Systematic Review of the Diagnostic Accuracy of C-Reactive Protein to Detect Bacterial Infection in Nonhospitalized Infants and Children with Fever

Sharon Sanders, BSc(Pod), MPH, Adrian Barnett, BSc(Statistics), PhD, Ignacio Correa-Velez, MBBS, PhD, Mark Coulthard, MBBS, FRACP, and Jenny Doust, BA, BEcons, MBBS, FRACGP, Grad Dip Clin Epi, PhD

Objective To determine the accuracy of C-reactive protein (CRP) for diagnosing serious bacterial and bacterial infections in infants and children presenting with fever.

Study design Systematic review of diagnostic accuracy studies. We included studies comparing the diagnostic accuracy of CRP with microbiologic confirmation of (a) serious bacterial and (b) bacterial infection.

Results For differentiating between serious bacterial infection and benign or nonbacterial infection (6 studies), the pooled estimate of sensitivity was 0.77 (95% CI, 0.68, 0.83); specificity, 0.79 (95% CI, 0.74, 0.83); positive likelihood ratio, 3.64 (95% CI, 2.99, 4.43); and negative likelihood ratio, 0.29 (95% CI, 0.22, 0.40). In multivariate analysis, CRP is an independent predictor of serious bacterial infection. 3 studies investigating the accuracy of CRP for diagnosing bacterial infection could not be pooled, but all showed a lower sensitivity compared with studies using serious bacterial infection as the reference diagnosis.

Conclusions CRP provides moderate and independent information for both ruling in and ruling out serious bacterial infection in children with fever at first presentation. Poor sensitivity means that CRP cannot be used to exclude all bacterial infection. *(J Pediatr 2008;153:570-4)*

Although fever is a common reason for children to be brought to medical attention, it remains a diagnostic and management challenge. Most children with fever will have a self-limiting illness that resolves in a few days without active intervention. Some children, however, benefit from antibiotic treatment, and some substantially so. Few clinical features distinguish those who benefit from those who do not, and doctors' clinical judgment frequently is not able to distinguish children with bacterial infection from nonbacterial infection.[1] Because both doctors and patients are aware of the potential benefits of antibiotics for some patients and the potential risks of not treating a life-threatening infection in a small minority, there is an incentive to prescribe antibiotics, despite the costs, adverse effects, and increasing antibiotic resistance that result from this practice.[2-4]

C-reactive protein (CRP) rises in response to infectious and inflammatory diseases and shows greater elevations in serious bacterial than in other bacterial infections. It may distinguish those children who have a bacterial infection that could benefit from antibiotics from those who do not.[5-7] Our aim in this review was to evaluate the diagnostic accuracy of CRP in infants and children with an initial complaint of fever (with or without signs of respiratory tract infection).

METHODS

Because clinical assessment and prior diagnostic testing may change the spectrum of patients being assessed and therefore the diagnostic accuracy of a test,[8] we limited this review to studies conducted in children who came to medical attention initially with complaint of fever. Studies that included children who had been admitted to hospital (other than in an emergency department observational ward) were excluded from the review.

We included studies that compared a blood or serum CRP measurement with a reference standard of a microbiologic diagnosis of (a) serious bacterial infection (versus benign bacterial or nonbacterial infection) or (b) bacterial infection (versus nonbacterial infection). We excluded studies in which more than 10% of participants were neonates, and the reference standard was the diagnosis of a specific disease (eg,

From The School of Medicine (S.S., J.D.), The University of Queensland, Royal Brisbane Hospital Complex, Queensland, Brisbane, Australia; The School of Population Health (A.B.), The University of Queensland, Herston, Queensland, Australia; Refugee Health Research Centre (I.C.-V.), La Trobe University, Victoria, Australia; and Intensive Care, Royal Children's Hospital (M.C.), Herston, Queensland, Australia.

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Correspondence (no reprints): Ms. Sharon Sanders, The School of Medicine, The University of Queensland, Level 2, Edith Cavell Building, Royal Brisbane Hospital Complex, Brisbane, QLD 4029, Australia. E-mail: s.sanders@uq.edu.au.

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meningitis, gastroenteritis, or arthritis) or studies conducted in subgroups of patients with specific medical conditions, such as cancer or renal failure. No language restriction was applied. Ethics approval was not required to conduct this study.

Identification of Studies

We searched the databases Medline and EMBASE from inception to December 2007 using the following terms: C-reactive protein (MeSH) OR C-reactive protein (text word) OR CRP (text word) AND (bacterial infections (MeSH) OR virus diseases (MeSH) OR bacteria* (text word) OR virus (text word) OR viral (text word) AND (child (MeSH) OR child* (text word) OR infant (MeSH) OR infant* (text word). We checked the reference lists of all included papers and review articles and forward searched any identified papers. 2 reviewers screened the titles and abstracts from the electronic searches against the inclusion and exclusion criteria. Disagreements were resolved by discussion with a third reviewer.

Quality Assessment

Quality of the included studies was assessed independently by 2 reviewers using QUADAS,[9] a validated tool for assessing quality of diagnostic studies. We used the 11-item version as recommended by the Cochrane Diagnostic Test Accuracy Working Group, which contains items relating to patient spectrum, reference standard, disease progression bias, verification bias, review bias, incorporation bias, test execution, study withdrawals, and indeterminate results. 2 of the 11 items were deemed not relevant due to the objectivity of the CRP test and were omitted. 1 item that asks whether patients received the same reference standard regardless of the index test result was split into 2 because it was possible that a different reference standard was applied but performance of the reference test was not related to the outcome of the index test. Percentage agreement and the κ statistic were calculated to assess the interobserver variation of the initial assessment of both reviewers.

Data Extraction

Data were extracted by 2 reviewers independently on predesigned and piloted forms. Where necessary, we contacted authors for data or clarifying information.

Data Analysis

Data from each study were extracted in 2×2 tables. We combined the categories of invasive bacterial and localized bacterial infection in the category of bacterial infection for the purpose of the 2×2 tables; similarly, we categorized mixed bacterial and viral infections (1 study) and proven or possible bacterial infections (1 study) as bacterial. In a sensitivity analysis, these categorizations had a negligible effect on the results. Heterogeneity in study results was examined graphically using plots of sensitivity versus 1 minus specificity. Clinical heterogeneity was examined using descriptions of study characteristics.

Where there was sufficient homogeneity of results, we used a random-effects bivariate model to obtain summary estimates of sensitivity and specificity and corresponding 95% confidence intervals. This model estimates and incorporates the correlation that may exist because of the trade-off between sensitivity and specificity due to changes in the threshold in the index test for defining disease used between studies. It is equivalent to a hierarchical summary receiver operating characteristic curve analysis in most situations.[10] The model also estimates the diagnostic odds ratio, a measure of overall test accuracy equivalent to the ratio of true to false test results.[11] Statistical codes were kindly provided by Roger Harbord of Bristol University.[10] Stata 9 was used for all analyses.

RESULTS

Study Characteristics

The search retrieved 1770 potentially relevant titles and abstracts. Of these, 10 studies assessing a total of 2046 participants met the inclusion criteria for the review. All of the studies were conducted in emergency departments. 36 studies examining the diagnostic accuracy of CRP in children admitted to hospital were excluded. Characteristics of the studies investigating CRP for the identification of serious bacterial

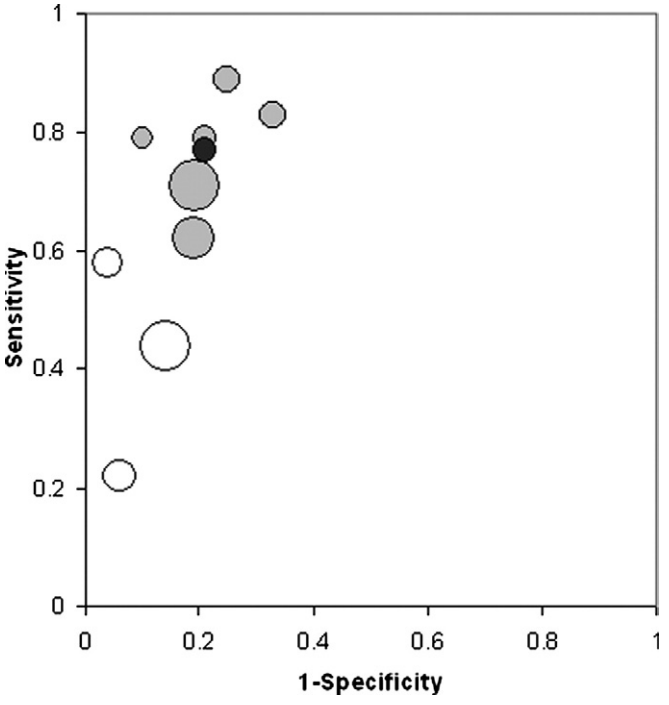

Figure. Results of studies estimating the sensitivity and specificity of C-reactive protein for the detection of serious bacterial infection and bacterial infection. Grey circles indicate serious bacterial infection; white circles indicate bacterial infection; the black circle indicates summary point for serious bacterial infection (summary estimate from the random-effects bivariate analysis). Each circle represents the sensitivity and specificity of the individual studies included in the review. The size of the circle is proportionate to study size.