Sensitivity of Erythrocyte Sedimentation Rate and C-reactive Protein in Childhood Bone and Joint Infections

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Abstract In addition to the examination of clinical signs, several laboratory markers have been measured for diagnostics and monitoring of pediatric septic bone and joint infections. Traditionally erythrocyte sedimentation rate (ESR) and leukocyte cell count have been used, whereas C-reactive protein (CRP) has gained in popularity. We monitored 265 children at ages 3 months to 15 years with culture-positive osteoarticular infections with a predetermined series of ESR, CRP, and leukocyte count measurements. On admission, ESR exceeded 20 mm/hour in 94% and CRP exceeded 20 mg/L in 95% of the cases, the mean ($\pm$ standard error of the mean) being 51 ± 2 mm/hour and 87 ± 4 mg/L, respectively. ESR normalized in 24 days and CRP in 10 days. Elevated CRP gave a slightly better sensitivity in diagnostics than ESR, but best sensitivity was gained with the combined use of

ESR and CRP (98%). Elevated ESR or CRP was seen in all cases during the first 3 days. Measuring ESR and CRP on admission can help the clinician rule out an acute osteoarticular infection. CRP normalizes faster than ESR, providing a clear advantage in monitoring recovery.

Level of Evidence: Level II, diagnostic study. See Guidelines for Authors for a complete description of levels of evidence.

Introduction

Acute osteoarticular infections of childhood comprise essentially three entities, septic arthritis (SA), osteomyelitis (OM), and their combination (OM + SA). Historically these were diseases of high mortality [7], but even today sequelae are relatively common [13, 30]. In diagnostics and monitoring, clinicians pay attention to fever, malaise, or local symptoms such as swelling, pain, or restricted motion of the affected limb. Laboratory parameters are used to help the clinician with evaluation. ESR is still the main yardstick in monitoring the course of illness [1, 5, 24, 31]. Unfortunately, ESR increases rather arbitrarily and normalizes so slowly that active infection is likely to have resolved earlier than suggested by normalized ESR values [2, 27].

The serum CRP challenges the traditional position of ESR for diagnostics and followup of invasive bacterial infections such as osteoarticular infections of childhood [6, 20, 28]. Three reasons justify its active use. First, in the appropriate context, increased serum concentrations provide a good hint toward an invasive bacterial infection [4, 10, 18, 20–23, 26]. Second, the increases and decreases of CRP are so clear cut and fast (increased values are seen within 6 to 8 hours [16, 17], and the doubling time is only

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Each author certifies that his or her institution has approved the human protocol for this investigation, that all investigations were conducted in conformity with ethical principles of research, and that informed consent for participation in the study was obtained. This work was performed at Helsinki University Central Hospital.

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8 hours [9, 16]) that they have the potential to influence treatment. Furthermore, if the infection subsides, the levels decline by approximately 50% a day [22]. Third, as the CRP alternations may be hundreds-fold, quantitative measurements are easy [19], quick (in 5 minutes if needed), and inexpensive [8, 26].

A negative CRP measurement is of great value, because it is a strong argument against potential SA, OM, or OM + SA [6]. If in doubt, CRP should be checked after 6 to 8 hours, and if still less than 20 mg/L [19], the risk of acute osteoarticular infection is very low [12, 20, 28]. However, CRP is also useful in monitoring the course of disease [22].

Leukocyte count (WBC) is perhaps the most widely used nonspecific index for inflammation, and osteoarticular infections are no exception [12]. A common problem with the WBC is that it can be normal in as much as 80% of cases and thus is not a reliable indicator [12]. One study assessing the test characteristics of CRP in pediatric osteoarticular infections prospectively included only 39 cases of proven SA [10]. In earlier reports of samples of 44 to 100 patients, we suggested CRP is faster than ESR and WBC in predicting the effectiveness of therapy in SA, OM, and OM + SA [6, 28, 29].

We therefore (1) calculated the sensitivity of ESR and CRP in bacteriologically proven pediatric osteoarticular infections and (2) confirmed our earlier findings with a larger sample.

Materials and Methods

We collected data from a large prospective treatment study of pediatric osteoarticular infections done in Finland between 1983 and 2005. All children with ages 3 months to 15 years in the seven referral hospitals presenting with signs and symptoms suggesting an acute osteoarticular infection were enrolled, but only culture-positive cases were analyzed. We excluded neonates younger than 3 months and patients who were immunodeficient. The trial was designed, conducted, and analyzed independently of any medical companies or manufacturers. The trial was approved by the relevant ethical committees, and legal guardians gave informed consent for their children to participate.

Two hundred sixty-five patients fulfilled the inclusion criteria for the study. Of these, 134 had SA, 106 had OM, and 25 had OM + SA (Table 1). The mean and median ages of patients with SA was 6.7 and 6.5 years, for OM 9.4 and 10.0 years, and for OM + SA 6.2 and 5.6 years, respectively. The three most common causative agents in SA were *Staphylococcus aureus* in 60% (81 of 134), *Haemophilus influenzae* B in 17% (23 of 134), and

Table 1. Patient characteristics on admission (n = 265)

Parameter	Value
Males/females	161/104
Age (years)*	8.4 (4.0–11.3)
History (days)*	3 (2–4)
Diagnosis	
SA	134
OM	106
OM + SA	25
Agent cultured from	
Joint and blood	55
Bone and blood	21
Joint only	75
Bone only	33
Blood only†	81
Causative agent	
<i>Staphylococcus aureus</i>	199
<i>Haemophilus influenzae</i> type b	26
<i>Streptococcus pyogenes</i>	25
<i>Streptococcus pneumoniae</i>	12
Other‡	3
Initial value§	
ESR (mm/hour)	51 ± 2
CRP (mg/L)	87 ± 4
WBC (/mm ³)	12,600 ± 300
ESR normalization (< 20 mm/hour) (days)§	
All	23.5 ± 1.4
SA	25.4 ± 2.1
OM	18.7 ± 1.1
OM + SA	36.9 ± 7.8
CRP normalization (< 20 mg/L) (days)§	
All	10.3 ± 3.7
SA	10.6 ± 0.6
OM	8.4 ± 0.8
OM + SA	16.1 ± 2.5

* Values expressed as median, with interquartile range in parentheses; †with compatible signs and symptoms; ‡one case each of *Neisseria meningitidis* group B and W135 and *Streptococcus* group G; §values expressed as mean ± standard error of the mean; SA = septic arthritis; OM = osteomyelitis; OM + SA = osteomyelitis with adjacent septic arthritis; ESR = erythrocyte sedimentation rate; CRP = C-reactive protein; WBC = white blood cell count.

Streptococcus pyogenes in 12% (16 of 134). OM was caused overwhelmingly by *S. aureus* (93%, 99 of 106), which also was the most common causative organism in OM + SA (76%, 19 of 25).

In addition to routine blood culture, a sample was obtained from all patients by joint and/or bone via needle aspiration. The infections were categorized as SA, OM, or OM + SA with preset criteria. SA was defined as an acute

joint infection with bacteria yielding from joint and/or blood. Positive blood culture alone sufficed if the joint showed indisputable signs of acute arthritis and joint effusion was confirmed by aspiration and/or ultrasound. OM was diagnosed if bacteria grew from the bone. If only blood culture was positive, bone involvement was documented by radiograph or MRI. Finally, OM + SA was diagnosed if bacteria grew from the bone and joint or, if only blood culture was positive, involvement of both tissues was observed on radiographs and/or MRI.

Patients were treated according to a preset protocol with high doses of antimicrobials starting intravenously. Clindamycin or first-generation cephalosporins were used primarily, combined with ampicillin/amoxicillin in cases of suspected *H influenzae* B. Antibiotic treatment lasted

23 ± 1 days (mean $\pm$ standard error of the mean) for patients with SA, 24 ± 1 days for patients with OM, and 29 ± 4 days for patients with OM + SA. More extensive surgery than diagnostic aspiration/drilling was performed in 23 of 134 (17%) patients with SA, 45 of 106 (42%) patients with OM, and seven of 25 (28%) patients with OM + SA.

We used a preset schedule (Fig. 1) to check the ESR, CRP, and WBC values. During the first 14 days of treatment, ESR was measured six times, CRP nine times, and WBC three times. If a child was discharged earlier, the samples were taken at the outpatient department. The followup lasted for 12 months posthospitalization.

For ESR, any value exceeding 20 mm/hour was deemed increased, as were values greater than 20 mg/L for CRP

Fig. 1A–C The graphs show the pattern of increase and decrease of (A) ESR (mm/hour), (B) serum CRP (mg/L), and (C) WBC (per mm³) in patients with OM + SA, SA, and OM. Measurements were taken 1 to 29 days after admission and 2 weeks, 3 months, and 1 year after discharge.

[19, 20]. Leukocytosis was defined as greater than 15,000 per mm³. The data were recorded on special forms that were computerized and analyzed in Helsinki. StatView® (SAS Institute Inc, Cary, NC) was used in data calculations. Values are presented as mean $\pm$ standard error of the mean. Sensitivity for a particular test was the proportion of actual positives correctly identified and the Newcombe method was used to calculate the 95% confidence intervals (CIs). A researchers' meeting was held once a year.

Results

The initial ESR (51 ± 2 mm/hour; range, 20–130 mm/hour) was elevated in 94% of the patients (248 of 265), whereas the primary CRP value (87 ± 4 mg/L; range, 20–311 mg/L) was elevated in 95% of the patients (251 of 265). Of the 14 patients (six with SA, seven with OM, one with OM + SA) whose first CRP measurement on admission was less than 20 mg/L, 71% (10 of 14) showed an initial ESR greater than 20 mm/hour (range, 21–59 mm/hour). The sensitivity of elevated ESR on admission to detect an osteoarticular infection was 94% (95% CI, 90%–96%). Using CRP alone gave only a slightly better sensitivity of 95% (95% CI, 91%–97%), but combining these two markers gave a sensitivity of 98% (95% CI, 96%–99%) (261 of 265). An elevated ESR or CRP within the first 3 days was seen in all patients (100% sensitivity; 95% CI, 99%–100%).

The observed peaks of the ESR and CRP generally were reached on Day 2 (Fig. 1). The average peak ESR and CRP were 67 ± 2 mm/hour and 107 ± 5 mg/L, respectively. After peaking, ESR started a slow descent; the 20-mm/hour level was reached on Day 24 (± 1.4 days). CRP started a more rapid normalization, descending to less than 20 mg/L in 10 ± 0.5 days. ESR and CRP normalized fastest in patients with OM, whereas normalization was slowest in patients with OM + SA (Table 1). ESR, CRP, and WBC values typically were highest in patients with OM + SA; the lowest values were characteristic of OM (Fig. 1). We observed no correlation between CRP or ESR elevation and the proportion of patients undergoing surgery. Fever lasted on average 3.5 ± 0.3 days in patients with SA, 2.0 ± 0.2 days in patients with OM, and 3.4 ± 0.5 days in patients with OM + SA, respectively.

Discussion

Diagnosing and monitoring pediatric osteoarticular infections start with a clinical evaluation. Attention is directed to local symptoms and signs such as tenderness, swelling, or restricted motion of the affected limb or general

symptoms such as fever, malaise, or refusing food. Unfortunately, many inflammatory conditions such as transient synovitis, reactive arthritis, or juvenile rheumatoid arthritis can clinically mimic septic infection [8]. To counter this problem, ESR and CRP have been used to diagnose osteoarticular infections for decades, but the sensitivities of these markers have not been described in previous reports of these infections [6, 8, 12, 28]. The benefits of CRP for monitoring patients have been described, but owing to the rarity of septic osteoarticular infections, the study sizes tend to be small, as are studies comparing the behavior of laboratory markers in SA, OM, and OM + SA [6, 12, 28]. We therefore calculated the sensitivity of ESR and CRP in pediatric osteoarticular infections in a large prospective series of patients with bacteriologically confirmed infections, and confirmed with a larger sample our preliminary findings [6, 28, 29] suggesting CRP is faster than ESR and WBC in predicting the effectiveness of therapy in SA, OM, and OM + SA.

Our study has some limitations. First, as comparing ESR and CRP was not our primary study purpose, the schedules of measuring these markers differed slightly. We do not believe this compromises our results as the schedules were stringent enough to fairly accurately describe the behavior of both markers (Fig. 1). Second, we did not include and thus cannot apply our data to patients who are immunodeficient. Third, as our study was performed in an industrial country, our results may not be directly applicable in developing nations, where the cheaper price and wide availability still might favor the use of ESR [14].

Sensitivity to detect a bacterial osteoarticular infection on admission was 94% for ESR and 95% for CRP, higher than reported previously [10, 28]. Most importantly, combining these two markers provided an even better sensitivity of 98%. Among 265 patients, there were no cases of confirmed osteoarticular infection in which ESR and CRP remained normal 3 days after admission, virtually ruling out bacterial osteoarticular infection if ESR and CRP remain normal for 3 days. This information benefits clinicians when pondering whether to start antimicrobial treatment for a suspected osteoarticular infection.

In monitoring the course of diseases, CRP proved a good yardstick [6, 12, 28]. The pattern followed by the ESR and CRP values (WBC was not measured with the same schedule) was similar in SA, OM, and OM + SA: such rapid ascent that increased values usually were seen on admission, a peak on the second or third day of treatment, and then a fast descent, provided no complications developed. The speed of normalization differed substantially in favor of CRP, being at least 13 days quicker than for ESR. Other investigators reported, if CRP in OM was not clearly descending on the fourth day of treatment, a complication was likely [22]. In another study of patients in intensive

care, continuously high CRP often suggested nonsurvival of the patient [11]. There were differences among SA, OM, and OM + SA. OM induced a low CRP response, SA induced a greater response, and OM + SA induced the greatest response. We believe this finding reflected the initially more localized inflammation in OM, whereas in SA the entire joint was soon affected and massive inflammation was quickly manifested with its well-known symptoms and signs of acute arthritis. In OM + SA, CRP response was understandably the greatest, albeit CRP alone did not always distinguish OM + SA from SA or OM [29]. Regardless, an exceptionally high CRP value on admission was a warning sign to the clinician to take into account this possibility.

A physician who puts CRP in the context of the entire clinical situation gains much from sequential CRP measurements. We recommend ESR be measured on arrival, but only at arrival because, in some rare cases, the first CRP value was less than 20 mg/L. We assume the inflammatory process in these patients was too weak to trigger CRP production, and in this respect, ESR provided additional information in diagnostics. For monitoring, we favor using CRP only [6, 28]. Modern technology has made it possible to measure CRP quantitatively from a finger prick whole-blood sample. A precise value is obtained so quickly that the procedure is easily possible even on site (eg, in the doctor's office) [3, 15, 25]. A complex hospital laboratory is not needed (unless many samples are analyzed) if the small instrument is at hand. CRP is an inexpensive and useful method to diagnose and monitor acute osteoarticular infections of childhood.

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