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C-Reactive Protein in Patients with Bacteremia

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Quantitative measurement of C-reactive protein (CRP) in serum has been proposed as a sensitive and, for some populations, a specific indicator of infection. To determine whether early measurement of CRP in serum could differentiate patients with bacteremia from a control group of patients whose blood cultures yielded contaminants, we measured CRP concentrations quantitatively by rate nephelometry in serum samples that had been obtained from patients on the same day as blood samples that yielded bacteria or fungi. Of the 36 episodes of bacteremia, 3 (8.5%) occurred in patients with normal concentrations of CRP in serum and 2 (5.5%) in patients with minimally elevated levels. Of the 21 episodes associated with contaminated blood cultures, only 2 (9.5%) occurred in patients with normal CRP levels. Of the patients with marked elevations of CRP (>10 mg/dl), 18 (86%) had infection, although not all of these patients had bacteremia. We conclude that a normal concentration of CRP in serum does not eliminate the possibility of bacteremia. Moderate elevations (1 to 10 mg/dl) of CRP levels are common in both patients with contaminated blood cultures and in those with bacteremia. If the CRP concentration in serum is greater than 10 mg/dl and if other causes of marked elevations of CRP levels are eliminated, CRP concentration in serum may be a relatively specific indicator of infection. However, elevations of CRP concentrations are neither completely sensitive nor specific for detecting infection in patients with bacteremia.

Early diagnosis and treatment of infection is critical in the care of normal and immunodeficient patients. Excluding infection from the differential diagnosis avoids the use of potentially harmful antibiotics and, just as importantly, clarifies the clinical situation. Physicians are always on the alert for a method that promises to be either sensitive or specific for the early detection of infection. In the past several years, a number of investigators have concluded that measurement of the level of C-reactive protein (CRP) is a sensitive and, in certain clinical settings, specific method for the early detection of infection (1–3, 5, 7–9, 11–13, 15, 16, 18). CRP is synthesized by hepatocytes and is normally found in plasma (4). Although its precise biological function is unknown, CRP is classified as an acute-phase reactant; the concentration of CRP may rise 10^3-fold in response to tissue injury or infection (4, 14). The concentration of CRP in serum can now be quickly, reliably, and easily measured in the clinical laboratory by nephelometric and enzymatic immunoassays (6, 19). The proper application for measurement of CRP concentration in clinical medicine, however, has yet to be fully defined.

We determined CRP concentrations in the sera of patients with positive blood cultures in a general hospital to determine whether this measurement is uniformly sensitive for the early detection of bacteremia in a group of patients who are unequivocally infected with bacteria and whether a CRP concentration in serum could be defined as specific for bacteremic infection in this group of patients.

MATERIALS AND METHODS

The patients were those whose blood cultures yielded either bacterial or fungal isolates during a period of 10 consecutive weeks at Stanford Hospital. There were 126 such patients. Serum samples drawn on the same day as the blood samples were obtained from the clinical chemistry laboratory. The serum samples were obtained from 58 of the 126 patients with positive blood cultures. Two patients each had two discrete clinical episodes that produced positive blood cultures, and one patient had three such episodes. Each episode was considered independently, and therefore a total of 62 episodes (49%) were included in this study. Serum samples were stored at −20°C before determination of the CRP concentration.

The hospital charts of all the patients were reviewed without prior knowledge of the CRP levels in serum. Organisms recovered from the blood cultures were classified as pathogens, nonpathogens (contaminants), or indeterminate. For classification of a gram-positive bacterial isolate as a pathogen, an appropriate clinical setting was necessary. The appropriate clinical setting required either multiple positive blood cultures (for the majority of patients) or a single positive blood culture with a demonstrable source of bacteremia. Organisms were classified as nonpathogens if they were of recognized low pathogenic potential (e.g., coagulase-negative staphylococci in an immunocompetent patient) without a clinically evident source, and if the episode that prompted the blood culture to be taken resolved without measures directed specifically against the organism recovered from the blood culture.

CRP levels were determined by rate nephelometry with the Beckman immunochemistry analyzer and CRP kit (Beckman Instruments, Inc., Fullerton, Calif.) (6). According to the package insert, the range of CRP levels measured by this instrument is 0.6 to 120 mg/dl; the level of CRP in the sera of normal control patients when this method is used is less than 0.8 mg/dl (6). The manufacturer specifies a coefficient of variation of 1 to 4% for multiple determinations on a single sample. We verified this claim before use.

RESULTS

The 58 patients ranged in age from 13 months to 90 years, with average and median ages of 53 and 60 years, respective-

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ly; 56% of the patients were male. Seven patients had either leukemia or lymphoma, 10 had cancer as a significant underlying disease directly related to their hospitalization, and 1 was the recipient of a heart transplant; 24% of the patients had undergone a surgical procedure within 4 weeks of the positive blood culture.

Of the blood culture isolates, 36 (58%) were classified as pathogens, 21 (34%) were classified as nonpathogens, and 5 (8%) were indeterminate (Fig. 1). All gram-negative bacilli (22 cases) were classified as pathogens. The vast majority of isolates classified as nonpathogens were coagulase-negative staphylococci (20 [95%] of 21). Five patients had isolates that were classified as indeterminate. In four of these five patients it could not be determined whether the organisms were contaminants or whether they were implicated in intravenous catheter-related sepsis in patients with multiple potential causes of fever. In eight cases, patients with blood culture isolates classified as nonpathogens were found to have an infection caused by an organism different from that recovered from the blood, e.g., a febrile patient with a single blood culture yielding coagulase-negative staphylococci but with a urine culture that grew more than 10^5 CFU of gram-negative bacilli per ml.

For each of the patient categories, a wide range of CRP levels was evident. For patients with bacteremia (pathogens), contaminated blood cultures (nonpathogens), and indeterminate isolates, the average CRP concentrations (± standard deviations) were 13.1 ± 10.4, 9.2 ± 9.6, and 4.8 ± 4.9 mg/dl, respectively. Three (8.5%) of 36 patients with bacteremia had CRP levels in the normal range, and two other patients with bacteremia had minimally elevated CRP levels (1.0 and 1.7 mg/dl, respectively); 39% of the patients with bacteremia had levels greater than 10 mg/dl. Eight of the patients with bacteremia had undergone a major surgical procedure within 4 weeks of CRP determination; four of these had CRP levels greater than 10 mg/dl.

The range of CRP levels for patients determined to have contaminated blood cultures was similar to that found in bacteremic patients (Fig. 1). Thus, CRP levels in sera drawn on the same day as the blood cultures did not differ significantly between patients with pathogens and patients with contaminants isolated from blood cultures.

The five bacteremic patients noted above, with CRP levels either in the normal range or minimally elevated, could not be clinically distinguished from bacteremic patients with higher CRP levels. One of these five bacteremic patients, who had a CRP level of 1.7 mg/dl in serum, was admitted to the hospital in a coma due to myocardial infarction. Despite significant recovery, he had intermittent fever. On day 11 after admission (date of CRP determination), four separate blood cultures grew *Staphylococcus aureus*. Purulent pericarditis was subsequently discovered during surgery. Two of the patients with gram-negative bacteremia and normal CRP levels in serum were ill for at least 2 and 7 days, respectively, before the positive blood cultures were drawn. Another patient with a normal CRP level in serum was an 82-year-old man who was admitted to the hospital with a fever of 39°C. *Streptococcus pyogenes* grew on two separate blood cultures, and the patient responded to appropriate antibiotic therapy. It was not clear from review of his hospital chart how long he was ill before admission. The last of these five patients, who had a CRP level of 1.0 mg/dl in serum, was in the midst of a 4-month hospitalization to determine the etiology of more than 30 episodes of gram-negative bacteremia presumed to be of either biliary or renal origin.

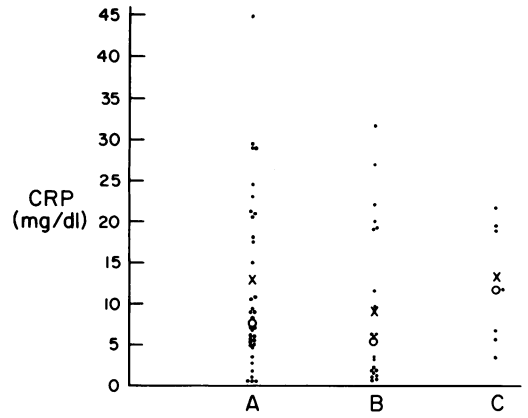

FIG. 1. CRP levels in sera of patients with bacteremia (A), contaminated blood cultures (B), or contaminated blood cultures but with demonstrable infection (C). The patients in group C are included in group B. ○, Mean CRP level; ×, median CRP level.

Some investigators have considered CRP levels greater than 10 mg/dl in serum to be markedly elevated and perhaps to denote a special group of patients (5, 10, 15, 18). In this study, 14 (67%) of 21 patients with CRP levels greater than 10 mg/dl were bacteremic. Of the seven nonbacteremic patients, we considered four to have a bacterial infection even though the blood culture isolate was considered to be a contaminant. Thus, 18 (86%) of the 21 patients with CRP levels greater than 10 mg/dl were infected, with or without bacteremia. Two of the three patients who had CRP levels greater than 10 mg/dl and had neither bacteremia nor a concurrent infection had undergone surgery 2 and 3 days earlier, respectively. The last patient had chronic rheumatoid arthritis and was admitted to the hospital with progressive lung infiltrates that caused her death. At autopsy, no definite etiology of the lung infiltrates was determined.

Of the 11 nonbacteremic patients with CRP levels between 1 and 10 mg/dl, three had bacterial infections even though the blood culture isolate was a contaminant, and another, whose condition was very complicated, had undergone aortic valve replacement within 4 weeks of the CRP determination.

DISCUSSION

With the advent of rapid methods for measurement of CRP concentrations, a number of investigations have evaluated the correlation of either single or serial levels of CRP in serum with the presence or absence of infection in diverse clinical settings. Several studies have reported that methods of measuring CRP levels in serum are very sensitive for the detection of infection or bacteremia in infants (16) and in patients with leukemia (11, 12, 15, 18), systemic lupus erythematosus (8), pulmonary infiltrates (9), or pelvic inflammatory disease (7). Rare instances have been reported in which the CRP level in serum was normal in a patient with either proven or strongly suspected bacterial infection (9, 16). Some investigators chose to monitor serial CRP levels in serum to detect the presence of infection, usually because a significant proportion of the patients in the study group had elevated levels of CRP in their sera when uninfected (2, 3, 5, 8, 11, 12, 15, 18). In these studies, very high CRP levels in serum were often found to correlate with the presence of infection (2, 11, 12, 15).

The fact that elevated levels of CRP have been found in the sera of patients with no evidence of bacterial infection

makes interpretation of CRP determinations difficult with regard to the etiology of the rise. Common viral infections, such as those due to influenza virus, rubella virus, cytomegalovirus, herpes simplex virus, and enterovirus commonly cause moderate elevations of CRP levels in serum and occasionally cause elevations to levels greater than 10 mg/dl (17). Morley and Kushner, in a large study at Cleveland Metropolitan Hospital (10), found a wide range of disease processes associated with CRP levels between 1 and 10 mg/dl in serum; these included deep venous thrombosis, cutaneous vasculitis, pericarditis, chronic infection such as tuberculosis, collagen vascular diseases, malignancies, pancreatitis, bronchitis, alcoholic hepatitis, and some cardiovascular disorders. Recent surgery is also a cause of elevated CRP levels in serum (5).

Many of these studies were plagued by lack of appropriate definitions of patient groups and infections; lack of information about the time of CRP determination with respect to the clinical consideration of infection has made it difficult to interpret results and thus to evaluate the clinical usefulness of CRP measurement. Furthermore, even if these problems were not present, the conclusion of many of these studies, i.e., that CRP is relatively sensitive and specific for the detection of infection, was based upon either the uniformly low CRP levels found in control groups and the uniform likelihood of infection in patients with elevated CRP levels, or the use of the patient as his or her own control and the measurement of serial CRP levels. Unfortunately, a physician is rarely able to compare the CRP levels in the serum of his or her patient with the appropriate control value in the initial assessment of a patient for the presence of infection, because the CRP levels in appropriate control groups are frequently not available.

Our data show that, for patients in our hospital, elevated levels of CRP in serum did not differ significantly among patients with bacteremia, patients infected but without bacteremia, and patients who were apparently ill enough for infection to be considered and blood cultures taken, but in whom no infection could be found. Furthermore, some patients with bacteremia had levels of CRP in the normal range, and therefore little reliance can be placed on a normal level of CRP as an indication that bacteremia is absent in an ill patient. However, 18 (85%) of 21 patients with marked elevations (greater than 10 mg/dl) of CRP levels were infected; the three uninfected patients with marked CRP elevations were either severely ill or had recently undergone surgery. Thus, CRP levels greater than 10 mg/dl may reliably indicate infection in hospitalized patients. Other studies have also reported that very high levels of CRP suggest the presence of infection (2, 10–12, 15). Recent surgery or significant trauma should probably be excluded as causes of marked CRP elevation.

Because of the discrepancies in the results from different laboratories and conflicting conclusions among various workers about the diagnostic utility of CRP measurements, further carefully constructed and controlled studies are necessary. Measurement of CRP levels is not likely to be a completely reliable screening test for infection, since a significant minority of patients do not respond to infection by an elevation in their CRP levels. Marked elevations of CRP concentrations to levels greater than 10 mg/dl may be a strong clue to the presence of infection, but the entire clinical situation must be assessed for other factors that may cause a rise in CRP levels independent of infection. Serial or even single determinations of CRP levels in serum are most likely to be useful for detection of infection in patients for whom CRP control values are available from appropriately defined study control groups.

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