalcitonin in its ability to discriminate between different microbiological aetiologies, infectious and non-infectious causes of systemic inflammatory response syndrome, and to predict outcome in critical illness. In a meta-analysis comparing the ability of procalcitonin and CRP to discriminate between bacterial and viral or non-infective causes of inflammation in hospitalised patients, it was concluded that procalcitonin was superior to CRP.[14]

In studies of less severely ill patients, procalcitonin values are generally lower than values in patients with critical illness. In a study on LRTI, Polzin *et al,* found that procalcitonin was elevated in patients with community or hospital-acquired pneumonia and in patients hospitalised with acute exacerbation of chronic obstructive pulmonary disease when compared to healthy controls. But the median procalcitonin value in the patients was below the usual cut-off point suggestive of bacterial infection of 0.5 ng/ml.[15] However, Hedlund and Hansson showed that with a cut-off point of 0.5 ng/ml, procalcitonin was able to distinguish between classical and atypical bacterial aetiology in adults hospitalised with community-acquired pneumonia.[16]

Christ-Crain *et al,* performed a study in which patients with LRTI were treated by standard of care or by a procalcitonin-guided protocol according to which use of antibiotics were more or less encouraged with procalcitonin values of ≥0.5 ng/ml and ≥0.25 ng/ml.[11] Antibiotic treatment was reduced in the procalcitonin-guided group without affecting outcome. For patients with community-acquired pneumonia, only a small reduction in prescribing was observed, but more substantial reductions were seen in patients with acute exacerbation of chronic obstructive pulmonary disease or acute bronchitis. The majority of patients were treated in the hospital setting.

Data from the present study show that very few patients treated in primary care have procalcitonin values above either cut-off point, and application of a treatment strategy based on a cut-off point of 0.25 ng/ml in this setting would mean withholding antibiotics in 36 of 47 (77%) patients with pneumonia.

Few studies have evaluated patients treated in primary care, and none has been conducted in a well-defined group of adult patients with LRTI. The ability of procalcitonin to differentiate between aetiologies of LRTI in children in primary care has been studied by Korppi and Remes.[17] They found no association between procalcitonin levels and aetiology, or between procalcitonin levels and severity of disease, defined as the need for in-patient treatment. In the current study of adults, both procalcitonin and CRP levels were significantly associated with bacterial aetiology and subsequent risk of hospitalisation, but the accuracy of both tests were low. The difference between the current findings and the findings by Korppi and Remes must be interpreted in the context of the different assays used, as well as the different populations. In the study of children, the less sensitive LUMItest® was used, and the median procalcitonin of 0.45 ng/ml in patients in primary care did not differ from the median found by the same group in hospitalised children. In these patients, Korppi and Remes did find a marginally higher procalcitonin level in pneumococcal pneumonia compared with viral pneumonia, but the likelihood ratios were too low to be of clinical value.[18]

Implications for clinical practice and future research

Procalcitonin has not been previously considered as a relevant inflammatory marker in primary care. Introduction of the test in this setting will undoubtedly be discussed when the results from a primary care study from the Basel Institute for Clinical Epidemiology, University Hospital Basel, Switzerland are published.[19]

In the current study, elevated procalcitonin and CRP were significantly associated with pneumonia, bacterial aetiology, and risk of hospitalisation in adults with LRTI treated in primary care. At the chosen cut-off points, procalcitonin did not perform better than CRP, and high PPVs were found for both inflammatory markers associated with low sensitivities.

The majority of patients had procalcitonin values below the functional sensitivity level of the test, and a more sensitive method is needed to evaluate fully procalcitonin levels in LRTI in primary care. However, the results indicate that even using a more sensitive test would not be able to identify accurately patients with pneumonia, bacterial infection, or adverse outcome.

It is possible that procalcitonin can be used to discriminate between patients with mycoplasma and other bacterial infections. This may have therapeutic consequences in countries where β-lactam antibiotics are used as first choice empiric treatment for pneumonia in primary care. Introduction of a sensitive, rapid test without the need of a centrifuged venous blood sample is required if procalcitonin is to be routinely used in primary care.

Supplementary information

Additional information accompanies this paper at http://www.rcgp.org.uk/bjgp-suppinfo

Funding body

We are grateful for financial support from the following contributors: ML Jørgensen and Gunnar Hansens Fond, Praktiserende Lægers Uddannelses Fond, The Danish Lung Association, The Danish Medical Association, Institute of Clinical Research, University of Southern Denmark, Fonden for Lægevidenskabelig Forskning m.m. ved Fyns Amts Sygehusvæsen, Overlægerådets Legatudvalg, Odense University Hospital, Højbjerg Fonden, Fyns Amts Forskningsråd. Funded by The Danish Medical Research Council

Ethics committee

The protocol was approved by the Medical Ethics Committee of Funen and Vejle Counties and by the Danish Data Protection Agency (reference number 20000008)

Competing interests

The authors have stated that there are none

Acknowledgements

We wish to thank the participating GPs and patients, and the study nurses at the Research Unit of infectious diseases at Odense University Hospital.

REFERENCES

1. Raherison C, Peray P, Poirier R, *et al*. Management of lower respiratory tract infections by French general practitioners: the AIR II study. Analyse Infections Respiratoires. *Eur Respir J* 2002; **19(2):** 314–319.
2. Huchon GJ, Gialdroni-Grassi G, Leophonte P, *et al*. Initial antibiotic therapy for lower respiratory tract infection in the community: a European survey. *Eur Respir J* 1996; **9(8):** 1590–1595.
3. Gonzales R, Barrett PH Jr, Crane LA, Steiner JF. Factors associated with antibiotic use for acute bronchitis. *J Gen Intern Med* 1998; **13(8):** 541–548.
4. Metlay JP, Kapoor WN, Fine MJ. Does this patient have community-acquired pneumonia? Diagnosing pneumonia by history and physical examination. *JAMA* 1997; **278(17):** 1440–1445.
5. Plouffe JF, McNally C, File TM, Jr. Value of noninvasive studies in community-acquired pneumonia. *Infect Dis Clin North Am* 1998; **12(3):** 689–699, ix.
6. 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(3):** 234–240.
7. Hopstaken RM, Muris JW, Knottnerus JA, *et al*. 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(490):** 358–364.
8. van der Meer V, Neven AK, Van Den Broek PJ, Assendelft WJ. Diagnostic value of C reactive protein in infections of the lower respiratory tract: systematic review. *BMJ* 2005; **331(7507):** 26.
9. Holm A, Nexoe J, Bistrup LA, *et al*. Aetiology and prediction of pneumonia in lower respiratory tract infection in primary care. *BJGP* 2007; **57(540):** 547–554.
10. Meisner M. Pathobiochemistry and clinical use of procalcitonin. *Clin Chim Acta* 2002; **323(1–2):** 17–29.
11. Christ-Crain M, Jaccard-Stolz D, Bingisser R, *et al*. Effect of procalcitonin-guided treatment on antibiotic use and outcome in lower respiratory tract infections: cluster-randomised, single-blinded intervention trial. *Lancet* 2004; **363(9409):** 600–607.
12. Morgenthaler NG, Struck J, Fischer-Schulz C, *et al*. Detection of procalcitonin (PCT) in healthy controls and patients with local infection by a sensitive ILMA. *Clin Lab* 2002; **48(5–6):** 263–270.
13. Assicot M, Gendrel D, Carsin H, *et al*. High serum procalcitonin concentrations in patients with sepsis and infection. *Lancet* 1993; **341(8844):** 515–518.
14. Simon L, Gauvin F, Amre DK, *et al*. Serum procalcitonin and C-reactive protein levels as markers of bacterial infection: a systematic review and meta-analysis. *Clin Infect Dis* 2004; **39(2):** 206–217.
15. Polzin A, Pletz M, Erbes R, *et al*. Procalcitonin as a diagnostic tool in lower respiratory tract infections and tuberculosis. *Eur Respir J* 2003; **21(6):** 939–943.
16. Hedlund J, Hansson LO. Procalcitonin and C-reactive protein levels in community-acquired pneumonia: correlation with etiology and prognosis. *Infection* 2000; **28(2):** 68–73.
17. Korppi M, Remes S, Heiskanen-Kosma T. Serum procalcitonin concentrations in bacterial pneumonia in children: a negative result in primary healthcare settings. *Pediatr Pulmonol* 2003; **35(1):** 56–61.
18. Korppi M, Remes S. Serum procalcitonin in pneumococcal pneumonia in children. *Eur Respir J* 2001; **17(4):** 623–627.
19. Briel M, Christ-Crain M, Young J, *et al*. Procalcitonin-guided antibiotic use versus a standard approach for acute respiratory tract infections in primary care: study protocol for a randomised controlled trial and baseline characteristics of participating general practitioners [ISRCTN73182671]. *BMC Fam Pract* 2005; **6:** 34.