Systematic review of the diagnostic accuracy of C-reactive protein to detect bacterial infection in nonhospitalized infants and children with fever

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CRD summary
The review assessed the accuracy of C-reactive protein for diagnosing bacterial infections in febrile children and used robust reviewing and meta-analytic methods. The authors’ conclusion that C-reactive protein provided moderate and independent information for ruling-in and ruling-out serious bacterial infection, but cannot be used alone to exclude bacterial infection, is likely to be reliable.

Authors' objectives
To determine the accuracy of C-reactive protein for diagnosis of bacterial infection in infants and children who presented with fever.

Searching
MEDLINE and EMBASE were searched from inception to December 2007. Search terms were reported. Searches were based on test and target condition. No language restriction was applied. Bibliographies of reviews and included studies were screened for additional articles.

Study selection
Studies that assessed the diagnostic accuracy of blood or serum C-reactive protein against a reference standard of microbiological diagnosis of either serious bacterial infection versus benign bacterial or non-bacterial infection, or bacterial infection versus non-bacterial infection, in children who initially presented with fever were eligible for inclusion. The diagnostic threshold for C-reactive protein used by the included studies ranged from 6mg/L to 70mg/L. Studies that included children admitted to hospital (other than the emergency department observational ward) were excluded, as were studies where more than 10% of the population was neonates. Studies where the reference standard was the diagnosis of a specific disease (for example, meningitis, gastroenteritis or arthritis) and studies in subgroups of patients with specific conditions (such as cancer, renal failure) were excluded.

Two reviewers assessed studies for inclusion. Disagreements were resolved by discussion with a third reviewer.

Assessment of study quality
The methodological quality of included studies was assessed using a modified 11-item version of the QUADAS tool, which contained items related to patient spectrum, reference standard, disease progression bias, verification bias, review bias, incorporation bias, test execution, withdrawals and indeterminate results.

Two reviewers independently assessed study quality. Interobserver variation was assessed using the kappa statistic.

Data extraction
Data to populate 2x2 contingency tables (numbers of true positives, false negatives, false positives and true negatives) for serious bacterial infection and bacterial infection were extracted independently by two reviewers using piloted forms. The categories of invasive and localised bacterial infection were combined as bacterial infection, as were mixed bacterial and viral infections (one study) and proven or possible bacterial infections (one study).

Accuracy data were reported as sensitivity and specificity, and positive and negative likelihood ratios, with 95% confidence intervals (CIs).

Methods of synthesis
Between-study statistical heterogeneity was assessed by visual examination of study results plotted in receiver operating
characteristic (ROC) space. Clinical heterogeneity was assessed using the descriptions of study characteristics.

Where there was sufficient homogeneity of results, a random-effects bivariate model was used to calculate summary estimates of sensitivity and specificity, with 95% CIs.

**Results of the review**

Ten studies (n=2,046) were included in the review. All studies were conducted in emergency departments. Fever was not defined in four studies. Withdrawals and handling of uninterpretable results were poorly reported by almost all studies. None of the studies reported sufficient information to judge whether reference standard tests were interpreted blind to the C-reactive protein result.

Seven studies (n=1,091) assessed the accuracy of C-reactive protein in differentiating between serious bacterial infection and self-limiting or non-bacterial infection; six studies reported sensitivity and specificity; and five used multivariate modelling to assess the additional information provided by C-reactive protein over clinical features. The prevalence of serious bacterial infection ranged from 11% to 29%. The summary estimates of sensitivity and specificity were 0.77 (95% CI 0.68 to 0.83) for sensitivity and 0.79 (95% CI 0.74 to 0.83) for specificity. The positive and negative likelihood ratios were 3.64 (95% CI 2.99 to 4.43) for positive and 0.29 (95% CI 0.22 to 0.40) for negative. In all five studies that used multivariate analysis, C-reactive protein was an independent predictor of serious bacterial infection.

Three studies (n=722) assessed the accuracy of C-reactive protein to differentiate between bacterial and viral infections. The reported prevalences of bacterial infection were 28%, 35% and 82%. The corresponding sensitivities were 0.44 (95% CI 0.35 to 0.54), 0.58 (95% CI 0.44 to 0.72) and 0.22 (95% CI 0.15 to 0.28). Specificities were 0.86 (95% CI 0.82 to 0.90), 0.96 (95% CI 0.91 to 1.00) and 0.94 (95% CI 0.86 to 1.00). Given the significant between-study heterogeneity, no pooled estimates were generated.

**Authors' conclusions**

C-reactive protein provided moderate and independent information for both ruling-in and ruling-out serious bacterial infection in children who presented with fever. Poor sensitivity precluded use of C-reactive protein to exclude all bacterial infection.

**CRD commentary**

The article presented a clearly stated research question, appropriately defined by the inclusion criteria of the review. The search strategy covered a range of sources and no language restrictions were applied, which increased the likelihood that all relevant data were retrieved. Measures to minimise error and bias in the review process were reported and the methodological quality of included studies was assessed and incorporated in the results of the review. Where appropriate, rigorous meta-analytic methods were used to generate pooled estimates of diagnostic accuracy. The authors conclusions are a reasonable interpretation of the data presented and are likely to be reliable.

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

**Practice:** The authors stated that C-reactive protein test results should be considered in the context of other clinical information and should not be relied upon alone to exclude bacterial infection.

**Research:** The authors made no recommendations for future research.

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**Bibliographic details**

Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.