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Evaluating the evidence for the implementation of C-reactive protein measurement in adult patients with suspected lower respiratory tract infection in primary care: a systematic review

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Background. Excessive prescription of antibiotics in patients with lower respiratory tract infection (LRTI) is common in primary care and might be reduced by rapid point-of-care (POC) C-reactive protein (CRP) testing. However, the exact benefits of this test are unclear.

Objective. To review the available evidence for the role of POC CRP measurement in (i) guiding antibiotic prescription, (ii) predicting aetiology, (iii) prognosis and (iv) diagnosis (pneumonia) in LRTI patients.

Methods. For each research question, studies were retrieved through an electronic literature search in Medline, Embase and the Cochrane Library using synonyms for CRP and LRTI combined with different relevant subheadings. Study quality was assessed using validated instruments and predefined outcome measures were extracted from each study.

Results. The search yielded 13 articles, each answering one or more questions; one was excluded by insufficient internal validity. (i) One of four studies showed a significant reduction in the antibiotic prescriptions when applying POC CRP measurement [relative risk (RR) 0.6, 95% confidence interval (CI) 0.5–0.7]. (ii) Three studies on aetiology demonstrated that an elevated CRP was associated with bacterial [odds ratio (OR) 2.46–4.8] and one with viral (OR 2.7) aetiology. (iii) Results on the prognostic value were contradictory, providing evidence for faster symptom resolution (RR 1.16, 95% CI 1.1–1.3), higher mortality rate (RR 2.5, 95% CI 1.2–5.1) and no difference in outcome in patients with high CRP levels. (iv) Four studies showed that CRP had limited value as a single predictor of pneumonia. When combined with clinical assessment, its value increased according to two of these studies (receiver operating characteristic area from 0.7 to 0.9). However, methodological flaws and/or wide CIs limit the generalizability of findings in all studies.

Conclusion. The evidence for the benefits of POC CRP measurement in LRTI patients in primary care is limited, contradictory and does not support its use to guide treatment decisions yet.

Keywords. Antibiotic prescription, aetiology, C-reactive protein, diagnosis, point-of-care, primary care, prognosis.

Introduction

Excessive prescription of antibiotics in patients with lower respiratory tract infection (LRTI) is a substantial problem in Western Europe. In the Netherlands, inappropriate prescribing in LRTI is as high as 86%.[1] Excessive use of antibiotics drives the development of antimicrobial resistance, medicalization of patients and increases health care costs.[2,3]

Point-of-care (POC) C-reactive protein (CRP) measurement may reduce diagnostic uncertainty, consequently unnecessary antibiotic prescription and even increase patients' adherence to therapy.[4,5] It is a rapid quantitative test which can be performed at the GP's office and requires a droplet of blood obtained by finger prick. Results are available within 2 minutes. Most POC analyzers detect CRP levels between 5 and 200 mg/l with a level of <20 mg/l indicating a healthy

patient or non-severe infection. Average purchasing costs are €1837—with an additional of €4—per test.[6–8]

Recently issued Dutch guidelines, serving as a protocol for GPs, advocate the use of POC CRP testing in LRTI patients at intermediate risk of severe infection,[9] while the diagnostic value of this test in (these) LRTI patients can be questioned. For example, a systematic review, including hospitalized patients and children, showed that CRP measurement was insufficiently sensitive and specific to act as a diagnostic tool to predict bacterial aetiology or radiographic pneumonia.[10] It is unknown to what extent these results are applicable to an adult primary care population, with a different pretest probability.

Strikingly, implementation of POC CRP testing in Scandinavian countries resulted in excessive use of the test and continuous suboptimal use of antibiotics in primary care.[11,12] An observation of routine practice showed that the POC CRP level does influence antibiotic prescribing, but the use of POC CRP testing in itself does not substantially reduce the overall amount of antibiotic prescriptions [relative risk (RR) 1.1].[2] These observations urge (Dutch) professionals to be critical when implementing POC CRP measurement in daily practice on a large scale. We will therefore review the available evidence for the effect of POC CRP measurement on the management of adult patients with suspected LRTI presenting in primary care and the rationale behind CRP measurement in these patients. We will focus on (i) prescription of antibiotics, (ii) prediction of aetiology, (iii) prognosis and (iv) diagnosis (i.e. pneumonia).

Methods

Search strategy

An electronic literature search by title and abstract was performed in Medline, Embase and the Cochrane Library, from January 1975 to July 2010. The search was limited to published studies only. Search terms and medical subheadings differed per research question (Table A1). No methodological filters were applied and no articles were excluded by language. The search was supplemented by screening of related articles, references and citations of relevant studies and (inter-) national guidelines on LRTI. Authors and/or publicists were contacted when the full text version was not available.

Study selection and data extraction

Based on title and abstract, two authors (MFE and FPP) independently selected full text articles based on predefined inclusion and exclusion criteria. These inclusion and exclusion criteria were the same for all the four research questions. Studies using adult patients (≥16 years of age) consulting their GP with a probable LRTI were included if CRP was measured in (a part) of those patients. 'Probable LRTI' had to be defined as the presence of clinical criteria suggesting LRTI or a diagnosis of LRTI made by the physician, small differences in definitions of LRTI between studies were accepted.

Exclusion criteria were letters, editorials, reviews and single case reports. Studies that only described upper respiratory infections, patients with confirmed pneumonia or bronchitis and/or immunocompromised patients (HIV) were also excluded. Studies describing hospitalized patients or patients presented on the emergency department were excluded, as a hospital-based population consists of more severely ill patients and would produce a higher pretest probability of antibiotic prescriptions, (bacterial) pneumonia and poor prognosis. In studies on diagnosis, for example, this would lead to an overestimation of the discriminatory value of CRP in all LRTI patients.[13,14] Studies not presenting data for LRTI patients in primary care separately were excluded as well. In addition, specific inclusion and exclusion criteria were formulated to match each different research question as follows.

Antibiotic prescription. Studies that evaluated the effect of CRP measurement on antibiotic prescription were only included if a POC CRP test was used in a study setting (i.e. excluding cohort studies describing daily practice). Studies needed to provide a RR or quantitative information from which a RR could be extracted.

Aetiology. Aetiologic studies had to provide the negative (NPV) and positive predictive value (PPV) of CRP measurement compared to a reference test consisting of sputum cultures, throat swabs and/or serology. Because aetiologic testing in the general population is not feasible, the prevalence of bacterial colonization in the community is unknown, the prevalence in LRTI patients presenting in primary care is ~380 per 1000 LRTI patients.[15]

Prognosis. To determine the prognostic value of CRP we included articles providing the RR, or data from which it could be calculated, of persisting symptoms and/or mortality for different CRP cut-off points.

Diagnosis. Studies that evaluated the diagnostic properties of CRP were only included if chest radiography was used as a reference test; international guidelines define community-acquired pneumonia (CAP) as clinical symptoms suggestive for LRTI combined with radiographic findings suggestive for CAP.[16,17] The NPV and PPV of CRP measurement had to be provided. The reported prevalence of CAP in the community ranges from 8 to 12 per 1000 inhabitants,[18,19] the incidence in

LRTI patients ranges from 60 per 1000 overall to 130 per 1000 in winter seasons.[15,20,21]

Per article, one of two authors (MFE and FPP) extracted all relevant data and the second author verified if the retrieved data matched the original article. Before comparison of the aforementioned outcome measures, relevant study data were retrieved and compared. These data included design (including randomization and blinding); inclusion and exclusion criteria; selection procedures; demographic data, co-morbidity and signs and symptoms of participants; performance of CRP measurement and reference tests (setting and timing); follow-up and statistical analysis methods. CRP cut-off values were displayed as described in the original studies. Authors were contacted if the original data were required for comparison, data were not reanalysed.

Quality assessment

Study quality was independently evaluated by two authors (MFE and FPP). To assess study quality and identify sources of bias, the QUADAS (Quality Assessment of Studies of Diagnostic Accuracy) was used for diagnostic studies and the Cochrane validity score was used for randomized controlled trials (RCTs) and the remaining cohort studies.[22,23] A score was calculated by dividing the amount of items the study was scored on by the amount of positive results (Supplementary Table 1, see online supplementary material). This resulted in a percentage which was labelled 'validity score'. Studies with a low validity score (<50%) were excluded from this review. The initial agreement between authors was evaluated and Cohen's Kappa was calculated. Disagreements were solved after discussion with the entire study group.

Results

After applying the inclusion and exclusion criteria, 13 articles originating from 10 studies were retrieved. Each article answered one or more research questions. Five articles discussed antibiotic prescription, four aetiology, three prognosis and three diagnosis. Figure 1 illustrates the flow of articles through the review process. Two articles were derived from the same study [20,24] and all three articles by Hopstaken *et al.* are subanalyses derived from data from one RCT described elsewhere.[21,25–27]

Quality assessment

Table 1 shows the results of the assessment of relevance and quality. Initial agreement between the two quality assessors was 97% ($\kappa = 0.97$). Overall quality of the included studies varied from low to excellent. One study on antibiotic prescription had a low internal validity (validity score 17%); the appraisal revealed major methodological flaws (Supplementary Table 1, see online supplementary material), it was therefore excluded from this review.[28]

Study characteristics

Table 2 lists the main characteristics of the 12 retrieved articles derived from 9 original studies. All studies discussed LRTI only or displayed results for LRTI separately from other conditions. One paper discussed both adults and children; data on adults only were retrieved by contacting the author.[29] The relevant outcome measures were provided in all retrieved articles.

Synthesis of results

Details of study results are listed in Table 2, subdivided by research question.

Can rapid POC CRP measurement in primary care reduce antibiotic prescription? Comparison of study populations of the four studies on this subject shows comparable duration of symptoms and frequencies of fever. The incidence of cough in these groups, however, varies from 40% to 100%. Overall, the RR of an antibiotic prescription at index consultation ranged from 0.58 to 0.96 in the POC CRP group compared to the control group.[4,29–31] One study, with the lowest validity score (56%), showed that prescribing antibiotics based on the results of rapid POC CRP measurement can reduce the amount of antibiotic prescriptions significantly. A difference between the POC CRP and the control group was found [RR 0.58, 95% confidence interval (CI) 0.5–0.7], remaining significant after 28 days of follow-up (RR 0.77, 95% CI 0.6–0.9). However, controls had abnormalities on chest auscultation more often than cases, which might have influenced antibiotic prescription.[31] Patient's outcome was comparable for the intervention and control group in this study, suggesting that the withholding of antibiotics did not compromise patient outcome. Concordantly, two additional studies showed no significant difference in patient outcome.[4,30] Diederichsen *et al.*,[29] however, showed that patients in the CRP group had a slightly longer duration of symptoms compared to the control group.

Can CRP levels identify bacterial aetiology in LRTI? Different patient characteristics were described in each study restricting the comparability of study populations. The population in the study by Melbye *et al.*,[30] for example, shows significantly less fever and cough and a shorter duration of symptoms as compared to the remaining study populations. High CRP values, measured in the laboratory, were generally associated with a confirmed aetiological diagnosis in all four studies. One author identified an association between an elevated CRP (>50 mg/L) and viral aetiology [odds ratio (OR) 2.7, 95% CI 1.4–5.2]. However, this association was only observed when comparing patients with viral LRTI to patients with microbiologically

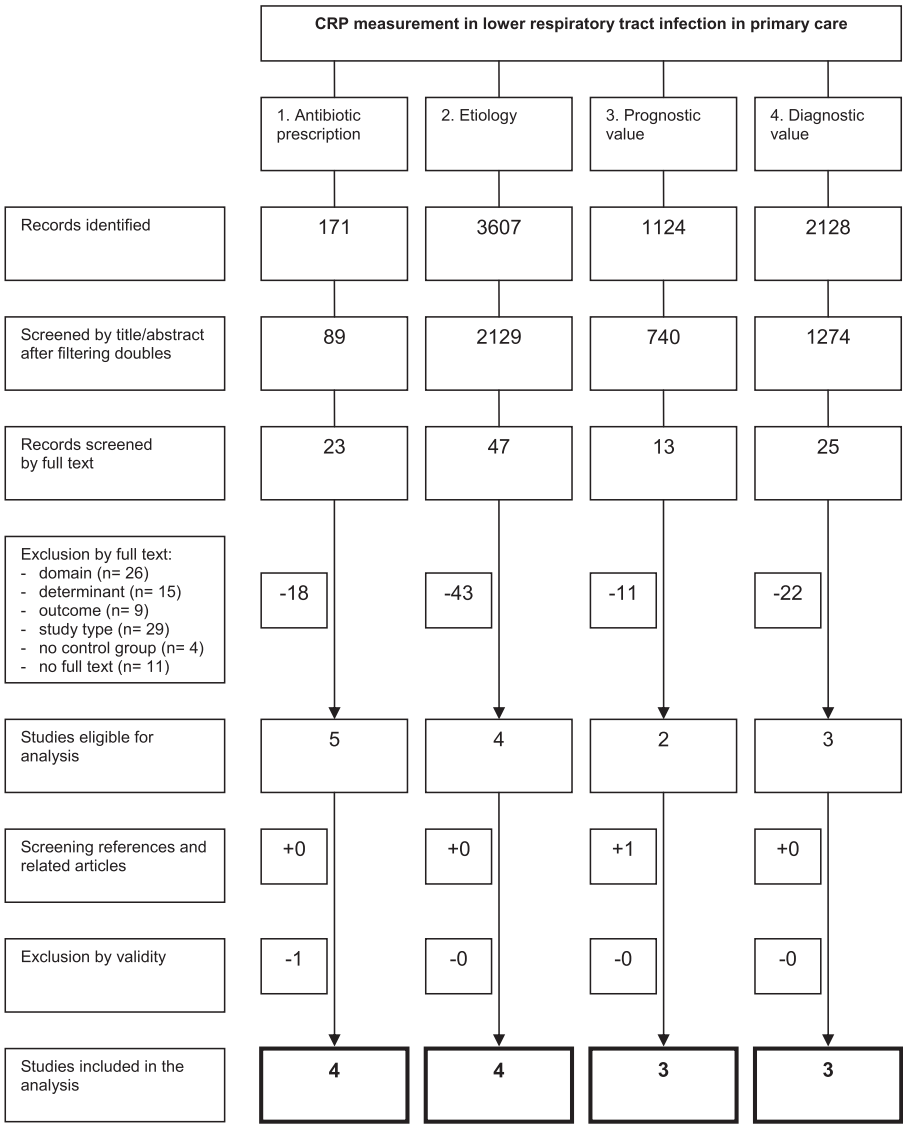

FIGURE 1 *Flowchart*

unexplained LRTI and may have been due to the fact that patients with microbiologically unexplained LRTI were less ill and therefore less likely to show strong acute-phase responses.[25]

Holm *et al.*[24] showed contrasting results; an elevated CRP (>20 mg/L) was associated with bacterial aetiology (OR 2.58, 95% CI 1.51–4.43) compared to all other causes of LRTI. Furthermore, Macfarlane *et al.* compared a group of patients with bacterial and atypical LRTI to a group with viral and unexplained LRTI, using a CRP cut-off value of >50 mg/l. The OR for CRP predicting bacterial/atypical LRTI was 2.46 (95% CI 1.3–4.6).[15] The study by Graffelman *et al.* also showed an association between bacterial LRTI and high CRP levels compared to viral LRTI. CRP cut-off values of >20 and >50 mg/l yielded ORs of 4.8 (95% CI 1.3–18) and 2.6 (95% CI 1.0–6.5), respectively. In the multivariate analysis, CRP did not have additional value to history and physical examination alone in predicting bacterial aetiology of LRTI.[32]

Does CRP level in LRTI patients have prognostic value? Study populations of the three retrieved studies differ greatly, for example, the population used by Seppa *et al.* consisted of mainly elderly patients. There was a wide variety between groups in incidence of cough, fever, abnormalities on chest auscultation and duration of symptoms. One study showed that CRP, measured in the laboratory, was not a significant predictor of symptom resolution.[26] Strikingly, a study by Melbye *et al.* showed that a CRP level of ⩾11 mg/l was associated with a shorter duration of illness (calculated RR 1.16 95% CI 1.1–1.3) when compared to patients with a CRP <11 mg/L measured at index consultation, but this difference was not statistically significant. Because patients with higher CRP levels were prescribed

TABLE 1 *Validity score[a] and relevance of the retrieved articles by research question*

Research question	Author (year)	Validity score[a] (%)	Relevance		
			Domain	Determinant	Outcome
Antibiotic prescription			Adults, LRTI, primary care	POC CRP measurement	Antibiotic prescription
	Cals (2009)	56	+	+	+
	Cals (2010)	89	–	+	+
	Diederichsen (2000)	63	–	+	+
	Kavanagh (2011)	17	–	+	+
	Melbye (1995)	86	+	+	+
Aetiology			Adults, LRTI, primary care	CRP measurement	Microbiological diagnosis
	Graffelman (2004)	80	+	+	+
	Holm (2007)	91	+	+	+
	Hopstaken (2005)	100	+	+	+
	Macfarlane (2001)	91	+	+	+
Prognostic value			Adults, LRTI, primary care	CRP measurement	Prognosis
	Hopstaken (2006)	89	+	+	+
	Melbye (1995)	78	+	+	+
	Seppa (2001)	80	–	+	+
Diagnostic value			Adults, LRTI, primary care	CRP measurement	Radiographic pneumonia
	Holm (2007)	83	+	+	+
	Hopstaken (2003)	100	+	+	+
	Macfarlane (2001)	83	+	+	+

(+), variables used in the article meet the variables aimed for in this review; (–), variables used in the article do not meet the variables aimed for in this review.
[a]Validity score: the percentage of (+) scored with the different validated tools.

antibiotics more often, the observed effect might be a result of prescription bias. However, antibiotic prescriptions had no significant influence on duration of illness in this study. Another study, performed in elderly patients, found that a CRP level of ⩾100 mg/l was an independent risk factor of mortality within 30 days (RR 2.5, 95% CI 1.2–5.1). The influence of antibiotics was not accounted for, while the prevalence of pneumonia was relatively high in this population.[33]

Can CRP predict radiographically confirmed pneumonia? Study populations differ greatly, the population used by Melbye *et al.* showed less signs of illness than the populations used in the remaining two studies. The retrieved studies showed different diagnostic properties. Overall, radiographic confirmed pneumonia was present in 13%–17% of patients studied. The PPV and NPV of CRP, measured in the laboratory, ranged from 0.17 to 0.42 and from 0.88 to 0.99, respectively. Macfarlane *et al.* identified an association between an elevated CRP (⩾50 mg/l) and radiographic confirmed pneumonia (OR 5.4, 95% CI 2.7–11.0). Holm *et al.*[20] found that a CRP level of ⩾20 mg/l was an independent predictor of pneumonia (OR 2.83, 95% CI 1.33–6.04). Hopstaken *et al.*[21] evaluated three CRP cut-off points; 10, 20 and 50 mg/l and found an OR for pneumonia of 14.1 (95% CI 1.9–105.6), 9.9 (95% CI 2.9–33.7) and 21.4 (95% CI 7.2–63.9), respectively.

Two studies evaluated the diagnostic value of CRP combined with clinical assessment. Holm *et al.* combined a CRP of ⩾20 mg/l with a clinical diagnosis of pneumonia based on history taking and physical examination, resulting in an OR of 4.97 (95% CI 2.60–9.52). The PPV and NPV in this case were 0.32 and 0.91, respectively. These authors also evaluated the use of either an elevated CRP or a clinical diagnosis of pneumonia as a predictor of pneumonia. They found that the PPV was lower (0.20) and the NPV higher (0.95).[20] Hopstaken *et al.* designed a prediction rule, using various signs and symptoms combined with CRP. The performance of this model versus signs and symptoms alone was shown in receiver operating characteristic analysis: the area under the curve was 0.9 versus 0.7, respectively.[21]

Discussion

The studies included in our systematic review showed limited evidence for the usefulness of rapid POC CRP measurement in adult patients suspected of LRTI in primary care. Only one study provided evidence that a reduction in antibiotic prescriptions may be achieved when POC CRP measurement is applied.[31] Two studies showed limited value of CRP in diagnosing pneumonia, although the diagnostic value increased when

TABLE 2 *Study characteristics*

Research question	Author (year, country)	Study design	Domain	*N*	Reference standard	Outcome	CRP cut-off point (mg/L)	Outcome measure						Validity (%)
								RR (95% CI)	OR (95% CI)	Sn	Sp	PPV	NPV	
Antibiotic prescription	Cals (2009, The Netherlands)	Cluster RCT	Adults with [a]	431	X	% Antibiotic prescriptions, at index consultation	X	0.6* (0.5–0.7)*						56
						At 28 days		0.8* (0.6–0.9)*						
	Cals (2010, The Netherlands)	RCT	Adults with LRTI[a] and rhinosinusitis	258	X	% Antibiotic prescriptions	X							89
			Subgroup: LRTI[a]	107		At index consultation		0.8* (0.5–1.2)*						
	Diederichsen (2000, Denmark)	RCT	Children and adults with all types RTI[b]	812	X	% Antibiotic prescriptions	X							63
			Subgroup: Adults with chest infection	418		At index consultation		0.96* (0.78–1.18)*						
	Melbye (1995, Norway)	RCT	Adults with LRTI[c]	239	X	% Antibiotic prescriptions, at index consultation	X	1.0* (0.8–1.2)*						86
						At 21 days		1.0* (0.8–1.2)*						
Aetiology	Graffelman (2004, The Netherlands)	PC	Adults with LRTI[d]	137	Sputum culture	Bacterial versus viral	>20 UV		4.8 (1.3–18.0)	0.89	0.35	0.49	0.81	80
					Throat swab		MV		–	–	–	–	–	
					Serology		>50 UV		2.6 (1.0–6.5)	0.66	0.57	0.52	0.70	
							MV		–	–	–	–	–	
	Holm[b] (2007, Denmark)	PC	Adults with LRTI[e]	682	Sputum culture + PCR Blood culture	Bacterial versus non-bacterial	⩾50 UV		2.6 (1.5–4.4)	0.56	0.64	0.28	0.87	91
	Hopstaken (2005, The Netherlands)	POC	Adults with LRTI[f]	236	Sputum culture/ oral washing	Viral versus bacterial/ unexplained	>10 UV		1.7 (0.8–3.7)	0.80	0.31	0.23	0.85	100
					Nose/throat swab/ Serology		>20 UV		1.7 (0.9–3.4)	0.65	0.48	0.25	0.84	
							>50 UV		2.7 (1.4–5.2)	0.51	0.72	0.33	0.85	
	Macfarlane (2001, UK)	PC	Adults with LRT illness[g]	316	Sputum culture Throat swab/ serology	Bacterial/ atypical versus viral/ unexplained	⩾50 UV		2.5* (1.3–4.6)*	0.62*	0.60*	0.23*	0.89*	91

TABLE 2 *Continued*

Research question	Author (year, country)	Study design	Domain	*N*	Reference standard	Outcome	CRP cut-off point (mg/L)	RR (95% CI)	Outcome measure OR (95% CI)	Sn	Sp	PPV	NPV	Validity (%)
Prognosis	Melbye (1995, Norway)	RCT	Adults with LRTI[c]	239	Clinical course	Symptom improvement	>11 UV	1.2* (1.1–1.3)*						89
	Hopstaken (2006, The Netherlands)	PC	Adults with LRTI[f]	240	Clinical course	Symptom resolution	? UV MV	? NS						78
	Seppa (2001, Finland)	PC	Elderly with severe LRTI[h]	950	X	Mortality due to LRTI	⩾100 MV	2.5 (1.2–5.1)						80
Diagnostic value	Holm[a] (2007, Denmark)	PC	Adults with LRTI[e]	682	Chest radiography	Transient non-malignant infiltrate	⩾20 UV		5.0 (2.6–9.9)	0.73	0.65	0.24	0.94	83
							⩾20 MV		2.8 (1.3–6.0)	–	–	–	–	
	Hopstaken (2003, The Netherlands)	PC	Adults with LRTI[f]	243	Chest radiography	Infiltrate	⩾10 UV		14.1 (1.9–105.6)	0.97*	0.31*	0.17*	0.99*	100
							⩾20 UV		9.9 (2.9–33.7)	0.91*	0.51*	0.22*	0.97*	
							⩾50 UV		21.4 (7.2–63.9)	0.88*	0.75*	0.34*	0.98*	
	Macfarlane (2001, UK)	PC	Adults with LRT illness[g]	289	Chest radiography	Infiltrate	⩾50 UV		5.4 (2.7–11.0)*	0.66*	0.89*	0.42*	0.88*	83

*, calculated; ?, not specified, X, not applicable; NS, not significant; PC, prospective cohort; Sn, sensitivity; Sp, specificity; UV, univariate analysis; MV, multivariate analysis.

[a]⩾ 18 years of age and cough >4 weeks and physician suspects LRTI and at least one symptom out of the following categories (shortness of breath, wheezing, chest pain, abnormal lung auscultation) and (fever, perspiration, headache, myalgia, general unwell-being).

[b]> 18 years of age and LRTI defined as chest infection.

[c]> 18 years of age and physician suspects pneumonia, bronchitis or asthma and at least one symptom out of the following categories (cough, shortness of breath) or (chest pain which increases by coughing or deep inspiration).

[d]⩾ 18 years of age and abnormal lung auscultation and at least two symptom out of the following category [fever (>38°C) (reported in the last 48 hours), shortness of breath or cough, tachypnoea or general unwell-being or confusion).

[e]⩾ 18 years of age and first consultation with this complaint and physician suspects LRTI.

[f]⩾ 18 years of age and physician suspects LRTI and new or increasing cough and at least one symptom out of the following categories (shortness of breath, wheezing, chest pain, abnormal lung auscultation) and [(reported) fever (⩾38°C), perspiring, headache, myalgia].

[g]⩾ 16 years of age and previously well and acute illness (<21 days) and cough is main complaint and LRTI is most likely diagnosis and at least one symptom out of the following category (sputum production, shortness of breath, wheezing, chest pain/discomfort).

[h]⩾ 65 years of age and physician suspects LRTI.

CRP measurement was combined with clinical assessment.[20,21] Patients with pneumonia generally have a poorer prognosis and their disease is more often caused by bacteria compared to other forms of LRTI. It can reasonably be expected that if CRP is an indicator of pneumonia, it would be an indicator of prognosis and aetiology as well. Results of the majority of the retrieved studies do not reflect this association. CRP cannot be used as a predictor in distinguishing bacterial from viral aetiology and results on the prognostic value are contradictory. Notably, most studies, especially those on diagnosis and aetiology, showed wide CIs which limit the generalizability of findings.

Our review has several strengths and limitations. We aimed to include all papers that evaluated the value of CRP measurement in adults with LRTI in primary care. By defining broadly formulated search syntaxes per research question and screening related articles, citations and references, we attempted to create a complete overview of studies on this topic. We also assessed methodological quality of the included studies by means of validated instruments. The preferred association measures were not always provided in the articles and comparing of data has been made possible after contacting authors for the crude data. All studies describe West European patients, allowing extrapolation of results to European primary care.

However, due to several reasons, results of the displayed studies cannot be extrapolated to daily practice without reservations. Firstly, the golden standards used in aetiologic and diagnostic studies are of limited value. In practice, aetiological agents cannot always be detected, even when sputum cultures, throat swabs and serological examination are used. In addition, chest radiographs do not provide absolute diagnostic certainty, especially in the early stages of pneumonia. Therefore, the correlations displayed in this review might be underestimated.

Secondly, in all studies, patient selection bias may have resulted in incomparable study groups. In four articles discussing antibiotic prescription, aetiology, prognosis and/or diagnosis, inclusion and exclusion criteria were poorly defined and inclusion of patients was largely dependent on the GP's opinion.[20,24,29,33] This pragmatic study design was possibly chosen in order to mimic daily practice. Furthermore, in the majority of studies, characteristics of non-participants were not provided. Macfarlane *et al.*, however, did report these characteristics in the study on aetiology and diagnosis. Non-participants had significantly milder illness judged from the presence of symptoms like wheezing, dyspnoea and chest pain.[15] As such, the value of CRP as an indicator of bacterial aetiology and pneumonia may have been overestimated here. In contrast, in the study by Holm *et al.*, discussing aetiology and diagnosis, characteristics of participants and non-participants were reported and comparable.[20,24]

Thirdly, the only study showing a decrease in antibiotic prescriptions due to POC CRP measurement scored relatively low on the Cochrane validity score.[31] Because the authors chose to randomize GPs and not patients, characteristics of the two patient populations showed important differences. For example, the control group contained more patients with abnormalities on chest auscultation, possibly accounting for the higher prescription rate in these patients. All other studies showed no differences in antibiotic prescription when POC CRP tests were used compared to controls.

In the systematic review by van der Meer *et al.*,[10] the diagnostic value of CRP measurement in LRTI patients was discussed profoundly. Due to the differences in target population described in the introduction of this review, only two studies on diagnosing pneumonia were used in this review as well.[21,34] This resulted in a different pretest probability of pneumonia and different test characteristics (sensitivity: this review 66%–97% versus van der Meer *et al.* 10%–98%, specificity: this review 31%–89% versus van der Meer *et al.* 44%–99%). In contrast to this review, van der Meer did not discuss the diagnostic value of CRP when combined with signs and symptoms. Our results suggest that CRP measurement might have an added value in detecting radiographic pneumonia, distinguishing the conclusion by van der Meer *et al.*

By issuing the guideline on LRTI, the Dutch College of General practitioners places the use of POC CRP measurement in a practical perspective. In this guideline, a clinical rule is provided to identify low-risk patients whom should not receive antibiotics or a POC CRP test. High-risk patients are identified based on the GPs professional opinion and should receive antibiotics or be referred tot the hospital immediately. GPs are advised to use POC CRP measurement only in the remaining patients labelled as 'patients at intermediate risk of severe infection' and prescribe antibiotics according to test results. However, a different prevalence of (bacterial) pneumonia can be expected in this subgroup, thus influencing the pretest probability and the predictive value of CRP. Until now, studies that address this subgroup of patients have not been performed.

Downright introduction of POC CRP measurement for LRTI patients in primary care might have adverse effects. Implementation of CRP measurement in a group largely consisting of low-risk patients leads to a minimal reduction in antibiotic prescriptions at the expense of an increase in health care costs.[11,12] The estimated costs of inappropriate use of POC CRP measurement in Sweden, for example, are as high as €1 million annually.[11] The cost-effectiveness of large-scale implementation of POC CRP in the Netherlands can be extrapolated from one study performed in our country. Based on the available evidence, it would lead to a mean increase of health care costs of €160

per patient.[35] However, the number of patients included in this study was too small to prove that the withholding of antibiotics based on POC CRP level warrants patient safety.

Apart from CRP, other biomarkers used for guiding diagnosis and treatment in respiratory tract infection have been evaluated, IL-6 and procalcitonin for example.[36] Procalcitonin seems the most promising, however, it cannot be measured in a POC setting yet. Besides biomarkers, other tools may reduce the amount of antibiotics prescribed in primary care. For example, communication skills training may have an equal effect to POC CRP measurement on the GPs tendency to prescribe antibiotics, presenting an alternative and less costly possibility.[31] From this perspective, POC CRP measurement might not be the most optimal solution to excessive antibiotic prescription in LRTI.

In conclusion, judging from the available evidence, the additional value of implementing POC CRP measurement in the management of LRTI in primary care is limited. Before implementing POC CRP measurement on a large scale, as advocated in Dutch guidelines, research must be done to evaluate the effects and safety of POC CRP measurement in LRTI patients at intermediate risk of severe infection.

Supplementary material

Supplementary material is available at *Family Practice* online.

Declaration

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Conflict of interest: none.

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Appendix

TABLE A1 *Search syntax per research question*

1. Search syntax 'Antibiotic prescription'

Domain		Determinant
Respiratory infection	Primary care	CRP
Acute cough	General practitioner	CRP
Acute coughing	General practitioners	C-reactive protein
LRT	GP	C reactive protein
LRTI	General physician	
RTI	General physicians	
LRI	General practice	
Lower respiratory tract	General practices	
Lower respiratory infection	Primary care	
Lower respiratory infections	Outpatient setting	
Respiratory infection	Outpatient care	
Respiratory infections	Family medicine	
Respiratory tract infection	Primary health care	
Respiratory tract infections	Ambulatory care	
Bronchitis		
Pneumonia		
CAP		

2. Search syntax 'Etiology'

Domain	Determinant	Outcome
Respiratory infection	CRP	–
Acute cough	CRP	–
Acute coughing	C-reactive protein	
LRT	C reactive protein	
LRI	Aetiology	
LRTI	Etiology	
RTI	Aetiologies etiologies	
Lower respiratory tract	Atiologic	
Lower respiratory infection	Aetiologic	
Lower respiratory infections		
Respiratory infection		
Respiratory infections		
Respiratory tract infection		
Respiratory tract infections		

3. Search syntax 'Prognostic value'

Domain	Determinant	Outcome
Respiratory infection	CRP	Prognosis
Acute cough	CRP	Complication
Acute coughing	C-reactive protein	Complications
LRT	C reactive protein	Morbidity
LRTI		Mortality
RTI		Prediction
LRI		Prognosis
Lower respiratory tract		Prognostic
Lower respiratory infection		Course
Lower respiratory infections		Outcome
Respiratory tract infection		
Respiratory tract infections		
Bronchitis		
Pneumonia		
CAP		

4. Search syntax 'Diagnostic value'

Domain	Determinant	Outcome*
Respiratory infection	CRP	Pneumonia
Acute cough	CRP	Pneumonia
Acute coughing	C-reactive protein	CAP
LRT	C reactive protein	
LRI		
LRTI		
RTI		
Lower respiratory tract		
Lower respiratory infection		
Lower respiratory infections		
Respiratory infection		
Respiratory infections		
Respiratory tract infection		
Respiratory tract infections		

Terms within the columns were connected by 'or', and the rows were connected by 'and'.