How useful is C-reactive protein in detecting occult bacterial infection in young children with fever without apparent focus?

Report by

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You are a specialist registrar in a paediatric day assessment unit and often see young children with high fever but no obvious focus of infection on physical examination. You wonder if a screening test can be done in such patients to identify those with occult bacterial infection. You know that in some units C-reactive protein (CRP) is measured routinely in all children with high fever. However, you are not sure if CRP measurement is a good screening test to detect occult bacterial infection in a young child with fever without apparent focus. You decide to find out more.

Structured clinical question

In young children with fever without apparent focus on physical examination and history [subject], is measurement of C-reactive protein a good screening test [intervention] to detect occult bacterial infection or bacteraemia [outcome]?

Search strategy and outcome

See table 1.

Primary sources

Medline (1951–2004) via Dialog DATA star: “C-reactive protein or acute phase reactant\$ or acute phase protein\$ or CRP AND fever without focus or fever of unknown origin or occult bacteraemia”.

Outcome: A total of 58 articles were found. This was limited to 23 articles by selecting those in the English language and human studies related to children (up to 18 years of age). Each abstract was read and six relevant studies were found. One of these studies (Berger *et al*⁶) was relevant but was designed to look at the use of CRP in differentiating bacterial and viral infection, and children with identifiable focus of infection were included in the study. Therefore this was excluded from the analysis. Five more relevant articles were obtained from the references of the above studies.^{7–11} However, designs of these studies were similar to those of Berger *et al*, and all included children with identifiable focus of infection in their analysis. Subsequently none of them were included in the analysis here.

Pubmed and Embase: No further relevant articles were found.

Secondary sources

Cochrane library and Bestbets website: No further relevant article was found.

Commentary

The management of febrile young children without apparent source of infection remains controversial, because there has been no test available with adequate sensitivity and specificity required to distinguish children with occult bacterial infection from non-bacterial illness. Blood culture is the gold standard to detect occult bacteraemia; however, results are not quickly available.

Five studies evaluating the use of various acute phase reactants in this clinical situation are appraised here. The

diagnostic nature of the question determines that the best possible research studies would be validating prospective cohort studies, but four of them were exploratory cohort studies and one was a retrospective analysis, and all of them had methodological flaws in them. Three prospective studies^{1 2 5} showed that CRP has better predictive value than other acute phase reactants, while one study⁴ found ANC to have better predictive value. Interestingly, in all of them mean CRP was significantly higher in children with serious bacterial infections compared with children with benign infections, and when taken in conjunction with other acute phase reactants, gave good probability of serious bacterial infection.

One may imagine that trend in CRP over time may be more important than a single CRP value, and a single very high CRP may have very high specificity and sensitivity to detect serious bacterial infections. However, none of these studies gave enough data to answer these two questions, and no other studies are available looking at the serial measurements of serum CRP to detect occult bacterial infection in paediatric population.

The incidence of serious bacterial infections was high in all the studies, ranging from 11.3% to 29%. The prevalence of occult bacteraemia in non-toxic appearing children between 3 and 36 months of age with temperatures higher than 39°C has declined to about 2% following the introduction of conjugate vaccine against *Haemophilus influenzae* type b.^{12 13} Recently, conjugate pneumococcal vaccine has been introduced in a few countries such as the USA, and has been shown to substantially reduce the rate of invasive pneumococcal disease in immunised children,¹⁴ so a screening test to detect occult bacterial infections in children attending emergency departments in these countries may be of little value, as the pre-test probability is much lower.

On the basis of published evidence, it can be concluded that high CRP can only suggest the presence of serious bacterial infection. Nevertheless, taken in conjunction with other acute phase reactants, it can contribute towards decision making.

CLINICAL BOTTOM LINE

- Children with serious bacterial infections and occult bacteraemia are more likely to have high CRP than children with benign infections. (Grade B)
- A single CRP value gives a probability but never a certainty of presence or absence of serious bacterial infection. (Grade B)
- The use of CRP alone or with other factors may enhance clinicians' abilities in the early recognition of clinically undetectable serious bacterial infection, allowing for a more selective strategy for determining which children need additional diagnostic studies and antibiotic therapy.

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Table 1 C-reactive protein in young children with fever without apparent focus

Citation	Study group	Study type (level of evidence)	Outcome	Key results	Comments
Kohli V <i>et al</i> (1993) ¹	100 children from 3 months to 3 years of age with temperature >38.5° of less than 3 days duration without an apparent focus on physical examination and history; normal CXR and a peripheral film negative for malarial parasites. Patients with underlying neoplastic or immunosuppressive condition or with a chronic liver, heart and renal disease and those who had already received antibiotics were excluded	Exploratory prospective cohort study (level IIb)	CRP, total and differential leucocyte count and ESR in children with laboratory or radiographically proven bacterial illness and non-bacterial illnesses	The sensitivity of serum CRP >4 mg/dl for diagnosis of bacteraemia was 95%, specificity 86% with and likely hood ratio of 6.8 None of the other acute phase reactants individually or in combination had better sensitivity or specificity than CRP The sensitivity of serum CRP >4 mg/dl for diagnosis of bacteraemia was 95%, specificity 86% with and likely hood ratio of 6.8 None of the other acute phase reactants individually or in combination had better sensitivity or specificity than CRP	High incidence of proven bacterial infection (25%) in the study population Children with possible but not proven bacterial infection (13%) were not included in statistical analysis Confidence interval of sensitivity and specificity values were not given
Pulliam <i>et al</i> (2001) ²	77 children from 1 to 36 months of age with temperature >39°C and clinically undetectable source of fever. Children with acute otitis media, acute pharyngitis, clinical pneumonia, acute respiratory tract infection, acute gastroenteritis, those with a history of antibiotic use during the past 7 days, a known underlying immunologic disease and who received vaccination during the previous two days were excluded	Exploratory prospective cohort study (level IIb)	WBC, absolute neutrophil count (ANC), Band count, CRP in children with laboratory or radiographically proven serious bacterial infections	Multivariate logistic regression analysis suggested CRP as an only predictor of serious bacterial infection (Beta=0.76, 95% CI: 0.64, 0.89) A CRP value of >7 mg/dl had sensitivity of 79%, specificity of 91%, likelihood ratio 8.3 (95% CI: 3.8, 27.3) to detect occult bacterial infection CRP concentration of >9 mg/dl had a likelihood ratio of SBI of 9 CRP had better predictive value than WBC or ANC	The incidence of occult bacterial infection in the study population was high (18%) There was possibility of sampling bias as well appearing children were more likely to be discharged from emergency department without having had any laboratory studies than those who were more ill appearing
Bleeker <i>et al</i> (2001) ³	231 children aged 1–36 months who attended a paediatric emergency ward with fever >38°C without apparent focus of infection. Reviewing standardised medical records collected patient data. Laboratory results were retrieved from computer documented hospital information system	Retrospective case reviews	Using multivariate logistic regression and ROC area the diagnostic value of predictors for serious bacterial infection from history, examination and laboratory tests was judged, resulting in a risk stratification	Independent predictors for SBI from laboratory tests were WBC count, CRP and the presence of >70 WBC in urinalysis (ROC area: 0.83). The risk stratification for serious bacterial infection ranged from 6–92%	High incidence of serious bacterial infection in the study population (25%) Retrospective study
Isaccman <i>et al</i> (2002) ⁴	256 febrile children between 3–36 months of age without apparent focus. Patients who had taken antibiotics within 48 hours of presentation and those who were known case of bacteraemia during the previous 48 hours were excluded	Exploratory prospective cohort (level IIb)	CRP, absolute neutrophil count (ANC), WBC in children with laboratory or radiographically proven occult bacterial infection	The sensitivity, specificity, and likelihood ratio of CRP value of >4.4 mg/dl was 63% (95% CI 43–82), 81% (76–81), 3.3 (1.7–4.3) respectively in detecting occult bacterial infection ANC had better predictive value for detection of occult bacterial infection than CRP	High incidence of occult bacterial infection in the study population (11.3%) Good sample size
Galetto-Lacour <i>et al</i> (2003) ⁵	99 children between age 1 week to 3 years with fever >38°C and no localising sign of infection seen at the emergency department. Children with fever lasting longer than 7 days, with known immunodeficiencies and who were treated with antibiotics during the two previous days were excluded	Exploratory prospective cohort (level IIb)	Procalcitonin (PCT), CRP, IL-6 levels and WBC with differential counts in children with laboratory or radiographically proven serious bacterial infection	The sensitivity, specificity, and likelihood ratio of CRP value of >4 mg/dl was 76% (95% CI 60–92), 79% (67–88) and 3.6 (1.8–7.6) respectively in detecting serious bacterial infection PCT and CRP performed better than IL-6 and/or band count in predicting the occurrence of serious bacterial infection	High incidence of serious bacterial infection (29%) in the study population Neonates from 1 week to 1 month of age were also included In non-toxic appearing children blood culture was only done if their leucocytes count was >15 g/l or band count was >1.5 g/l

5 Galetto-Lacour A, Zamora SA, Gervaix A. Bedside procalcitonin and C-reactive protein tests in children with fever without localizing signs of infection seen in a referral centre. *Pediatrics* 2003;**112**:1054–60.

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Does treatment with Echinacea purpurea effectively shorten the course of upper respiratory tract infections in children?

Report by

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You are a paediatric specialist registrar on a Sunday late shift in the accident and emergency department. A 4 year old boy presents with a two day history of fever (maximum temperature 38.8°C) and clinical signs of an upper respiratory tract infection (URTI). At home, his mother gave regular paracetamol to treat his fever and extracts from ivy to alleviate the cough. She asks you about Echinacea purpurea therapy for her son's illness.

Structured clinical question

In children with upper respiratory tract infection [patient], is treatment with Echinacea purpurea [intervention] effective for alleviating symptoms and shortening the course of URTI [outcome]?

Search strategy and outcome

Cochrane Database of Systematic Reviews: 1 relevant hit.

Pubmed: "Echinacea" AND ("respiratory infection" OR "cold"). Limits: "Randomized controlled trial" or "clinical trial". 15 hits, 7 relevant. "Echinacea" AND ("respiratory infection" OR "cold") AND ("children" OR "infants"). Limits: "Randomized controlled trial" or "clinical trial". 2 hits, 1 relevant. Embase: "Echinacea" AND "respiratory" AND "infection" AND "trial". No further relevant hits. "Echinacea" AND "respiratory" AND "infection" AND "children" AND "trial". No further relevant hits.

See table 2.

Commentary

In recent years, alternative medicines have gained much popularity. According to a recent survey, more than one third of the US population consumes herbal medicines regularly.¹¹ Reasons for the surge of herbal remedies include the widely assumed good tolerance of "natural" products and a supposed lack of side effects, a belief often paired with scepticism towards the efficacy of "conventional" medicine. Particularly in paediatric medicine, it seems in vogue to treat common childhood ailments using herbal medicines. Among the most commonly used remedies are Echinacea preparations, constituting approx. 10% of the total US market in herbal medicine, with annual sales worth over US\$300 million.¹¹ Complaints about an URTI account for about 40% of visits to paediatricians during winter months, and herbal

substances are increasingly being prescribed by medical practitioners despite a lack of convincing proof of their effectiveness or safety.¹² In particular, Echinaceas attributed immune modulating effects may not only be beneficial: Echinacea possibly reduces the effectiveness of corticosteroids, commonly used by asthmatics and for treating viral induced wheeze, and can cause hypersensitivity reactions in susceptible individuals.^{13 14}

Treatment of the common cold in children with Echinacea has only been investigated in one randomised, double blind, placebo controlled trial: Taylor *et al* examined the efficacy and safety of Echinacea purpurea in children with URTI. The authors studied a large cohort by using a stringent methodology, but the results failed to show an influence on duration of illness or severity of symptoms.¹ To further elucidate our clinical question, we extended our search to treatment trials in the adult population. A Cochrane review about Echinacea treatment, published in 1999, found no definite treatment effect and criticises methodological inconsistencies among the studies available.¹⁰ We reviewed six recent randomised controlled trials of adults receiving Echinacea treatment for symptoms of URTI (table 2). Neither the study populations, nor the preparations of Echinacea investigated in the trials were standardised, a fact that complicates the comparability of the results. The results are inconsistent; trials with a larger number of individuals failed to show a significant effect of Echinacea treatment, whereas smaller trials did document positive effects. Treatment with Echinacea purpurea was perceived as beneficial by a number of individuals, possibly due to the placebo effect.

Currently, there is a lack of evidence on the efficacy of Echinacea purpurea, especially in paediatric patients. Under the present circumstances, the use of Echinacea as a treatment for URTI cannot be suggested as being effective. In particular, Echinacea should be not be taken by patients with chronic immune mediated disease on treatment with corticosteroids and those with allergy to ragweed and related allergens.^{13 14}

CLINICAL BOTTOM LINE

- There is currently no evidence for the efficacy of Echinacea purpurea in the treatment of children with upper respiratory tract infections. (Grade A)
- Echinacea should be avoided by patients who receive corticosteroids and by those with allergy to ragweed and related allergens. (Grade B)

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