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# Serum C reactive protein in infective endocarditis

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SUMMARY C reactive protein (CRP) was measured serially in 29 patients with infective endocarditis. Twenty one patients were initially treated with antimicrobial drugs. In 13, serial measurement of CRP concentrations showed a progressive return to normal (less than 10 mg/l), which correlated with a satisfactory recovery. Of the remainder (eight patients), five had persistently high concentrations of CRP, indicating a failure to respond to antimicrobial treatment alone. Two of these five patients died and three underwent valve replacement. Of 11 patients treated with antibiotics and valve replacement, CRP concentrations returned to normal in nine. Two patients had infective complications and the CRP concentration did not return to normal. A transient rise in CRP concentration during an otherwise uneventful fall to normal was a sign of allergic reaction in two and of intercurrent infection in three more patients. Serial measurements of CRP concentrations in patients with infective endocarditis may be useful to monitor treatment and also to detect other infections and complications.

Infective endocarditis has a mortality of about 30% despite improvements in treatment with antimicrobial agents and valve replacement.[1] Although the infection usually responds to appropriate antibiotics, fever and intercurrent infection can develop and may complicate clinical assessment of the response to treatment. Although the serum bactericidal test is widely used to assess the response, there is little evidence to date that the test is of prognostic value.[2]

C reactive protein (CRP) is an acute phase protein of the serum, concentrations of which can increase rapidly in response to tissue injury, infection, or inflammation in healthy subjects. When the stimulus resolves, such as with effective antimicrobial treatment, the concentration falls rapidly.[3–5] The development of immunochemical assay methods means that serum CRP concentrations can now be measured quickly and accurately.

Serial CRP measurements have proved useful in monitoring the response to antimicrobial treatment in neonatal septicaemia,[6] infections of the central nervous system,[7,8] infections in leukaemia,[9] and peritonitis in patients receiving continuous peritoneal dialysis.[10]

We recently examined the clinical value of determining serial CRP concentrations in a prospective study of patients with infective endocarditis. Serial CRP measurements provided a useful and rapid index of the response to treatment in endocarditis and also indicated the duration of treatment.

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## Patients and methods

Twenty nine patients with infective endocarditis were studied between November 1983 and September 1986; 17 were male and 12 female, with a mean age of 43·6 years (range 14–71). Where possible, a blood sample was taken as soon as the diagnosis of endocarditis was confirmed in the laboratory. Thereafter, CRP concentrations were measured regularly every one to two days. CRP was estimated by fluorescence polarimetry (Abbott Laboratories, Diagnostic Division). The intra-assay coefficient of variation was less than 5% and a CRP concentration of 10 mg/l or less was regarded as normal.[11]

Tests for serum bactericidal titre (SBT) were performed on trough and peak serum samples for all patients receiving antibacterial treatment. Serial doubling dilutions of serum were prepared in Isosensitest broth (Oxoid Ltd) containing 50% (v/v) bovine serum (Oxoid Ltd). A 99·9% or greater kill of the initial $10^5$ colony forming unit inoculum of organisms was taken as the bactericidal end point.

Available clinical details about patients before inclusion in the study included the infecting organism, fever (> 37·5°C), the presence or absence of a prosthetic valve, and antimicrobial treatment.

## Results

Serum concentrations of CRP were measured in 29 patients with infective endocarditis (table 1). Twelve patients had prosthetic valve endocarditis, eight of whom presented within two months of surgery (early endocarditis) and four after this period (late endocarditis). Ten patients, including five drug addicts, had endocarditis on previously normal valves; seven patients had a congenital cardiac defect. The overall mortality was 28%.

The trough SBT during antibacterial treatment showed bactericidal activity of a dilution of 1 in 16 or greater in all 27 patients with bacterial endocarditis.

All patients showed a CRP response. Fig 1 shows the peak concentration in 25 patients at the time of diagnosis. Four patients, all of whom had been referred from other hospitals, had been treated with antimicrobial drugs for several days before CRP was measured. The peak of the CRP response was not related to the duration of symptoms. Although the numbers were small, there was some evidence that different species of micro-organism gave rise to different peaks of CRP (fig 1), but the differences were not significant.

Twenty one patients had been initially treated with antimicrobial agents alone (table 2). In 13 patients this was successful in that they did not require surgical intervention and their serum CRP concentrations started to fall within 24 hours of starting treatment. The mean time that the CRP concentration took to return to normal was 13 days (range six to 30). One patient with early prosthetic valve endocarditis died from mechanical problems with the valve soon after the start of treatment and when the CRP concentrations had started to decline. In two patients treatment was stopped after only two weeks when CRP was still raised (44 mg/l and 73 mg/l, respectively), and both patients relapsed. Despite successful treatment one patient, a drug addict with *Staphylococcus aureus* valvular infection, died from cardiac tamponade.

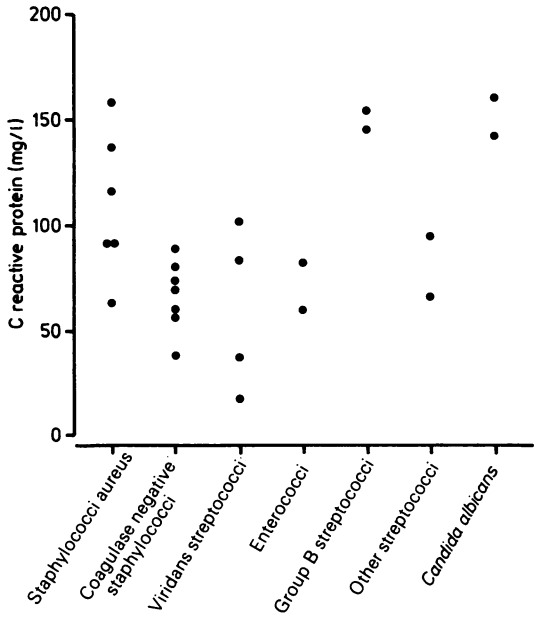


Fig 1 *Peak serum (CRP) concentrations in 25 patients with infective endocarditis.*

Five patients did not respond to antimicrobial agents alone and required valve replacement. Lack of response was shown by continuing fever and CRP concentrations which remained increased. Two of these five patients had group B streptococcus endocarditis, two had *Candida albicans* endocarditis, and the remaining one had *S aureus* endocarditis. The two patients with yeast endocarditis were not well enough to have valve replacement and both died. The other three patients had successful valve replacement.

Altogether, 11 of the 29 patients underwent valve replacement during treatment (table 2). All showed a characteristic rise of CRP two to three days after operation, but cardiac surgery can cause CRP to rise;

Table 1 *Details of 29 patients with infective endocarditis*

| *Causative organism* | *Age (mean and range)* | *Sex* | | *Valve type* | | *Clinical outcome (survived/total)* |
|---|---|---|---|---|---|---|
| | | *M* | *F* | *Native* | *Prosthetic* | |
| *Staphylococcus aureus* | 30·1 (17–64) | 6 | 2 | 8 | 0 | 7/8 |
| Coagulase negative staphylococci | 56·7 (46–71) | 4 | 5 | 1 | 8 | 6/9 |
| Viridans streptococci | 38·2 (14–59) | 1 | 3 | 4 | 0 | 4/4 |
| Enterococci | 59·0 (59–59) | 2 | 0 | 1 | 1 | 1/2 |
| Group B streptococci | 34·0 (28–40) | 2 | 0 | 1 | 1 | 1/2 |
| Other streptococci (*S pyogenes S milleri*) | 22·0 (18–26) | 1 | 1 | 2 | 0 | 2/2 |
| *Candida albicans* | 63·5 (63–64) | 1 | 1 | 0 | 2 | 0/2 |
| All episodes | 43·5 (14–71) | 17 | 12 | 17 | 12 | 21/29 |

Table 2 *Antibiotic treatment and management of 29 patients with infective endocardits*

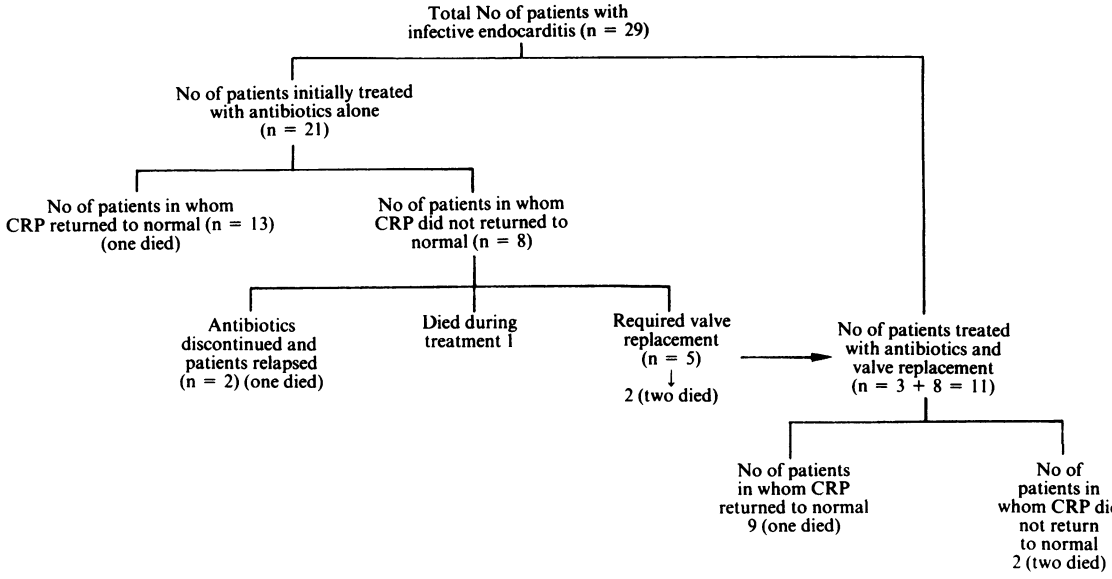


fig 2 shows valves observed in a control group of patients who had cardiac surgery with an uneventful postoperative course. The mean time after surgery when the serum CRP concentration returned to normal in nine of the 11 patients with endocarditis was 17 days (range eight to 24). Unfortunately, one patient died from a spontaneous splenic rupture. In two patients, CRP did not return to normal: one patient became superinfected with *C albicans* and died during an operation for valve re-replacement and the other died from a cerebral mycotic aneurysm (fig 3).

Three patients developed intercurrent infections during treatment for infective endocarditis: these included a chest infection with *Haemophilus influenzae*, vaginitis due to *C albicans* (fig 4), and a perineal abscess from which both *Bacteroides fragilis* and *Enterobacter cloacae* were cultured. All three infective episodes were accompanied by raised serum CRP concentrations which later fell when appropriate treatment was started. In general, raised CRP concentrations were associated with fever, but this was not observed with these three intercurrent infections.

Allergic reactions during treatment with high dose benzyl penicillin were seen in two patients. Both became feverish and a coincidental rise in CRP concentration was noted. When the penicillin was stopped CRP concentrations fell.

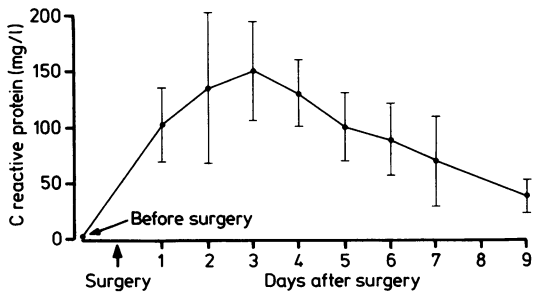


Fig 2 *Serum CRP concentration in normal subjects undergoing cardiac surgery.*

## Discussion

This study reports the results of serial CRP measurements in 29 patients with infective endocarditis. In 22 the CRP concentrations progressively returned to normal and this correlated with a satisfactory response to treatment. In this group a transient increase in CRP concentrations during the fall to within normal limits was a sign of allergic drug reaction in two patients and of intercurrent infection in three more. In the group of 21 patients initially treated with antimicrobial agents alone persistent high concentrations of CRP in five patients corresponded with a failure to respond to treatment (table 2). Two patients, whose treatment had been discontinued while CRP was still raised, relapsed. This suggests, perhaps, that CRP determining concentration may also be of value in decisions on the duration of treatment in infective endocarditis.

A rise in serum CRP is a non-specific acute phase

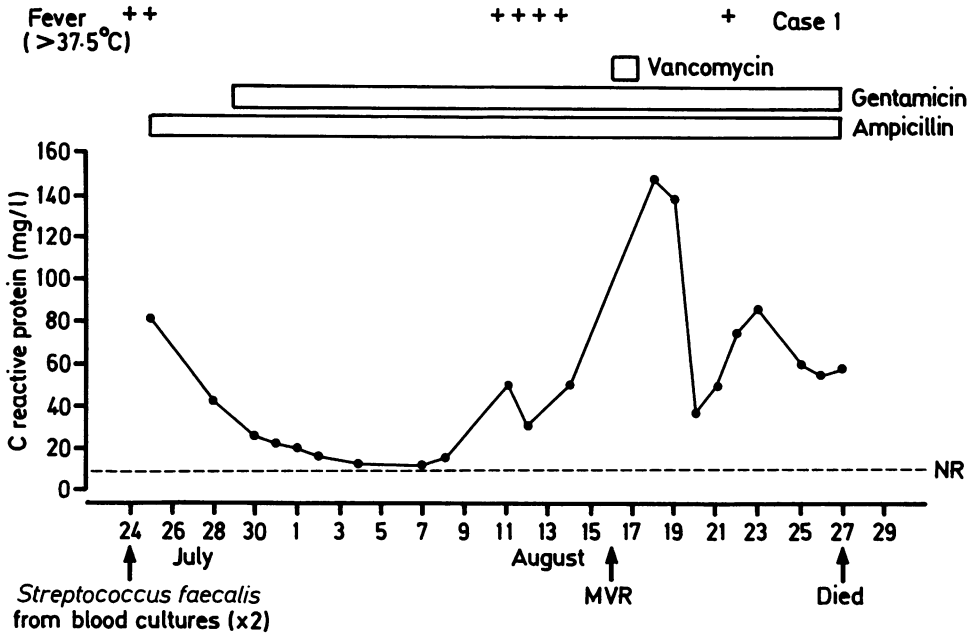


Fig 3 *Serial serum CRP concentrations in 59 year old man with S faecalis endocarditis. NR = normal range (< 10mg/l); MVR = mitral valve replacement.*

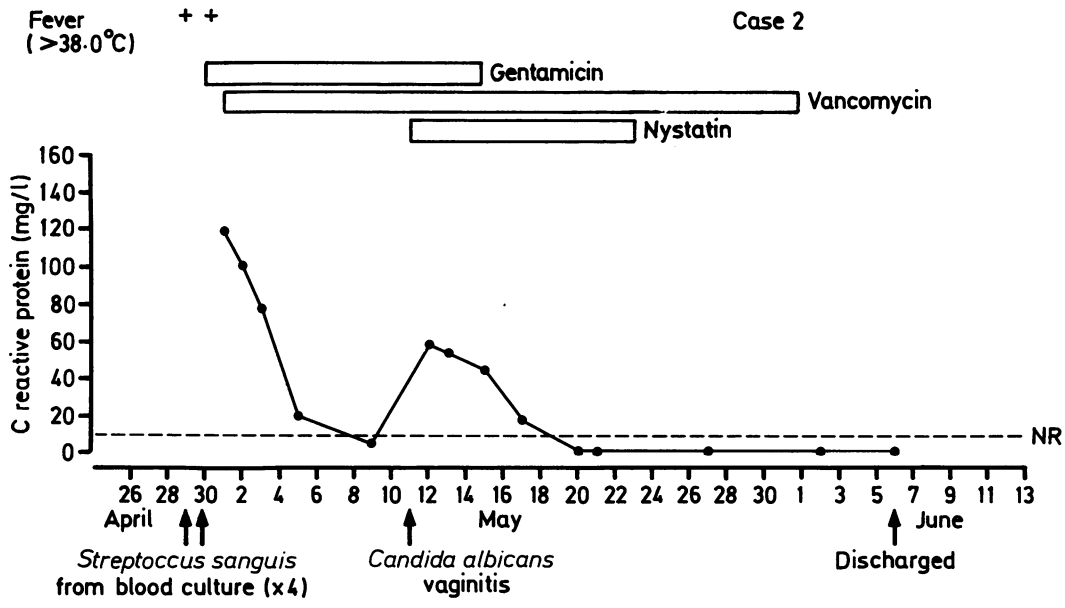


Fig 4 *Serial serum CRP concentrations in 49 year old woman with a ventricular septal defect. NR = normal range (< 10mg/l).*

response and is not diagnostic of infection, let alone endocarditis. Blood culture remains the cornerstone of diagnosis in infective endocarditis. Isolation of the causal organisms to determine appropriate treatment is most important.

Microbiologists generally use in vitro tests of the serum inhibitory titre and the serum bactericidal titre to assess the response to antimicrobial agents in infective endocarditis. Coleman reviewed 17 individual studies which attempted to correlate serum inhibitory titre and serum bactericidal titre with therapeutic outcome.[2] He concluded that there was insufficient evidence for these tests to be used as prognostic indicators in patients with endocarditis. In a multicentre collaborative evaluation Weinstein *et al* showed that serum bactericidal titre can predict bacteriological cure but not bacteriological failure or clinical outcome.[12] This may reflect the influence of other factors on the outcome besides the causal organism and appropriate treatment. Our study suggests that serial measurements of serum CRP concentrations are of more value than estimations of serum bactericidal titre both in prognosis and in predicting continuing infection in infective endocarditis.

The magnitude of the CRP response has been shown to correlate well with the severity of tissue damage in several infectious, inflammatory, and neoplastic disorders.[5] In our study there was some evidence that the magnitude of the CRP response correlated with the pathogenicity of the infecting organisms and the tissue damage of the infected valve.

Rapid and precise assays for CRP are now commercially available. This study shows that serial measurements of CRP can be used both to monitor the response to antimicrobial treatment in infective endocarditis and also to detect other infections and complications. As with many in vitro tests, however, CRP values must not be interpreted without knowing the clinical picture and other laboratory results.

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