Significance of C-reactive Protein During Febrile Neutropenia in Pediatric Malignancies

K SHREEDHARA AVABRATHA, ATK RAU, P VENKATARAVANAMMA AND *AARATHI RAU

*From the Departments of Pediatrics and *Pathology, Kasturba Medical College, Mangalore, India.*

Correspondence to:
Dr ATK Rau, Prof and Unit Chief, Department of Pediatrics, Kasturba Medical College Hospital, Attavar, Mangalore 575 001, Karnataka, India.
atkrau@sancharnet.in
Manuscript received: March 14, 2008; Initial Review : April 10, 2008; Accepted: August 27, 2008.

Fifty episodes of febrile neutropenia (FN) in 33 children with malignancies were studied to evaluate the usefulness of C-reactive protein (CRP) levels as an indicator of infection, and the efficacy of antibiotic therapy. Nineteen FN episodes occurred in children with documented infection whereas, 9 and 22 episodes occurred with probable infection and fever of unknown origin, respectively. CRP positivity during episodes of documented and probable infection was significantly higher than with febrile episodes of unknown origin. Blood culture was positive in 15 episodes; of these, CRP was positive in 11. CRP declined to normal on 7th day of antibiotic therapy. CRP is a useful indicator of infection in neutropenic children and also in determining the efficacy of antibiotic therapy.

Keywords: *C-reactive protein, Child, Febrile neutropenia, Infection, Neoplasm.*

Published online 2009 April 1. PII:S097475790800159-2

Diagnosis of potentially life threatening febrile neutropenia (FN) in pediatric malignancies is often missed or delayed. C-reactive protein (CRP), an acute phase reactant, synthesized by the liver during infection and acute inflammation, has been widely used as an indicator of infection(1). However, its role as an indicator of sepsis in immunocompromised patients has not been adequately studied. This study was undertaken to evaluate the usefulness of CRP as an indicator of covert infection in neutropenic children and in determining the efficacy of antibiotic therapy.

METHODS

This is a prospective study of 50 consecutive episodes of febrile neutropenia (FN) in children suffering from malignancies and undergoing therapy in a pediatric oncology unit of a teaching hospital. Children between 1-15 years of age with marrow/ biopsy evidence of malignancy and clinical features of FN were included. Those with liver disease were excluded from the study.

The diagnosis of FN was made as per standard criteria(2) *i.e.* absolute neutrophil count (ANC) of <500/cmm or a count of <1000/cmm with a predicted decline to 500/cmm, with single oral temperature of ≥38.3°C or a temperature of ≥38°C for ≥1 hour. All participants were subjected to thorough clinical examination and tests for hemoglobin, complete blood cell count, peripheral smear, blood culture and sensitivity, and CRP estimation (Humatex human CRP test kit, a latex agglutination slide test on undiluted serum). Antibiotics were then started. CRP estimation was repeated on day 7 and on the last day of antibiotic therapy, if extended. A value above 6 mg/L was considered positive.

The results of CRP were compared and associated with clinical findings and other laboratory results. SPSS version 11.5 was used for statistical analysis.

RESULTS

Fifty episodes of FN occurred in 33 children, 17 of

whom were males, with a mean age of 6.9 years. Thirty episodes of FN occurred in the intensive and 20 in the maintenance phases of chemotherapy. The commonest diagnosis was acute lymphoblastic leukemia (34 episodes in 24 patients).

Out of the 50 episodes of FN, 19 (38%) occurred in children with documented infection with clinical and/or radiological evidence of infection and culture positivity (Group I). In these, respiratory tract infections were the commonest (31.6%) followed by urinary tract infections (26.3%) and sepsis (21%). Cellulitis purely on clinical evidence was also included in this group. Nine episodes (18%) occurred in children with probable infection (Group II), in which there was an identifiable site of infection without a positive culture. The rest 22 (44%), were labeled as having fever of unknown origin (Group III).

ANC at presentation was <200/cmm in 19 episodes (38%), between 200-500/cmm in 17 episodes (34%) and >500/cmm in 14 episodes (28%). A majority of the documented and probable infection, occurred with ANC <200/cmm (73.7% and 55.6% respectively) while only a few episodes of documented and probable infection, occurred in children with ANC >500/cmm (10.5% and 22.2% respectively). Fifteen episodes grew organisms from tissue fluid cultures (*S. aureus*: 4; *P. aeuruginosa*: 3; *Citrobacter*: 1; *E.coli*: 4; *S. pneumoniae*: 2; and other: 1). CRP was positive in 11 of these episodes (***Table* I**).

Initial CRP positivity in the study groups revealed that while Group I (D1:15/19; D7:4/19) and II (D1:7/9; D7:2/9) had higher number of CRP positivity, Group I values, when considered in isolation, were significantly higher ($P<0.001$). In Group III, CRP was positive on D1 in 5/22 episodes and in 2/22 episodes on day 7. When CRP positivity in the various groups were analyzed on day 7 and at the end of antibiotic therapy (if later), it was found that in all three groups, CRP decreased as treatment progressed and the child responded to therapy.

DISCUSSION

Our findings corroborate the results of previous studies(3,4). However, Bodey, *et al.*(5) demonstrated 53% documented infections in their series, in contrast to the present study. This could be due to low culture yields, early initiation of empirical antibiotic therapy or better nursing care in our patients.

Of the 50 episodes of FN, true positives (*i.e.* CRP positive with documented infections) accounted for 15 episodes, false positive (*i.e.* CRP positive but cultures negative) in 12, false negative (*i.e.* CRP negative and culture positive) in 4 and true negative (*i.e.* CRP and culture negative) in remaining 19 episodes. The sensitivity was 55% and specificity 82% with a positive predictive value of 78%. Putto, *et al.*(6) have reported a sensitivity of 100% and specificity of 75% for CRP in infections while Peltola and Jaakkola(7) reported a sensitivity of 89% and specificity of 77% with a positive predictive value of 79%.

In Group I, CRP remained high in 4 children out of 15 on day 7 and on the last day of antibiotic

TABLE I CULTURE RESULTS IN FEBRILE NEUTROPENIA AND CRP POSITIVITY

Organism isolated	ANC <200/cmm (*n* =8)		ANC 200-500/cmm (*n*=5)		ANC >500/cmm (*n* = 2)	
	CRP+ve	CRP-ve	CRP+ve	CRP-ve	CRP+ve	CRP-ve
Staphylococcus aureus (*n*=4)	2	0	2	0	0	0
Pseudomonas aeruginosa (*n*=3)	1	1	1	0	0	0
Citrobacter species (*n*=1)	0	0	0	1	0	0
E. coli (*n*=4)	0	2	0	0	2	0
Genus *bacillus* (*n*=1)	0	0	1	0	0	0
S. pneumoniae (*n*=2)	2	0	0	0	0	0

WHAT THIS STUDY ADDS?

- Serial estimation of C-reactive protein can serve as a tool for diagnosing infection and monitoring the response to antibiotic therapy in febrile neutropenia.

therapy. Of these 2 died and 2 required augmentation of therapy. Other than these, in all 3 groups, CRP positivity uniformly decreased as the children improved. Thus, CRP can indicate persistent infection in children with FN. This correlates well with other studies(8,9). Though there are reports of procalcitonin(PCT) being a better marker of infection in FN, it is expensive and not readily available(10). In a pediatric study(11) involving 60 febrile episodes, periodic measurement of PCT was found to be more useful than CRP. However, both PCT and CRP levels were significantly higher in FN than in controls.

We conclude that, CRP is an easily available and significantly sensitive test to diagnose infection and monitor response to therapy in FN.

Contributors: ATK conceived the idea, provided the study design and stands as guarantor. Data was collected and analyzed by VP along with ATK and KSA. KSA, ATK and AR wrote the paper. The final manuscript was approved by all authors.

Funding: None.

Competing interests: None stated.

REFERENCES

1. Schofield KP ,Voulgari F , Gozzard DI, Leyland MJ, Beeching NJ. C-reactive protein concentration as a guide to antibiotic therapy in acute leukemia. J Clin Pathol 1982; 35: 866-869.
2. Hughes WT, Armstrong D, Bodey GP, Bow EJ, Calandra T, Feld R, *et al.* 2002 guidelines for the use of antimicrobial agents in neutropenic patients with cancer. Clin Infect Dis 2002; 34: 730-751.
3. Nachmann JB, Honig GR. Fever and neutropenia in children with neoplastic disease. Cancer 1980; 45: 407-412.
4. Bloomfield CD, Kennedy BJ. Cephalothin, carbenicillin and gentamicin combination therapy for febrile patient with acute non lymphocytic leukemia. Cancer 1974; 34: 431-437.
5. Bodey GP, Rodriguez V,Chang HY, Narboni G. Fever and infection in leukemia patients. Cancer 1978; 41: 1610-1622.
6. Putto A, Runskanen O, Meurman O, Ekblad H, Kurvenranta H, Mertsola J, *et al.* C-reactive protein in the evaluation of febrile illeness. Arch Dis Child 1986; 61: 24-29.
7. Peltola H, Jaakkola M. C-reactive protein in early detection of bacteremic versus viral infection in immunocompetent and compromised children. J Pediatr 1988; 113: 641-646.
8. Gronn M, SlordahL, Skrede S, Lie SO. C-reactive protein as an indicator of infection in immuno-suppressed child. Eur J Pediatr 1986; 145: 18-21.
9. Aslan V, Akay OM, Gulbas Z. C-reactive protein in the follow up and estimation of infections in acute leukemic patients. Turk J Haematol 2003; 20: 75-80.
10. Massaro KS, Costa SF, Leone C, Chamone D. Procalcitonin and C-reactive protein as severe systemic infection markers in febrile neutropenic adults. BMC Infect Dis 2007; 7: 137.
11. Secmeer G, Devrim I, Kara A, Ceyhan M, Cengiz B, Kutluk T, *et al*. Role of procalcitonin and CRP in differentiating a stable from a deteriorating clinical course in pediatric febrile neutropenia. J Pediatr Hematol Oncol 2007; 29: 107-111.