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Perspectives and Commentaries

Diagnosis and Surveillance of Infections in Cytopenic Cancer Patients

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(A COMMENT ON: Timonen T, Koistinen P. C-reactive protein for detection and follow-up of bacterial and fungal infections in severely neutropenic patients with acute leukaemia. *Eur J Cancer Clin Oncol* 1985, **21,** 557–562.)

ALTHOUGH mostly treatable, infections are still an important problem in oncology. The more aggressive and successful we become in treating many cancers, the more we tend to depress the immune system. We have made much progress in our ability to treat the unavoidable infectious complications of this depression. This is not to say that we would not benefit from even more potent drugs, particularly in viral and fungal infections, but one sometimes has the impression of being counterproductive. Most of the progress in this field comes from the ever widening use of the very useful concept of empiric coverage. The first step was the use of empiric broad-spectrum antibiotics at the first sign of fever in neutropenic patients. We now routinely use, especially in the most problematic situation like in bone marrow transplant patients, not only anti-fungal but also anti-viral and anti-parasitic empiric therapy. I believe we pay a price for that: the price is that we are selecting each time more aggressive and more resistant organisms that eventually lead to the patient's demise. Thus progress in this field, although more potent drugs are eagerly awaited, must come from a better way of detecting as quickly as possible if a patient is infected and with what, or possibly from better prevention of infection. More rapid and sensitive (but possibly less specific) means of detecting pathogens in the blood (various "isolator" systems) are one avenue of possible progress.

I think there might be another one.

We all know that neutropenic patients often have fever for reasons unknown but probably not infectious: febrile reactions to various blood product transfusions are but one example. Would it not be possible to distinguish between those patients who have an infectious process, worth investigating and treating empirically, and those who have "benign" fever for other reasons?

However non-specific, various ways of detecting the presence of an active infectious process by measuring the body's reactions to it have long been a fruitful area of research. These body reactions are mainly what is loosely called the "acute phase reaction". Some of the acute phase reactants are well known: the time-honoured sedimentation rate is one example. It was discovered around 1920 by Fahraeus, who was looking for an early test for the diagnosis of pregnancy [1]. However, apart from its lack of specificity, the raised sedimentation rate is a relatively slow reaction to an infection, thus reducing its usefulness in predicting quickly which patient is infected [2].

Study of the so-called "acute phase reaction" has led to the discovery of numerous compounds that rise in the blood, following rather non-specific stimuli that might be infectious in origin [3]. One such compound has been discovered as long ago as 1930 [4]: it is called the C-reactive protein (CRP). However it was long measured only as an "all or none" phenomenon.

It was only in the 1950s that Anderson and McCarty [5] introduced a semi-quantitative precipitation technique which enhanced its utility in distinguishing normal from pathological elevation, since small amounts of CRP are present in all normal individuals. Since then, much research has been done about this protein, its metabolism and

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its role in different disease states [6]. Serial measurements especially hold much promise because CRP levels have been shown to rise rapidly (within 6–12 hr [7]) with the initiation and fall rapidly upon cessation of inflammation. Admittedly, this elevation can be due to many other causes than acute infections, from rheumatoid disease to myocardial infarction, widespread malignancy and normal pregnancy.

Bearing in mind this lack of specificity, I think that serial measurement of CRP or other rapid acute phase reactants can be of some help in distinguishing the neutropenic patient who has a serious infectious problem necessitating initiation, change or addition of antimicrobials, from the one who just needs close surveillance. One paper specifically looks at the helpfulness of serial measurement [8]. The authors serially measured the CRP level in 20 consecutive, neutropenic adults with acute leukaemia and fever, 35 apyretic patients with acute leukaemia and 20 healthy adults were also followed serially as far as their CRP level was concerned.

Another control group consisted of the 20 patients included in the study group, when they were afebrile. The 20 patients had 35 episodes of pyrexia: the authors divided them in four groups. In group I (patients with septicemia), for all febrile episodes, the CRP level rose to more than 100 mg/l (mean value 195 mg/l with a range of 112–354). In group II (patients with microbiologically documented infections, excluding septicemias) the mean CRP value was 219 mg/l with a range of 36–440. In group III (patients with clinically documented infections) the mean was 147 mg/l with a range of 69–210. In group IV (patients with negative cultures, without signs of infection and no response to antibiotics) the mean was 86 mg/l with a range of 10–204. In all afebrile control patients with acute leukaemia, the CRP value was < 27 mg/l.

In 20 healthy adults, the mean value was < 10 mg/l.

Overall, in 84% of infections the peak value for CRP rose to more than 100 mg/l, compared to a level less than 10 mg/l for 87% of controls. There are other interesting findings in this study: in fungal infections, CRP levels rose as high as in bacterial infections; very high CRP levels on apparently appropriate antibiotics decreased sharply after draining an abscess or performing a paracentesis for otitis media; some patients had persisting high levels of CRP when they had extramedullary bone infiltration by their leukaemia, etc. . . Other studies have shown similar results. In one study [9], the serum CRP level rose above or by, 100 mg/l in 25 patients with leukaemia who developed 34 episodes of infections. In another study, CRP level was elevated to at least 100 mg/l at the beginning of 32 of 34 episodes of infection, and subsequently rose above 100 mg/l in all 34 [10]. Similarly, CRP levels in the CSF have been shown to help differentiating bacterial meningitis from other CNS diseases [11] or bacterial from viral pneumonia [12].

Serial measurements of CRP levels have also been found to be helpful in diagnosing superimposed infection in SLE [13], in neonates [14] in distinguishing between pyelonephritis and cystitis in children [15], etc. . . Another use in serially measuring CRP levels is in following up patients with rheumatoid arthritis [16] or inflammatory bowel disease [17].

Obviously, there are drawbacks. We mentioned some of them apropos of the first paper referred to [8]: some patients obviously infected (although no septicemic patient in this study) did not mount a CRP response above 100 mg/l; some patients had elevated CRP levels that were not due to infection but to bone infiltration by their disease. Many other disease states can be associated with high CRP values, besides bacterial or fungal infections, although values are usually lower than in infections: for a review see Morley and Kushner [18].

In bone marrow transplantation, there is some controversy about CRP response in graft vs. host disease: in one report published in the literature [19], GVH alone was associated with high CRP values, thereby diminishing the value of this test to distinguish serious infection from another disease process in this setting. By contrast, another study from another London hospital [20], of a greater number of patients, showed significantly higher CRP levels in bone marrow transplant patients with major bacterial infections, with or without acute GVH vs. viral, fungal (contrary to the study in [8]) or acute GVH without bacterial infection. A bizarre exception in this latest study was streptococcal septicemia: the median serum CRP for eight patients with streptococcal septicemia was 14 mg/l with a range of 6–39 mg/l. The same investigators extended their study to the late post-transplant period and showed that chronic graft vs. host disease *per se* did not increase CRP levels [21]. These authors also emphasized the usefulness of serially measuring CRP levels in following-up response to antibacterial therapy in those patients. This was also insisted upon in another similar study [22].

There is also some controversy, alluded to above, about the CRP response in fungal infections. Contrary to the study in [8], one study did not show a consistent elevation in fungal infections [20]. However, in another study [23], where the author tried to distinguish patients with deep-seated fungal infections from patients with tran-

sient fungemia or superficial infections, there was a rise of the CRP above 100 mg/l in 76% of deep-seated fungal infections. In another study, it was suggested that patients who have persistent elevations of the CRP level with blood cultures that remain negative might suffer from an occult form of infection which might well be fungal, since the poor sensitivity of positive blood cultures in disseminated fungal infection is well known [24].

Other participants in the acute phase reaction have been studied intensively and some of them might turn out to be helpful for our purposes. However, none so far has been studied as extensively as the CRP level which is also one of the quickest to rise and one for which a rapid one hour test has been devised.

In summary, despite some uncertainties and its non-specificity we believe that serial measurement of CRP in cancer patients at risk of infection, if interpreted with much caution, in the light of other clinical and biological findings, can be a useful tool and can help in the day-to-day management of those patient's difficult problems. Certainly, it merits further study.

REFERENCES

1. Fahraeus R. *The Suspension Stability of the Blood.* Stockholm, Norstedt and Sön, 1921.
2. Peltola H, Rasanen JA. Quantitative C-reactive protein in relation to erythrocyte sedimentation rate, fever, and duration of antimicrobial therapy in bacteraemic diseases of childhood. *J Infect* 1982, **5,** 257–267.
3. Whicher JT, Dieppe PA. Acute phase proteins. *Clin Immunol Allergy* 1985, **5,** 425–446.
4. Tillet WS, Francis T Jr. Serological reaction in pneumonia with a nonprotein fraction from pneumococcus. *J Exp Med* 1930, **52,** 561.
5. Anderson HC, McCarty M. Determination of C-reactive protein in the blood as a measure of the activity of the disease process in acute rheumatic fever. *Am J Med* 1950, **8,** 445.
6. Gewurz H, Mold C, Siegel J, Fiedel R. C-reactive protein and the acute phase response. *Annu Rev Inter Med* 1982, , 345–372.
7. Kushner I, Broder MI. Serum CRP kinetics in acute myocardial infection (abstract). *Clin Res* 1972, **20,** 794.
8. Timonen T, Koistinen P. C-reactive protein for detecting and follow-up of bacterial and fungal infections in severely neutropenic patients with acute leukaemia. *Eur J Cancer Clin Oncol* 1985, **21,** 557–562.
9. Rose PE, Johnson SA, Meakin M, Mackie PH, Stuart J. Serial study of C-reactive protein during infection in leukaemia. *J Clin Pathol* 1981, **34,** 263–266.
10. Mackie PH, Crockson RA, Stuart J. C-reactive protein for rapid diagnosis of infection in leukaemia. *J Clin Path* 1979, **32,** 1253–1256.
11. Abramson JS, Hampton KD, Babu S, Wasilauskas BL, Marcon MJ. The use of C-reactive protein from cerebrospinal fluid for differentiating meningitis from other central nervous system diseases. *J Infect Dis* 1985, **151,** 854–858.
12. McCarthy PL, Frank AL, Masters SJ, Dolan TF Jr. Value of the C-reactive protein test in the differentiation of bacterial and viral pneumonia. *J Pediatr* 1978, **92,** 453–456.
13. Becler GK, Wamdbirger M, Hughes GRV, Pepys MB. Value of serum C-reactive protein measurement in the investigation of fever in systemic lupus erythematosus. *Ann Rheum Dis* 1980, **39,** 50–52.
14. Sabel KG, Wadsworth C. C–reactive protein (CRP) in early diagnosis of neonatal septicemia. *Acta Paediatr Scand* 1979, **68,** 825–831.
15. Jodal V, Lindberg V, Lincoln K. Level of diagnosis of symptomatic urinary tract infections in childhood. *Acta Paediatr Scand* 1975, **64,** 201.
16. Amos RS, Constable TJ, Crockson RA, Crockson AP, McConkey B. Rheumatoid arthritis: relation of C-reactive protein and erythrocyte sedimentation rates to radiographic changes. *Br Med J* 1977, **1,** 195–197.
17. Buckell NA, Lennard-Jones JE, Hernandez MA, Kohn J, Riches PG, Wadsworth J. Measurement of serum protein during attacks of ulcerative colitis as a guide to patient management. *Gut* 1979, **20,** 22–27.
18. Morley JJ, Kushner I. Serum C-reactive protein levels in disease. *Ann NY Acad Sci* 1982, **359,** 406–417.
19. Rowe IF, Worsley AM, Donnelly P, Catovsky D, Goldman JM, Galton D, Pepys MB. Measurement of serum C-reactive protein concentration after bone marrow transplantation for leukaemia. *J Clin Pathol* 1984, **37,** 263–266.
20. Walker SA, Rogers TR, Riches PG, White S, Hobbs JR. Value of serum C-reactive protein measurement in the management of bone marrow transplant recipients. Part I: early transplant period. *J Clin Pathol* 1984, **37,** 1018–1021.
21. Walker SA, Riches PG, Rogers TR, White S, Hobbs JR. Value of serum C-reactive protein measurement in the management of bone marrow transplant recipients. Part II: late post-transplant period. *J Clin Pathol* 1984, **37,** 1022–1026.
22. Schofield KP, Voulgari F, Gozzard DI, Leyland MJ, Beeching NJ, Stuart J. C-reactive protein concentration as a guide to antibiotic therapy in acute leukaemia. *J Clin Pathol* 1982, **35,** 866–869.

23. Kostiala I. C-reactive protein response induced by fungal infections. *J Infect* 1984, **8,** 212–220.
24. Kostiala AAI, Kostiala I, Valtonen VV, Teerenhovi L. Levels of C-reactive protein in patients with hematologic malignancies. *Scand J Infect Dis* 1985, **17,** 407–410.