Diagnostic value of C reactive protein in infections of the lower respiratory tract: systematic review
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CRD summary
This review concluded that testing for C reactive protein was neither sufficiently sensitive to rule out nor specific to rule in both an infiltrate on chest radiograph and bacterial aetiology of lower respiratory tract infection. The authors highlighted the poor methodological quality of the few available studies in this area. The authors' conclusions are supported by the evidence presented.

Authors' objectives
To evaluate the diagnostic accuracy of C reactive protein in detecting radiologically proved pneumonia; and to assess how well C reactive protein could discriminate between bacterial and viral infections of the lower respiratory tract.

Searching
The authors searched MEDLINE and EMBASE electronic databases from inception until April 2004; the search terms were reported. Methodological filters were applied to the electronic searches. Reference lists were checked for additional relevant publications. The search was limited to studies reported in English.

Study selection
Study designs of evaluations included in the review
The authors did not state any inclusion criteria relating to the study design.

Specific interventions included in the review
Studies of C reactive protein were eligible for inclusion in the review.

Reference standard test against which the new test was compared
To answer the first review objective, studies that used chest radiograph as the reference standard were eligible for inclusion in the review. To answer the second review objective, studies that used microbiological work-up as the reference standard were eligible for inclusion.

Participants included in the review
The participants of interest were patients with lower respiratory tract infection. The authors stated that studies of immunocompromised patients, patients treated in intensive care units, or patients with hospital-acquired pneumonia were excluded from the review. All but one of the studies addressing the first review question were conducted in adults; three studies were conducted in primary care, two in secondary care and one in a mixed population. The majority of the studies addressing the second review question were conducted in secondary care.

Outcomes assessed in the review
The authors did not state any inclusion criteria relating to the outcomes.

How were decisions on the relevance of primary studies made?
One reviewer selected studies for inclusion in the review.

Assessment of study quality
Guidelines of the Cochrane Methods Group on systematic reviews of screening and diagnostic tests were used to assess the quality of the included studies. The quality assessment criteria related to: the blind and independent assessment of the index test and reference standard; the use of a prospective, consecutive clinical population; interpretation of the index test independently of clinical information; the reference standard test being conducted before treatment
commenced; samples for the reference standard taken on the first day; and criteria relevant to the applicability of the results, such as setting, duration of illness and demographic information. Two reviewers independently assessed the validity of the included studies, and any disagreements were resolved through consensus. The kappa statistic was used as a measure of agreement for the quality assessment.

**Data extraction**
The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction.

The authors extracted data to calculate the sensitivity, specificity, and positive and negative likelihood ratios for three different cut-off values of C reactive protein. The authors of the primary studies were contacted for additional data if there were insufficient data in the publication to calculate these outcomes.

**Methods of synthesis**
How were the studies combined?
A statistical model based on that of Midgette et al. (see Other Publications of Related Interest) was used to summarise diagnostic test performance. Spearman’s correlation of true-positive rates and true-negative rates was calculated, along with areas under the curve for each study to follow inverse correlation. A summary receiver operating characteristic (sROC) curve was drawn where data were homogeneous.

How were differences between studies investigated?
The DerSimonian and Laird chi squared-test was used to test heterogeneity of areas under the curve. Subgroup analyses were performed for age, setting and gender, where sufficient data were available; other subgroup analyses (not predefined) were also investigated. Studies that met four specific methodological criteria were pooled separately from studies that did not meet all four criteria in a sensitivity analysis.

**Results of the review**
Seventeen diagnostic accuracy studies were included in the review, of which 13 provided quantitative data and were included in the analysis: 6 studies provided data for the evaluation of the diagnostic accuracy of C reactive protein in detecting radiologically proved pneumonia (1,178 patients) and 8 studies provided data for the assessment of how well C reactive protein can discriminate between bacterial and viral infections of the lower respiratory tract (1,096 patients). One of the studies was included for both questions.

The initial agreement between reviewers for the quality assessment was 82.5% (k=0.68).

Diagnostic accuracy of C reactive protein in detecting radiologically proved pneumonia.

The sensitivities ranged from 10 to 98% and the specificities from 44 to 99%. The area under the sROC curve for the subgroup of adults (5 studies) was 0.80 (95% confidence interval, CI: 0.75, 0.85). Other subgroup analyses were not performed because of a lack of data. Sensitivity analysis of the areas under the curves of studies that met the four quality criteria (area under the curve 0.84, 95% CI: 0.78, 0.90) and those that did not meet the criteria (area under the curve 0.74, 95% CI: 0.65, 0.83) showed robustness of the data.

Discrimination between bacterial and viral infections.

The sensitivities ranged from 8 to 99% and the specificities from 27 to 95%. An sROC curve for the subgroup of children (6 studies) could not be drawn because of statistical heterogeneity. Other subgroup analyses were not performed because of a lack of data. None of the studies met the four quality criteria, therefore a sensitivity analysis was not performed for methodological quality.

**Authors' conclusions**
Testing for C reactive protein was neither sufficiently sensitive to rule out nor sufficiently specific to rule in both an
infiltrate on chest radiograph and bacterial aetiology of lower respiratory tract infection. The methodological quality of the few available studies was generally poor.

**CRD commentary**

The review questions were clear and inclusion criteria were stated for the index test, reference standards and participants of interest. The authors searched two electronic databases and reference lists for English language studies, but no attempts were made to identify unpublished studies, thus allowing the possibility of publication and language biases. One reviewer selected studies for inclusion, but the authors did not state how many reviewers performed the data extraction; the possibility of reviewer bias or error cannot, therefore, be ruled out.

Adequate details of the included studies were presented and the authors assessed study quality using appropriate criteria. Heterogeneity was assessed and attempts were made to investigate sources of heterogeneity. There was a great deal of heterogeneity between the results of studies, particularly in relation to the second review question. Despite the limitations in the search strategy, highlighted above, the authors’ conclusions are supported by the evidence presented.

**Implications of the review for practice and research**

Practice: The authors stated that the current evidence does not consistently or sufficiently support the wide introduction of C reactive protein as a rapid test to guide antibiotic prescription.

Research: The authors stated that more methodologically sound diagnostic studies are required if conclusions regarding the diagnostic accuracy of C reactive protein in infection of the lower respiratory tract are to be drawn. They stated that the recent Standards for the Reporting of Diagnostic Accuracy Studies (STARD) guidelines will probably have an important role in this process.

**Bibliographic details**

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