Serum C-Reactive Protein, Erythrocyte Sedimentation Rate, and White Blood Cell Count in Acute Hematogenous Osteomyelitis of Children

Leila Unkila-Kallio, MD*; Markku J.T. Kallio, MD*; Juhani Eskola, MD†; and Heikki Peltola, MD*

ABSTRACT. Objective. The aim of this prospective study was to compare the clinical value of the erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and white blood cell (WBC) count in diagnosis and follow-up of acute hematogenous osteomyelitis in children.

Design. Forty-four children aged 2 weeks to 14 years with bacteriologically confirmed acute hematogenous osteomyelitis were examined. Staphylococcus aureus was responsible in 39 cases (89%), Haemophilus influenzae type b in 3 cases (7%), pneumococcus in 1 case (2%), and a microaerophilic streptococcus in 1 case (2%). ESR was measured at the time of admission and on days 3, 5, 7, 10, 14, 19, and 29 of treatment, and CRP was measured on the same days as ESR but also on days 2, 9, 12, 17, and 23. WBC count was examined at the time of admission and on days 5, 10, 19, and 29.

Results. ESR was elevated (≥20 mm/h) initially in 92% of the cases; the mean value was 45 mm/h, and the peak values (mean 58 mm/h) were reached on days 3 to 5. After this the levels slowly returned to normal in approximately 3 weeks (mean 18 days). CRP was elevated (≥19 mg/L) at the time of admission in 98% of the cases, the mean value being 71 mg/L. The peak CRP value was reached on day 2 (mean 83 mg/L). The decrease was very rapid, normal values being reached within a week (mean 6.9 days). The WBC count was a poor indicator of acute hematogenous osteomyelitis, since only 35% of the children had leukocytosis (WBCs > 12 x 10⁹/L) at the time of admission.

Conclusions. In patients with acute hematogenous osteomyelitis, CRP increased and especially decreased significantly faster than ESR, reflecting the effectiveness of the therapy given and predicting recovery more sensitively than ESR or WBC count. Pediatrics 1994;93:59-62.

C-reactive protein, erythrocyte sedimentation rate, white blood cell count, osteomyelitis.

ABBREVIATIONS. AHOM, acute hematogenous osteomyelitis; ESR, erythrocyte sedimentation rate; WBC, white blood cell; CRP, C-reactive protein.

Acute hematogenous osteomyelitis (AHOM) is a septic bone infection which is curable with appropriate antimicrobial treatment and adjunctive surgery.¹ The classic laboratory tests for diagnosing and for monitoring recovery from AHOM are the erythrocyte sedimentation rate (ESR) and the white blood cell (WBC) count.²–⁶

An increase in ESR, a nonspecific index of inflammation primarily reflecting concentration of fibrinogen and immunoglobulins in the plasma,⁷ is usually seen 24 hours or more after the onset of symptoms and signs of AHOM. Then the ESR slowly returns to normal within approximately 3 to 4 weeks,⁸–¹⁰ provided treatment has been adequate. Up to 25% of patients have normal ESRs in the early stages of the disease,¹¹ and the WBC count is normal even more often than the ESR.¹²

The serum C-reactive protein (CRP) concentration has proved a useful measure in invasive childhood infections¹³–¹⁹ including AHOM.²⁰ Of special relevance is the finding that besides differential diagnosis, sequential determination of CRP is of great clinical value in monitoring the course of the illness, no matter whether the inflammation is caused by infection¹³,²⁰–²⁴ or, for example, trauma.²⁵ This is because CRP tends to increase several hundred fold after a triggering stimulus, and the rise may occur within 6 hours.²² With a doubling time of approximately 8 hours,²⁶ peak values are mostly reached within 50 hours.²²

The usefulness of CRP in meningitis²³,²⁴,²⁷ and possibly also in orthopaedic infections²⁵,²⁶ led our group to set up a prospective study of AHOM. The aim of this prospective study was to compare the clinical values of CRP, ESR, and WBC count in AHOM of childhood.

PATIENTS AND METHODS

The series comprised 44 children aged from 2 weeks to 14 years (median 9 years, mean 8 years) with bacteriologically confirmed AHOM collected prospectively from eight centers in Finland during the period from 1981 to 1992. The data were collected, checked, and analyzed at the Children's Hospital, University of Helsinki. The study protocol was approved by the Ethical Committee of the hospitals involved.

In all children the diagnosis of AHOM was based clinically on the characteristic signs and symptoms of bone infection, and microbiologically on a positive blood or tissue culture. In addition, a typical plain roentgenogram and/or a positive scan at some stage in the course of the illness was observed. Patients with subacute osteomyelitis (a history of greater than 2 weeks at the time of admission), penetrating wounds, spine infections, or chronic illness were excluded.

Staphylococcus aureus was responsible in 39 cases (89%), Haemophilus influenzae type b in 3 cases (7%), pneumococcus in 1 case (2%), and a microaerophilic streptococcus in 1 case (2%). Blood culture was positive in 31 (74%) of those 42 cases in which it had been obtained. The culture obtained locally from the bone was positive in 24 (71%) of 34 cases. Both cultures were positive in 12 (38%) of the 32 cases. The lower extremities were the site of AHOM in 57%, the upper extremities in 11%, and other bones of the skeleton were involved in 32%.

Erythrocyte sedimentation rate was measured by the conventional Westergren tube method at the time of admission and on
days 3, 5, 7, 10, 14, 19, and 29 of treatment. C-reactive protein was measured quantitatively from a finger-prick sample using the turbidimetric- or nephelometric method in the same days as ESR but also on days 2, 9, 12, 17, and 23. The upper normal limit for CRP is 19 mg/L and for ESR, 19 mm/h.

In addition to ESR and CRP, the WBC count was examined at the time of admission and on days 5, 10, 19, and 29. Values of less than 12 × 10⁹/L were regarded as normal. A body temperature greater than 37.5°C was considered to be fever.

Blood cultures were obtained before antimicrobial treatment was instituted. First-generation cephalosporins or cefuroxime was used at random (data to be published), and the treatment was started intravenously but switched to the oral route within a few days. The mean duration of medication was 23 days (median 20.5 days).

After a preliminary analysis of the material, the cases were divided into two groups according to length of history: The “short-history group” (n = 12, 27% of the series) comprised those children in whom symptoms and signs had persisted for 48 hours or less before diagnosis. The remaining patients comprised the “longer history group” (n = 32, 73%).

Student’s unpaired t test was used for testing the significance of differences between the means of the different groups.

RESULTS

Erythrocyte sedimentation rate was initially elevated (≥20 mm/h) in 35 (92%) of 38 cases; the mean value was 45 ± 22 mm/h (Table 1, Figure). In three patients ESR was normal at the time of admission. The values increased during the following days, reaching a peak on days 3 to 5 (mean 58 ± 24 mm/h), and then falling to normal in approximately 3 weeks; the mean (±SD) time required for ESR to reach the value of 19 mm/h or less was 18 ± 10 days. In 10 patients the return to normal required more than 21 days.

Except for one case with a normal (<20 mg/L) initial value, the CRP was clearly elevated at the time of admission (98%); the mean value was 71 ± 45 mg/L (Table 1, Figure). As a reflection of the rapid increase, the mean peak value was reached on day 7. The CRP fell to normal sooner than the ESR, since values of less than 20 mg/L were measured within a week; the mean (±SD) time until normalization was only 6.9 ± 4.8 days, whereas that of ESR was 18 ± 10 days (P < .001). In three cases the CRP required longer than 12 days to normalize, but all these patients had also a joint involvement, not infection localized to the bony tissue only.

TABLE 1. Mean Values (±SD) of Serum C-Reactive Protein (CRP), Erythrocyte Sedimentation Rate (ESR), and White Blood Cell (WBC) Counts in Bacteriologically Confirmed Acute Hematogenous Osteomyelitis in Children

<table>
<thead>
<tr>
<th>Time</th>
<th>CRP, mg/L</th>
<th>ESR, mm/h</th>
<th>WBC, ×10⁹/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>71 ± 45</td>
<td>47 ± 21</td>
<td>11.0 ± 5.4</td>
</tr>
<tr>
<td>2</td>
<td>85 ± 60</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>84 ± 65</td>
<td>58 ± 24</td>
<td>6.9 ± 3.5</td>
</tr>
<tr>
<td>5</td>
<td>40 ± 46</td>
<td>55 ± 26</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>23 ± 28</td>
<td>51 ± 25</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>&lt;20</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>&lt;20</td>
<td>36 ± 27</td>
<td>7.2 ± 1.6</td>
</tr>
<tr>
<td>12</td>
<td>&lt;20</td>
<td></td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>&lt;20</td>
<td>35 ± 29</td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>&lt;20</td>
<td>23 ± 20</td>
<td>6.1 ± 1.9</td>
</tr>
<tr>
<td>23</td>
<td>&lt;20</td>
<td>14 ± 9</td>
<td>6.0 ± 2.1</td>
</tr>
</tbody>
</table>

* The day of admission is day 0.

White blood cell count was a poor indicator of infection (or inflammation). Only 34% of the children had leukocytosis (WBC counts > 12 × 10⁹/L) at the time of admission (Table 1), and a normal WBC count whenever measured was found in 28 (65%) of 43 children.

Defervescence occurred, on average, in 1.8 days (range 0 through 6 days). The duration of illness (mean ± SD) before the start of antimicrobial treatment was 5 ± 3 days (range 1 through 14, median 4 days). No relapse of AHOM was found in this series.

Length of History and CRP, ESR, and WBC Levels

Short-History Group. In the short-history group (up to 2 days), the mean ESR was slightly elevated (33 mm/h) at the time of admission, whereas the CRP was more clearly elevated (66 mg/L) and the WBC count was modestly elevated (14.6 × 10⁹/L) (Table 2). At the time of admission, one patient had a normal ESR, whereas the CRP was increased in all cases. The peak value for ESR was reached on day 5 and for CRP on day 2 (P < .01).

TABLE 2. Initial Mean (±SD) and Ranges of Erythrocyte Sedimentation Rate (ESR), C-Reactive Protein (CRP), and White Blood Cell (WBC) Counts, and Days of Fever After Institution of Therapy in Acute Hematogenous Osteomyelitis of Children According to the Length of the History

<table>
<thead>
<tr>
<th>Time</th>
<th>ESR, mm/h</th>
<th>CRP, mg/L</th>
<th>WBC, ×10⁹/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>33 ± 16</td>
<td>66 ± 54</td>
<td>26 ± 180</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>10–62</td>
<td>20–91</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>74 ± 42</td>
<td>4.4–18.5</td>
</tr>
<tr>
<td>5</td>
<td>14.6 ± 7.6</td>
<td>19.7 ± 3.5</td>
<td>10–179</td>
</tr>
<tr>
<td>7</td>
<td>11.6 ± 9.8</td>
<td>7.4 ± 2.4</td>
<td>4.4–18.5</td>
</tr>
<tr>
<td>10</td>
<td></td>
<td>10.2–15.6</td>
<td>4.4–18.5</td>
</tr>
<tr>
<td>14</td>
<td></td>
<td>20–91</td>
<td>4.4–18.5</td>
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<tr>
<td>23</td>
<td></td>
<td>20–91</td>
<td>4.4–18.5</td>
</tr>
<tr>
<td>29</td>
<td></td>
<td>20–91</td>
<td>4.4–18.5</td>
</tr>
</tbody>
</table>

* NS, not significant.
Longer History Group. In the longer history group (more than 2 days), both ESR and CRP were more elevated at the time of admission, the mean values being 52 mm/h for ESR and 74 mg/L for CRP; the mean WBC count, in contrast, was normal (mean 9.7 x 10^9/L) (Table 2). There were two patients with normal ESR and one patient with normal CRP at the time of admission. The peak value for CRP was again reached significantly faster than for ESR (p < .001) — for CRP on day 2 and for ESR on day 5. Whereas the ESR levels were significantly higher in the longer history group at the time of admission (p < .01), the groups did not differ in CRP values. The WBC counts were higher in the short-history group (p < .01). Half the cases in the short-history group had normal WBC counts, and 70% of the longer history group had normal WBC counts initially.

Except for fever that lasted longer in the longer history group (Table 2), no other significant differences were found in the indices investigated.

Surgery and CRP
A surgical procedure (needle aspiration, drilling, or opening) was performed in 27 patients (61%). Surgery performed in this series did not influence the daily values of ESR, CRP, or WBC.

DISCUSSION
To our knowledge, CRP has only once been used for the diagnosis and monitoring of the course of AHOM. Based on those elementary data that represented only a subgroup of bacteremic children and on a study on septic arthritis, we launched this prospective study. Now, with experience derived from 44 patients who had bacteriologically confirmed AHOM of much the same etiology (89% were caused by S. aureus), and the same randomized treatment and monitoring, we are convinced that serum CRP is of great value for monitoring AHOM. The critical question is, how does CRP behave compared with ESR, the test used hitherto? We see three points in favor of CRP over ESR.

First, CRP is a simple test, carried out with readily available laboratory equipment, nephelometer or turbidimeter, that requires only a finger-prick sample, not venipuncture, as for ESR. Easiness of sampling has the practical consequence that CRP can—and should—be done daily or at least every other day in the early phase of illness. As the test result is available within an hour or so, the information reflects the actual situation, not that prevailing the previous day.

Second, CRP increases and, especially, decreases more rapidly than ESR. C-reactive protein values were markedly elevated (mean 71 mg/L) at the time of admission, peaked during the following 48 hours, and returned to normal within a week. Erythrocyte sedimentation rate was normal at the time of admission in three cases and reached the peak level on days 3 to 5 but required almost 3 weeks for normalization (Figure), as is known from previous studies. The rapidity with which CRP increases and decreases has major clinical relevance, since the test has the potential for detecting complications sooner than any other laboratory index of which we are aware. As all the patients in this series recovered uneventfully, we could not document this hypothesis, but monitoring bacterial meningitis—another bacteremic infection—by daily CRP determinations has taught us that these tests are worth doing. Whatever the other conditions prevailing (local and general signs, extent of fever, leukocytosis, etc), if the CRP is decreasing, the inflammation is likely to be subsiding. In case of doubt, a CRP determination should be repeated after 6 to 12 hours, and should the favorable trend have continued, resolution of the infection is even more likely. Such information is not obtainable from sequential ESR determinations, which lag far behind those of CRP (Table 1, Figure).

Third, the length of the history did not influence the CRP values at the time of admission, i.e., in cases in which symptoms and signs had lasted for 48 hours at most the CRP was clearly increased, although ESR levels were still low (Table 2).

The finding that the extent of surgery (needle aspiration, drilling, opening) did not influence the CRP levels was surprising, because operations tend to induce CRP production, peak values being reached on day 2. We assume that the inflammation due to AHOM had a proportionally far greater effect than the minor surgery performed; hence, the potential slight increase in CRP was masked by the general trend of the curve (Figure).

The WBC counts were normal at the time of admission in 65% of the cases, but higher if the history had been short (Table 2). Despite this, WBC obviously did not contribute much to the diagnosis or follow-up of AHOM.

Occasionally one may be faced with a case in which ESR but not CRP is elevated (one case in this series). Our interpretation of these rare cases is that the infection has been too localized to trigger CRP production by the hepatocytes.

Because the kinetics of CRP and of ESR are dissimilar, we recommend initial determination of both indices, then CRP every 24 to 48 hours for approximately a week, until values less than 20 mg/L are achieved, and ESR twice a week (Figure). During the follow-up period, CRP should be determined, since a secondary rise is a warning sign of recrudescence.

In our circumstances, we do not see why treatment of AHOM should be continued until ESR has normalized, and we think it suffices if CRP has normalized and remains so. We agree, however, that there may well be considerable differences in the natural course of AHOM in various parts of the world. First, therefore, the potential of CRP should be determined for the locality, and only then should general recommendations be formulated on the use of this test for the diagnosis and monitoring of the course of AHOM.

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REFERENCES


CRITICISM OF ORGAN TRANSPLANTATION

The field of organ replacement now epitomizes a very different and powerful tendency in the American health care system and in the value and belief system of our society’s culture: our pervasive reluctance to accept the limits to the biological and human condition imposed by the aging process and our ultimate mortality.


Submitted by Student

C-REACTIVE PROTEIN IN HEMATOGENOUS OSTEOMYELITIS