C-Reactive Protein (CRP)

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A Test for Assessing Infection and Inflammation

- C-reactive protein (CRP) is an acute phase protein produced in response to inflammation, infection, and tissue injury.[1]
- CRP is used to assess the course of bacterial infections and chronic inflammation, and to evaluate response to therapy.[2, 3]
- High Serum CRP levels are strongly linked to low serum albumin levels among dialysis patients, independent of nutritional status.[4, 5]
- High Serum CRP levels correlate with erythropoietin (EPO) resistance and altered iron availability in hemodialysis patients.[6, 14]
- Mildly elevated CRP levels may indicate cardiovascular disease.[16]

CRP and the Acute Phase Response

The acute phase response is a nonspecific early response that begins when injury or invading pathogens stimulate the release of cytokines and other factors (Figure 1). In response to injury, local inflammatory cells secrete a number of cytokines into the bloodstream. This mobilizes the body's immune reaction (including the liver responding) by producing a large number of acute-phase reactants. Each of these acute phase reactants plays an important role in the body's reaction to infection.

As shown in Figure 1, the acute phase response is triggered by the cytokines interleukin-6 (IL-6), interleukin-1 (IL-1), and tissue necrosis factor (TNF) released by macrophages and other cells at the injury site. These factors induce fever and stimulate the liver to produce CRP and other acute phase proteins. The acute phase response mobilizes other immune and inflammatory responses as immune cells are recruited to the area and blood supply to the site increases. During an acute phase response, albumin and prealbumin production by the liver drops, in part to allow synthesis of acute phase proteins.[1]

Serum CRP levels increase dramatically during infection or injury.[1] CRP levels can rise during bacterial and viral infections, rheumatic and malignant disease, myocardial infarction, tuberculosis, tissue necrosis, and surgery.[2, 3] Levels usually peak 2 to 3 days after an acute stimulus, and fall over 1 to 2 weeks after infection or inflammation subsides. CRP is thus an early marker for infection, inflammation, and tissue injury. CRP tests have been used widely to assist in the detection and management of chronic inflammatory diseases,[3] infections and surgical complications,[2, 3] and to assess risk factors for cardiovascular disease.[7, 17]

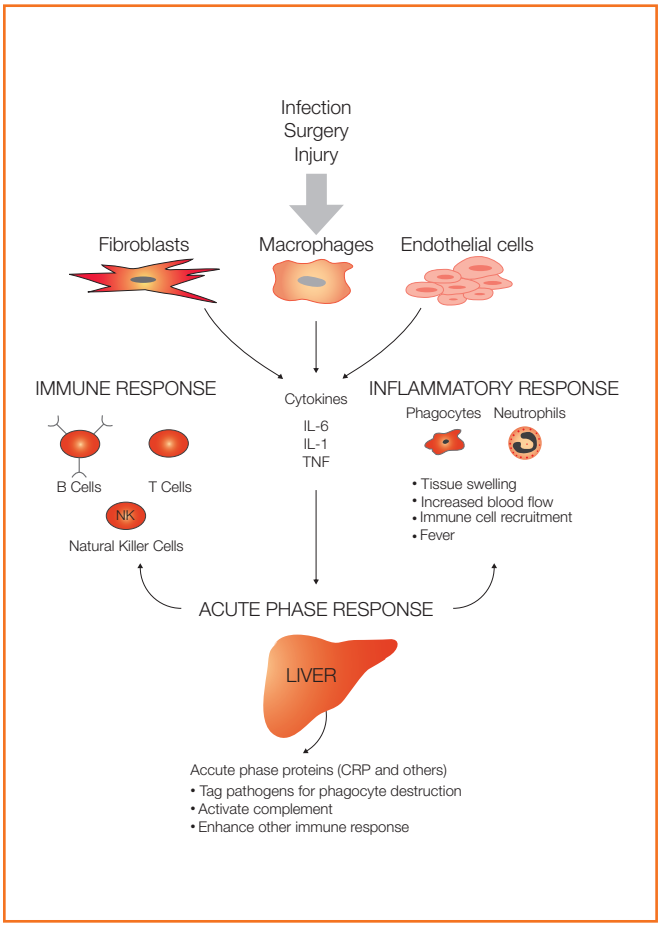

Figure 1

Chronic inflammation is common among patients with chronic renal failure. CRP levels aid in detecting occult infections and chronic inflammation.

Clinical Applications

CRP tests may help clinicians:

- Elucidate decreased serum albumin and prealbumin levels in patients, especially when nutritional status is normal
- Clarify resistance to EPO therapy[6]
- Assess the course of acute bacterial infections and evaluate response to treatment[2, 3]
- Detect occult infections or chronic inflammation[3]
- Help detect infections or other causes of chronic inflammation
  - Rheumatic fever and rheumatoid arthritis[11]
  - Systematic lupus erythematosus[3]
  - Myocardial infarction[11]
  - Malignancy
  - Coronary Artery Disease[16]

Relevance in Patients with Kidney Disease

CRP as a predictor of albumin levels due to inflammation
Inflammation is an important predictor of low serum albumin levels among dialysis patients, independent of nutritional status.[4, 5] Low albumin is often indicative of malnutrition, but chronic inflammation appears to be the culprit in at least half of patients with such levels.[4] This may explain why nutritional therapy does not increase serum albumin in some patients, suggesting underlying inflammation. High CRP levels correlate with increased mortality,[8] regardless of nutritional status, suggesting an independent role for chronic inflammation.[4] CRP tests may help clinicians manage patients with low albumin, especially in cases of adequate nutrition.

CRP as a marker for inflammation and infection
Inflammation is common among patients with chronic renal failure. These patients have significantly higher CRP levels than the general population.[4, 5, 9] While the cause of chronic inflammation in this population is unclear, low-grade infections, uremia, vascular access surgery, dialysis membrane bioincompatibility, and bacterial contaminants in dialysate may play a role.[9] CRP testing has been used to evaluate the course of acute infections and postsurgical complications, and to assess response to antimicrobial therapy.[2, 3, 10]

CRP levels rise more rapidly during inflammation and infection, and return to normal more quickly and consistently than other serum markers (e.g., erythrocyte sedimentation rates).[2, 11] Serial CRP measurements have been used to assess peritonitis,[10] abdominal sepsis,[10] and endocarditis,[2] and to track response to treatment. In some cases, CRP is useful for detecting occult infections, even before clinical signs of relapse occur, allowing earlier and more effective treatment.[2, 10] CRP levels also aid in detecting occult infections and chronic inflammation, and provide early warning of complications after surgery.[2, 3]

CRP as a predictor of erythropoietin resistance
Inflammation is associated with EPO resistance and altered iron availability in hemodialysis patients.[6, 12] Patients with high CRP levels require higher doses, even with adequate intravenous iron.[6, 12] Chronic inflammation reduces iron availability (by causing iron to be sequestered in ferritin), suggesting that EPO resistance may result from a functional iron deficiency.[6, 12] Cytokines produced during inflammation also may inhibit endogenous EPO production.[6] CRP tests may be useful for evaluating and managing EPO resistance, particularly in patients with high ferritin levels but low total saturated iron values.

CRP as an indicator of cardiovascular disease
Recent research has implicated that mildly elevated levels of CRP is as predictive of cardiovascular disease in the general population. Since heart disease is a leading cause of death in the dialysis population, CRP has become of great interest in the treatment of ESRD. Values < 1mg/L are associated with low risk, while values > 3mg/L are associated with high risk, and with values between 1 and 3 as intermediate risk of cardiovascular disease.[15]

Test Methodology
CRP assays have been developed for automated chemistry analyzers. These assays provide excellent sensitivity and reproducibility.

Specimen Collection
Pregnancy, diet, intrauterine devices, oral contraceptives, and anti-inflammatory drugs may affect test results. CRP levels vary widely among patients, but usually are tightly regulated and consistent in individual patients.[3, 13] Additional sampling may be necessary to establish individual treatment ranges or therapy response curves.[13]

Specimen Requirements: 0.5 mL serum (SST GEL tube)
TAT: 1 day
Test Set-up: M-Sat
CPT Code: 86140

REFERENCES

1. Steel DM and Whitehead AS. The Acute Phase Response. In: *Humoral Factors*. E Sim (ed) Oxford. IRL Press. 1993; 1-29.
2. Adeeb TM, et al. Serial C-Reactive Protein Measurements in Infective Complications Following Cardiac Operation: Evaluation and Use in Monitoring Response to Therapy. *Ann Thor Surg*. 1982; 34 (2): 166-175.
3. Young B, et al. C-Reactive Protein: A Critical Review. *Pathology*. 1991; 23: 118-124.
4. Kaysen GA, Stevenson Ft, Depner TA. Determinants of Albumin Concentration in Hemodialysis Patients. *AM J. Kid. Dis*. 1997; 29 (5): 658-668.
5. Yeun JY, Kaysen GA. Acute Phase Proteins and Peritoneal Dialysate Albumin Loss are the Main Determinants of Serum Albumin in Peritoneal Dialysis Patients. *Am J. Kid. Dis*. 1997; 30 (6): 923-927.
6. Barany P, et al. High C-Reactive Protein is a Strong Predictor of Resistance to Erythroprotein in Hemodialysis Patients. *Am. J. Kid. Dis*. 1997; 29 (4): 565-568.
7. Ridker PM, et al. Inflammation, Aspirin, and the Risk of Cardiovascular Disease in Apparently Healthy Men. *N Engl J Med*. 1997; 336 (14): 973-979.
8. Bergstrom J, et al. Elevated Serum C-Reactive Protein is a Stronger Predictor of Increased Mortality and Low Serum Albumin in Hemodialysis (HD) Patients. *J Am Soc Nephrol*. 1995; 6: 573 (abstr).
9. Haubitz M, et al. Chronic Induction of C-Reactive Protein by Hemodialysis But Not by Peritoneal Dialysis. *PD Internat*. 1996; 16: 158-162.
10. Schentag JJ, et al. C-Reactive Protein as an indicator of Infection Relapse in Patients with Abdominal Sepsis. *Arch Surg*. 1984; 119: 300-304.
11. Fischbach FT. A Manual of Laboratory and Diagnostic Tests. Fifth Edition. Philadelphia: Lippincott. 1996; 551-552.
12. Rosenlof K, et al. Iron Availability is Transiently Improved by Intravenous Iron Medication in Patients on Chronic Hemodialysis. *Clin Nephrol*. 1995; 43 (4): 249-255.
13. Gambino R. C-Reactive Protein-Undervalued, Underutilized. *Clin Chem*. 1997; 43 (11): 2017-2018.
14. Bradbury BD, et al. Impact of Elevated C-reactive protein levels in Erythropoiesis-Stimulating Agent (ESA) Dose and Responsiveness in Hemodialysis Patients. *Nephrol Dial Transplant*. 2009; (3): 919-925.
15. Pearson TA, et al. Marker of Inflammation and Cardiovascular Disease: Application to Clinical and Health Practice: a Statement for Healthcare Professionals from the Centers for Disease Control and Prevention and the American Heart Association. Circulation 2003; 107: 499-511.
16. Kessler M, et al. Predictors of Cardiovascular Event in Patients with End-Stage Renal Disease: an Analysis From the Fosinopril In Dialysis Study. *Nephrol Dial Transplant (12)*. 2007; 3573-3579.
17. Honda H, et al. Serum Albumin, C-reactive protein, Interleukin 6 and Fetuin A as Predictors of Malnutrition, Cardiovascular Disease, and Mortality in Patients with ESRD. *Am J Kidney Dis*. (1) 2007; 138-48.
18. Koenig W, et al. Increased Concentrations of C-Reative Protein and IL-6 but not IL-18 Are Independently Associated With Incident Coronary Events in Middle-Aged Men and Women. *Art Thromb Vascular Bio*. 2006; 26: 2745-2751.

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