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SHORT REPORT

Accuracy of lipopolysaccharide-binding protein (LBP) and fibrinogen compared to C-reactive protein (CRP) in differentiating pneumonia from acute bronchitis in primary care

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Abstract

Aims: To assess the diagnostic value of lipopolysaccharide-binding protein (LBP) and fibrinogen compared to C-reactive protein (CRP) for pneumonia in primary care patients with lower respiratory tract infection (LRTI).

Methods: Receiver operating characteristic curves summarising test accuracies for LBP, fibrinogen and CRP for pneumonia were constructed. The respective areas under the curve (AUCs) were calculated and compared with that of body temperature, an acknowledged clinical sign to differentiate pneumonia from acute bronchitis in primary care.

Results: 11 of 95 patients had radiographically confirmed pneumonia (11.7%). The AUC was 0.90 for CRP, 0.92 for LBP and 0.86 for fibrinogen. Body temperature yielded an AUC of 0.63. Differences between the AUCs were not significant for the three blood tests, but highly significant when compared to body temperature ($p<0.001$).

Conclusion: LBP and fibrinogen are equally strong predictors of pneumonia in patients with LRTI, but they do not perform better than CRP.

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Introduction

The non-specific nature of symptoms and signs in lower respiratory tract infection (LRTI) makes differentiation between pneumonia and acute bronchitis difficult for clinicians in primary care. Optimal management for LRTI (a common reason to consult in primary care) should only involve antibiotic treatment for patients with pneumonia and not for most patients with acute bronchitis.[1] However, antibiotic prescribing rates of up to 80% for LRTI are reported in many countries.[2,3] Increasing antimicrobial resistance, possible side effects and societal costs, stress the need to optimise management. Performing chest radiography on all patients with LRTI is not feasible on economical and logistic grounds. Accurate, diagnostic markers to guide physicians are therefore needed, preferably as point of care tests.[4] In recent years, several biomarkers have been suggested.[5-8]

C-reactive protein (CRP) is a better marker of pneumonia than any clinical symptom or sign, leucocyte count, or the erythrocyte sedimentation rate (ESR), and may therefore guide rational antibiotic treatment in primary care situations.[6,9] Procalcitonin is promising, but point of care testing is not possible.[5] Lipopolysacharide-binding protein (LBP) and fibrinogen are other acute phase proteins used to diagnose and monitor infection in critical care.[7,10] These two markers may perform better, but their additional value for primary care is not known.

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In the present study we assessed the diagnostic accuracy of LBP and fibrinogen for pneumonia in primary care patients with LRTI, and we compared accuracy with CRP.

Methods

Consecutive eligible adult patients who presented to their general practitioner (GP) with signs and symptoms of LRTI were included in this cohort study in the Netherlands. Eligibility criteria have been described in detail elsewhere.[6] Venous blood samples were taken in the general practice directly after consultation. Spare blood samples were stored in -80 degrees Celsius in the University Hospital, Maastricht until analysed in January 2006. LBP was measured with an immunometric assay (Immulite; Siemens Medical Solutions Diagnostics). CRP and fibrinogen were measured using standard laboratory procedures. Chest radiographs (lateral and postero-anterior) were performed on every patient. Two independent blinded radiologists assessed the radiographs for the presence or absence of infiltrates. If the two radiologists disagreed, a third radiologist conducted an independent, decisive assessment. The conclusive finding of a pulmonary infiltrate was regarded as evidence of pneumonia. Laboratory results were not available to investigators, radiologists or physicians until after patient classification (pneumonia or acute bronchitis) had taken place. Sampling was performed before possible antibiotic treatment was started.

We assessed the sensitivities and specificities of all possible cut-off points and constructed receiver operating characteristic (ROC) curves for LBP, fibrinogen and CRP. To compare the overall diagnostic accuracy of the blood tests, the respective areas under the curve (AUCs) were calculated. The AUC of the ROC curves were also compared with the AUC of a physical sign with acknowledged diagnostic accuracy in previous studies on clinical prediction of pneumonia: i.e. body temperature. Differences between the AUCs were tested for significance by the DeLong equality test. Statistical analysis was performed using SPSS and STATA. The study was approved by the local ethics committee and written consent was obtained from all patients for the additional blood sampling.

Results

Blood samples of 95 patients were available for LBP and fibrinogen analysis. Eleven patients had radiographically-confirmed pneumonia (11.7%). Baseline characteristics are summarised in Table 1. Demographics and symptoms and signs of this subgroup were comparable to the original trial cohort.[6] Median values of LBP, fibrinogen and CRP for all 95 LRTI patients are shown in Table 2.

Table 3 shows sensitivities, specificities, positive and negative predictive values of various cut-off points for CRP,

Table 1. Baseline characteristics of study population.

	n=95	(%)
Demographics		
Mean age (SD)	52.4	(15.8)
Male	43	(45.3)
Smoking	35	(36.8)
Symptoms & signs		
Recent cough (<29 days)	85	(89.5)
Dry cough	25	(26.3)
Auscultation abnormality	80	(84.2)
Fever (≥38ºC)	18	(18.9)
Co-morbidity		
Asthma	15	(15.8)
COPD	20	(21.1)
Chest radiograph		
Infiltrate (pneumonia)	11	(11.7)
Antibiotic prescription	77	(77.9)

Table 2. C-reactive protein (CRP), fibrinogen and lipopolysaccharide-binding protein (LBP) values.

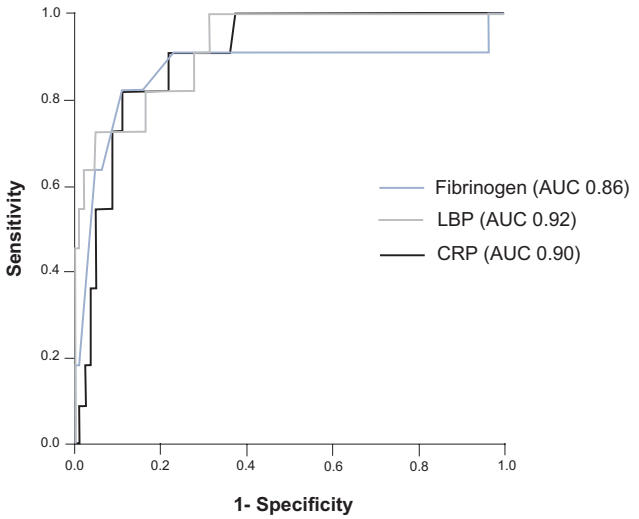
	Pneumonia (n=11)	No pneumonia (n=84)	All patients (n=95)
CRP (mg/L)	145 (36-213)	17 (2-216)	26 (2-216)
Fibrinogen (g/L)	5.5 (1.8-8.9)	4.0 (0.6-5.7)	4.1 (0.6-8.9)
LBP (mg/L)	44.7 (17.1-87.6)	11.3 (3.8-48.6)	12.1 (3.8-87.6)

Values are median (range).

Table 3. Sensitivities, specificities, positive and negative predictive values (PPV, NPV;%) of C-reactive protein (CRP), lipopolysaccharide-binding protein (LBP), fibrinogen and fever at different cut-off values for patients with pneumonia.

	Sensitivity	Specificity	PPV	NPV
CRP >10	100	36.1	17.2	100
CRP >20	100	50.6	21.2	100
CRP >100	81.8	84.3	40.9	97.2
LBP >10	100	33.7	16.7	100
LBP >20	81.8	79.5	34.6	97.1
LBP >30	72.7	90.4	50.0	96.2
Fibrinogen >4	90.9	54.9	21.3	97.8
Fibrinogen >5	81.8	89.0	50.0	97.3
Fever (≥38ºC)	36.4	83.1	22.2	90.8

Figure 1. ROC curves showing sensitivity and specificity of C-reactive protein (CRP), Lipopolysacharide-binding protein (LBP) and fibrinogen for pneumonia at different cut-off points.



LBP and fibrinogen for pneumonia in addition to the presence of fever (≥38ºC).

The Figure shows ROC curves illustrating the sensitivity and specificity of CRP, LBP and fibrinogen. The area under the ROC curve was 0.90 for CRP, 0.92 for LBP and 0.86 for fibrinogen. Body temperature yielded an AUC of 0.63. Differences between the AUCs were not significant for the three blood tests, but highly significant when compared to body temperature (p<0.001; DeLong equality test).

Discussion

LBP, fibrinogen and CRP were equally strong predictors of pneumonia in this primary care study of patients with LRTI. Accuracies were much higher than that of the best diagnostic test available from history and physical examination – the presence of fever (temperature ≥38ºC).

In a previous study we showed that the diagnostic accuracy of CRP for pneumonia was superior to any clinical finding as well as to leucocyte count and ESR.[6] Quantitative CRP point of care tests are commercially available and have been widely used in several European countries for many years. They have proved to be reliable and robust for routine use in general practice.[11,12] LBP and fibrinogen seem to be equally strong predictors for pneumonia, but at present they are not available as point of care tests. The results of this study do not directly advocate developing these two biomarkers as near patient tests for primary care settings. However, our study is the first to test the accuracy of LBP and fibrinogen for pneumonia in primary care. New, larger studies would be necessary for definite conclusions.

Interpretation of ROC curves, including choosing optimal cut-off values, differs for the setting in which the test is used. Intensive care physicians are primarily interested in finding evidence of pneumonia that justifies antibiotic treatment; hence, a highly specific test with optimal performance of the test on high cut-off values of the test is most valuable for them. In contrast, in primary care – where pneumonia is by far outnumbered by presenting cases of self-limiting acute bronchitis – physicians specifically need additional tools to rule out pneumonia. For that reason, the test needs to perform well at low cut-off points in the primary care setting. A CRP cut-off point of 20 mg/l fits this need and could lead to a considerable and safe reduction of unnecessary antibiotic prescriptions in general practice. The large differences in incidence and illness severity between patient settings, and forthcoming implications for management, underline the importance of primary care studies in addition to studies in highly selected populations. This may also explain why many promising markers often studied and developed in critical care perform relatively poorly in differentiating primary care infections.

We explicitly chose to study the diagnostic accuracy of these biomarkers in differentiating pneumonia from acute bronchitis, and not the distinction between bacterial and viral infection, nor the distinction between patients with or without COPD co-morbidity. As much as the latter two distinctions are relevant, the first distinction is the most important issue to primary care physicians – i.e. does this patient have pneumonia and hence do I need to treat this patient with antibiotics?

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Conflict of interest declaration

The authors have no conflict of interest.

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OBITUARY

Dr Ian Gregg 1925-2009

Ian Gregg was well known for his pioneering work in asthma, and its treatment and monitoring in general practice and by the patient at home. He was particularly instrumental in getting the peak flow meter accepted as a valuable indicator of airway resistance change before and during an asthma attack. Perhaps his best known work was in establishing normal peak flow values (Nunn & Gregg, *Br Med J* 1989;**298**:1068-70).

Ian was educated at Westminster, and after leaving in 1943 joined the Army. He spent much time in India, which he loved, and became fluent in Urdu. On demobilisation he went up to Wadham College, Oxford, and then qualified at Westminster Hospital Medical School in 1954. House jobs followed at the Westminster, Brompton, and St Stephen's Hospitals.

Ian's ambitions were always in general practice, and from 1958 to 1982 he was a principal at practices in Roehampton and later at Kingston-upon-Thames. He continued research as a clinical assistant at the Westminster. In 1962 Ian observed the increase in airway resistance in many asthmatic patients without symptoms, and in 1964 published his classic paper on the use of the Wright peak flow meter in general practice (*J Coll Gen Pract* 1964;**7**(2):199-214)

From 1982 until 1987 he was senior lecturer at Southampton University. He travelled widely, lecturing, presenting research, helping and advising industry, and making many friends.

Ian Gregg died on 26 April 2009.

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