C reactive protein in the evaluation of febrile illness

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SUMMARY We studied prospectively 154 febrile children to determine the diagnostic value of the quantitative serum C reactive protein concentrations (CRP). Children with acute otitis media, acute tonsillitis, or treated with antibiotics during the two previous weeks and infants less than 2 months of age were excluded. Ninety seven children were from private paediatric practice and 57 were patients who had been admitted to hospital. The comparison group consisted of 75 children with confirmed bacterial infections whose CRP values were recorded retrospectively. In the study group 35 (23%) children had a confirmed viral infection, 92 (59%) had a probable viral infection as judged from the clinical picture and outcome of the illness, and 27 (18%) had a bacterial or probable bacterial infection. When the duration of the disease was more than 12 hours and the CRP value less than 20 mg/l, all children had a confirmed or probable viral infection. Nine children (one from the study group and eight from the comparison group) were found to have a septic infection and a CRP value of 20 mg/l or less. In all these cases, however, the duration of the symptoms was less than 12 hours. In addition CRP ≤ 20 mg/l was found in five (14%) children with urinary tract infection in the comparison group. CRP values of 20–40 mg/l were recorded in children with both viral and bacterial infections. A CRP value ≥ 40 mg/l detected 79% of bacterial infections with 90% specificity. Our data show that determination of serum CRP concentrations is a valuable tool in evaluating children who have been ill for more than 12 hours.

Febrile children comprise one of the most important problems in paediatric practice. The major diagnostic goal is to distinguish bacterial and treatable infections from viral ones. Recent studies have shown serum C reactive protein (CRP) determination to be useful in the diagnosis of invasive bacterial infections.^{1–3} We studied the value of CRP in evaluating febrile children with a special attention to respiratory virus infections.

Patients and methods

Study group. From March 18 to May 31 1984, 154 consecutive febrile children with respiratory tract infection or without localising signs of infection were studied prospectively. Of these, 97 were outpatients from private paediatric practice and 57 were patients who had been admitted to our Department of Pediatrics. Fever were defined as an axillary temperature of 38°C (100.4°F) or higher. Children with acute otitis media, acute tonsillitis, or treated with antibiotics during the two previous weeks and infants less than 2 months of age were excluded.

Children with acute otitis media were excluded because they are routinely treated with antibiotics. Children with tonsillitis were excluded because a separate study was being carried out of tonsillitis.

There were 70 girls and 84 boys. Seventy eight (51%) children were less than 2 years old, 42 (27%) between 2 and 6 years, and 34 (22%) over 6 years old. The mean age was 3 years 4 months with a range of 2 months to 14 years.

The outpatients received a questionnaire for follow up of the symptoms and signs of the disease. Re-examination was performed in 83 of 97 outpatients seven days after the first visit, and the questionnaire was returned. The follow up was conducted by telephone in another 13 patients, and one patient returned the questionnaire by mail. The inpatients were treated in the hospital until afebrile and were not routinely re-evaluated.

Blood was taken for routine haematologic tests (total white blood cell counts (WBC) and differential counts, erythrocyte sedimentation rate (ESR), and CRP). Nasopharyngeal mucus aspirates for rapid diagnosis of virus was taken from 135 children.

Further studies were performed only on specific clinical indications. Urine analysis with culture was performed in 68 patients, throat culture for β haemolytic streptococci in 34 patients, blood culture in 29 patients, chest roentgenogram in 27 patients, bacterial antigen (*Haemophilus influenzae* type B, *Streptococcus pneumoniae*, *Neisseria meningitidis*) detection from the urine in 14 patients, lumbar puncture in 11 patients, and bacterial antigen detection in serum in eight patients. Pneumococcal antibodies from paired sera were studied in 20 children.

Comparison group. The comparison group for CRP concentrations, total WBC counts, and ESRs in bacterial infections included 75 children with proved bacterial disease treated in the same hospital from January 1 1982 to February 28 1984. The case records of these children were reviewed retrospectively. There were 22 boys and 53 girls, and the mean age was 2 years 9 months with a range of 2 months to 16 years. Thirty six patients had urinary tract infection (bladder tap culture positive), 21 meningitis (spinal fluid culture positive), 11 epiglottitis (blood culture positive), five septicaemia, and two cellulitis with a positive blood culture.

Determination of CRP. The CRP values of the patients who had been admitted to hospital were determined on admission quantitatively by turbidometry (Multistat III, IL) using standards from Behringwerke AG and antiserum from Dakopatts AS. In the outpatients the CRP was quantified with a rapid liquid phase immunoprecipitation technique⁴ using reagents (CRP kit cat no D-147 and CRP Buffer cat no D-179) from Orion Diagnostica, Finland.

Enzyme immunoassay for viral antigens. Nasopharyngeal secretion specimens were collected by suction through nostrils with a disposable mucus extractor (Vygon, Ecouen, France). The specimen volume obtained was usually 0.5–2.0 ml. The specimens were tested parallel for respiratory syncytial virus, adenovirus, influenza A and B virus, and parainfluenza virus type 1, 2, and 3 antigens by analogous enzyme immunoassays. The indirect enzyme immunoassay was used as described previously.⁵

Enzyme immunoassay for pneumococcal antibodies. IgM, IgA, and IgG antibodies to pneumococci were assessed by an enzyme immunoassay with a 14 valent pneumococcal polysaccharide vaccine (Pneumovax^R; Merck, Sharp and Dohme) as antigen. The antigen was coupled (1.4 μ g/ml) onto

polystyrene microtitre plates (Linbro/Titertek, Flow Laboratories, Hamden, Connecticut). The coupling buffer was 0.05M phosphate buffered saline (pH 7.4). The same buffer supplemented with 1% normal sheep serum was used for saturating the plates and as an assay buffer. Sera were diluted 1:100 for incubation. After incubation conjugated antibodies to human IgM, IgA, or IgG (Orion Diagnostica, Espoo, Finland) were added. P-nitrophenylphosphate (Orion Diagnostica) was used as substrate, and the optical density was measured at 405 nm by a vertical beam photometer (Titertek/Multiskan, Eflab Oy, Helsinki, Finland). A standard curve was prepared for each immunoglobulin class. The results were expressed as relative units (EIU), where one unit was 1/100 of corresponding antibody concentration in the reference serum.

Statistics. Statistical analysis was carried out by the one way analysis of variance and the Tukey-Kramer method using logarithmic CRP and ESR values. P values less than 0.05 were considered significant.

Results

Disease range. In the study group 35 children (23%) had a confirmed viral disease, 27 (18%) had a bacterial or probable bacterial disease, and 92 (59%) had a probable viral infection. Sixty (65%) patients with probable viral infection had respiratory symptoms. Eighty one (88%) of the children with probable viral infection recovered within a week without treatment with antibiotics. The remaining 11 patients were treated with antibiotics for various reasons.

The viruses found by direct antigen detection were parainfluenza type 3 (14 cases), influenza B (12), parainfluenza type 1 (7), adenovirus (3), and respiratory syncytial virus (1). One patient had both parainfluenza type 3 and respiratory syncytial virus simultaneously. One child had parainfluenza type 3 virus at the first visit and influenza B virus at the follow up visit. Table 1 shows the diagnoses of the patients. The aetiological agent of all urinary tract infections was *Escherichia coli*. The causative agent in the two cases of meningitis was *Haemophilus influenzae* type B, cultured from the spinal fluid and the blood. Sixteen children had lobar pneumonia with high fever, and they all responded to treatment with antibiotics within 12–24 hours, fulfilling the clinical criteria of bacterial pneumonia. Pneumococcal antibodies were raised in four of these patients (IgM 7.4–13.1, IgM 7.5–30.1, IgM 12.5–24.5, and IgA 0.6–22.3, respectively). One patient was positive for pneumococcal antigen in the urine and

Table 1 Diagnoses of patients of the study group

Outpatients (n=97)		Patients who had been admitted to hospital (n=57)	
Disease	No	Disease	No
<i>Proved or suspected viral diseases</i>			
Upper respiratory tract infection	52 (19)*	Fever without localising signs	8 (1)*
Fever without localising signs	32 (6)*	Laryngitis	7 (4)*
Pharyngitis	3	Whooping cough	7
Urticaria	2	Upper respiratory tract infection	7 (4)*
Laryngitis	1	Febrile convulsions	3 (1)*
Whooping cough	1	Exanthem subitum	2
Exanthem subitum	1	Purpura non ultra descriptus	1
<i>Proved or suspected bacterial diseases</i>			
Lobar pneumonia	2 (2)**	Lobar pneumonia	14 (4)**
Streptococcal pharyngitis	2 (2)**	Urinary tract infection	5 (5)**
Urinary tract infection	1 (1)**	Meningitis	2 (2)**
		Pneumococcaemia	1 (1)**

*Confirmed viral infection (positive for nasopharyngeal secretion).

**Bacterial culture or antigen detection in serum/urine positive or serologically confirmed bacterial infection.

Table 2 C reactive protein values (CRP), white blood cell count (WBC), and erythrocyte sedimentation rate (ESR) in patients with bacterial, viral, and probable viral infections

	CRP (mg/l)		WBC count ($\times 10^9/l$)		ESR (mm/h)	
	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
Study group:						
Bacterial infections	27	98 (67)	27	18.1 (6.7)	23	57 (30)
Viral infections	35	13 (12)	35	8.5 (4.5)	32	16 (11)
Probable viral infections	92	17 (20)	92	9.2 (5.3)	84	16 (12)
Comparison group:						
Septic infections	39	115 (71)	39	18.7 (7.8)	31	46 (32)
Urinary tract infections	36	89 (61)	36	19.8 (6.3)	33	53 (33)

serum, and one patient had a positive blood culture for *Haemophilus influenzae* type B.

CRP, WBC count, and ESR. Table 2 shows the mean (SD) values of CRP, WBC count, and ESR. The differences between bacterial and viral diseases and probable viral infections were significant ($p < 0.05$) in all these laboratory tests. There was no significant difference between viral and probable viral diseases, nor in bacterial infections between the study group and the comparison group.

Because CRP values may not begin to rise in some patients until 12–22 hours after onset of stimulus,⁶ patients who had been sick for less than 12 hours were excluded from the calculations of the sensitivity and specificity of CRP, WBC count, and ESR for bacterial infections. In three patients of the study group the duration of symptoms was less than 12 hours; one had pneumococcaemia, one bacterial pneumonia (confirmed serologically), and one meningitis. One of these patients had CRP < 20 mg/l. Table 3 shows the sensitivity, specificity, and predic-

tive values of CRP, WBC count, and ESR for bacterial infections in the study group. Of the patients with viral or probable viral infection, 75% had CRP less than 20 mg/l. Of the patients with CRP ≥ 40 mg/l, 59% had bacterial infection, and 90% of patients with viral or probable viral infection had CRP < 40 mg/l (Figure).

Of the patients with bacterial disease, 67% had WBC count $\geq 15 \times 10^9/l$, and 87% of patients with viral or probable viral infection had WBC count $< 15 \times 10^9/l$. ESR ≥ 30 mm/h detected 91% of patients with bacterial infections, and 89% of patients with viral or probable viral infection had ESR < 30 mm/h.

In the comparison group there were eight patients with septic bacterial infections with duration of symptoms for less than 12 hours and CRP ≤ 20 mg/l. In addition there were five children with urinary tract infection with CRP ≤ 20 mg/l.

Outcome and treatment. Eighty three outpatients attended the follow up visit. Eight children had otitis

Table 3 Sensitivity,* specificity,[†] positive predictive value,[‡] and negative predictive value[§] of C reactive protein concentrations (CRP), white blood cell count (WBC), and erythrocyte sedimentation rate (ESR) for bacterial infections in the study group of 151 children who had been ill for more than 12 hours (values are %)

		Sensitivity	Specificity	Positive predictive value	Negative predictive value
CRP (mg/l)	≥20	100	75	43	100
	≥40	79	90	59	96
	≥80	63	98	88	93
WBC (×10 ⁹ /l)	≥10	96	66	35	99
	≥15	67	87	50	93
	≥20	38	97	69	93
ESR (mm/h)	≥30	91	89	61	98
CRP (mg)/WBC (×10 ⁹ /l):	≥20/≥15	67	95	70	94
	≥40/≥15	58	96	74	92
	≥80/≥20	33	100	100	89
ESR (mm/h)/WBC (×10 ⁹ /l):	≥30/≥15	59	95	68	92

*Probability that test results will be positive when bacterial disease is present.

[†]Probability that test results will be negative when bacterial disease is not present.

[‡]Probability that bacterial disease is present when results of test are positive.

[§]Probability that bacterial disease is not present when results of test are negative.²⁰

media, six of whom had had a confirmed viral disease at the first visit. Fourteen children had minor respiratory symptoms, and one had wheezy bronchitis. All but one of the children with a new viral infection (influenza B) and otitis were afebrile. The children contacted by phone or by mail had recovered uneventfully.

Seven of the 97 outpatients were treated with antibiotics at the first visit. Of these, two had alveolar pneumonia, one had urinary tract infection, and two had influenza B virus infection. Two patients with streptococcal pharyngitis were treated after their throat culture proved positive. In the other eleven outpatients treated, antibiotics were started during follow up or at the follow up visit. Eight of the treated children had acute otitis media, one had lymphadenitis, one had upper respiratory tract infection, and one had a positive throat culture for β haemolytic streptococci group G, although she did not have pharyngitis. All 22 bacterial infections of patients who had been admitted to hospital were treated with antibiotics. Altogether, 18 outpatients (19%) and 32 patients who had been admitted to hospital (56%) were treated with antibiotics.

Discussion

This study differs from previous studies of CRP in that rapid detection of respiratory virus antigens in nasopharyngeal mucus permitted us to diagnose the specific viral aetiology within 30 hours in 35 (23%) patients. The results show that the quantitative CRP test is a valuable tool for distinguishing viral infections from bacterial infections in febrile children. If the duration of the illness was more than 12 hours and the CRP value was less than 20 mg/l all children investigated had viral or probable viral infection. Seventy six (78%) of the 97 febrile children studied in private practice and 19 (34%) of the patients who had been admitted to hospital belonged to this group. There were nine children (one in the study group and eight in the comparison group) with CRP ≤ 20 mg/l who had an invasive bacterial infection. In all cases the duration of the disease was 12 hours or less, which suggests that the CRP test is good for screening only in patients who have been sick for more than 12 hours. McCabe and Remington reported CRP values less than 20 mg/l in 14% of 36 patients with bacteraemia.⁷ The study, however, did not report the exact duration of the symptoms of the patients. CRP was ≤ 20 mg/l in five (14%) of the patients with urinary tract infection in the comparison group of this study, suggesting that the infection would have been in bladder level. Jodal *et al* have shown that serum CRP concentrations will not increase in cystitis.⁸

A CRP value exceeding 20 mg/l has been suggested as a screening limit for bacterial infections.¹ In this study we found its sensitivity for bacterial infection to be 100%, but the false positive rate was 25% and the positive predictive value only 43%. Our data prefer CRP value 40 mg/l as a screening limit, because its specificity (90%) and positive predictive value (59%) are better and sensitivity is still 79%. Raised CRP values (≥ 40 mg/l) were found in one (3%) of 35 patients with confirmed viral infection and in 13 (14%) of the 91 patients with probable viral illness. We have shown previously that in children who were admitted to hospital with adenovirus, influenza, parainfluenza, or respiratory syncytial virus infection CRP values more than 40 mg/l were recorded in 38%, 20%, 0%, and 13% of patients, respectively.⁹ Some of these patients may have undergone a concomitant bacterial infection, which remained undiagnosed. On the other hand, it is probable that some viral infections, especially adenovirus infections,¹⁰ may induce so much tissue damage that CRP values will be raised.

Many previous studies have evaluated the value of WBC count, ESR, and CRP in the detection of serious bacterial infections.¹¹⁻¹⁵ No test alone or in combination has 100% sensitivity and specificity for bacterial infections. Rasmussen and Rasmussen have shown that WBC and differential counts have little value in distinguishing bacterial infections from viral infections.¹¹ McCarthy *et al* found a clinically useful association between a WBC count $\geq 15 \times 10^9/l$ and ESR ≥ 30 mm/h and pneumonia or bacteraemia in children less than 2 years old with temperatures $\geq 40^\circ\text{C}$.¹⁶ In a further study they showed that ESR ≥ 30 mm/h was more sensitive than a positive slide test for CRP (1:50) in bacteraemia, pneumonia, and other bacterial infections, but it was less specific than a positive CRP test or a high WBC count.¹⁷

In this study the best single indicator of bacterial infection was ESR ≥ 30 mm/h with a sensitivity of 91% and a specificity of 89% (Table 3). In confirmed viral and probable viral infections ESR was less than 30 mm/h in 89% and 88%, respectively. The differences between ESR ≥ 30 mm/h and CRP ≥ 40 mg/l, however, were small, and the CRP test has several other advantages over ESR. CRP can be measured quantitatively with a simple and inexpensive method in 15 minutes.⁴ It increases within hours and, most important, CRP decreases during successful treatment with a half life of three days.¹⁸ The decrease is much more rapid than that of ESR.¹² The rapid decrease of CRP permits the use of this test during the follow up of patients with bacterial infections. Peltola *et al* have recently shown that a reincrease of CRP during the treatment of bacterial meningitis reflects complications.¹⁹

The determination of CRP combined with a careful clinical examination was useful when the necessity of treatment with antibiotics was being considered. Only seven of 97 outpatients were treated with antibiotics at the first visit. The uneventful recovery of 79 (88%) of the untreated outpatients justifies our antibiotic policy.

In conclusion, our data show that determination of CRP is a valuable tool in evaluating febrile children. When the duration of the illness is 12 hours or more and serum CRP concentration less than 20 mg/l and there is no identifiable focus of bacterial infection—that is, otitis, tonsillitis, cystitis, etc—the disease is most probably a benign viral infection. CRP values of 20–40 mg/l may be recorded both in viral and bacterial infections. Most febrile children with CRP $\geq$ 40 mg/l have a bacterial infection. Finally, it should be emphasised that no laboratory test will replace careful clinical judgment of a febrile child.

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