C-REACTIVE PROTEIN AS A PREDICTOR OF INFECTIONS

Deepali Danave[1], K. V. Ingole[2]

[1]Associate Professor, Department of Microbiology, Dr. Vaishampayan Memorial Government Medical College, Solapur.
[2]Professor and HOD, Department of Microbiology, Dr. Vaishampayan Memorial Government Medical College, Solapur.

ABSTRACT

BACKGROUND

C-reactive protein (CRP) is a plasma protein of the pentraxin family and an acute phase reactant, which displays high sensitivity as a general inflammation marker. CRP testing has been employed in the detection of a variety of conditions as infections, myocardial infarction, sepsis, necrosis and trauma.

The objective of the study is to investigate the impact of routine CRP ordering on clinical decision-making in hospitalised febrile children and neonates with suspected neonatal sepsis and adult patients with infections.

MATERIALS AND METHODS

During two months period, 153 such clinically diagnosed cases of infections were referred for CRP testing. Blood samples were collected from these patients and sent to the laboratory for detection of CRP. Sera were separated and subjected to latex agglutination test. Testing was carried out as per manufacturer's instructions. Positive or negative status of the samples for CRP was reported. The test kits used were Immun-Star CRP (Latex slide test) by Star Diagnostics Pvt. Ltd. Mumbai, India.

RESULTS

In our study, 24.18% (37 samples) tested positive for CRP out of 153 samples (Table 1). There was no significant difference in the sex-wise distribution of positive samples (Table 2). But the positivity was very high in paediatric age group (86.48%) as compared to adults (13.51%; Table 3). Maximum referrals for CRP testing were obtained from NICU, PICU, Paediatric wards (Table 4).

CONCLUSION

We conclude that routine CRP ordering for diagnostic purposes for infections fails to inform decision-making in the majority of cases and it only leads to inflated hospital bills.

KEYWORDS

C-reactive Protein, Neonatal, Paediatric Infections.

HOW TO CITE THIS ARTICLE: Danave D, Ingole KV. C-reactive protein as a predictor of infections. Journal of Evolution of Research in Medical Microbiology 2017; Vol. 3, Issue 2, July-December 2017; Page: 1-3.

BACKGROUND

C-reactive protein (CRP) is a plasma protein of the pentraxin family and an acute phase reactant, which displays high sensitivity as a general inflammation marker. [1]CRP was discovered in Oswald Avery's laboratory during the course of studies of patients with *Streptococcus pneumoniae* infection.[2] Sera obtained from these patients during the early, acute phase of the illness were found to contain a protein that could precipitate the "C" polysaccharide derived from the pneumococcal cell wall. Forty years later, Volanakis and Kaplan identified the specific ligand for CRP in the pneumococcal C polysaccharide as phosphocholine, part of the teichoic acid of the pneumococcal cell wall.[3] Although phosphocholine was the first defined ligand for CRP, a number of other ligands have since been identified. CRP can activate the classical complement pathway, stimulate phagocytosis, and bind to immunoglobulin receptors (Fc`*g*R). CRP consists of five identical, noncovalently associated 23-kDa protomers arranged symmetrically around a central pore. The term "pentraxins" has been used to describe the family of related proteins with this structure.[4]

Financial or Other, Competing Interest: None.
Submission 23-04-2017, Peer Review 10-08-2017,
Acceptance 16-08-2017, Published 18-12-2017.
Corresponding Author:
Dr. Deepali Danave,
Department of Microbiology,
Dr. Vaishampayan Memorial Government Medical College, Solapur.
E-mail:milliondollarbaby@rediffmail.com

In humans, plasma levels of CRP may rise rapidly and markedly, as much as 1000-fold or more, after an acute inflammatory stimulus, largely reflecting increased synthesis by hepatocytes. CRP induction is part of a larger picture of re-orchestration of liver gene expression during inflammatory states, the *acute phase response*, in which synthesis of many plasma proteins is increased, whereas that of a smaller number, notably albumin, is decreased. At least 40 plasma proteins are defined as acute phase proteins, based on changes in circulating concentration of at least 25% after an inflammatory stimulus. This group includes clotting proteins, complement factors, anti-proteases, and transport proteins. These changes presumably contribute to defensive or adaptive capabilities. [4]

CRP testing has been employed in the detection of a variety of conditions as infections, myocardial infarction, sepsis, necrosis and trauma. The CRP level is widely used to detect bacterial infections in children with fever and in neonates with suspected sepsis.[5] We decided to investigate the impact of routine CRP ordering on clinical decision-making in hospitalised febrile children and neonates with suspected neonatal sepsis and adult patients with infections.

MATERIALS AND METHODS

The study was carried out from June 2011- July 2011 in a tertiary care centre. The subjects chosen were paediatric and adult patients from indoor admissions. These patients were clinically diagnosed with acute infections, sepsis. 153 such clinically diagnosed cases were referred for CRP testing.

Blood samples were collected from these patients and sent to the laboratory for detection of CRP. Sera were separated and subjected to latex agglutination test. Testing was carried out as per manufacturer's instructions. Positive or negative status of the samples for CRP was reported. Since this was a screening test determination of titres was not done. The test kits used were Immun-Star CRP (LATEX SLIDE TEST) by Star Diagnostics Pvt. Ltd. Mumbai, India.

RESULTS

Positive	37 (24.18%)
Negative	116 (75.8%)
Total	**153**
Table 1. Distribution of Total Samples	

Males	18 (48.64%)
Females	19 (51.35%)
Total	**37**
Table 2. Sex-wise Distribution of Positive Samples	

Age Group	**Males**	**Females**	**Total**
Paediatric < 12 years	17	15	32 (86.48 %)
Adult >12 years	1	4	5 (13.51 %)
Total	**18 (48.64 %)**	**19 (51.35 %)**	**37**
Table 3. Age-wise and Sex-wise Distribution of Positive Samples			

Ward	**Males**	**Females**	**Total**
NICU	7	10	17
PICU	4	1	5
Paediatric ward	6	4	10
Adults	1	4	5
	18 (48.64 %)	19 (51.35 %)	37
Table 4. Ward-wise Distribution of Positive Samples			

Acute phase response with high CRP release	
Infection	Bacteria, mycobacteria, viruses, and fungi
Post -infectious allergic complications	Rheumatoid arthritis and erythema nodosum
Inflammatory diseases	Crohn's disease, psoriatic arthritis, systemic vasculitis, and Reiter's disease
Necrosis	Myocardial infarction and acute pancreatitis
Trauma	Surgeries, fractures, and burns
Acute Phase response with low CRP Release	
Systemic lupus erythematosus, scleroderma, ulcerative colitis and dermatomyositis.	
Table 5. C-Reactive Protein in Certain Pathologies[6]	

DISCUSSION

C-reactive protein (CRP) is a phylogenetically highly conserved plasma protein, with homologs in vertebrates and many invertebrates, that participates in the systemic response to inflammation. Its plasma concentration increases during inflammatory states, a characteristic that has long been employed for clinical purposes. CRP is a pattern recognition molecule, binding to specific molecular configurations that are typically exposed during cell death or found on the surfaces of pathogens. Its rapid increase in synthesis within hours after tissue injury or infection suggests that it contributes to host defence and that it is part of the innate immune response.[4]

C-reactive protein (CRP) is an acute-phase reactant that is synthesised by the liver within six hours after the onset of inflammation and tissue necrosis.[7] Its rapid synthesis, short half-life and rapid decline with recovery, together with an association between greater increases and serious bacterial infections, have made the CRP test popular. This test is often requested to help discriminate viral infections from bacterial infections or monitor the response to antibiotics. The CRP level is widely used to detect bacterial infections in children with fever and in neonates with suspected sepsis. However, recent evidence on the utility of the CRP test in patients with various infections suggests that there are great variations in the sensitivity, specificity, and predictive values of this test, which may compromise its diagnostic accuracy. [8-10]

In our study, 24.18% (37 samples) tested positive for CRP (Table 1). There was no significant difference in the sex-wise distribution of positive samples (Table 2). But the percentage of positivity was very high in paediatric age group (86.48%) as compared to adults (13.51%)- Table 3. Maximum referrals for CRP testing were obtained from NICU, PICU, paediatric wards (Table 4). In our setting, CRP is ordered routinely on children presenting with symptoms and/or signs suggestive of acute infection as a baseline test for infections. Similarly, CRP is ordered routinely on all neonates with suspected neonatal sepsis in the neonatal intensive care unit.

Currently, it is well known that CRP levels may rise due to several processes of inflammatory aetiology (Table 5). But the lack of specificity may concern many physicians when assessing CRP in the clinical scenario. In addition, despite its wide use as a diagnostic tool for several acute paediatric infections, CRP testing rarely impacts clinical decision-making. Additionally, these are inexpensive techniques, an important aspect regarding its routine use in clinical practice. Therefore, we conducted this study to determine how often the results of CRP testing impact clinical decision-making regarding paediatric patients requiring hospital admission.

In recent years, a plethora of studies have demonstrated an association between slightly elevated CRP plasma levels, between 3 and 10 mg/mL, and the risk of developing cardiovascular disease, metabolic syndrome, and colon cancer. It is felt that many of these conditions involve a low level of underlying chronic inflammation that could be reflected by these minor increases. Minor increases in CRP levels have also been reported to be associated with a number of medical conditions that do not appear to be inflammation-associated, as well as with several genetic polymorphisms of the CRP and other genes, ethnicity, various dietary patterns, and obesity.[4]

The majority of the ordered CRP tests do not have a solid evidence base to support their use as diagnostic tools for the accurate detection of bacterial infections. Most of the CRP tests ordered during the initial workup of neonatal sepsis and performed to investigate or follow up in children with bacterial infections are non-evidence based. This questionable practice is most likely influenced by the rapidly increasing literature on the utility of CRP levels for different infections in children and neonates.

Overuse of laboratory testing is common in hospital practices and has been attributed to the defensive behaviour of physicians, a lack of experience, uncertainty, "routine"

practice, a lack of awareness of the associated costs, the use of protocols and guidelines, and other factors.[12] Inappropriate testing may increase patient anxiety, inflate health care costs, waste health resources, and affect the quality of care. Unfortunately, interventions aiming at improving appropriate laboratory ordering have been unsuccessful,[11] further adding to the complexity of the problem.

Routine CRP ordering for the detection of bacterial infections needs further scrutiny by practising physicians. The evidence in support of the diagnostic utility of CRP levels for infections is weak and is mostly based on studies of low levels of evidence.[12] The CRP test results seem to have a small impact on decision-making and may contribute to the unnecessary elevation of health care expenditures. Better quality studies are needed to address the utility of CRP testing for infections and to define a consistent optimal cut-off value that can discriminate bacterial from viral infections or other diseases.[12]

CONCLUSION

We conclude that routine CRP ordering for diagnostic purposes for infections fails to inform decision-making in the majority of cases and it only leads to inflated hospital bills.

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