Early Detection of Sequela-Prone Osteomyelitis in Children with Use of Simple Clinical and Laboratory Criteria

Irmeli Roine, Adriano Arguedas, Idis Faingezicht, and Francisco Rodriguez

To determine which clinical or laboratory criteria best reflected the prognosis for 83 children with acute hematogenous osteomyelitis (AHO), they were compared with outcomes after a follow-up of at least 2 months (for 78%, 6 months). Twenty-eight children (34%) developed sequelae. They had higher serum C-reactive protein (CRP) concentrations (days 1–6 of treatment; $P = .0004$ to $<.0001$) and higher clinical scores ($P = .0001$) than did patients who had an uneventful recovery. The frequency of sequelae increased from 3% to 73% ($P = .0001$) when CRP concentrations exceeded the defined cutoff limits and the clinical scores were $>1$. Age, the duration of symptoms at diagnosis, and the type and duration of intravenous antimicrobial therapy or surgical management did not differ ($P > .05$) between children with and without sequelae. Both CRP determinations and clinical evaluations with use of a scoring system enable early detection of sequela-prone AHO in children and are most accurate when used together.

Acute hematogenous osteomyelitis (AHO) remains a frequent childhood disease in developing countries. It is associated with a notable risk of sequelae [1–7], which are not known to be predictable [8]. Generally they are detected after the patient is discharged, most within a follow-up period of 6–12 months [2].

In Costa Rica, AHO sequelae such as recurrent osteomyelitis, pathological fractures, and growth alterations are seen repeatedly. If the sequela-prone cases could be identified earlier, modification in management might improve prognosis. We studied how accurately sequelae were predicted with use of the following criteria, all of which have previously been associated with adverse outcome: a delay in diagnosis [3, 4] or surgical drainage [1], short duration of antimicrobial therapy [1], high serial serum C-reactive protein (CRP) concentrations [9] or erythrocyte sedimentation rates (ESRs) [5], and slow clinical response to treatment [3, 10].

Methods

Patients

The study series included 83 consecutive, prospectively observed, previously healthy children aged 6.7 ± 3.7 (mean ± SD) years (range, 3 months to 13.5 years; 87% were >2 years old). They were selected on the basis of having attended a follow-up visit 2 months (1.5 ± 0.6 months) after hospitalization for AHO during the period of August 1992 to October 1994 at the National Children's Hospital (San José, Costa Rica). Patients with AHO who did not comply with this follow-up visit ($n = 23$) or were <1 month of age were excluded from analysis, as were patients with penetrating osteomyelitis. Sixty-five of the 83 children (78%) attended further follow-up visits for 14 ± 7 months (all for at least 6 months and 85% for >8 months).

Osteomyelitis was diagnosed when, in addition to the typical symptoms and signs of AHO [8, 11], one of the following was noted: pus or a positive bone culture (54 children; 65%); a positive $^{99m}$technetium methylene diphosphate (Tc) scan and later typical [11] radiographic changes (16 children; 19%) or a positive Tc and/or $^{67}$gallium citrate scan (13 children; 16%). Osteomyelitis was considered acute if symptoms had been present for a maximum of 10 days [12] and if the plain radiograph obtained on admission was normal [13]. The age of the patients, the duration of symptoms, the site of infection, and the etiology are presented in table 1.

The guidelines for antimicrobial and surgical management of AHO in our hospital have been presented previously [9]. Rifampin or an aminoglycoside may be added to an oxacillin regimen for 10 days if the physician in charge considers the initial clinical response to be suboptimal. Oral therapy is initiated when there is clear improvement and the patient is afebrile. The agent given is either cephalexin (75 mg/[kg·d] in four doses) [14] or trimethoprim-sulfamethoxazole (TMP-SMZ; 40 mg/[kg·d] in two doses), whichever is more practical.

Bone drilling is performed in the first few days of hospitalization for most patients with presumed AHO. If pus is obtained, aspiration and surgical lavage follow. All adjacent septic joints are drained.

Collection of Data

Local inflammation, pain, and motility were graded daily (as marked, diminished, or absent) by an infectious disease
specialist and one or two weeks a time by an orthopedic surgeon. This information was used in the present study with other prospectively collected clinical data to construct a score consisting of five elements reflecting early recovery and the extent of disease.

Each of the following elements was worth one point (Table 2): axillary temperature >37.4°C for >7 days; marked local swelling or warmth for >10 days; marked local pain or limited motility for >10 days; the need for further surgical drainage after its initial performance at presentation (repeated drainage of another focus, when indicated by the orthopedic surgeon); and the presence of more than one focus of osteomyelitis or septic shock. CRP levels were determined 1–3 times per week (3.0 ± 1.6 times per patient per 6 days), and the ESR was determined 1–2 times per week (1.2 ± 0.7 times per patient per 7 days).

Evaluation of Outcome

Follow-up visits were scheduled for all patients at approximately 2, 6, and 12 months after hospitalization for AHO. Outcome was evaluated by an orthopedic surgeon and a pediatrician and on the basis of a radiograph (obtained for 79 of the 83 patients [95%]). Slight sequelae were defined as local swelling or pain or limited motility and radiographic changes consisting of lytic lesions limited to less than one-third of the bone shaft, a periosteal reaction, or sclerosis. Severe sequelae were defined as any symptom at the site of infection and radiographic changes consisting of lytic lesions extending over one-third of the bone shaft or lesions within the growth zone.

Statistical Analysis

Categorical data were compared by means of the \( \chi^2 \) test, with correction for continuity and continuous data with use of analysis of variance (ANOVA). Sensitivity and specificity were calculated according to the methods of Galen [15]. Mean daily serum CRP concentrations when available and mean ESRs on days 1–3, 4–7, and 8–12 of treatment were calculated for >40% of the patients. If more than one value was available for the same patient during these days, we used the mathematical average. For the purpose of comparison, CRP concentrations were likewise calculated for days 1–3 and 4–7 of treatment. Continuous data are expressed in the text as means ± SD, if not indicated otherwise. A \( P \) value <.05 was considered significant.

Results

Sequelae

Twenty-eight (34%) of the 83 children had sequelae at 2 months; those were slight in 12 and severe in 16. Four of the children with severe sequelae also had a pathological fracture, two had recurrent infection, and three had both. Patients with slight sequelae had usually recovered without further treatment by the 6-month follow-up visit (8 of 9; 3 of the 12 children were lost to follow-up). In contrast, most children with severe sequelae (11 of 13; the 3 other children were lost to follow-up) continued to have (at least) restricted motility (5 also had growth arrest) for ≥6 months. The five children with recurrent osteomyelitis recovered eventually with prolonged antimicrobial therapy. Two children who had been asymptomatic at

| Table 2. A clinical scoring system of 0–5 points, reflecting early recovery and extent of disease of acute hematogenous osteomyelitis in childhood. Each of the five elements is worth one point. A score of ≥1 was associated with adverse outcome of acute hematogenous osteomyelitis in childhood. |
|-----------------|------------------|
| **Element**     | **Points**       |
| Axillary temperature >37.4°C for >7 d | 1 |
| Marked local swelling or warmth for >10 d | 1 |
| Marked local pain or limited motility for >10 d | 1 |
| Additional surgical drainage after the initial one | 1 |
| More than one focus of osteomyelitis or septic shock | 1 |
Factors Associated with Sequelae

Children with sequelae at 2 months had higher clinical scores (ANOVA, $P = .0001$; table 1), higher CRP concentrations during days 1–6 of treatment (ANOVA, $P = .0004$ to $P = .0001$; figure 1), and higher ESRs during days 4–7 of treatment (ANOVA, $P = .002$) than did children without sequelae at 2 months.

The frequency of sequelae increased (figure 2) from 3% to 17% to 73% at 2 months ($\chi^2$, $P = .0001$), according to the presence of none, one, or both of the following factors: (1) a clinical score of $\geq 1$ and (2) a CRP concentration on days 1–6 of treatment that exceeded the mean ($\pm SD$) of the CRP concentration in children with an uneventful recovery (cutoff limits in figure 2). The frequency of long-lasting sequelae (present for $\geq 6$ months) increased from zero to 7% to 44% ($\chi^2$, $P = .0004$), according to the presence of these factors (figure 2).

Fifteen of the 16 children with severe sequelae had both of the factors described above, and one child had one factor. Nine of the 12 children with slight sequelae had both factors, 2 had one factor, and 1 had no factor. The sensitivity of the combined presence of the two factors to identify children with sequelae was 86% and 92% for sequelae at 2 months and at $\geq 6$ months, respectively, and the specificity was 81% and 69%, respectively.

As expected [16, 17], a staphylococcal etiology ($\chi^2$, $P = .007$) and adjacent septic arthritis ($\chi^2$, $P = .02$) were associated with sequelae (table 1).

Oral treatment with TMP-SMZ was associated with sequelae ($\chi^2$, $P = .02$), but a retrospective analysis showed that it had been indicated for children with higher (ANOVA, $P = .0001$) clinical scores (2.7 ± 1.7 points; $n = 14$) compared with those of children who did not receive TMP-SMZ (0.9 ± 1.3 points; $n = 69$).

Factors That Did Not Predict Sequelae

Age, duration of symptoms on admission, and type and duration of intravenous antimicrobial treatment or surgical management did not differ (ANOVA and $\chi^2$, $P > .05$) between children with and without sequelae (tables 1 and 2).

Although a higher ESR on days 4–7 of treatment was associated with forthcoming sequelae, a cutoff value of 55 mm/h (the mean rate [$\pm SD$] found on days 4–7 in children without sequelae at 2 months) had a low sensitivity of 57% and 50% and a specificity of 84% and 79% for distinguishing children with sequelae at 2 months and children with sequelae at $\geq 6$ months, respectively.

Discussion

Our major finding was that the children who develop sequelae can be identified early in the course of treatment. It is of great importance for developing countries that this was...
achieved by a simple clinical score and easily determined [18] CRP concentrations. Two-thirds of the patients who had a clinical score ≥1 and a CRP concentration exceeding the cutoff concentration had sequelae at 2 months; half of them had severe sequelae followed by prolonged invalidity, and several had permanent damage. On the other hand, only one of 28 children with sequelae had neither factor. An unexpected finding was that the development of sequelae was not fully explained by a delay in diagnosis, lack of surgical intervention, or too-short antimicrobial treatment.

Determination of the CRP value is a simple way of measuring the magnitude of the inflammatory response [19]. High concentrations after the third day of treatment have previously been associated with short-term adverse outcome and the development of extensive radiographic changes [9]. The new finding of the present study is that even the values on admission are significant.

It is logical that clinical signs of severity such as slow recovery, prolonged fever, multifocal osteomyelitis, or the need for repeated surgery reflect a suboptimal outcome [3, 10]. The benefit of the present study was to score these aspects and to show that, indeed, together they are a very reliable predictor of outcome. Scoring, however, requires clinical experience in osteomyelitis and follow-up preferably by the same person to adequately register the change from marked to diminished inflammatory signs.

Delay in diagnosis is considered one of the major causes of sequelae from AHO [3, 4], but for our patients it was not a significant association (ANOVA, P > .05). Three explanations are possible. First, the extent of bone necrosis (an important basis of development of sequelae [20]) is not determined by the duration of infection alone. Other factors, such as the number of infecting microorganisms or their capacity to induce inflammatory mediators, are fundamental in the outcome of bacterial meningitis [21] and could play a similar role in AHO. In addition, some staphylococci are known to cause more severe osteomyelitis than others [22].

Second, a delay in diagnosis of 1–10 days, as in our patients, may not be critical. Previously, limits of 5 days [3] and 10 days [2, 16] have been proposed; our results suggest the latter would be accurate. Third, our results may lack statistical power because of the number of patients.

Antimicrobial therapy of <3 weeks’ duration is another well-known risk factor for adverse outcome [1, 5], although other investigators claim that a 7–21-day regimen is as effective as one of >21 days [2]. Our patients with sequelae received antimicrobials for clearly longer periods (intravenous: ANOVA, P = .0001; total: ANOVA, P = .0006) than did children without sequelae. Even management with prolonged antimicrobial therapy, with a combination of two antimicrobials (table 3), and with surgical drainage was often not enough to stop the development of extensive radiographic changes and sequelae in cases of AHO with high CRP concentrations and thus a severe inflammatory response (ANOVA, P = .0004 for CRP value on day 1 with forthcoming sequelae).

### Table 3. Antimicrobial and surgical management of acute hematogenous osteomyelitis in 83 children, as related to outcome at 2 months.

<table>
<thead>
<tr>
<th>Variable</th>
<th>No sequelae (n = 55)</th>
<th>Sequelae (n = 28)</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preadmission antimicrobial therapy† (d)</td>
<td>0.7</td>
<td>1.5</td>
<td>.06</td>
</tr>
<tr>
<td>Intravenous antimicrobial(s) received</td>
<td></td>
<td></td>
<td>.08</td>
</tr>
<tr>
<td>Oxacillin alone</td>
<td>41 (75)</td>
<td>14 (50)</td>
<td></td>
</tr>
<tr>
<td>Oxacillin in combination†</td>
<td>10 (18)</td>
<td>10 (36)</td>
<td></td>
</tr>
<tr>
<td>Other§</td>
<td>4 (7)</td>
<td>4 (14)</td>
<td></td>
</tr>
<tr>
<td>Duration of iv antimicrobial therapy (d)</td>
<td>11</td>
<td>18</td>
<td>.0001</td>
</tr>
<tr>
<td>Total duration of antimicrobial therapy (d)</td>
<td>38</td>
<td>65</td>
<td>.0006</td>
</tr>
<tr>
<td>Oral TMP-SMZ therapy</td>
<td>5 (9)</td>
<td>9 (32)</td>
<td>.02</td>
</tr>
<tr>
<td>Bone drilling</td>
<td>40 (73)</td>
<td>22 (79)</td>
<td>.79</td>
</tr>
<tr>
<td>Days since onset of pain when performed</td>
<td>5.9</td>
<td>7.5</td>
<td>.08</td>
</tr>
<tr>
<td>With aspiration and surgical lavage</td>
<td>33 (60)</td>
<td>19 (68)</td>
<td>.97</td>
</tr>
</tbody>
</table>

NOTE. Data are mean values or no. of patients; numbers in parentheses are percentages.

* Obtained by ANOVA (continuous variables) and χ² (categorical variables) tests.
† At doses considered insufficient for acute hematogenous osteomyelitis.
‡ With ampicillin (9), rifampin (6), an aminoglycoside (4), or cefotaxime (1).
§ Vancomycin (5), including for the 2 oxacillin-resistant strains, cefotaxime for H. influenzae infection (1), penicillin for S. pneumoniae infection (1), ceftazidime for Salmonella ansera + Enterobacter cloacae infection (1).

It was not possible to evaluate the role of oral TMP-SMZ in adverse outcome, because it had frequently been administered to children with high clinical scores whose outcome, as such, is suboptimal. In any case, we would avoid using it as oral treatment for patients with AHO and a clinical score ≥1 until more information is available with regard to its efficacy [23].

In conclusion, many patients with AHO (14 of 28; 50%) who developed sequelae could have been identified at presentation, and almost all of them (27 of 28; 96%) within the first 10 days of treatment. A delay in diagnosis or in surgical and antimicrobial management did not explain satisfactorily why some patients developed sequelae, a finding suggesting that there are other important factors involved in the process that remain to be identified.

### Acknowledgments

The authors thank C. Fonseca, M.D., for interpreting the bone scans; M. L. Herrera, B.S., for the bacterial cultures and susceptibility testing; J. F. Herrera, B. S., for CRP determinations; and the residents and students of the infectious diseases ward at National Children’s Hospital for helping to run the study.

### References