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Research Paper

## C-REACTIVE PROTEIN AS A GUIDE FOR THE TREATMENT RESPONSE OF OPPORTUNISTIC INFECTIONS IN HIV

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CRP is an acute phase protein whose levels increase with the infection and inflammation. The present study was conducted at Victoria Hospital Bangalore, where a total of 171 HIV patients were enrolled with a note on their opportunistic infections (OI), CRP level and treatment history of the underlying OI. 58 asymptomatic patients acted as control with CRP level less than 6 mg/L, showing no base line rise in CRP. Of the 86 tuberculosis patients, 23 had no history of treatment and CRP was found to be 41.2 mg/L. 3 patients of TB, with 1 day treatment history, had a mean CRP of about 36.6mg/L. 6 patients of TB, with a treatment history of 2days, showed a mean CRP of about 17 mg/L. 7 patients with 3 days treatment history, showed a mean CRP of 10.7mg/L. A graph of CRP and no of days of treatment, showed a negative correlation ( $r = -0.2427$ ) between them. Graphically it was found that, CRP elevated on or after 23 days of treatment of underlying OI could indicate treatment failure. CRP can be used as an indicator for the treatment response of the underlying OI in HIV positive patients.

**Keywords:** Opportunistic infections, CRP, Tuberculosis

### INTRODUCTION

CRP is an acute phase protein whose levels increase with the infection and inflammation. CRP is an important component of the innate immune system, which is synthesized in the hepatocytes, primarily in response to IL-6 and other cytokines. Normally its serum concentration is less than 6mg/L, but during inflammation its level may increase 10,000-folds (Pepys and Hirschfield, 2003). Increase in CRP level can be detected as

early as 5-10 hours after tissue damage. Opportunistic infections accounts for the majority of death in untreated patients with HIV. These infections usually are a result of activation of latent infections which are normally kept in check by robust immune system. The treatment response of the individual to the underlying opportunistic infections varies considerably and depends on the immune power (CD4 COUNT). CRP levels increases with infection and there exists a negative correlation between CRP and CD4 count

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[Melchior JC et al, (1999)]. The actual frequency of opportunistic infections varies in different regions of the world. Elevated levels of CRP can usually be demonstrated in case of acute myocardial infarction, rheumatoid arthritis, bacterial and viral infections, acute rheumatic fever, with or without carditis, and in several types of malignancies, particularly those with metastasis. HIV is a progressive infection accompanied by destruction of the immune system largely through depletion of CD-4 cells. Fever, which is the result of cytokine mediated effects during acute phase response caused by tissue injury or inflammation leads to changes in serum protein levels. Fever and the rise in circulating concentrations of CRP are commonly used in clinical medicine for diagnosis of various infections and to monitor the response to Therapy (Pepys and Hirschfield, 2003). Fever and other symptoms in an HIV infected individual are normally caused by opportunistic infections, which do cause a rise in CRP concentration (Florence *et al.*, 2002; and Sullivan *et al.*, 1996). However the relation between CRP concentration and Human Immuno deficiency Virus is still unclear. At present CD-4 count and HIV-RNA assay are potent markers of prognosis of HIV infection. But measurement of HIV-RNA level is highly expensive and is not used in most hospitals. Low values of CRP have been shown to predict longer survival within HIV-infected individuals (Grützmeier and Sandström, 1999). It has been suggested that the measurement of CRP levels may be an inexpensive method for the study of prognosis of HIV infection and can be used as a vital tool to monitor the anti-retroviral therapy (Grützmeier and Sandström, 1999). Infections in people living with HIV reflect the immune suppression of the host. Hence, CRP

can be used as a marker of degree of immune suppression. CRP is produced as a result of the opportunistic infection (Florence *et al.*, 2002; and Sullivan *et al.*, 1996); a decreased level of CRP is thus an indicator of good treatment response to the underlying infection and hence this study was under taken with same aim.

## MATERIALS AND METHODS

The present study was conducted for a period of two months at ART center, Victoria Hospital, Bangalore. During which 171 patients were enrolled, among which 58 were asymptomatic and acted as controls. All Patients above the age of 18 years seropositive for HIV-antibodies and attending ART center at Victoria hospital Bangalore were included in the study. Patients below age of 18 years, Patients on ART therapy, and Patients clinically diagnosed with AIDS were excluded.

The pre-ART patients were enrolled for the study with their informed consent. Patients were explained about the study in detail in simplest manner possible as they could understand in their own mother tongue. Signature of the patient was taken on the consent form as a mark of their approval in presence of the ART counselor. Permission from the KSAPS (Karnataka state AIDS prevention society) was also taken to conduct the study. A generalized proforma was filled up with clinical history of the patient, diagnosed OI, treatment history and past clinical history.

### Analytical Methods

**Sample:** The blood sample was collected under standard precautions at ART center for measurement of CD4 count in an EDTA vial and for CRP in a sterile plane vial without anticoagulant. The samples were immediately

brought to the Microbiology lab for further processing. For CRP measurement, the serum sample was used and processed in the serology lab of microbiology. CRP estimation was done by latex slide and tube test a diagnostic reagent kit for the in vitro detection of CRP in human serum by qualitative and semi quantitative rapid latex slider test. The principal behind the test is an immunological reaction between CRP as an antigen and latex particles that have been coated with mono specific anti human CRP sensitized to detect the level of greater than 6micrograms per ml.

## RESULTS

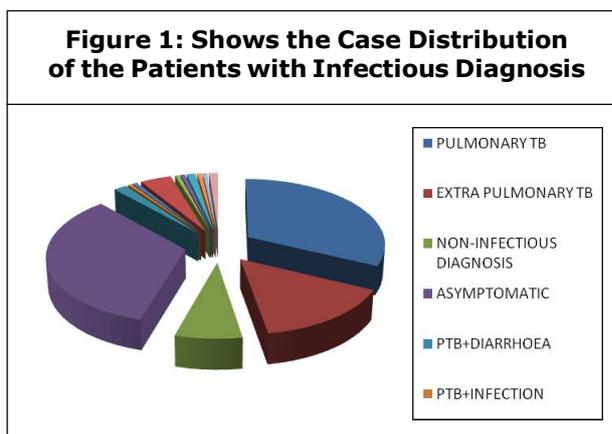
A Total of 171 patients were enrolled for the study, out of which 58 were asymptomatic and acted as control with serum CRP level less than 6 mg/ L. The remaining 113 patients were symptomatic patients with infectious or non infectious diagnosis. 101 patients were with infectious diagnosis and 12 were with non-infectious diagnosis. Table 1 shows the case distribution.

Figure 1 shows the case distribution of the patients with infectious diagnosis. All the patients with infectious diagnosis were positive for the CRP test in early days of their treatment that is treatment history of less than 5 days. Out of the 101 patients having infectious diagnosis 86 patients were with tuberculosis (TB), with 55 patients being pulmonary tuberculosis (PTB), 26 being extra pulmonary tuberculosis (EPTB) and remaining 5 patients with co-infection. 7 patients were with diarrhea, 2 febrile patients, 2 herpes and 2 cases of oral thrush and remaining 2 of less common co-infections.

Off the tuberculosis patients, 39 patients had no history of treatment for the underlying infection (0 day of treatment). Out of 55 patients of PTB

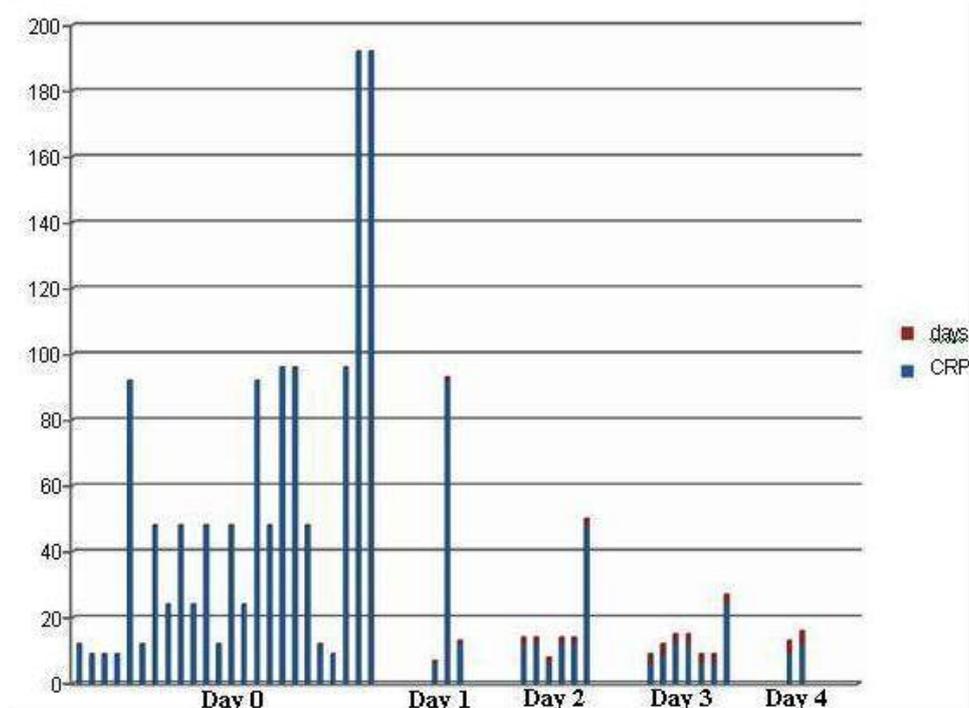
**Table 1: Shows The Case Distribution**

Opportunistic Infections	Sample Size
Pulmonary Tb (Ptb)	55
Extra Pulmonary Tb (Eptb)	26
Non-infectious Diagnosis	12
Asymptomatic	58
Ptb+Diarrhoea	3
Ptb+Infection	1
Eptb+Diarrhoea	1
Diarrhoea	7
Diarrhoea+Infection	1
Diarrhoea+Oralthrush	1
Herpes	2
Cns Infection	1
Oral Thrush	1
Febrile	2
Total	171



18 were freshly diagnosed cases and showed a very high level of CRP (mean 50 mg/L). Out of 26 cases of EPTB, 5 patients were with no treatment history and showed a high level CRP of about 32.4 mg/L. Hence the mean CRP for tuberculosis was 41.25 mg/L. 5 patients with diarrhea had no treatment history for diarrhea and showed a mean CRP of about 21 mg/L. 3 patients of EPTB were with a 1 day history of treatment and had a mean value of CRP of about 36.6 mg/ L. 6 patients (3 each of PTB and EPTB) were

**Figure 2: Showing CRP Levels of Patients With Tuberculosis (TB) During the Early Days of Their Treatment. First Set of CRP Level is of the Freshly Diagnosed Cases Showing a Very High Level of CRP. Second, Third, Fourth and Fifth Sets of CRP are of the Patients on Treatment for TB Since One, Two, Three and Four Days Respectively. There is Decrease in the Levels of CRP With Treatment, Being High on First Day and Least on Fourth Day of Treatment.**



with a treatment history of 2 days and showed a mean CRP of about 17 mg/L. 7 patients with 3 days treatment history, showed a mean CRP of 10.7 mg/L. 2 patients of EPTB with 4 days of treatment history had a mean CRP value of 10.5 mg/L. CRP was found to be high with opportunistic infection. CRP was much higher in bacterial infection than in the fungal or viral infection. Asymptomatic patients gave negative result for CRP test. There was direct correlation between CRP levels and Opportunistic infection and did not vary with age, sex, or other parameters. Patients with non infectious diagnosis like sinusitis, migraine, hypertensive diabetics also showed, slight rise in CRP with high CD4 count. But treatment of the under lying

non infectious disease did not lower the CRP level much. There was no baseline rise in the levels of CRP in HIV infected patients. CRP test was positive in cases of only opportunistic infection with no treatment history or treatment history of less than 5 days.

## STATISTICAL ANALYSIS

A graph of CRP along x-axis and number of days of treatment for OI along the y-axis is plotted. CRP was the independent variable with CD4 count being dependent Variable. Z-test method of significance was employed for the analysis. No statistical software's were used for the analysis and was done manually with the help of

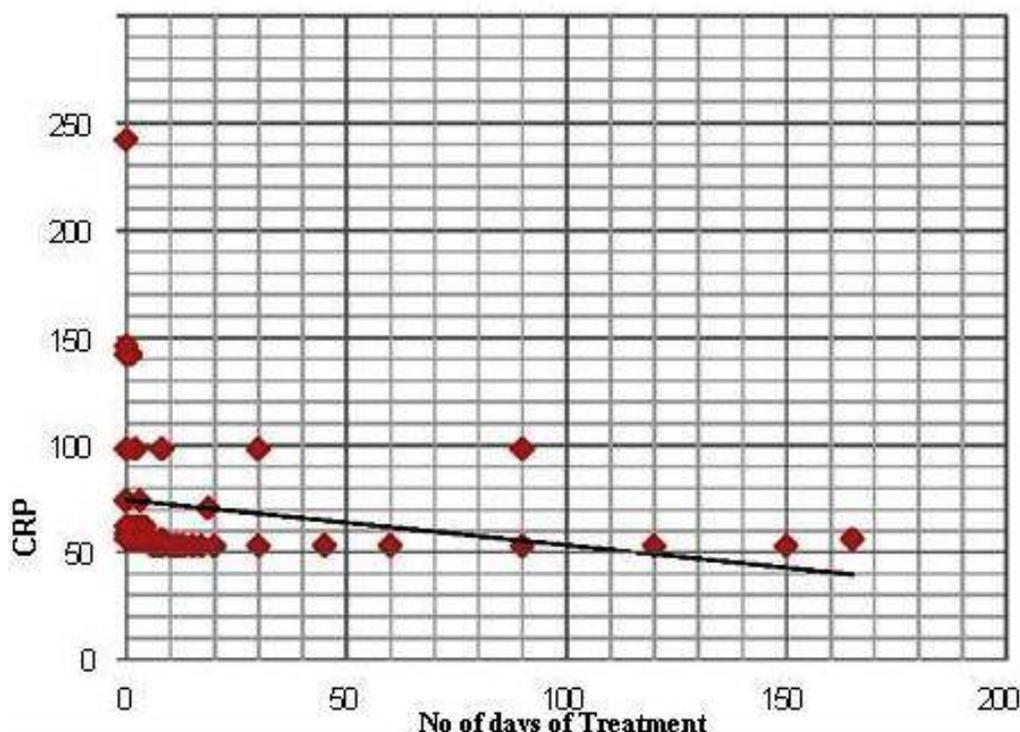
an expert statistician. It showed a negative correlation ( $r = -0.24247$ ) between them, which is highly significant ( $p < 0.01$ ) at 1% level of significance. The linear regression line of CD4 count on CRP was drawn as shown in the Figure 3.  $y = 24.4379 - 0.21045x$  is the equation of the line ( $r = -0.2424$  and  $p < 0.01$  ( $|z| = 2.589$ )). Substituting  $y=5.9$  in the above equation we graphically get an assumption that, CRP positive test even after 23.2 days of treatment of underlying opportunistic infection could probably indicate treatment failure.

### DISCUSSION

The asymptomatic HIV patients showed negative test for CRP ( $<6$  mg/L), which suggests that there was no baseline rise in CRP in HIV patients.

Noursadeghi M and Miller RF (2005) proposed that the base line CRP levels in the general population are  $<3$  mg/L. In HIV positive patients it was found to be higher than the general population and it was 5.9 mg/L and possibly reflects sustained acute phase response as a consequence of HIV infection. Lau *et al.* (2006) showed in their study, lower level of CRP concentration predicts longer survival within HIV infected population. For a population with on-going HIV infection, level of CRP was shown to be relatively low ( $<4$  mg/L), which indicates HIV is not a highly inflammatory state. Baseline of 3.52 mg/L was suggested by Kannangai *et al.* (2008). In our present study all asymptomatic patients with No clinical symptoms gave negative results for CRP done by latex agglutination method, which detects CRP greater than or equal to

**Figure 3: Graph Comparing CRP (mg/L) and No of Days of Treatment of Underlying Opportunistic Infections**



6 mg/L concentration. As suggested by Noursadeghi and Miller (2005) there might be slight/no elevation of CRP in HIV patients, but is insignificant.

Infectious cases were all positive for CRP. CRP was very high in case of combination of opportunistic infections. Lawn *et al.*, (2001) suggested that the serum CRP in HIV infected persons increase only in presence of opportunistic infections. Chalmers *et al.* (2008) showed elevated CRP in patients with Pneumocystis Carini Pneumonia (120 mg/L) and TB as high as 44 mg/L, which correlated with our study, where TB patients had an average CRP of 42 mg/L.

With the treatment of underlying opportunistic infection the CRP level decreased progressively and showed a negative test. Sage *et al.* (2010) showed in those with CRP value that remain elevated after >4 days of treatment there was a greater risk of treatment failure and increased mortality.

## CONCLUSION

From the study we conclude that CRP is a very sensitive marker infection and inflammation, in HIV and can identify opportunistic infections at the earliest. CRP test can be done as a bed side procedure in any of the primary health set ups. It is seen that, CRP levels decrease with treatment of underlying opportunistic infection and thus CRP can be used as an indicator for the treatment response of the underlying opportunistic infections in HIV positive patients. CRP positive test even after 23 days of treatment of underlying opportunistic infection could indicate treatment failure.

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