Can CRP Predict Bacterial Infection in Children with Fever?

The following piece (in italics) is presented with kind permission from the *Archimedes* section of *Archives of Disease in Childhood*. This is followed by examination of the evidence along the lines of EURECA.

ARCHIMEDES

Maheshwari N. How useful is C-reactive protein in detecting occult bacterial infection in young children with fever without apparent focus? Arch Dis Child 2006; 91: 533-535.

Clinical scenario: *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

Primary sources: *Medline (1951–2004) via Dialog DATA star, using the following search phrases: C-reactive protein, acute phase reactant, acute phase protein, CRP, fever without focus, fever of unknown origin, 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(1-6). One of these studies(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.(6), 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 study(4) found absolute neutrophil count 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 bacteremia 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 Hemophilus 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 immunized 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.

EURECA

The clinical scenario depicted here is fairly common in day to day practice and pediatricians often initiate antibiotic therapy in such situations. Many would rightly send blood samples for culture and take further steps based on the results. Therefore, the question addressed in this piece from *Archimedes* has considerable relevance in the Indian setting from two perspectives; first, whether CRP can be used to determine if an episode of fever is related to bacterial infection (that therefore justifies the use of antibiotics); second and perhaps more important, whether the results of CRP analysis (single or multiple) can strengthen the decision to stop antibiotics even before blood culture results are available. A third issue could be whether CRP in

conjunction with one or more clinical and/or laboratory parameters can resolve these issues. *Archimedes* has tried to find evidence to address the first of these. Their search strategy was reliable, easily reproducible and transparent. They have presented the pooled information from the available data in a tabular form. Currently, there is limited experience in combining data from diagnostic test studies into a meta-analysis, hence their presentation represents current best practice. In terms of EURECA, the clinical question, intervention (CRP test) and the findings are all relevant to the Indian context.

In order to obtain current evidence, an updated literature search duplicating the Archimedes search strategy, for the period 1 January 2005 to 31 December 2007 was performed. This yielded 122 citations that were narrowed down to 52 using the limits in *Archimedes*. Of these, five were relevant(15-19). Two of the studies(15,16) also evaluated pro-calcitonin and one was conducted in children with malignancies(17). One study(18) compared the predictive value of CRP (and other potential markers) in children with fever of greater than 12 hours duration versus fever of shorter duration. Another evaluated three different methods of performing CRP analysis(19). The Cochrane Library yielded two additional citations(20,21); however neither was a systematic review. One of these(20) was a randomized controlled trial that compared antibiotic prescription rates in children with respiratory infection having a CRP test versus those who did not. The study found no difference between the two groups suggesting limited value of the test on prescription behavior. The other was a four arm trial which showed that neonates with 'highly probable sepsis' and 'probable sepsis' had higher CRP level than those with 'possible sepsis' or no sepsis(21). BestBETs registered a title to evaluate CRP in children with pneumonia on 13 September 2006, but no data was presented(22). **Table I** summarises the details of all the relevant studies. The additional data pointed in the same general direction as the Archimedes evidence, suggesting that the findings are robust.

It is important for pediatricians to realize that there is no such thing as a positive or negative CRP. The test does not provide a dichotomous (yes/no)

TABLE I DETAILS FROM RELEVANT STUDIES

No.	Study design	Participants n (age)	CRP level analysed	Prevalence of bacterial infection	Main results
1.	Prospective cohort(1)	100 (3 mo to 3 yr)	>4 mg/dL	25%	Sensitivity = 95%; Specificity = 86%; LR + 6.8
2.	Prospective cohort(2)	77 (1-36 mo)	>7 mg/dL	18%	Sensitivity = 79%; Specificity = 91%; LR + 8.3 (9.0 if 9 mg/dL used)
3.	Retrospective(3)	231 (1-36 mo)	ROC method used	25%	CRP predictive of serious bacterial infection
4.	Prospective cohort(4)	256 (3-36 mo)	>4.4 mg/dL	11.3%	Sensitivity = 63%; Specificity = 81%; LR + 3.3
5.	Prospective cohort(5)	99 (1wk-36 mo)	>4 mg/dL	29%	Sensitivity = 76%; Specificity = 79%; LR + 3.6
6.	Prospective cohort(15)	72 (1-36 mo)	>5 mg/dL	11.1%	Sensitivity = 75%; Specificity = 68.7%
7.	Prospective cohort(16)	408 (1wk-36 mo)	ROC method used	23.1%	CRP predictive of serious bacterial infection
8.	Prospective cohort(17)	Children with malignancies	>9 mg/dL		Sensitivity = 70%; Specificity = 73%; NPV = 51%; PPV = 85%

Abbreviations: CRP = C-reactive protein; LR += Likelihood ratio of positive test; NPV = negative predictive value; PPV = positive predictive value; ROC=Receiver operator characteristics

result, but yields a value that has to be interpreted in light of the level in 'normal' subjects. The 'normal' value itself may vary depending upon subject characteristics and laboratory methodology; hence the cut-off used varies widely from as low as 1 mg/dL(23, 24) to as high as 9 mg/dL(17). It would be interesting to study how CRP performs if all studies use a uniform cut-off value.

The impact of age of children (newborn, infant or older), clinical characteristics and "gold standard' used also need to be worked out. The last of these is particularly noteworthy because blood culture is the usual gold standard for comparing all potential markers of bacterial infection. However, it is well known that blood culture does not always yield an organism in cases that manifest with clinical profile, laboratory results, course and outcome conforming to bacterial infection. It is unclear how CRP behaves as a 'diagnostic' test in situations where blood culture is 'negative'.

Can the evidence presented in *Archimedes* (updated and appraised in EURECA) be used in our setting? Only one of the studies was conducted in

Indian children(5); it showed very high sensitivity, specificity and likelihood ratio. It is not clear whether this highly optimistic result (other studies in different settings reported more conservative results) is due to participant characteristics, study methodology or reflects genuinely better performance of the CRP test in Indian children. Nevertheless, it may be concluded that current evidence shows CRP to be at best suggestive, but not confirmatory of bacterial infection. Therefore, this 'external' evidence can be 'extended' to the local setting. In addition, the test is reasonably simple to perform, easily accessible and affordable. However recent literature suggests that procalcitonin may be a more reliable and valid acute phase reactant that can address the clinical question being considered; however this tool is still under evaluation. Besides it is not widely available in the Indian scenario at present.

EURECA CONCLUSION

In children having fever without obvious focus, measurement of C-reactive protein may suggest (but not confirm) the presence of bacteremia (bacterial

infection). The critically appraised evidence is relevant, current and extendible to the Indian context.

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