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The value of C-reactive protein in emergency medicine

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ABSTRACT

C-reactive protein (CRP) is a commonly used tool in emergency department (ED), especially in febrile and infectious patients. It was identified in 1930 and was subsequently classified into an "acute phase protein", an early indicator of infectious or inflammatory situations in the ED, CRP must be a diagnostic reference and no single value can be indicated to rule in or rule out a specific diagnosis or disease. CRP is a comprehensively assisted tool for evaluation and diagnosis of tissue damage (rheumatologic diseases, stroke, cancer, pancreatitis, burn injury, sepsis and gout) and infection (urinary tract infection, pelvic inflammatory disease, meningitis and lung infection). It can be used for treatment monitoring and severity evaluation in pneumonia, pancreatitis, pelvic inflammatory disease (PID), and urinary tract infections (UTI). Otherwise, it also plays the role of prognostic indicator of acute coronary syndrome. C-reactive protein adds little to the diagnosis of pneumonia, urinary tract infections, and pancreatitis. A single CRP value should not straightly make the decision to treat these patients. That is, CRP has no role in diagnosing these clinical entities, and a normal CRP level should never delay antibiotic coverage in ED. Faster and more interpretable tools such as image studies (X-ray, sonography and computed tomography) are available to help diagnose suspected cases of aortic dissection, appendicitis, cholecystitis, pancreatitis, pneumonia and stroke in ED.

1. Introduction

C-reactive protein (CRP) is a commonly used tool in emergency department (ED), especially in febrile and equivocal infectious patients. It was identified in 1930 and was subsequently classified into an "acute phase protein", an early indicator of infectious or inflammatory situations[1]. And then CRP has been considered as a screening test for tissue inflammation, a biomarker of disease activity, monitor of reflector therapy and as a predictive or prognostic tool of many acute and chronic diseases[2,3]. Actually we can not distinguish the bacteremia from nonbacteremic infection by CRP level, and physicians must take the detailed history of fever onset to improve the accurate prediction of bacteremia before the results of blood cultures came out[4]. Although CRP nowadays is used to be a prognostic and predictive factor in acute coronary syndrome, infectious and inflammatory diseases, high variability of association between an elevated CRP and a bacterial aetiology of the infection was poor: sensitivity ranged from 8% to 99% and specificity from 27% to 95%[5]. However, it is not used to differentiate among the many sources of potential tissue destruction. Serial CRP measurements may be helpful to monitor a patient's response to medical intervention. In this article, we will review and discuss the CRP value and applications in common medical emergencies in ED.

2. Pathophysiology

CRP has several properties with function of being a bacterial opsonin, promoting phagocytosis, accelerating chemotaxis, and activating platelets. In the nomination of C-reactive protein (CRP), it shows binding reactivity with pneumococcal C-polysaccharide, the cell wall carbohydrate of Streptococcus pneumoniae, so we called it as C-reactive protein[6]. CRP is synthesized by hepatocytes and is stimulated by cytokines, particularly IL-6, IL-1, and tumor necrosis factor (TNF) after tissue injury or inflammation[7]. Levels in healthy individuals are normally less than 1 mg/L,

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and a value above 10 mg/dL is more likely to indicate when patients encounter bacterial, viral or fungal infections or tissue inflammation or damage[2]. A cutoff value of 17 mg/dL or more for CRP reaches a sensitivity of 74% and a specificity of 75% in predicting the existence of infection[8]. The functional properties of CRP include the ability to activate complement pathway and the ability to modulate the action of phagocytic cells. Although CRP rises with tissue injury or ischemia, in septic patients with fulminant hepatic failure, it is more to be a marker of severe liver dysfunction rather than be used as a marker of infection[9].

2.1. Acute coronary syndrome (ACS)

Acute coronary syndrome (ACS) is a commonly seen medical emergency in ED daily practice and it includes acute ST elevation myocardial infarcts, non-ST elevation myocardial infarcts and unstable angina. Risk factors of ACS are hyperlipidemia, smoking, hypertension, diabetes mellitus (DM), obesity, low levels of physical activity, family history of ACS, and depressive symptoms[10]. There are many researches describing elevation of serum C-reactive protein (CRP) levels is related to increased risk of myocardial infarction[3,11-13]. CRP possesses activation of peripheral leukocytes with producing plaque-destabilizing mediators and results in infectious diseases trigger manifestations of atherosclerosis, in which CRP elevation might lead to the onset of cardiovascular events[14]. The earliest research from Italy in 1994 reported by Liuzzo and colleagues, and they found elevated CRP predicts a poor outcome in patients with unstable angina[15]. High-sensitivity CRP (hsCRP) is being increasingly used as a tool for cardiac risk evaluation and as a prognostic factor in acute coronary syndrome (ACS). In the prognosis of ACS, baseline CRP level is an independent predictor of both early (30 days) and late (1 year) mortality in patients with ACS being intervened with an early invasive strategy, especially in Troponin positive patients[16].

Although the hs-CRP value showing the maximum likelihood ratio for predicting cardiac events was 1.45 mg/dL, however, in large patient cohort managed in a single-center chest pain unit (CPU) (n=958), measurement of hs-CRP did not increase the diagnostic accuracy for ACS. Routine hs-CRP as a diagnostic tool should not be recommended in the CPU setting nowadays[17,18]. The important role of CRP in CAD after transplanted heart is to intervene with statins by reducing CRP, may prevent the severe progression of graft atherosclerosis and prolong survival[19]. For ACS, the higher CRP levels, the worse prognosis and the higher cardiac events possibility.

2.2. Aortic dissection

Aortic dissection (AD) is one of the cardiovascular emergencies in ED practice. It occurs when the aortic intima tears and blood flows into the aortic media creating a false lumen. Risky factors include uncontrolled hypertension, connective tissue disorders, congenital aortic valve disorder, syphilis infection, illicit drug usage and medial degeneration of aorta. An Austria study in 2002 suggested elevated admission CRP levels in patients with symptomatic aortic aneurysm or dissection were independently associated with poor prognosis. CRP levels higher than 6.3 mg/dL show a high risk for short-term mortality[20]. Increased CRP levels were independently associated with mortality. Another study from Japan in 2010 concluded peak CRP is a strong predictor for adverse long-term events in patients with type B acute aortic dissection[21]. For aortic dissection, the higher CRP values, the worse prognosis and outcome.

2.3. Appendicitis

Acute abdominal pain is a common complaint in ED patients and a Taiwan report (n=143) about acute abdominal pain concluded elevated CRP along with leukocytosis, the diagnostic value was much improved, reaching specificity of 89% and positive predictive value of 88%. Thus, CRP is a helpful reference for disposition decision-making in patients with acute abdominal pain[22]. Diagnosis of appendicitis always relies on prudent history taking and physical examinations. Some inflammatory parameters (such as CRP) could be references in the diagnosis of acute appendicitis[23]. A normal CRP along with a normal WBC count and normal neutrophil count is unlikely to be a case of appendicitis[24]. Although early in the course of appendicitis, the white blood cell (WBC) count has shown the best diagnostic sensitivity among laboratory tests, there are 21% of appendicitis is normal levels of WBC count before appendectomy[23]. In appendicitis, after 12-24 h of symptoms, CRP is deemed to be useful, especially when serial levels show an increase. An Ireland report (947 appendectomies) in 2010, highlight the importance of obesity when interpreting the significance of an elevated CRP level in children with suspected diagnosis of appendicitis and CRP is not a reliable biomarker of inflammation in extremely obese children presenting with suspected appendicitis[25]. A meta-analysis study (n=3 436) by Hallan concluded CRP is an examination of medium accuracy in diagnosing acute appendicitis. The sensitivity varied from 0.40 to 0.99, and the specificity from 0.27 to 0.90[26]. Although CRP is a marker helpful to decision making in acute abdominal pain in the ED, we should not make decision in equivocal appendicitis case by single CRP level, and computed tomography (CT) is a better choice[22]; there is no substitute for serial and prudent clinical examinations during an observation period for abdominal pain, especially the initial epigastric pain or peri-umbilical pain.

A study of perforated appendicitis (n=155) from Switzerland in 2010 reported hyperbilirubinemia (>20 mmol/L) to be a statistically significant marker of perforation in acute appendicitis. However, CRP overmatches bilirubin for implication of perforation in acute appendicitis[27]. A Taiwan report (568 appendectomies) studied the cutoff values of CRP concentration taken as the first, second, and third days after onset of symptoms that distinguish acute appendicitis

from other acute abdominal diseases were 1.5, 4.0, and 10.5 mg/dL, respectively; the values that distinguish perforated appendicitis from other acute abdominal diseases were 3.3 mg/dL (first day), 8.5 mg/dL (second day), and 12.0 mg/dL (third day)[28]. From above, CRP is a tool of reference in predciting appendicitis and perforated appendicitis. Of them, higher CRP level might be found in laboratory data.

2.4. Cholecystitis

There are relative small amount of documents mentioned about CRP in cholecystitis. Patients exhibiting one of the local signs of inflammation, such as Murphy's sign, pain or tenderness in the right upper quadrant (RUQ), as well as one of the systemic signs of inflammation, such as fever, elevated white blood cell count (WBC), and elevated C-reactive protein level, are diagnosed as having acute Cholecystitis[29]. Level of CRP also predicts the severity of acute cholecystitis (>10 mg/dL is strongly related to tissue necrosis)[8]. CRP can not play a suitable role in diagnosis of cholecystitis, but can be a factor indicating severity of cholecystitis and response to therapy.

2.5. Gout

Not every gout patient had high level exceeding normal range of uric acid; similarly, CRP is not a reliable test for diagnosis of gout. Patients who had gout and high levels of uric acid in their blood did not necessarily also have high levels of C-reactive protein. Like that as we all know, not every gout patient had hyperuricemia. A Japan study in 2011 suggests that hyperuricemia may not result in an increase in serum CRP level, while benzbromarone may have a favorable effect on CRP[30].

2.6. Meningitis

A Finland study in 1999 described seral CRP can distinguish Gram negative bacterial meningitis (n=55) from viral meningitis (n=182). The mean CRP level in Gram negative bacterial meningitis is 11.5 mg/dL, and in viral meningitis is less than 2 mg/dL[31]. Compared with CRP, procalcitonin can be used in the early diagnosis of bacterial meningitis and may be a useful adjunct in differentiating bacterial and non bacterial meningitis than CRP or leukocyte count and diminishing the value of lumbar puncture performed 48-72 h after admission to assess treatment efficacy[32]. For meningitis, CRP plays a role of distinguishing bacteria from non-bacteria aetiology infection.

2.7. Pancreatitis

CRP might be valuable in the assessment and monitoring of acute pancreatitis. C reactive protein response and its rate of change in acute pancreatitis reflect different severity. Higher concentrations of C reactive protein (>10mg/dL) were sustained in severe attacks, and give a warning of the following severe local inflammation in the patient whose initial illness is relatively mild and whose clinical course is initially benign[33]. Erythrocyte sedimentation rate (ESR) can predict severe acute pancreatitis with a slightly inferior performance to CRP. Combined ESR and CRP at 24 h can predict severe acute pancreatitis accurately[5]. For pancreatitis, CRP is a tool of evaluation in severity rather than making diagnosis.

2.8. Pelvic inflammatory disease

Currently C-reactive protein is used in the management of chorioamnionitis, preterm premature rupture of membranes, pelvic inflammatory disease (PID), and urinary tract infection (UTI) in gynecology[34]. A Slovenia study in 1998 documented 96.1% of pelvic inflammatory disease (PID) patients had increased CRP values. In successful treatment, the CRP values decreased significantly in PID patients without tubo-ovarian abscess (TOA) on day 3-4, in patients with TOA on day 6-8 and reached normal values in both groups on day 18-21. Improves in clinical condition were most concurrent with decreases in CRP values[35]. Another study from Finland in 1987 reported 55 PID cases had the mean CRP level of 7.6 mg/dL. CRP greater than 1 mg/dL had good sensitivity (93%) and specificity (83%) in the diagnosis of PID. Furthermore, CRP levels became normal much sooner than did erythrocyte sedimentation rate (ESR) following effective antibiotic therapy, suggesting that it is useful in monitoring therapeutic response[36]. For PID, CRP is a tool of monitoring therapeutic efficacy.

2.9. Pneumonia

There are many aspects and tools to diagnose pneumonia including history taking, chest X ray, auscultation of breathing sound or high resolution computed tomography (HRCT). Composition of some parameters/blood tests such as white blood cell count (WBC) and CRP are adjuvant and helpful to diagnosis. For pneumonia, CRP plays the roles of prognosis prediction and therapy reflector rather than making diagnosis. An UK study in 2008 studied 570 pneumonia cases, and found admission CRP<10 mg/dL has reduced risk for 30-day mortality, need for mechanical ventilation and/or inotropic support, and complicated pneumonia. Failure of CRP to fall by 50% or more at day 4 leads to an increased risk for 30-day mortality, need for mechanical ventilation and/or inotropic support, and complicated pneumonia. CRP is an independent biomarker of severity in community-acquired pneumonia[37]. A Brazil study in 2010 documented daily CRP measurements in patients with nosocomial pneumonia may be useful in the prediction of patients with poor outcome, and detect patients with inappropriate antimicrobial therapy[38].

2.10. Sepsis

Sepsis is the major cause of mortality in critically ill patients and physicians encountered it in ED and intensive care unit (ICU) in daily practice. Although CRP is used to be a monitoring factor for complication or treatment failure, it is not reliable and meaningful in the early post-operative period. Tissue damages may lead to pseudo-elevation of CRP rather than sepsis. A Brazil study in 2009 did not show any correlation between CRP and infection among patients with systemic inflammatory response syndrome (SIRS) and septic shock during the early postoperative period[39]. C-reactive protein is a valuable laboratory test in the assessment of febrile infants aged ≤3 months old and may serve as a better diagnostic marker of serious bacterial infection (SBI) than total WBC count[40]. For the diagnosis of late-onset neonatal sepsis (LONS), the procalcitonin (PCT) test showed better accuracy than the CRP test[41]. Procalcitonin (PCT) has emerged as the most studied and promising sepsis biomarker. For diagnostic and prognostic purposes in critical care, PCT is superior to CRP and other traditional markers of sepsis[42].

2.11. Stroke

Elevation of CRP is obviously seen after ischemic stroke attack than intracranial hemorrhage (ICH). Brain tissue ischemia and damage result in surge of CRP after stroke episode. Prudent physical examinations and review of systems are helpful to detect other infectious condition co-incidence stroke. An Iran study in 2011 reported serum level of hs-CRP in ischemic patients was higher than in hemorrhagic group (18.92 mg/dL vs. 2.65 mg/dL). Hs-CRP might be considered as a helpful method for the initial diagnosis of the type of stroke (ischemic infarcts or hemorrhagic)[43]. Higher WBC, CRP, and blood glucose are associated with increased mortality in spontaneous intracranial hemorrhage (sICH) patients. Only CRP elevation portends higher risk of death independently of other indicators of sICH severity[44]. CRP is a marker of increased 1-year risk in ischemic stroke. CRP at discharge is better related to later outcome and could be of greater utility for risk stratification. These findings are consistent with that elevated CRP may predict future cardiovascular events or death[45].

2.12. Urinary tract infection

Urinary tract infection (UTI) is a commonly seen disease in ED daily practice. An elevated serum CRP concentration is not accurate in localizing the site of a urinary tract infection in girls who do not have clinical signs of acute pyelonephritis[46]. ESR and differential leukocyte count are two valuable tests in febrile UTI and may be useful for localization of UTI level, but the total leukocyte count and CRP level as in qualitative methods are not useful, and many patients with febrile UTI do not have leukocytosis[47].

3. Summary

In the ED, CRP must be a diagnostic reference and no single value can be indicated to rule in or rule out a specific diagnosis or disease. CRP is a comprehensively assisted tool for evaluation and diagnosis of tissue damage (rheumatologic diseases, cancer, pancreatitis, burn injury, sepsis) and infection (urinary tract infection, pelvic inflammatory disease, lung infection). It can be used for treatment monitoring and severity evaluation in pneumonia, pancreatitis, pelvic inflammatory disease (PID), and urinary tract infections (UTI). C-reactive protein adds little to the diagnosis of pneumonia, urinary tract infections, and pancreatitis. A single CRP value should not straightly make the decision to treat these patients. That is, CRP has no role in diagnosing these clinical entities, and a normal CRP level should never delay antibiotic coverage in ED. Faster and more interpretable tools such as image studies (X-ray, sonography and computed tomography) are available to help diagnose suspected cases of aortic dissection, appendicitis, cholecystitis, pancreatitis, pneumonia and stroke in ED.

Conflict of interest statement

The authors declare that there are no conflicts of interest.

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