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Diagnostic properties of C-reactive protein for detecting pneumonia in children

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Summary
Background: The diagnostic value of C-reactive protein (CRP) level for pneumonia in children is unknown. As a first step in the assessment of the value of CRP, a diagnostic study was performed in children at an emergency department (ED).
Methods: In this cross-sectional study, data were retrospectively collected from children presenting with suspected pneumonia at the ED of Antonius Hospital Nieuwegein in The Netherlands between January 2007 and January 2012. Diagnostic outcome was pneumonia yes/no according to independent radiologist. (Un)adjusted association between CRP level and pneumonia and diagnostic value of CRP were calculated.
Results: Of 687 presenting children, 286 underwent both CRP measurement and chest radiography. 148 had pneumonia (52%). The proportion of pneumonia increased with CRP level. Negative predictive values declined, but positive predictive values increased with higher CRP thresholds. Univariable odds ratio for the association between CRP level and pneumonia was 1.2 (95% CI 1.11–1.21) per 10 mg/L increase. After adjustment for baseline characteristics CRP level remained associated with pneumonia.
Conclusions: CRP level has independent diagnostic value for pneumonia in children presenting at the ED with suspected pneumonia, but low levels do not exclude pneumonia in this setting. These results prompt evaluation of CRP in primary care children with LRTI.

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Introduction

Lower respiratory tract infections (LRTIs) are common in children and among the most frequent reasons for consulting a general practitioner (GP).[1] LRTIs comprise acute bronchitis, bronchiolitis and pneumonia. While the latter usually requires antibiotic treatment, the former two are generally self-limiting and complications are rare when antibiotics are withheld.[2]

Nonetheless, most children diagnosed with acute bronchitis and bronchiolitis are prescribed antibiotics. A large survey in Dutch general practice including over 75 000 children in 2001 showed that 83.5% of all children presenting with acute bronchitis still received antibiotics,[3] and recent studies confirmed these high prescription numbers.[4] Aside from the costs, the high prescription rates are undesirable because of needless exposure of patients to possible side effects,[5] medicalisation of self-limiting illness[6] and increasing development of bacterial resistance.[7]

An important reason for the high prescription rates could be diagnostic uncertainty of the GP. It is difficult to distinguish pneumonia from other LRTIs using history and clinical examination only,[8,9] and it is neither feasible nor desirable to perform a chest radiograph in all children with suspected LRTI.

C-reactive protein (CRP) measurement might be helpful in the diagnostic management of LRTI in children. CRP is an acute phase protein synthesized by the liver in response to IL-6. Plasma levels of CRP are generally very low in healthy persons, but can rise rapidly in case of acute inflammation.[10,11] Studies have shown that CRP could be helpful in the distinction of pneumonia from other LRTIs in adults.[12] However, these results cannot be assumed to be completely applicable to children, due to differences in immunity, causal agents, anatomy and physiology.[13]

While there are some studies reporting on the ability of CRP to discriminate between viral and bacterial infections in children with pneumonia,[14] hardly any data is available on the diagnostic value of CRP to distinguish between pneumonia and other LRTIs like acute bronchitis in children. We are aware of only one previously published study which investigated the ability of CRP to discriminate between presence or absence of pneumonia in children with LRTI in secondary care. Babu et al.[15] compared CRP levels of 30 children with pneumonia to those of 30 children with normal chest radiographs. The results showed 100% sensitivity, specificity and predictive values when using a threshold for CRP of 35 mg/L. However this study was very small and its methodology had serious flaws.

Therefore, a logical first step in the assessment of the diagnostic value of CRP in children to detect pneumonia, seemed to be an observational study in secondary care, because the prevalence of the target disorder, pneumonia, is relatively high in this group and both CRP and chest radiographs are part of the routine diagnostic work-up in this setting.

The aim of this study was to determine the diagnostic value of CRP in children visiting the emergency department (ED), referred by their GP with suspected pneumonia.

Methods

Design and study population

This was a diagnostic cross-sectional study with retrospective data collection. Eligible patients were children (aged under 18), visiting the ED of the Antonius Hospital Nieuwegein in the Netherlands between January 2007 and January 2012, suspected of pneumonia. Immunocompromised children were excluded from analysis, as well as children with chromosomal disorders (e.g. Down syndrome), developmental disorders, current malignancies and children with chronic pulmonary disorders other than asthma or recurrent viral wheezing.

Diagnostic outcome

The diagnostic outcome or reference test was pneumonia presence or absence according to the chest radiograph. All chest radiographs, taken during first presentation, were reassessed in May 2012 by an independent chest radiologist (PdJ) with 10 years experience in pediatric chest imaging. This radiologist was blinded for earlier reports, as well as for symptoms and signs of the presenting children. The chest radiographs were classified as pneumonia, no pneumonia or inconclusive. For analysis, the latter two groups were combined. A radiograph was said to show pneumonia when it contained an opacity which was judged to be real (no composition of vessels or bones) and acute (no residual scars).[16]

The original radiology reports performed during the actual presentation at the ED were used to calculate the interobserver variability. The proportional agreement was calculated as well as Cohen's Kappa (κ) to determine the level of agreement. A κ below 0.20 indicates poor agreement, a κ of 0.21—0.40 fair, a κ of 0.41—0.60 moderate, a κ of 0.61—0.80 good and a κ of 0.81—1.00 indicates very good agreement between two observers.[17]

Analysis

The analyses were performed using SPSS 17.0. The main analyses were done in the children of whom results of both CRP level and a chest radiograph from the day of presentation were available. Data were expressed as mean and standard deviation (SD) for continuous variables and percentages and 95% confidence interval (CI) for categorical variables.

Missing data were imputed for white blood cell count (WBC), duration of fever and body temperature at first presentation. Missing information regarding the use of antibiotics or prednisone in the two weeks prior to presentation and history of wheezing or asthma were not imputed but assumed to be negative when missing, because lacking information here was more likely to mean a negative result.

Patient characteristics including CRP level were compared between the children with and without pneumonia, where children with inconclusive radiograph results were included in the group without pneumonia, using *t*-tests for continuous and chi square tests for categorical

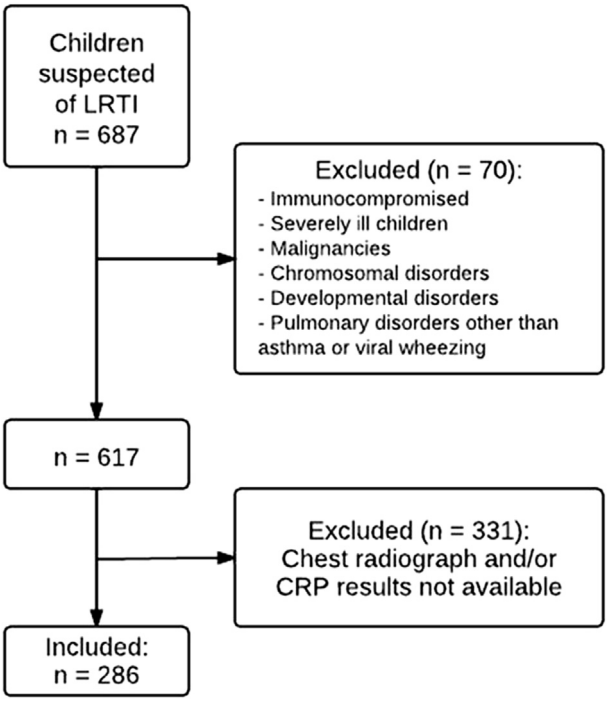

Figure 1 Study patients.

variables. The proportion of pneumonia was determined for the following ranges of CRP level; below 20 mg/L, 20—50 mg/L, 50—100 mg/L, 100—200 mg/L and above 200 mg/L and univariable test characteristics (sensitivity, specificity, predictive values and likelihood ratio's) of CRP level for pneumonia were calculated for the different thresholds. The area under the receiver operating characteristic (ROC) curve was calculated as a measure of discrimination of CRP level.

After checking linearity of the association between continuous variables (CRP, age, duration of symptoms), logistic regression was used to calculate the univariate odds ratio (OR) for the association between CRP level and other patient characteristics and the diagnostic outcome pneumonia.

Results

Fig. 1 shows the included and excluded children. Out of 687 children, 286 remained for analysis. 70 children were excluded based on their health status, and another 331 because CRP and/or chest radiography results were not available. The included children were slightly older and less frequently had a history of wheezing compared to the 331 children with missing results (Table 1).

The mean age of the 286 included children was 4.4 years, 54% were male and their mean CRP level was 90 mg/L. According to the chest radiographs 148 (52%) had pneumonia. The mean CRP level was higher in children with than in those without pneumonia, respectively 141 mg/L and 34 mg/L. Mean WBC level was 18 $\times$ 10^9/L in children with pneumonia and 13 $\times$ 10^9/L in children without pneumonia. On average, the children in the pneumonia group were older, had a longer period of (anamnestic) fever prior to presentation and less often had a history of viral wheezing. Other characteristics between the two groups did not differ (Table 2).

The proportion of pneumonia increased with rising CRP levels. In children with a CRP level below 20 mg/L, 28% had pneumonia. For children with CRP levels of 20—50 mg/L, 50—100 mg/L, 100—200 mg/L and above 200 mg/L, the proportion was 42%, 48%, 80% and 94% respectively (Table 3).

Sensitivity, specificity, predictive values and positive and negative likelihood ratios for various thresholds are shown in Table 4. Where negative predictive values (NPVs)

Table 1 Baseline characteristics of children presenting with LRTI: in- and excluded children.

	Included children: CRP and chest radiograph performed (N = 286)		Excluded children: CRP test and/or chest radiograph not performed (N = 331)	
	Study group	Missing, N (%)	Study group	Missing, N (%)
Age, years	4.4 (4.3)	0	3.3 (3.3)	0
Male gender, N (%)	154 (54)	0	190 (57)	0
CRP, mg/L	89.3 (110.4)	0	65.0 (78.5)	303 (92)
WBC, $\times 10^9$/L	15.3 (8.3)	9 (3)	14.3 (8.4)	299 (90)
Duration of fever, days	4.3 (4.0)	34 (12)	3.2 (3.4)	40 (12)
Body temperature, °C	38.7 (1.2)	86 (30)	38.2 (2.9)	125 (38)
Antibiotics given before first contact, N (%)	81 (28)	7 (2)	80 (24)	0
Prednisone given before first contact, N (%)	8 (3)	7 (2)	4 (1)	0
History of wheezing, N (%)	55 (19)	32 (11)	93 (28)	34 (10)
History of asthma, N (%)	24 (8)	32 (11)	30 (9)	34 (10)
Chest X-ray				
Pneumonia, N (%)	148 (52)	0	91 (28)	159 (48)
No signs of pneumonia, N (%)	126 (44)		73 (22)	
Inconclusive, N (%)	12 (4)		8 (2)	

Presenting numbers are mean (SD), unless specified otherwise CRP, C-reactive protein; WBC, white blood cell count; mg/L, milligrams per Liter.

Table 2 Baseline characteristics of included children ($N = 286$).

Variable	Pneumonia ($N = 148$)	No pneumonia ($N = 138$)	P value
Age, years	5.2	3.6	0.002
Male gender, %	55	52	0.585
CRP, mg/L	140.8	34.1	<0.001
WBC, $\times 10^9$/L	17.5	12.7	<0.001
Duration of fever, days	4.9	3.2	<0.001
Body temperature, °C	38.8	38.6	0.076
Antibiotics given before first contact, %	33	24	0.102
Prednisone given before first contact, %	3	3	0.927
History of wheezing, %	16	27	0.036
History of asthma, %	8	11	0.462

Presenting numbers are mean, unless specified otherwise. CRP, C-reactive protein; WBC, white blood cell count.

declined, positive predictive values (PPVs) rose with increasing thresholds for CRP level.

Univariately, CRP level, WBC level, age, duration of fever prior to presentation and a history of wheezing were associated with pneumonia (Table 5). OR for CRP per 10 mg/L elevation was 1.2 (95% CI 1.11–1.21). After adjustment for other variables, the OR for CRP per 10 mg/L remained 1.2 (95% CI 1.10–1.22).

The ROC for CRP for the detection of pneumonia is shown in Fig. 2 and the accompanying ROC area was 0.79 (95%CI 0.73–0.84).

The proportions of agreement between the original radiograph reports and the evaluation of the independent radiologist were 82% for the non-pneumonia group and 78% for the pneumonia group. Cohen's kappa for reassessment of the chest radiographs was 0.61 (95%CI 0.52–0.70).

Discussion

Main findings

In this study on the diagnostic value of CRP for pneumonia in children visiting the ED with suspected LRTI, CRP level was independently associated with pneumonia. High CRP levels (>200 mg/L) had high PPVs, but low CRP levels did not result in high NPVs for pneumonia (maximum of 79% with CRP threshold of 10 mg/L).

Table 3 Proportion of pneumonia by CRP level.

CRP category (N of children)	Pneumonia N (%)	No pneumonia N (%)
<20 mg/L (101)	28 (28)	73 (72)
20–50 mg/L (59)	25 (42)	34 (58)
50–100 mg/L (40)	19 (48)	21 (52)
100–200 mg/L (35)	28 (80)	7 (20)
>200 mg/L (51)	48 (94)	3 (6)
Total (286)	148 (52)	138 (48)

CRP, C-reactive protein; mg/L, milligrams per liter.

Strengths and limitations

This is the first study on diagnostic accuracy of CRP for pneumonia in children in which a sufficiently large number of pneumonia cases was included. The 148 children with pneumonia according to their chest radiograph allowed for a robust analysis of the associations between several CRP levels and pneumonia presence or absence.

Nevertheless, our study has some limitations. Firstly, this study was conducted with retrospective data collection. Because tests were not performed in all presenting children, this could have led to a certain selection of children. However, according to baseline characteristics, children in whom both tests were performed did not seem to be more ill than those with missing results on CRP measurement and/or chest radiograph. The only difference was that children in the latter group were younger (3.3 vs. 4.4 years, respectively) and more often had a history of wheezing (28% vs. 19% respectively). Notably, the differences between the two groups are not likely to affect the relationship between CRP and pneumonia, and therefore we believe confounding caused by possible selection bias is most likely to be very limited.

Another possible limitation is the use of chest radiographs as a reference test for pneumonia. It is known that chest radiographs are an imperfect gold standard for pneumonia. Viral bronchiolitis, for example, can cause signs on chest radiographs which can sometimes be identical to the signs of bacterial pneumonia. Furthermore, the assessment of chest radiographs is susceptible to individual interpretation.[18] In order to use a uniform standard for all children, all chest radiographs in this study were judged by an independent, experienced radiologist.

In our analysis, the inconclusive chest radiographs were classified as 'no pneumonia'. For that reason, there may be some misclassification, e.g. inconclusive chest radiographs of children with pneumonia. If so, this could have influenced the outcome. On the other hand, only a very small number of cases was considered inconclusive ($N = 12$).

Comparison with previous studies

As mentioned earlier, very little research has been done on the diagnostic value of CRP for pneumonia in children. The sole study investigating this issue in children with LRTI was published by Babu et al.[15] Their results included sensitivity, specificity and predictive values of 100% using a CRP threshold of 35 mg/L, which differ considerably from our study results. An explanation might be the very small number of children in Babu's study. Moreover, in our study, a more heterogeneous group of children with signs of LRTI were studied, whereas in Babu's report children with bronchiolitis were excluded from analysis. Furthermore, 37% of the pneumonia cases in Babu's study had signs of substantial malnutrition, which may have affected the immune status and, therefore, the outcome.

A recent study in children with fever, conducted by Mintegi et al.,[19] investigated the value of CRP in diagnosing

Table 4 Test characteristics of CRP level per threshold.

CRP threshold	Sensitivity (%)	Specificity (%)	Negative predictive value (%)	Positive predictive value (%)	Positive likelihood ratio	Negative likelihood ratio
10 mg/L	90	40	79	62	1.50	0.25
20 mg/L	81	53	72	65	1.72	0.36
50 mg/L	64	78	67	75	2.91	0.46
75 mg/L	55	87	65	82	4.23	0.52
100 mg/L	51	93	64	88	7.29	0.53
200 mg/L	32	97	58	93	10.67	0.70
250 mg/L	23	99	56	97	23.00	0.78

CRP, C-reactive protein; mg/L, milligrams per liter.

pneumonia in 188 children younger than 36 months presenting in pediatric emergency departments. These children had no symptoms of LRTI, but presented with high fever without source. A threshold of 100 mg/L CRP level was used to divide the children in two groups and the proportion of pneumonia was determined in both groups. When comparing the two groups, an OR of 3.42 was found. Predictive values were not calculated in this study.

In contrast with the lack of studies in children, several studies were performed in adults. Falk et al.[12] conducted a systematic review and compared results of eight studies. Using a threshold of 20 mg/L resulted in pooled positive and negative likelihood ratios of 2.10 and 0.33, respectively. These resemble those found in our study: 1.72 and 0.36 respectively. Heterogeneous results were found in Falk's study when using higher thresholds. Using 100 mg/L as threshold, positive and negative likelihood ratios varied between 2.30 and 51.80 and between 0.35 and 0.92, respectively. The wide range of these results makes it hard to compare outcomes with the present results. In our study, positive and negative likelihood ratios for a threshold of 100 mg/L were 7.29 and 0.73 respectively.

The interobserver variability was accompanied by a kappa of 0.61 in our study which is slightly higher than results in earlier studies in adults.[18,20] The fact that adults have more abnormalities on their radiographs than children, due to for example previous infections (scar tissue) or pulmonary or cardiac disorders, may explain the difference. As in other studies, the proportional agreement in positive cases was lower than those in negative cases. This could mean that some children were wrongly considered not to have pneumonia.

Implications for practice/research

Even though the probability of pneumonia decreased with lower CRP levels, pneumonia was present in 28% of children with CRP levels below 20 mg/L. This is also reflected in the relatively low negative predictive values; e.g. a threshold of 10 mg/L for CRP resulted in an NPV of 79%. This means that in this secondary care setting low values of CRP cannot rule out pneumonia in children with suspected LRTI. High values on the other hand, make the diagnosis pneumonia more likely, reflected by high positive predictive values.

The children included in this study were all suspected of having pneumonia. The pre-test probability was 52%. Depending on the threshold used, measurement of CRP could alter this to 62–97% given a high CRP level.

In general practice, pre-test probability of pneumonia is probably much lower. Therefore, CRP measurement might be even more beneficial in that setting. In case of LRTI, CRP measurement is easier to obtain than chest radiographs and is also less expensive. CRP testing, preferably with point of care (POC) systems, might help to select children with a serious infection and may help to reduce unnecessary use of antibiotics. In a recent study in adults with LRTI, CRP POC testing safely reduced the number of prescribed

Table 5 Univariable and multivariable association of CRP with pneumonia.

	Univariable			Multivariable		
	Or	95% CI	*P* value	Or	95% CI	*P* value
CRP per 10 mg/L	1.2	1.11–1.21	<0.001	1.2	1.10–1.22	<0.001
Age, years	1.1	1.03–1.16	0.003	1.1	0.99–1.15	0.094
Male gender	1.1	0.72–1.81	0.584	1.0	0.53–1.86	0.988
WBC, $\times 10^9$/L	1.1	1.05–1.12	<0.001	1.1	1.00–1.10	0.025
Duration of fever, days	1.3	1.05–1.21	0.001	1.1	1.01–1.19	0.037
Body temperature, °C	1.1	0.94–1.39	0.178	0.9	0.69–1.20	0.510
Antibiotics given before first contact	1.5	0.92–2.61	0.103	1.9	0.91–3.82	0.089
Prednisone given before first contact	0.9	0.23–3.82	0.926	1.1	0.20–5.87	0.921
History of wheezing	0.5	0.28–0.97	0.039	0.8	0.40–1.76	0.634
History of asthma	0.7	0.31–1.70	0.463	0.8	0.26–2.17	0.597

CRP, C-reactive protein; mg/L, milligrams per liter; WBC, white blood cell count.

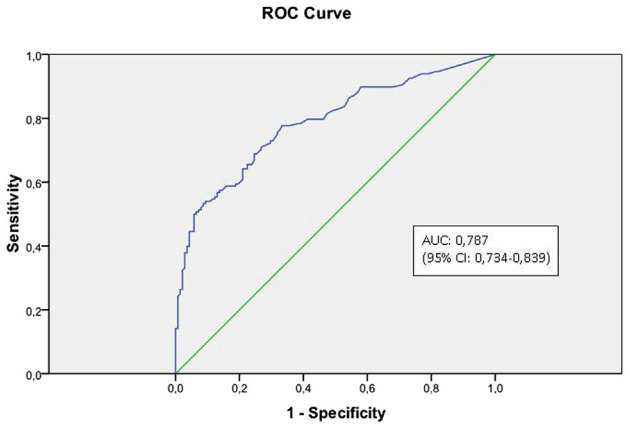

Figure 2 Reciever operating characteristic curve (ROC area) of CRP for pneumonia.

antibiotics.[21] Our study results are encouraging to start a prospective, multicenter study in general practice to gain more insights in the discriminative value of CRP in children.

Conclusion

This diagnostic study in an Emergency Department setting showed that CRP measurement could be of additional value in differentiating pneumonia from other LRTIs. High values of CRP show PPVs up to 97%. The high PPVs implicate that it would be justifiable to start treatment for pneumonia in children with high CRP levels, without awaiting the results of chest radiographs.

For primary care, merits are expected to be larger, because of less distinct clinical pictures, the impracticality of making chest X-rays in all symptomatic children and lower probability of pneumonia in this setting. A prospective study in general practice is therefore warranted.

Conflict of interest

M.J. Koster: none declared.
B.D.L. Broekhuizen: none declared.
M.C. Minnaard: none declared.
W.A.F. Balemans: has received a fee of 600 euro for organising and being one of the speakers on a symposium about RSV infections in children by Abbot in 2010 and 2011. Furthermore, WB is a member of the paediatric medical advising committee of GSK in the Netherlands and is member of the organising committee of a yearly asthma course for paediatricians, sponsored and organised with support of GSK in 2010, 2011 and 2012; the fee for this work is 1900 euro each year.

WB is a speaker on a yearly course on asthma in children for paediatric SHO's in 2011 and 2012. This course is sponsored by Teva pharma. The fee is 750 euro per course.

R.M. Hopstaken: has received travel funds from Axis-Shield (Norway) and Orion Diagnostica (Finland), both manufacturers of point-of-care CRP devices.

T.J.M. Verheij: has received an unconditional research grant and consultancy fees from Pfizer.

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