Use of C-Reactive Protein in Differentiation Between Acute Bacterial and Viral Otitis Media

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ABSTRACT. *Objectives.* **The objectives of this investigation were: (1) to determine degree of elevation of serum C-reactive protein (CRP) in uncomplicated acute otitis media (AOM); (2) to compare serum CRP levels in bacterial and viral otitis media; and (3) to determine whether a single serum CRP level, obtained early in the course of AOM, could be used to differentiate between viral and bacterial otitis media.**

Design and methods. **Sera were obtained from otherwise healthy infants and children with AOM who were 3 months to 7 years of age between 1989 and 1991. Tympanocentesis, bacterial and viral studies of the middle ear fluids, virologic studies of nasal wash specimens, measurements of serum antibody titers to respiratory viruses, blood counts, and quantitation of serum CRP concentrations were performed. After the initial tympanocentesis, an oral antibiotic was given for the next 10 days. The patients were clinically reevaluated over next 4 weeks.**

Outcome measures. **Serum CRP concentrations were compared among subjects with AOM who were divided into four groups based on the results of bacteriologic and virologic studies: group I, Bacterial infection (n = 82); group II, bacterial and viral infections (n = 69); group III, viral infection (n = 12); and group IV, no identifiable pathogen (n = 22).**

Results. **There was no statistical difference in serum CRP values among the four groups. The ranges of CRP were less than 0.6 to 22.8, less than 0.6 to 17.8, less than 0.6 to 2.0, and less than 0.6 to 6.8 mg/dL in groups I through IV, respectively. However, when CRP values in bacteria-positive cases were compared with CRP concentrations in bacteria-negative cases (1.58 ± 3.16 vs 0.64 ± 1.24 mg/dL), the difference was statistically significant. Furthermore, a significantly higher proportion of bacteria-positive cases had serum CRP concentrations greater than 2 mg/dL, compared with those in bacteria-negative cases. There was no correlation between initial CRP values and clinical findings and/or the clearance of bacteria from the middle ear. After 10 days of antibiotic treatment, CRP values returned to normal (<0.6 mg/dL) in all cases.**

Conclusion. **In AOM, the range of serum CRP varied from less than 0.6 to 22.8 mg/dL. High CRP values (>2.0 mg/dL) were associated with 22% of cases of bacterial AOM but only with 6% of nonbacterial AOM. High levels of serum CRP were found to be very specific in detecting bacterial AOM, and no cases of viral AOM without a concurrent bacterial infection were found to exhibit high serum levels of CRP.** ***Pediatrics*** **1995;95:664–669;** ***C-reactive protein, acute otitis media, viral otitis media.***

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Received for publication Jul 7, 1994; accepted Sep 8, 1994.

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ABBREVIATIONS. AOM, acute otitis media; CRP, C-reactive protein; MEF, middle ear fluid; WBC, white blood cell.

Acute otitis media (AOM), a very common pediatric disease, is generally considered to be a bacterial infection and is treated with antibiotics.[1] In the last decade, however, several studies have shown that AOM has both viral and bacterial causes.[2–4] Nevertheless, bacterial and viral otitis media cannot be differentiated on clinical grounds alone, and more definitive diagnostic procedures such as cultures of the middle ear fluids are not generally performed. In addition, the necessity of antibiotic therapy in AOM has been a subject for debate, because many infants and children with AOM resolve their infections without therapy.[5–7] Thus it is desirable to determine the cause of AOM early in the course of the disease to differentiate between bacterial and viral causes and to decide whether antibiotics can be withheld in some specific cases.

In the literature, one of the parameters used to differentiate between serious bacterial illness and viral infections has been the quantitation of serum C-reactive protein (CRP), a prototypic acute-phase reactant predominantly synthesized by the hepatocytes.[8–16] Normal values of serum CRP are very low; the median value in healthy adults is less than 0.8 mg/dL, with 90% having less than 0.3 mg/dL and 99% having less than 1.0 mg/dL.[17,18] 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.[14,19,20]

In contrast to the studies of systemic infections, very little information is available on serum CRP levels in local mucosal diseases such as AOM. Serum CRP has been shown to be elevated in bacterial otitis media, compared with otitis with sterile effusion,[21–24] but no data exist on serum CRP levels in viral otitis media or the use of serum CRP levels to differentiate between viral and bacterial otitis media.

The purposes of this study were to determine degree of elevation of serum CRP in uncomplicated

AOM, to compare serum CRP levels in both bacterial and viral otitis, and to determine whether a single serum CRP level, obtained early in the course of AOM, could distinguish between viral and bacterial otitis media.

METHODS

Samples and Treatment of Patients

Sera were obtained from 185 otherwise healthy infants and children with AOM who were enrolled in two antibiotic efficacy trials between October 1989 and April 1991 as previously described.[4] The diagnosis of AOM was based on symptoms of fever, irritability or earache, signs of inflammation of the tympanic membrane (red or yellow color or bulging), and the presence of middle ear fluid (MEF) as documented by tympanocentesis. No patient received antibiotics in the previous week. At enrollment, tympanocentesis was performed in all subjects, and MEF was obtained for bacterial and viral studies. A nasal wash specimen was also obtained for rapid viral antigen detection and viral cultures. Venous blood samples were obtained at enrollment for determination of serum CRP, white blood cell (WBC) count, and acute viral antibody titers, and at 9 to 12 days for convalescent viral antibody titers. After enrollment and specimen collection, each patient was given an antibiotic (Cefpodoxime proxitil, clarithromycin, or amoxicillin-clavulanate) for 10 days. Each child was clinically assessed 3 to 5 days (visit 2), 9 to 12 days (visit 3), and 1 month (visit 4) after initiation of therapy. Clinical outcome was defined as good when AOM seemed to be improved or cured on visit 2 and/or 3 and defined as poor (persistent otitis) if there was no clinical improvement or a persistence of bacteria in MEF (bacteriologic failure) on visit 2 and/or 3.

Diagnosis of Bacterial and/or Viral Otitis Media

The subjects were divided into four groups based on the presence or absence of bacteria and/or virus in the MEF and nasal wash specimen and the rise in serum titers of antibodies to a respiratory virus. The definition of each group and the number of patients in each group are shown in Table 1. Our previous studies[4,25] did not show significant differences in the degree of inflammation and clinical and bacteriologic outcomes between AOM patients with viral infection of the middle ear alone and those with AOM and viral respiratory tract infection (no virus in MEF) as documented by detection of virus in the nasal wash specimen or positive viral serologic studies.

CRP Assay

Sera were stored at −70°C until they were analyzed. Serum CRP was quantified by rate nephelometry using automated instrumentation and CRP reagents (Beckman Instruments, Inc, Diagnostic Systems Group, Brea, CA). The system was calibrated by using a standard test serum (CRP calibrate serum, Beckman Instruments) based on well-characterized primary standards prepared by the manufacturer. The range of serum CRP measured by this instrument was from 0.4 to 72 mg/dL. The coefficient of variation for the procedure was 5% or less. In this laboratory, serum CRP concentrations in 100 healthy children were less than 0.6 mg/dL.

Statistical Methods

Student's t test, χ^2 analysis, and Pearson correlations were used for statistical analysis of categorical data, and the Kruskal-Wallis test was used to compare the group means of data not normally distributed. $P < .05$ was considered to be statistically significant.

RESULTS

A summary of the demographic and clinical features of patients in each group is found in Table 2. Fifty seven percent were boys, and 43% were girls. Thirty nine percent were white, 32% black, and 29% hispanic. The ages ranged from 3 months to 7 years; the mean age was 27 months. The mean duration of symptoms of AOM at time of presentation was 2.3 days. Table 3 details the microbiologic data of the four groups.

Serum CRP concentrations were measured in both acute and/or convalescent sera from all patients. Serum CRP concentrations varied from less than 0.6 to 22.8 mg/dL. Figure 1 shows data on CRP concentrations in acute sera of each patient group. The ranges of CRP were less than 0.6 to 22.8, less than 0.6 to 17.8, less than 0.6 to 2.0, and less than 0.6 to 6.8 mg/dL, respectively, in groups I through IV. Using analysis of variance, no statistical differences were detected among the four groups. To determine whether the site of viral infection affects CRP concentrations, 69 patients in group II were divided into three subgroups based on the site of viral infection. Seventeen patients had virus or virus antigen in the MEF without presence of the virus or antigen in nasal wash specimen; CRP values in these patients ranged from less than 0.6 to 9.86 mg/dL (mean ± SD, 2.65 ± 4.56). Eighteen cases had both viral infection of the ear and respiratory tract (positive nasal wash specimen and/or viral serologic studies); CRP values in this group ranged from less than 0.6 to 5.0 mg/dL (mean ± SD, 1.0 ± 1.09). The last subgroup consisted of 34 patients with AOM, for whom viral infection of the respiratory tract was diagnosed but no virus or virus antigen was detected from the MEF. CRP values in the last group ranged from less than 0.6 to 7.85 (mean ± SD, 1.45 ± 1.69). No statistical differences were detected among these three subgroups (analysis of variance). Of 12 patients in group III, only 1 had a virus in the MEF; 11 patients had no pathogens in the MEF and positive nasal wash specimens and/or viral serologic studies. The number in group III was too

TABLE 1. Categorization of Patients (n = 185) with AOM According to the Presence or Absence of Bacteria or Viruses

Groups	Categorization	No. in Each Group
I	Bacterial infection, (bacteria alone in MEF, no evidence of viral infection*)	82
II	Bacterial and viral infection, (bacteria and virus in MEF or bacteria in MEF plus evidence of respiratory viral infection*)	69
III	Viral infection (virus alone in MEF or no pathogen in MEF plus evidence of respiratory viral infection*)	12
IV	AOM associated with no identifiable pathogen	22

* Evidence of respiratory viral infection indicates detection of a virus in a nasal wash specimen, or positive viral serologic studies. Viral serologic studies (respiratory syncytial virus, parainfluenza virus types 1, 2, and 3, influenza A and B viruses, and adenovirus) were performed in all patients with of AOM who had no virus or virus antigen detected from MEF or nasal wash specimens. A fourfold or greater rise in titers was considered a positive result.

TABLE 2. Demographic and Clinical Features in Each Group

	Group I Bacterial Infection (n = 82)	Group II Bacterial and Viral Infections (n = 69)	Group III Viral Infection (n = 12)	Group IV No Detectable Pathogen (n = 22)
Sex				
Male	41	45	7	12
Female	41	24	5	10
Age (mo)				
Range	3–89	3–65	4–75	3–81
Mean	23.4	24.9	30.4	29.9
Race				
White	28	32	4	8
Hispanic	28	19	3	4
Black	26	18	5	10
Duration of AOM Symptoms (d)				
Range	1–7	0–7	0–7	1–7
Mean	2.5	2.4	2.6	1.9
Fever >38.5°C (%)	16 (20%)	15 (21%)	3 (25%)	2 (9%)
Laterality of AOM				
Unilateral	14 (17%)	12 (17%)	7 (58%)	5 (23%)
Bilateral	68 (83%)	57 (83%)	5 (42%)	17 (73%)
WBC count > 15 000/mm³	45 (55%)	38 (55%)	2 (18%)	7 (31%)
Absolute neutrophil count (>5000/mm³)	62 (75%)	36 (52%)	3 (27%)	7 (31%)

small to analyze statistically the effect of the site of viral infection on CRP concentration.

To determine whether bacterial infections (with or without viral infection) are associated with elevated serum CRP values, we compared serum CRP concentrations in patients with bacterial infections (groups I and II) with those without bacterial infections (groups III and IV) (Table 4). Patients with bacterial infections (n = 151) tended to have higher CRP levels (P = .09, χ^2 analysis) compared with those without bacterial infections (n = 34). Because of the skewed distribution, a rank order analysis was performed (Kruskal-Wallis test), and the difference between the two groups was found to be significant (P < .006) (Fig 2).

Because increased CRP levels of 2 mg/dL or higher are often associated with acute bacterial infections,[8,26] we compared the proportion of sera with CRP values higher than 2 mg/dL in bacteria-positive cases and the bacteria-negative group (Table 5). A significantly higher proportion of bacteria-positive cases had CRP values higher than 2.0 mg/dL (P = .03, χ^2 analysis).

To determine the usefulness of a single CRP value in differentiating bacterial infection from nonbacterial disease, we calculated sensitivity, specificity, and predictive values of serum CRP in bacteria-positive and bacteria-negative groups, using 2.0 mg/dL as the cutoff value. The sensitivity of a CRP value higher than 2 mg/dL in the diagnosis of bacterial infection was 22%, whereas the specificity was 94%; the positive predictive value was 94.2%; and the negative predictive value was 21%.

To determine whether high CRP levels are associated with persistent otitis (outcomes at visits 2 and 3; see "Methods"), we compared CRP levels in patients with good and poor outcomes. CRP levels were not different in the two groups (P = .46). Similarly, CRP levels were not different in patients with unilateral or bilateral otitis media (P = .31).

CRP was also determined in 145 convalescent

TABLE 3. Microbiologic Data in Four Patient Groups*

Study Group	Number (%)	Microorganisms (n)
I (bacterial infection)	82 (44%)	*Streptococcus pneumoniae* (23) *Hemophilus influenzae* (22) *Moraxella catarralis* (10) Group A streptococci (3) *Staphylococcus aureus* (2) Others (22)†
II (bacterial and viral infections)	69 (37%)	Respiratory viruses (53), with SP, HI, and/or MC Herpes viruses (9), with SP, HI, and/or MC Enteroviruses (7), with SP, HI and/or MC
III (viral infection)	12 (7%)	Respiratory viruses (6) Herpes viruses (4) Enteroviruses (2)
IV (no detectable pathogen)	22 (12%)	No pathogen

* All bacteria were isolated from the MEF; viruses were detected both in the MEF or nasal wash specimens. Respiratory viruses are respiratory syncytial virus, influenza virus A or B, parainfluenza virus, adenovirus, and rhinovirus. Herpes viruses are herpes simplex virus or cytomegalovirus. Enteroviruses are coxsackieviruses, echoviruses, and enteroviruses.
† Twenty-two cases were associated with two or more bacterial pathogens.

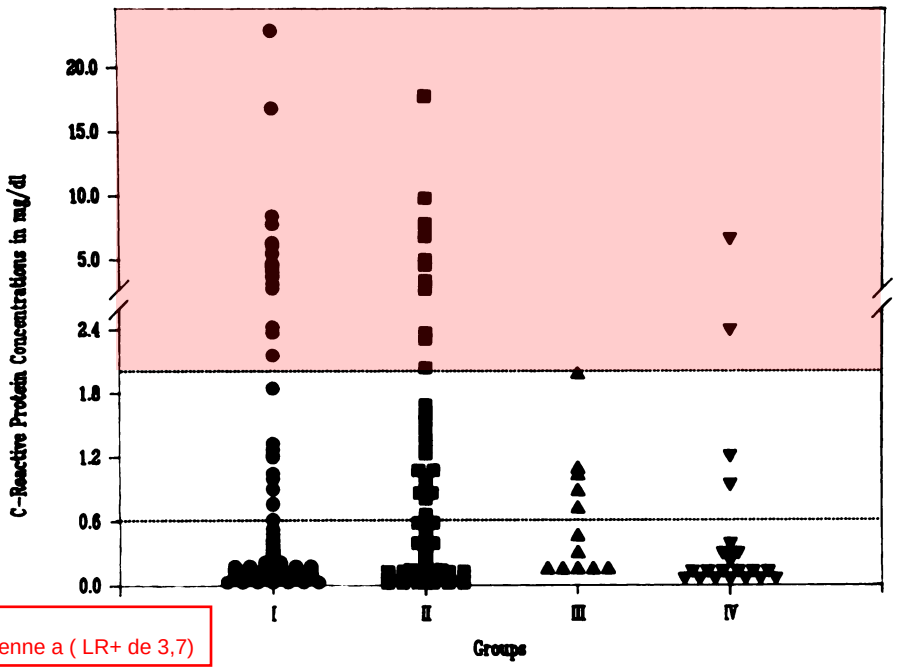

Fig 1. Serum CPR concentrations (milligrams per dL) in patients from groups I through IV. Group I, bacterial infection; group II, bacterial and viral infections; group III, viral infection; group IV, AOM associated with no identifiable pathogens.

Une CRP < 20 mg/l n'exclue rien (LR- de 0,8)
Une CRP > 20 mg/l est en faveur d'une infection bactérienne a (LR+ de 3,7)

TABLE 4. Comparison of CRP Values in Bacterial and Non-bacterial AOM*

Groups	No. of patients	Mean ± SD
I and II (bacteria positive)	151	1.6 ± 3.2
III and IV (bacteria negative)	34	0.6 ± 1.2

* Chi square analysis; P = .09.

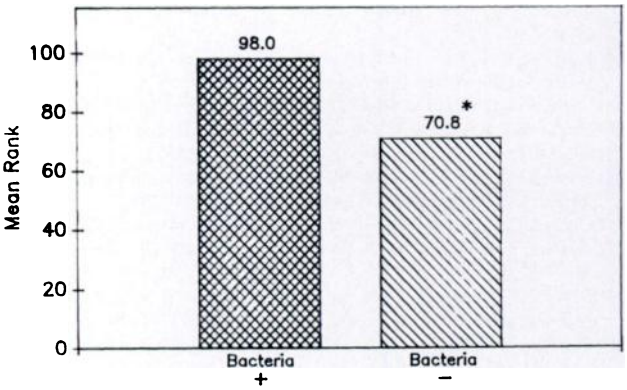

Fig 2. Kruskal-Wallis rank order analysis comparing bacteria-positive and bacteria-negative groups (P < .006).

TABLE 5. Comparison Between Bacteria-positive and Bacteria-negative Groups Using a Serum CRP Cutoff Value of 2.0 mg/dL*

CRP mg/dL	Bacteria-positive Cases (Groups I and II)	Bacteria-negative Cases (Groups III and IV)
≤2.0	118 (78%)	32 (94%)
>2.0	33 (22%)	2 (6%)

* Chi square analysis; P = .03.

- Très peu d' OMA virales ont une CRP > 20 mg/L (6%)
- 80% des OMA bactériennes ont une CRP basse < 20 mg/l

samples drawn between days 9 and 12; none was higher than 0.6 mg/dL.

We also found higher WBC counts in the bacteria-positive group when compared with the bacteria-negative group (P = .03, Pearson correlation). The increase in WBC was principally attributable to a rise in neutrophils. The WBC counts, absolute neutrophil counts, and band counts and serum CRP values were analyzed in all four groups. Significant correlations (Pearson correlation) were found between serum CRP and WBC counts (P = .0008), and between serum CRP values and absolute neutrophil counts (P = .0001), but there was no correlation between serum CRP levels and band counts (P = .46).

DISCUSSION

The cause of AOM can be determined only by tympanocentesis, an invasive method not routinely performed in clinical practice. Numerous studies have used fever, WBC count, and serum CRP levels to differentiate bacterial illness from viral infection.[27-31] In our study, fever and duration of illness were also found to be poor indicators of the cause of AOM.

There are five previous reports of serum CRP levels studied specifically in AOM.[21-24,32] None studied MEF for viral cause, and all defined their data as bacteria positive and/or sterile effusion, although Principi et al[21] obtained paired sera for viral serologic studies. Quantitative CRP in AOM was studied by Rosen et al[32] in 1983. No statistically significant differences were found when their bacteria-positive and -negative cases, as defined by cultures of nasopharyngeal swabs, were compared. No diagnostic tympanocenteses were done in that study. Therefore, the cause of the middle ear disease may not have been accurately determined, because nasopharyngeal cultures are not highly correlated with causative organisms in AOM.[1] Principi et al[21] found elevated serum CRP values (>1.5 mg/dL) in 71% and 67% of subjects in bacterial and sterile AOM (with serologic evidence of respiratory viral infection), respectively, and

concluded that there was no statistical difference between CRP values and AOM cause.

The current study thus seems to be the first one to compare blood CRP and WBC count in documented cases of either bacterial or viral AOM. In the study, highly elevated serum CRP levels were found to be associated with bacterial AOM, and those patients had higher CRP levels than those without bacterial infection. This is in agreement with studies by Komoroski et al,[22] Del Beccaro et al,[23] and Karma et al.[24] Ruuskanen et al[33] demonstrated that in viral AOM, serum CRPs are usually normal. However, adenoviral infection may be associated with very high CRP levels, probably because of liver involvement. In this regard, our data conflict with those of Ruuskanen et al. None of our patients with viral infections, including adenoviral infection (group III), had serum CRP values greater than 2.0 mg/dL.

Opinions also vary on what serum CRP levels should be used as a cutoff index in categorizing the severity of inflammatory responses and in helping to define disease categories. Some have used 1.0 mg/dL,[34] whereas others use 2.0 mg/dL.[11,26] One study suggested that a CRP level of greater than 4.0 mg/dL can be used to exclude a viral cause for illness in children.[20] In our study, a cutoff value of greater than 2.0 mg/dL seemed specific in excluding viral middle ear infection, although the sensitivity in detecting bacterial ear infection was low.

Because of the low sensitivity of this test (22%) and the high specificity (94%), a serum CRP value of less than 2.0 mg/dL would fail to differentiate between viral and bacterial causes of AOM, but a serum CRP level of more than 2.0 mg/dL would highly suggest bacterial otitis media. In that case, if a decision to initiate antibiotic therapy were to be based on high serum CRP, a large number of children with bacterial otitis media would be missed. Therefore, serum CRP levels cannot be used to help decide whether antibiotic treatment can be withheld in some cases of AOM.

It is of great interest that a high correlation was found in our study between serum CRP levels and absolute neutrophil count, and that both parameters were specific in detecting bacterial AOM. This suggests that bacterial AOM 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.[35] Therefore, it is likely that the quantitation of these types of cytokines in the peripheral blood may aid not only in predicting the microbial cause of AOM, but also in understanding the systemic effects of AOM in such patients.

ACKNOWLEDGMENTS

This study was funded in part by a grant from the National Institutes of Health (DC-01738).

We thank Mary Douglas for technical assistance and Sandra Fuentes for manuscript preparation.

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CONGRESSIONAL STUDY QUESTIONS VALUE OF OUTCOMES RESEARCH

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Clinical practice guidelines themselves came under fire in the Office of Technology Assessment report because of *how they are developed and disseminated*. Simply issuing them to physicians often has no effect, and unless they promote "extremely compelling" practices or are issued by credible organizations, they may have the unintended effects as clinicians try to circumvent them . . .

The report is available for $20 from the US Government Printing Office. S/N 052-003-01389-4. Call 202/512-1800.

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Noted by J.F.L., MD

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Pediatrics 1995;95;664

PEDIATRICS®
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