Review Article

Clinical Utility of Acute-phase Reactants in Medicine

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Abstract

Acute-phase response is the sum of the systemic and metabolic changes occurred by release of acute-phase proteins in response to an inflammatory stimulus. The most important ones of these acute-phase reactants are erythrocyte sedimentation rate, C-reactive protein, fibrinogen, procalcitonin and ferritin. The most widely used ones are ESR and CRP while fibrinogen and ferritin are less commonly used. The other acute-phase reactants have limited role in routine clinical use. ESR and C-reactive protein have traditionally been used as markers for inflammation in infectious and noninfectious conditions. These markers have significant role in early diagnosis, in differentiating infectious from noninfectious causes, as a prognostic marker and in antibiotic guidance strategies. Procalcitonin and CRP are most commonly used in this regard. Although CRP is more specific than ESR, yet because of the high cost and limited availability, it has restricted clinical usage in developing countries. Not all acute-phase reactants behave the same way when stimulated; the concentration of some increases while others decrease in plasma.

Keywords: Acute-phase reactants, Erythrocyte sedimentation rate, C-reactive protein, Fibrinogen, Ferritin, Procalcitonin.

Introduction

Infectious as well as noninfectious conditions are a major cause of morbidity and mortality worldwide. There has been increased use of acute-phase reactants (APRs) in the management and prognosis of these conditions. Acute-phase reactants are serum proteins whose concentrations either increase (positive acute-phase proteins) or decrease (negative acute-phase proteins) with inflammation, tissue injury, tissue infarction, burns, surgery, advanced cancer, various immunologically or crystal-induced inflammatory conditions. This response is called as acute-phase reaction (also called as acute-phase response). These reactants rise under the influence of certain stimulators (cytokines) like interleukin 6 (IL-6), tumor necrosis factor α (TNF-α), IL-1, transforming growth factor β and IL-8. These are released by a variety of cells involved in inflammatory process but most importantly monocytes and macrophages. The positive acute-phase proteins are C-reactive protein (CRP), fibrinogen, serum ferritin, procalcitonin (PCT), serum amyloid protein A (SAA), ceruloplasmin, complement components C3 and C4, α-1 acid glycoprotein, α-1 anti-chymotrypsin, and α-1 anti-trypsin (Table 1). The negative acute-phase proteins are serum albumin, serum transferrin, transthyretin and retinol. The erythrocyte sedimentation rate is a non-protein APR that changes in response to serum fibrinogen levels and viscosity. Therefore, ESR is an "indirect" APR. Procalcitonin as a marker in bacterial infections has gained a lot of focus in the last decade. There is increasing evidence to support its usefulness in differentiating viral from non-viral infections.

Table 1.Important Acute-Phase Reactants (adapted from NEJM 1999)1

Positive acute-phase proteins	CRP, fibrinogen, serum amyloid A, ferritin, C3, C4, C9, C1 inhibitor, plasminogen, plasminogen-activator inhibitor 1, tissue plasminogen activator, α-1 protease inhibitor, α-1 anti-chymotrypsin, ceruloplasmin, haptoglobin, hemopexin, secretory type II phospholipase A2, mannose binding lectin, procalcitonin
Negative acute-phase proteins	Albumin, transferrin, transthyretin, retinol

Erythrocyte Sedimentation Rate (ESR)

It is the rate at which red cells settle down on their own weight when an anticoagulated blood is suspended in a straight column for one hour. It is conventionally read as mm of descent in first hour. It can be estimated by Wintrobe's and Westergren's method but the latter has been accepted worldwide as a standard method for measuring ESR.[2] There are three phases of erythrocyte sedimentation, namely, aggregation or rouleaux formation, falling of red cells through the plasma, and final period of packing. The aggregation or rouleaux formation of red cells is enhanced by fibrinogen, gammaglobulins and other plasma proteins. All conditions which increase fibrinogen levels, like pregnancy, collagen vascular diseases, malignancies, heart diseases, also raise the ESR. It is an indirect estimation of rise of acute-phase proteins. It is influenced by a variety of factors such as shape, size and number of red cells, plasma viscosity, and temperature of surrounding and presence of immunoglobulins. These disadvantages together with presence of a better alternative in the form of CRP have led to a decreased use of ESR in clinical practice. However, it is still useful in certain places where CRP is not available or is expensive.

The normal ESR increases with age. The normal range in adult males and females is 0-15 and 0-20 mm 1st hour, respectively. Its rise and fall is slower, as compared to CRP. ESR rises within 24-48 hours of the onset of inflammation and falls back slowly with resolution. Mild to moderate increase in ESR is a non-specific marker of inflammation, but extreme elevation (defined as >100 mm 1^{st} hour) is seen in only a few conditions, namely temporal arteritis, polymyalgia rheumatica and multiple myeloma. The main use of ESR is in follow-up of patient response to therapy, like in rheumatoid arthritis and tuberculosis. Hence ESR is not a disease-specific marker; therefore, it should be correlated with CRP or other markers when clinical suspicion of infection or inflammation is high.

C-reactive Protein (CRP)

This protein was first found in a case of Pneumococcal pneumonia patient. It was seen to be bound to the polysaccharide "capsule" antigen; hence the name.[3] It is synthesized in the liver under the stimulation of IL-6. It rises thousand-fold upon an acute inflammatory stimulus. The normal values of CRP is <1 mg/dL; level of between 1 and10 mg/dL is mild elevation, whereas level >10 mg/dL is considered very high. Very high values are found in acute bacterial infection, major trauma and systemic vasculitis. However, it is a non-specific test even when it is in the range of very high level. Its main use is not for diagnosis but for the follow-up in response to treatment, of which classical example is rheumatoid arthritis. It is also prudent to note here that some laboratories give the concentration of CRP in mg/dL while others give in mg/L. Not all acute-phase reactants behave the same way when stimulated. For example, in SLE, which is a systemic inflammatory disorder, the ESR may rise but CRP may be normal. This is the only condition where ESR outperforms CRP. However, in the presence of bacterial infection, serositis and synovitis in SLE, the CRP level also rises. The rise of CRP as compared to ESR is faster and more reliable in inflammatory conditions. This along with the automated technology used in estimation of CRP as compared to manual method for ESR, has led to higher use of CRP among the clinicians. The high-sensitive CRP (hsCRP) rises acutely in myocardial infarction and also correlates with infarct size. The only difference between high-sensitivity CRP (hsCRP) and standard CRP is that hsCRP assay is designed to measure very low levels of CRP. It begins to rise after 12-24 hours and peaks within 2-3 days of inflammatory stimulus. Extremely high CRP elevation of more than 500 mg/L is mainly associated with severe bacterial infections. Low levels of elevated CRP, with values between 2 mg/L and 10 mg/L, may be seen with "metabolic inflammatory" states such as smoking, uremia, cardiac ischemia, and other low-level noninfectious inflammatory conditions. That is why clinical correlation is needed with all these markers.

Fibrinogen

An important acute-phase reactant, after ESR and CRP, is fibrinogen. It is, like CRP, also synthesized in liver; therefore the level of both decreases in liver damage. Fibrinogen is also an important component of coagulation. It rises in inflammatory diseases as well as

in malignancies like kidney, stomach and breast. Its normal range in serum is 200-400 mg/dL. When measured as an acute-phase reactant, it rises later than CRP, but it has a long half-life; therefore, its level does not decrease even after the inflammatory stimulus has been settled. These disadvantages make it less useful as an acute-phase reactant as compared to CRP and ESR. Fibrinogen along with haptoglobin, which is another acute-phase reactant, is helpful in various stages of wound healing. Fibrinogen as stated above is an important determining factor in ESR. Therefore, all conditions that lead to high fibrinogen levels also raise ESR and vice-versa. Fibrinogen is also used as a disease activity marker in Familial Mediterranean fever. Low levels of fibrinogen may be seen in liver diseases, prostate and lung cancers, bone lesions, malnutrition and some bleeding disorders. Afibrinogenemia, hypofibrinogenemia and dysfibrinogenemia are congenital diseases which are characterized with the lack or low levels of fibrinogen.

Procalcitonin (PCT)

Procalcitonin is the peptide prehormone of calcitonin that under normal conditions is secreted by C-cells of the thyroid gland in response to hypercalcemia or as a result of medullary carcinoma of thyroid. In systemic inflammatory conditions and, in particular, bacterial infections, PCT secretion is stimulated by various cytokines such as IL-1, IL-6, and tumor necrosis factor-alpha. In viral infections, the PCT production is downgraded, likely from increased interferon gamma production.4 Detectable within 3-4 hours and peaks within 6-24 hours, which is earlier than both CRP and ESR. Elevated levels are not seen in other noninfectious inflammatory conditions such as polymyalgia, inflammatory bowel disease, polyarteritis nodosa, systemic lupus erythematosus, gout, and temporal arteritis. It has also been reported to be high in Addisonian crisis, malaria and severe fungal infections, and medullary carcinoma of thyroid. It is more sensitive and specific than CRP for distinguishing bacterial from noninfectious causes of inflammation. Serum and CSF PCT level can be more useful in the diagnosis of bacterial meningitis and in distinguishing bacterial from viral meningitis.

Ferritin

Ferritin is an intracellular iron-binding protein. Its main role in clinical medicine is for estimation of total iron stores of the body but is also used as an acute-phase reactant. It is frequently ordered for workup of microcytic hypochromic anemia. However it may be high in anemia of chronic disease, giving a false impression of iron overload state, when actually it has risen in response to inflammation. Normal values are different for men and women, specifically 27-328 ng/mL and 9-125 ng/mL, respectively. Low levels are a specific indicator of iron deficiency. As mentioned above, high levels suggest iron overload, infection, inflammation, malignancy and excess alcohol intake. It rises in cases of hepatocyte damage in liver diseases, whereas fibrinogen and CRP levels decrease, as discussed above. It also rises in adult-onset stills disease and is an important diagnostic marker of hemophagocytic lyphohistiocytosis (HLH) syndrome. Other tests may be ordered when confronted with a high ferritin level. High transferrin saturation will complement a high ferritin level in iron overload states while a high ESR and CRP suggests underlying inflammatory diseases.[6]

Serum Amyloid A (SAA)

Just like CRP and fibrinogen, it is also synthesized by liver in response to chemokines such as IL-6, TNF-α, and IL-1. Its level in serum, like CRP, rises to several hundred folds upon stimulation by these chemokines; however, the rise of serum amyloid A (SAA) is far greater than that of CRP.[5] It has been established that it promotes thrombus formation at multiple stages of atherogenesis.[7]

Cytokines

The hyponatremia associated with inflammatory conditions seems to be due to release of arginine vasopressin (AVP) in response to IL-6. This cytokine is also responsible for thrombocytosis seen in inflammatory conditions. In addition to IL-6, the other cytokines like IL-1β, TNF-α, IFN γ, are responsible for cachexia seen in severe inflammatory disorders. Cytokines are also responsible for anemia of chronic disease, anorexia, lethargy and somnolence. Measurement of plasma concentration of cytokines for clinical benefit has been offset by their very short half-life and presence of blocking factors.

Other Positive Acute-Phase Reactants

Haptoglobin is a plasma protein that binds free hemoglobin that is released after intravascular hemolysis. The free hemoglobin is toxic since it has heme iron which is a potent oxidant. Therefore, the main role of haptoglobin is to detoxify the free hemoglobin. Not only haptoglobin but also hemopexin have anti-inflammatory and antioxidant properties and are protective against reactive oxygen species. Alpha-1 chymotrypsin is an inhibitor of proteolytic enzymes and production of superoxide anions. Ceruloplasmin (Cp) is a

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plasma protein that binds copper. One molecule of Cp can bind seven atoms of copper. In fact it accounts for around 95% of intravascular copper.

Secretory type I phospholipase A2 (sPLA2-I) is an enzyme that is secreted by pancreas while the type II is secreted by various other tissues. The main role of phospholipases is to break down the phospholipids from cell membranes leading to release of arachidonic acid and free fatty acids which is essential for making various pro-inflammatory lipid mediators.

Some of the acute-phase reactants are involved in innate immunity, like the mannose-binding proteins and the complement components. Mannose binding lectin (MBL), also known as mannan-binding lectin or mannose binding protein, is a plasma protein of lectin family. There are three ways of activation of complement system: the classical, the alternate and the lectin pathways. MBL is involved in pattern recognition; therefore, identifying self from non-self. It has a main role in the initial process of activation of lectin pathway of complement system, namely by identifying and binding to microorganisms. This it does by recognizing the specific carbohydrate pattern found on cell walls of bacteria, virus, fungi and protozoa. It also opsonizes old or damaged cells, so they can be taken up by macrophages. As an acute-phase reactant, it demonstrates a variable acute-phase response in the clinical setting of sepsis and septic shock.[8]

Many of the classical complement pathway components are acute-phase proteins, and have pro-inflammatory roles in the formation of immunity. Complement activation plays role in chemotaxis, increase of plasma proteins in the inflammation region, opsonization of the infectious agents and damaged cells.

Learning Points

- Acute-phase response is characterized by changes in the concentrations of a large number of proteins in response to tissue damage.
- The most commonly measured components of the acute-phase response are CRP and, indirectly, the ESR. With some exceptions, these markers of inflammation are elevated in the presence of infections, autoimmunity, trauma and malignancy.
- Mild to moderate elevation of ESR is non-specific but marked elevation (>100 mm 1st hour) is associated with diseases like temporal arteritis, multiple myeloma and polymyalgia rheumatica.
- CRP is used as a supportive marker for other acute-phase reactants, not only for diagnosis but also for follow-up in response to treatment.
- Procalcitonin may be used to differentiate bacterial infection from viral diseases.
- Hyperferritinemia should be evaluated for iron overload states from inflammatory conditions on the basis of serum transferrin saturation.
- ESR and CRP are most commonly used markers in resource limited country like India, while others are used in limited or specific conditions.
- While interpreting rise or fall of acute-phase reactants detailed clinical evaluation should always be done.

Conflict of Interest: None

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