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DAFTAR ISI

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DIAGNOSTIC OF C-REACTIVE PROTEIN IN FEBRILE CHILDREN

(Nilai Diagnostik C-Reactive Protein Pada Anak Demam)

Johanis[1], Aryati[1], Dominicus Husada[2], Djoko Marsudi[1], M. Y. Probohoesodo[1]

ABSTRACT

The measurement of C-reactive protein (CRP), an acute-phase protein synthesized by hepatocytes, is valuable to distinguish bacterial infection from non-bacterial infections in children. The aim of this study is to know the diagnostic properties of quantitative CRP associated with clinically bacterial and non-bacterial infection in febrile children. Febrile children which was studied were presenting in the Paediatric Emergency Department, their ages were up to 12 years, with axillary's temperature ≥38.5° C, and the clinically undetectable source of fever were enrolled in this consecutive study from September, 2009, up to August, 2010. Informed consent was obtained for the use of CRP evaluation. The CRP concentration was measured with immunoturbidimetry method (Pure auto S CRP latex (SS-type), Sekisui Medical Co., Ltd) and an auto photometer TMS 1024i. The main outcome result was the presence of the laboratory examination results, blood culture, or radio graphically. The receiver operator characteristic (ROC) curve was modelled for quantitative CRP to identify the optimal test value. Eighty-six patients were enrolled in this study. Forty-one (47.6%) had bacterial infection and 45 (52.3%) had non-bacterial infection. The CRP concentration was significantly different between the two groups (p=0.003). The ROC analysis demonstrated an area under curve (AUC) 0.689, standard error (SE) 0.059, and 95% confidence interval (CI): 0.573-0.805. The optimal cut-off point for CRP in this data set at 5 mg/L, achieved sensitivity of 0.61, specificity of 0.71, and likelihood ratio 2.11 (Kappa 0.003, McNemar 0.711) for the detection of bacterial infection in this population. The Quantitative CRP concentration is a valuable laboratory test for the evaluation of febrile children who are at risk of bacterial infection.

Key words: *C-reactive protein, febrile children*

ABSTRAK

Pemeriksaan C-reactive protein (CRP), merupakan protein fase akut yang disintesis oleh hepatosit, berguna untuk membedakan infeksi bakteri dengan infeksi non-bakteri pada anak. Tujuan penelitian ini adalah untuk mengetahui nilai diagnostik CRP kuantitatif yang berkaitan dengan infeksi bakteri dan non-bakteri secara klinis pada anak demam. Anak demam yang dirawat di Departemen Gawat Darurat Pediatri, berusia sampai dengan 12 tahun, dengan temperatur aksila ≥38,5° C, dan secara klinis belum diketahui penyebab panas diikutkan dalam penelitian konsekutif dari September 2009 sampai Agustus 2010. Informed consent untuk izin pemeriksaan CRP. Kadar CRP diperiksa dengan metode imunoturbidimetri (Pure auto S CRP latex (SS-type), Sekisui Medical Co., Ltd) dan fotometer otomatis TMS 1024i. Diagnosis ditegakkan berdasarkan hasil pemeriksaan laboratorium, kultur darah, atau radiografi. Kurva receiver operator characteristic (ROC) dibuat untuk menunjukkan nilai optimal pemeriksaan CRP kuantitatif. Delapan puluh enam pasien diikutkan dalam penelitian. Empat puluh satu (47,6%) menderita infeksi bakteri dan 45 (52,3%) menderita infeksi non-bakteri. Kadar CRP berbeda bermakna antara kedua kelompok (p=0,003). Analisis ROC menunjukkan area under curve (AUC) 0,689; standard error (SE) 0,059; dan 95% confidence interval (CI) 0573--0,805. Nilai potong optimal CRP untuk menemukan infeksi bakteri pada populasi ini adalah 5 mg/L, dengan nilai kepekaan 0,61; kekhasan 0,71; dan likelihood ratio 2,11 (Kappa 0,003; McNemar 0,711). Pemeriksaan CRP kuantitatif merupakan pemeriksaan laboratorium yang baik untuk evaluasi anak demam yang berkebahayaan infeksi bakteri.

Kata kunci: C-reactive protein, anak demam

INTRODUCTION

Febrile children comprise a substantial proportion of ambulatory paediatric visits. Both minor and life-threatening infectious diseases, including respiratory infections, such as: occult bacteraemia, and meningitis, are common in children. Although for distinguishing a child with a viral syndrome from one with bacterial is usually difficult, there may be a considerable overlap in the clinical appearance of children with fever without source, due to viral illness, and of those with occult bacteraemia. The management of febrile children needs to be structured to minimize the likelihood of these unfavourable outcomes.[1] Although untreated bacterial infections may cause serious complications, treating viral illnesses or noninfective causes of inflammation with antibiotics is not only ineffective, but also contributes to the development of resistance, increases costs, and adds to the risks of toxicity and allergic reactions. Studies undertaken by the World Health Organization indicate that, for every 100 respiratory infections, only

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20 require antibiotic treatment.[2] In the literature, one of the parameters used to differentiate between bacterial and viral infections has been the quantisation of serum C-reactive protein (CRP), a prototypic acute-phase reactant.[3,4]

In most diseases, the circulating value of CRP reflects ongoing inflammation and/or tissue damage much more accurately than do other laboratory parameters of the acute-phase response, such as plasma viscosity and the erythrocyte sedimentation rate. The CRP concentration is thus a very useful non-specific biochemical marker of inflammation, measurement of which contributes importantly to (a) screening for organic disease, (b) monitoring of the response to treatment of inflammation and infection, and (c) detection of intercurrent infection in immunocompromised individuals, and in the few specific diseases characterized by modest or absent acute-phase responses.[5]

Normal values of serum CRP are very low; in healthy children is less than 6 mg/L and in adults is less than 8 mg/L.[3,6] According to the data from the National Health and Nutrition Examination Survey (NHANES), the median serum CRP is 2.2 mg/L in adults and 0.4 mg/L in children under age 20.[7,8] Usually CRP concentration increases within 12 hours after tissue injury. Peak levels, 100 to 1000 times normal, are generally attained within 1 to 3 days after the injury appears and then fall rapidly once the inflammation ceases.[3] In the acute stage of bacterial infections, the CRP levels are moderately or highly increased, whereas in viral infections, the CRP levels are normal or slightly increased.[9] Children with serious bacterial infections and occult bacteraemia are more likely to have high CRP than children with benign infections.[10]

Several studies have looked at the diagnostic value of CRP for the detection of bacteraemia or occult bacterial infection (OBI) in children. Several reports have suggested that CRP may offer superior diagnostic accuracy compared with white blood cell count (WBC) in the detection of bacteraemia or OBI.[11] The aim of this consecutive study is to know the determination of the diagnostic properties of quantitative CRP associated with clinically bacterial and non-bacterial infection in febrile children.

METHODS

A consecutive study was conducted with subject recruitment from September, 2009, up to August, 2010. Children with age of 3 months until 12 years and measured axillary's temperature of ≥38.5° C who were seen in the Paediatric Emergency Department (ED) were eligible for the enrolment. But children with a previously identified chronic disease, prior surgery, immunizations in the 48 hours preceding the visit, or antibiotic treatment within the previous 48 hours were excluded. All subjects had received clinical care as determined by the treating paediatric emergency medicine physician. The institutional guidelines for the care of febrile included a complete blood count (CBC) with differential, absolute granulocyte count (AGC), blood culture, cerebrospinal fluid (CSF) cell count, protein level, glucose level analyses, Gram-staining, culture, and chest radiograph if pneumonia was presented, was suggested in the physical examination. During the study period, parents or caregivers of children who were having blood drawn for clinical evaluation were approached to participate in this study, and informed consent was obtained by an attending physician for the use of blood remaining after clinical tests. The medical record was reviewed for all children, regardless of chief complaint, to identify potentially missed cases. The infants' caregivers who had not been approached for consent during the ED visit were called by the treating physician and offered enrolment in the study as well.

The patients in this study were classified as having a definite bacterial infection or non-bacterial infection. Definite bacterial infection were (1) sepsis, as a whole-body inflammatory state (called a systemic inflammatory response syndrome or SIRS) and a positive blood culture result with a pathogen or suspected bacterial infection; (2) bacterial meningitis, as a positive CSF culture result with a pathogen or bacteraemia with CSF pleocytosis (>10 WBCs per μL); (3) bacterial pneumonia, as a chest radiograph interpreted by an attending radiologist indicating pneumonia with Bacterial Pneumonia Score (BPS) in the absence of pleural fluid, sputum, or blood culture result;[12] (4) respiratory diphtheria, as a greyish colour appeared, adherent membrane in the pharynx, palate, or nasal mucosa; (5) typhoid fever, as a positive serological test in the absence of blood culture result; (6) bacterial pharyngitis, as exudative pharyngitis, anterior cervical lymphadenitis, and scarlatiniform rash in the absence throat culture; (7) bacterial acute otitis media (AOM), as acute onset of symptoms (fever, irritability, or earache), signs of inflammation of the tympanic membrane, and presence of fluid in the middle ear; (8) bacterial endocarditic, as cardiac murmur, embolic phenomena, pulmonary infarcts, skin manifestations (petechiae, Osler's nodes or Jane way lesions), splenomegaly, and microscopic hematuria present. The final classification to definite bacterial infection or no bacterial infection was determined through consensus review by paediatricians.

Blood samples that remained after clinical tests were centrifuged at 3000 rpm for 10 minutes, and the serum was stored at –20° C before processing. Quantitative CRP concentration was measured at

the laboratory of Department of Clinical Pathology Dr.Soetomo Hospital, Surabaya, by using an particle enhanced immunoturbidimetry method with Pure auto S CRP latex (SS-type), Sekisui Medical Co., Ltd and an auto photometer TMS 1024i, Tokyo Boeki Medical System Ltd. This method employs latex agglutination immunoassay with monoclonal antibodies for measurement of CRP in serum or plasma. The CRP reacts with antihuman CRP mouse monoclonal antibody-coated latex, than an agglutination occurs. The CRP concentration is determined by measuring the change in absorbance, that results from the agglutination reaction. The system was calibrated by using a CRP calibrator (SS-type) serum which is traceable to CRM 470, based on well-characterized primary standard prepared by the manufacturer. The system was controlled by using Seronorm™ CRP Liquid in two levels. The range of serum CRP measured by this instrument was from 0.3 up to 300 mg/L. The coefficient of variation for the procedure was less than 5%. The CBC with differential was quantified by automated laboratory equipment.

The Mann–Whitney–Wilcoxon test or the 2-tailed *t* test and One-Sample Kolmogorov-Smirnov test were used as nonparametric tests to compare the mean values of continuous variables between subjects with and without bacterial infection. The X^2 test was used to assess the association between gender and an outcome of bacterial infection. WBC, AGC, and CRP level were assumed to be independent. $P<.05$ was considered to be statistically significant. Receiver operator characteristic (ROC) curve was fit for CRP individually, using the observed levels of the test, and compared using the maximum area under curve (AUC) criteria. Next, cut-off points were determined by the simultaneously maximizing the sensitivity and specificity. The ROC curves were fit using these cut-off points and compared using maximum AUC criteria and likelihood ratio tests where appropriate. Positive predictive value (PPV) and negative predictive value (NPV) with 95% confidence intervals (CIs) were tabulated. Statistical analyses were performed using the Statistical Program for the Social Sciences, Version 13.0 for Windows (SPSS, Chicago, IL).

RESULTS AND DISCUSSION

Forty-one (47.6%) patients had evidence of bacterial infection and 45 (52.3%) had no evidence of bacterial infection. Causes of bacterial infection included bacterial pneumonia (12), sepsis (7), bacterial meningitis (7), bacterial pharyngitis (6), respiratory diphtheria (4), typhoid fever (3), bacterial acute otitis media (1), and bacterial endocarditic (1). *Acitenobacter spp*, *Klebsiella pneumoniae*, coagulate-negative staphylococcus, extended spectrum beta-lactamases (ESBL)-producing *Klebsiella pneumonia* were the causative organisms of sepsis and *Streptococcus viridians* was the causative organism of bacterial endocarditic. Causes of non-bacterial infection included dengue infection (10), acute tonsillopharyngitis (15), viral bronchiolitis (15), measles (3), viral exanthema (1), and viral meningitis (1). The comparison of age, gender, and laboratory findings between the two (2) groups are shown in Table 1. The two (2) groups were indistinguishable in age and gender. WBC, absolute granulocyte count (AGC), and CRP concentration were significantly different ($P<.05$) between the 2 groups. The diagnostic properties of WBC, AGC, and CRP concentration are shown in Table 2. CRP was the only predictor for bacterial infection ($P<.0001$). The patients with evidence of bacterial infection, 39.0% had CRP <5 mg/L, 60.9% >5 mg/L, 53.6% >10 mg/L, 39.0% >20 mg/L, 19.5% >40 mg/L and 7.3% >80 mg/L. Of the patients with no evidence

Table 1. Characteristics of children had bacterial and non-bacterial infection

Characteristic*	Patients With Bacterial Infection (n = 41)	Patients With Non-Bacterial Infection (n = 45)	P Value
Age (month)	32.5 (26.2)	25.8 (21.4)	.196
Sex (% female)	36.6	51.1	.175
WBC (thousand/mm^3)	16.2 (7.8)	10.5 (5.1)	.006
Granulocyte† (thousand/mm3)	11.3 (7.2)	5.7 (3.9)	.002
Granulocyte (%)	66.0 (17.3)	52.5 (18.9)	.324
Lymphocyte (thousand/mm^3)	4.2 (2.2)	4.1 (2.3)	.982
Lymphocyte (%)	29.0 (15.4)	40.9 (17.1)	.325
Monocyte (hundred/mm^3)	686 (396)	653 (358)	.223
Monocyte (%)	4.9 (3.2)	6.5 (2.6)	.366
Haemoglobin (g/dL)	10.3 (1.5)	11.2 (1.7)	.400
Platelet (thousand/mm^3)	340.2 (168.6)	262.6 (137.2)	.126
CRP median (range) (mg/L)	14.06 (0.19-167.84)	1.55 (0.17-86.01)	<.001

* Values shown are means ±SD unless otherwise noted; †Absolute granulocyte count (AGC)

of bacterial infection, 71.1% had CRP <5 mg/L, 28.9% >5 mg/L, 15.6% >10 mg/L, but only 8.9% >20 mg/L, 6.7% >40 mg/L and 2.2% >80 mg/L. Ten patients with bacterial infection had CRP concentrations of <1 mg/L, two (2) with sepsis (age 9 and 16 months), two (2) with bacterial pneumonia (7 and 36 months old), four (4) with bacterial meningitis (12, 15, 15, and 48 months old), one (1) with respiratory diphtheria (24 months old), and one (1) with bacterial acute otitis media (60 months old). Three patients with bacterial infection had CRP >100 mg/L, two (2) with bacterial pneumonia (6 and 18 months old) and one (1) with respiratory diphtheria (72 months old). Three patients with non-bacterial infection had CRP >40 mg/L, one (1) with acute tonsillopharyngitis (75 months old, CRP 86.01 mg/L), one (1) with measles (30 months old, CRP 75.21 mg/L), and one (1) with dengue hemorrhagic fever grade I (5 months old, CRP 45.77 mg/L).

The ROC curve was constructed in Fig 1 (Kappa 0.003, McNemar 0.711), and demonstrated an AUC of 0.689 (standard error [SE]: 0.059, 95% confidence interval (CI): 0.573–0.805). When using the criteria of CRP cut-off point it was greater than or equal to 5 mg/L, the sensitivity was 0.61 (95% CI: 0.445–0.754), specificity 0.71 (95% CI: 0.555–0.832), positive predictive value 0.65 (95% CI: 0.486–0.799), negative predictive value 0.66 (95% CI: 0.515–0.792), and likelihood ratios of a positive and negative test result was 2.11 (95% CI: 1.255–3.549) and 0.54 (95% CI: 0.359–0.84), respectively. The level of 5 mg/L seemed more useful for the differentiation between bacterial and non-bacterial infections (see Table 3).

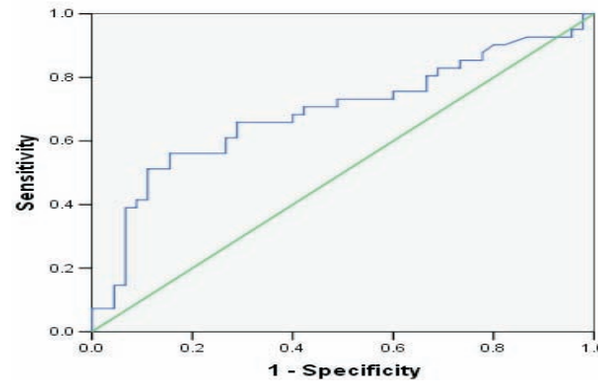

Figure 1. ROC for CRP concentration associated with bacterial infection, AUC 0.689 (SE: 0.059, 95% CI: 0.573-0.805)

The management of febrile children without apparent source of infection remains controversial, because there has been no test available with adequate sensitivity and specificity required to distinguish which children are at risk for bacterial infection. Total WBC is

Table 2. Predictors of bacterial infection

Variable	Cut-off Point	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	Likelihood Ratio (95% CI)
CRP (mg/L)	5	0.61 (0.44–0.75)	0.71 (0.55–0.83)	0.65 (0.48–0.79)	0.66 (0.51–0.79)	2.11 (1.25–3.54)
WBC (thousand/mm^3)	15	0.51 (0.36–0.65)	0.80 (0.66–0.89)	0.7 (0.52–0.83)	0.64 (0.51–0.75)	2.56 (1.32–4.93)
AGC (thousand/mm^3)	10	0.53 (0.38–0.67)	0.88 (0.76–0.95)	0.81 (0.63–0.91)	0.67 (0.55–0.78)	4.82 (2.01–11.57)

Table 3. Multilevel diagnostic values for CRP concentration

CRP (mg/L)	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	Likelihood Ratio (95% CI)	Posttest Probability
5	0.61 (0.44–0.75)	0.71 (0.55–0.83)	0.65 (0.48–0.79)	0.66 (0.51–0.79)	2.11 (1.25–3.54)	66%
10	0.53 (0.38–0.67)	0.84 (0.71–0.92)	0.75 (0.57–0.87)	0.66 (0.53–0.77)	3.45 (1.64–7.21)	76%
20	0.39 (0.25–0.54)	0.91 (0.79–0.96)	0.80 (0.58–0.91)	0.62 (0.50–0.72)	4.39 (1.59–12.06)	80%
40	0.19 (0.10–0.34)	0.93 (0.82–0.97)	0.72 (0.43–0.90)	0.56 (0.44–0.66)	2.93 (0.83–10.29)	73%
80	0.07 (0.02–0.19)	0.97 (0.88–0.99)	0.75 (0.30–0.95)	0.53 (0.42–0.64)	3.29 (0.35–30.41)	75%

the most commonly laboratory test used in this clinical situation. In this study, the mean total WBC and AGC were significantly different between those with bacterial infection and non-bacterial infection. Recent studies investigating the utility of WBC indices concluded that AGC is a much better test for detecting pneumococcal bacteraemia than WBC; with an approximate cut-off point of 10,000/mm^3.[11,13] It was found that total WBC and AGC have a similar profile as a screening test for bacterial infection. As a screening test for bacterial infection, a total WBC >15,000/mm^3 has a sensitivity of 0.51 and a specificity of 0.80, AGC >10,000/mm^3 has a sensitivity of 0.53 and a specificity of 0.88. This study demonstrates that CRP concentration is superior to other tests in predicting which febrile children have bacterial infection requiring antibiotic therapy.

CRP has been evaluated as a predictor of bacterial infection in febrile children using qualitative, semi quantitative, or quantitative. Although there is yet no test available that is 100% reliable, this study demonstrates that CRP is both more sensitive and more specific in distinguishing children with bacterial infection from those non-bacterial infection. CRP was found to have a good sensitivity and specificity, and when compared with WBC and AGC, CRP was found to be a better test. Recent prospective studies of febrile children have found CRP to be a more sensitive and specific predictor of bacterial infection compared with WBC.[13] The advantage of CRP is its rapid rise, less than 24 h from the beginning of an invasive infection. The rise in WBC may be even more rapid, though not as constant as the rise in CRP.[14] At the Dr.Soetomo Hospital Surabaya; CRP is measured by immunoturbidimetry automated assay available 24 h/d. The turnaround time is 45 minutes, and the cost of the test is equal for a CBC with differential count.

CRP is a predominantly synthesized by the hepatocytes, under transcriptional control by the cytokine interleukin-6, although other sites of local CRP synthesis and possibly secretion have been suggested. CRP belongs to the highly conserved pentraxin protein family and contributes to innate immunity against infection and to handling of autologous ligands. The autologous ligands of CRP include phospholipids and ribonucleoproteins from necrotic and apoptotic cells. CRP binds phosphocholine (PC) with the highest affinity for the precise molecular mechanism of this interaction. PC is universal in phospholipids in cell membranes and plasma lipoproteins, and is common in complex polysaccharides of plants, fungi and bacteria, whilst CRP also binds specifically to small nuclear ribonucleoprotein particles. Similar considerations may apply to the binding of CRP to its bacterial ligands. CRP itself is deposited in the infarcted tissue and showed complexed or aggregated CRP activates complement, with pro-inflammatory effects. This promotes beneficial and scavenging functions, but it also enhances tissue injury. CRP may thus be a significant therapeutic target and its molecular structure–function relationships are therefore potentially of practical importance.[15]

De novo hepatic synthesis starts very rapidly after a single stimulus such as tissue injury, infection, and inflammation, serum CRP concentration rises above 5 mg/L by about 6 hours and peaking around 48 hours. The plasma half-life of CRP is about 19 hours with a 50% reduction daily after the acute-phase stimulus resolves.[4] CRP is constant under all conditions of health and disease, so that the sole determinant of circulating CRP concentration is the synthesis rate, which thus directly reflects the intensity of the pathological process stimulating CRP production. When the stimulus for increased production completely ceases, the circulating CRP concentration falls rapidly at almost the rate of plasma CRP clearance.[5] Serum CRP assays are universally used to monitor disease activity and response to therapy.[15]

The most commonly used cut-off point for a positive CRP value in children with bacterial infection is 40 mg/L or higher.[16,17] This study demonstrates a lower cut-off point at 5 mg/L maximizing the sensitivity and specificity. Low levels of CRP do not rule out the possibility of bacterial infection in children. On the other hand, viral infection without bacterial involvement is very improbable if CRP is >40 mg/L. Our results suggest that high CRP values rule out viral infection as a sole aetiology of infection; bacterial infection and antibiotic treatment should be considered in these cases.

The initial value of CRP may be low, even in patients with severe bacterial infection. The causative of low CRP in bacterial infection is still unknown. The data suggest that paediatricians should consistently be aware of the possibility of bacterial infection even if the initial CRP test result is low and that serial CRP measurements appear to be practical.[18]

In the previous studies, CRP was useful for the screening of bacterial pneumonia. The previous results suggest a good specificity for the CRP concentration of 20 or 40 mg/L as the screening limit. The diagnosis of pneumonia is difficult, and this difficulties are greatest when diagnosing the cases in infants. The clinical symptoms and signs of pneumonia may be confusing, and even radiological diagnosis is difficult at that age. Moreover, infants have lower responses than older children in non-specific host response parameters. In addition, mixed viral-bacterial infections are common in infants, and *S. pneumonia* is the most common bacterial pathogen. CRP has limited capacity to differentiate between bacterial and viral pneumonia. *S. pneumonia* is the only significant bacterial cause of community-acquired pneumonia in normally healthy

children before school age. In school-aged children, *M. pneumonia* and *C. pneumonia* are equally, or even more important than *S. pneumonia*. Pneumonia, when suspected to be of bacterial origin, should be treated with antibiotics. Elevated values of CRP offers some evidence for bacterial aetiology in cases of pneumonia, but low values do not rule it out. CRP is recommended as the first-line method, and the value of 5 mg/L as the screening limit.[14] Occult bacteraemia also may occur in children with otitis media. When disease caused by *haemophilic influenza* type B was common, 5% to 10% of bacteraemia children subsequently developed bacterial meningitis and other focal bacterial infection.[1] CRP has also been found to be valuable in the diagnosis of bacterial meningitis.[13]

The association of CRP with age or sex did not significantly differ.[19] There is a strong positive association between baseline CRP concentration and BMI, and weight loss lowers the CRP value. The source of a substantial portion of base-line IL-6 production and perhaps also synthesize and secrete some of the baseline CRP itself.[5,20] In a large representative sample of US children, CRP concentration was significantly elevated among children with a BMI ≥85th percentile. Excess body weight may be associated with a state of chronic low-grade inflammation in children.[19] The CRP concentration increased as BMI increased. The majority of individuals who were not overweight exhibited CRP concentrations of less than 2 mg/L.[21] Importantly, acute-phase CRP values show no diurnal variation and are unaffected by eating. Liver failure impairs CRP production, but no other intercurrent pathologies and very few drugs reduce CRP values unless they also affect the underlying pathology providing the acute-phase stimulus.[5]

CRP concentrations can remain within normal limits in chronic inflammatory diseases such as systemic lupus erythematosus, dermatomyositis, ulcerative colitis, graft versus host disease, and leukaemia, even in the presence of severe tissue damage.[4] The immunologic status did not influence the CRP response.[22]

It is interest that increasing CRP, WBC, and AGC in bacterial infection was found in this study, suggesting that these parameters were specific in detecting bacterial infection. This suggests that bacterial infection may lead to the simultaneous production of not only interleukin-6, which is known to be the principal cytokine responsible for the enhanced production of CRP by hepatocytes, but of other cytokines, such as interleukin-8 and tumor necrosis factor-α, which are active in demarginating their neutrophils through the activating properties. These cytokines are likely produced by stimulated monocytes and macrophages during infections.[3]

Several limitations of this study deserve to be acknowledged. It was a consecutive study, the entry of patients based on the clinician's determination of the need for laboratory tests rather than discreet entry criteria, and the small number of patients with the outcome of interest. Entry criteria into the derivation set were designed to assess the utility of the CBC as a prediction tool for bacterial infection in a population of patients with suspected bacterial infection derived from a paediatric ED comprised of fellowship-trained paediatric emergency physicians. In summary, quantitative CRP concentration is a valuable laboratory test in the evaluation of febrile children who are at risk for bacterial infection, with a better sensitivity and specificity value than the total WBC or AGC. The use of CRP alone may enhance clinicians' abilities in the early recognition of clinically bacterial infection, allowing for a more selective strategy for determining which children need additional diagnostic studies and antibiotic therapy.

REFERENCES

1. Baraff LJ, Schriger DL, Bass JW, Fleisher GR, Klein JO, McCracken GH, Jr, Powell KR. Practice guideline for the management of infants and children 0 to 36 months of age with fever without source. Pediatrics 1993; 92: 1–12.
2. Simon L, Gauvin F, Amre DK, Saint-Louis P, Lacroix J. Serum procalcitonin and C-reactive protein levels as markers of bacterial infection: a systematic review and meta-analysis. Clinical Infectious Diseases 2004; 39: 206–17.
3. Tejani NR, Chonmaitree T, Rassin DK, Howie VM, Owen MJ, Goldman AS. Use of C-Reactive Protein in Differentiation Between Acute Bacterial and Viral Otitis Media. Pediatrics 1995; 95: 664–669.
4. Weitkamp JH, Aschner JL. Diagnostic use of C-reactive protein (CRP) in assessment of neonatal sepsis. NeoReviews 2005; 6: e508–e515.
5. Pepys MB, Hirschfield GM. C-reactive protein: a critical update. J. Clin. Invest. 2003; 111: 1805–1812.
6. Macy EM, Hayes TE, Tracy RP. Variability in the measurement of C-reactive protein in healthy subjects: implications for reference intervals and epidemiological applications. Clinical Chemistry 1997; 43(1): 52–58.
7. Ford ES. C-reactive protein concentration and cardiovascular disease risk factors in children findings from the national health and nutrition examination survey 1999–2000. Circulation 2003; 108: 1053–1058.
8. Ford ES, Giles WH, Myers GL, Rifai N, Ridker PM, Mannino DM. C-reactive protein concentration distribution among US children and young adults: findings from the National Health and Nutrition Examination Survey, 1999–2000. Clinical Chemistry 2003; 49(8): 1353–1357.
9. Sasaki K, Fujita I, Hamasaki Y, Miyazaki S. Differentiating between bacterial and viral infection by measuring both C-reactive protein and 2′-5′-oligoadenylate synthetase as inflammatory markers. J Infect Chemother 2002; 8: 76–80.
10. Maheshwari N, Phillips B. How useful is C-reactive protein in detecting occult bacterial infection in young children with fever without apparent focus? Arch Dis Child 2006; 91: 533–535.

11. Isaacman DJ, Burke BL. Utility of the serum C-reactive protein for detection of occult bacterial infection in children. Arch Pediatr Adolesc Med. 2002; 156: 905–909.
12. Moreno L, Krishnan JA, Duran P, Ferrero F. Development and validation of a clinical prediction rule to distinguish bacterial from viral pneumonia in children. Pediatric Pulmonology. 2006; 41(5): 331–337.
13. Pulliam PN, Attia MW, Cronan KM. C-reactive protein in febrile children 1 to 36 months of age with clinically undetectable serious bacterial infection. Pediatrics 2001; 108: 1275–1279.
14. Korppi M, Heiskanen-Kosma T, Leinonen M. White blood cells, C-reactive protein and erythrocyte sedimentation rate in pneumococcal pneumonia in children. Eur Respir J 1997; 10: 1125–1129.
15. Thompson D, Pepys MB, Wood SP. The physiological structure of human C-reactive protein and its complex with phosphocholine. Structure February 1999; 7: 169–177.
16. Galetto-Lacour A, Zamora SA, Gervaix A. Bedside procalcitonin and C-reactive protein tests in children with fever without localizing signs of infection seen in a referral center. Pediatrics 2003; 112: 1054–1060.
17. Korppi M, Kröger L. C-reactive protein in viral and bacterial respiratory infection in children. Scand J Infect Dis. 1993; 25(2): 207–13.
18. Kono T, Otsuka M, Ito M, Misawa M, Hoshioka A, Suzuki M, Migita T, Seki I. Negative C-reactive protein in children with bacterial infection. Pediatrics International 1999; 41: 496–499.
19. Ford ES, Galuska DA, Gillespie C, Will JC, Giles WH, Dietz WH. C-reactive protein and body mass index in children: findings from the Third National Health and Nutrition Examination Survey. The Journal of pediatrics 2001; 138(4): 486–492.
20. Feezor RJ, Oberholzer C, Baker HV, Novick D, Rubinstein M, Moldawer LL, Pribble J, Souza S, Dinarello CA, Ertel W, Oberholzer A. Molecular characterization of the acute inflammatory response to infections with Gram-negative versus Gram-positive bacteria. Infection and Immunity 2003; 71(10): 5803–5813.
21. Brasil AR, Norton RC, Rossetti MB, Leão E, Mendes RP. C-reactive protein as an indicator of low intensity inflammation in children and adolescents with and without obesity. J Pediatr (Rio J) 2007; 83(5): 477–480.
22. Peltola H, Jaakkola M. C-reactive protein in early detection of bacteremic versus viral infections in immunocompetent and compromised children. J Pediatr. 1988; 113(4)oct: 641–646.