Group A β-Hemolytic Streptococcal Osteomyelitis in Children

Ekopimo O. Ibia, MD, MPH*; Menfo Imoisi, MD, MPH*§; and Andreas Pikis, MD*§

ABSTRACT. Objective Little attention has been given to acute hematogenous osteomyelitis (AHO) caused by group A β-hemolytic Streptococcus (GABHS), although up to 10% of cases are caused by this microorganism. The objective of this study was to define the clinical and laboratory characteristics of AHO caused by GABHS. Methods. Between January 1983 and June 1999, 29 patients were treated at Children's National Medical Center with AHO caused by GABHS. The characteristics of these patients were compared with those of 28 patients with AHO caused by Streptococcus pneumoniae and those of a matched sample of 45 patients with AHO caused by Staphylococcus aureus. Results. Median ages of children with GABHS, S pneumoniae, and S aureus AHO were 36.0, 13.7, and 96.0 months, respectively. On admission, patients with GABHS AHO had a mean temperature of 38.9 ± 1.3°C and a mean white blood cell count of 17,000 ± 7800/mm³, findings similar to those from patients with S pneumoniae AHO. Patients with S aureus AHO had significantly lower admission temperature (38.1 ± 1.1°C) and white blood cell count (10,600 ± 4900/mm³). Varicella infection was the risk factor in 5 cases (17%) of GABHS AHO, whereas none of the cases of AHO caused by S pneumoniae and S aureus was associated with varicella infection. Adjacent septic arthritis occurred in 22%, 28%, and 61% of children with GABHS, S aureus, and S pneumoniae AHO, respectively. Admission erythrocyte sedimentation rate and frequency of bacteremia were similar in all groups. However, time to normalization of erythrocyte sedimentation rate was longer for GABHS and S aureus than for S pneumoniae AHO. GABHS, like S pneumoniae, affected fewer nonextremity bones compared with S aureus. Conclusions. GABHS should be considered in preschool- and early school-aged children who are suspected of having AHO and whose clinical and laboratory features are characterized by high fever and marked leukocytosis. It should also be highly considered in any child with AHO associated with varicella infection. Pediatrics 2003;112:22–e26. URL: http://www.pediatrics.org/cgi/content/full/112/1/e22; acute hematogenous osteomyelitis, group A β-hemolytic streptococcus, varicella.

ABBREVIATIONS. AHO, acute hematogenous osteomyelitis; GABHS, group A β-hemolytic Streptococcus; WBC, white blood cell; ESR, erythrocyte sedimentation rate.

Although acute hematogenous osteomyelitis (AHO) seems to have become less prevalent in industrialized countries, the diagnosis and management of AHO continue to challenge clinicians who care for children with this infection. Staphylococcus aureus is the predominant cause of AHO (40%–80% of cases), and group A β-hemolytic Streptococcus (GABHS) is the next in frequency. Other organisms, including Streptococcus pneumoniae, Haemophilus influenzae type b, and Kingella kingae, are less frequently associated with AHO. In the United States, the widespread use of conjugate vaccine against H influenzae since the late 1980s has virtually eliminated AHO caused by this organism. In addition, the recent approval by the Food and Drug Administration of a new 7-valent conjugate vaccine against S pneumoniae should have a significant impact on the incidence of invasive diseases caused by this bacterium.

Despite numerous studies pertaining to AHO, many important aspects of this infection remain to be elucidated fully. In fact, the majority of studies of AHO analyzed all cases as a group but not according to the causative agent. Because S aureus is the most frequent causative agent, published data have emphasized the characteristics of S aureus AHO with apparent marginalization of other less frequent causative microorganisms. Scattered reports in the literature have focused on AHO caused by specific organisms such as H influenzae and S pneumoniae. However, to the best of our knowledge, no published studies have addressed the characteristics of AHO caused by GABHS, the second most common causative agent of AHO in children. In this article, we provide information on the clinical and laboratory characteristics of childhood AHO caused by GABHS and compare these characteristics with those of AHO caused by S aureus and S pneumoniae.

METHODS

We selected for review all medical records of children who were aged 2 months to 18 years and carried a discharge diagnosis of AHO caused by GABHS from Children's National Medical Center (Washington, DC) between January 1993 and June 1999. These patients were compared with those who were diagnosed during the same period with AHO caused by S pneumoniae or S aureus. For S pneumoniae AHO, we reviewed the medical records of all patients; however, for S aureus AHO, we selected for review only the medical records of patients who were treated within 6 months of each case of GABHS or S pneumoniae AHO. When there was >1 case of S aureus AHO within the 6 months, the medical
record of the first case only was selected for review. Patients who were enrolled in this study were identified by reviewing all medical records classified under International Classification of Diseases, Ninth Revision, Clinical Modification codes 730 (osteomyelitis, periostitis, and other infections involving bones), 711 (pyogenic arthritis), and 716 (arthropathy, not otherwise specified). In addition, for patients who were treated between 1983 and 1993, we reviewed the outpatient clinic records kept by the Division of Infectious Diseases. For patients who were treated between 1994 and 1999, we also searched the hospital’s laboratory information system (Sunquest Information Systems, Raleigh, NC) to ascertain the microbiologic data obtained during the relevant illness episode.

The diagnosis of AHO was based on the following criteria: presence of localized pain/tenderness and other typical features of osteomyelitis of no more than 2 weeks’ duration, typical plain radiograph and/or a positive bone scan, and bacteriologic evidence of infection (positive blood and/or bone/synovial fluid culture). Patients with AHO were considered to have adjacent septic arthritis when a microorganism was isolated from the synovial fluid and/or purulent fluid was aspirated from the joint. Synovial fluid with white blood cell count (WBC) $>$50,000/mm$^3$ was considered purulent. Patients with acute osteomyelitis occurring after an open wound, fracture, or bone surgery and patients with mixed cultures were excluded from the study.

A standardized form was used for data abstraction from medical records. The following data were obtained: demographics, administration of antibiotic therapy before admission, type and duration of clinical symptoms, surgical procedures, antibiotic therapy administered, and outcome. Laboratory data collected included initial total and differential WBC count, erythrocyte sedimentation rate (ESR) and time to return to normal, sources of microbial cultures, and radiologic examinations.

Statistical Analysis

For continuous variables, 1-way analysis of variance was used to examine the differences among the 3 groups. For pairwise comparisons, where indicated, we conducted post hoc analyses using Bonferroni adjustments for multiple comparisons. However, because of unequal variances, we conducted the Dunnett C procedure for pairwise comparison of the mean ages, with the GABHS AHO group serving as control. For categorical variables, $\chi^2$ test (or Fisher exact test if indicated) was used to evaluate differences in proportions among the 3 groups. For assessing the time to normalization of ESR among the 3 groups, a survival fit was constructed using the Kaplan-Meier distribution and the Wilcoxon rank sum tests. For all statistical tests, we used 2-sided probabilities with $P < .05$ considered to be statistically significant.

RESULTS

A total of 426 infants and children with AHO were identified during the 16.5-year study period. An organism was identified in 300 patients. $S$ aureus was the most frequent etiologic agent, causing 43% of all bacteriologically proven cases. The 29 children with GABHS AHO represented 10% of cases of established cause. There were 31 (10%) cases with $S$ pneumoniae and 46 (15%) cases with mixed organisms, primarily involving combinations of various staphylococci and streptococci.

Of the 109 cases of AHO (GABHS, 29; $S$ pneumoniae, 31; and $S$ aureus, 49) that met inclusion criteria, 2 charts (1 each of $S$ aureus and $S$ pneumoniae AHO) were unavailable from the medical records department. Three other cases of $S$ aureus (poorly controlled type 1 diabetes, 2; sickle cell anemia, 1) and 2 cases of $S$ pneumoniae AHO (sickle cell anemia, 1; acute lymphocytic leukemia, 1) were excluded. The major demographic, clinical, and laboratory characteristics of patients with AHO caused by GABHS, $S$ pneumoniae, and $S$ aureus are summarized in Table 1.

Demographics

Children with GABHS AHO had a median age of 36.0 months (mean: 49.4 $\pm$ 38.7; range: 4–129), whereas those with AHO caused by $S$ pneumoniae and $S$ aureus had median ages of 13.7 months (mean: 36.5 $\pm$ 45.5; range: 2–192) and 96.0 months (mean: 94.4 $\pm$ 59.5; range: 2–208), respectively ($P < .0001$).

### TABLE 1. Comparison of Characteristics of Children With AHO Caused by GABHS, $S$ pneumoniae, and $S$ aureus

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>AHO</th>
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<tbody>
<tr>
<td></td>
<td>GABHS ($n = 29$)</td>
</tr>
<tr>
<td>Demographics</td>
<td></td>
</tr>
<tr>
<td>Age (mo, median)</td>
<td>36.0</td>
</tr>
<tr>
<td>Gender (male/female)</td>
<td>17/12</td>
</tr>
<tr>
<td>Race (white/nonwhite)</td>
<td>8/21</td>
</tr>
<tr>
<td>Clinical features</td>
<td></td>
</tr>
<tr>
<td>Antecedent event present</td>
<td></td>
</tr>
<tr>
<td>Upper respiratory tract infection [n (%)]</td>
<td>5 (17)</td>
</tr>
<tr>
<td>Varicella [n (%)]</td>
<td>5 (17)</td>
</tr>
<tr>
<td>Minor non penetrating trauma [n (%)]</td>
<td>9 (31)</td>
</tr>
<tr>
<td>Previous antibiotic therapy [n (%)]</td>
<td>5/28 (18)</td>
</tr>
<tr>
<td>Duration of previous antibiotic therapy (d, mean $\pm$ SD)</td>
<td>2.6 $\pm$ 1.7</td>
</tr>
<tr>
<td>Admission temperature ($^\circ$C, mean $\pm$ SD)</td>
<td>38.9 $\pm$ 1.3</td>
</tr>
<tr>
<td>Adjacent arthritis [n (%)]</td>
<td>8 (28)</td>
</tr>
</tbody>
</table>

Bone involvement$^*$

| Tubular bones (n) | 17 | 16 | 27 | .98   |
| Cuboid bones (n) | 10 | 10 | 8 | .10   |
| Other bones$^+$ (n) | 3 | 2 | 14 | .026   |
| Multilocality (n) | 2 | 2 | 4 | .71   |

Initial laboratory findings

| Peripheral WBC count ($\times10^3$/mm$^3$, mean $\pm$ SD) | 17.0 $\pm$ 7.8 | 16.3 $\pm$ 5.5 | 10.6 $\pm$ 4.9 | <.0001 |
| ESR (mm/first h, mean $\pm$ SD) | 48.0 $\pm$ 12.6 | 50.7 $\pm$ 7.4 | 47.0 $\pm$ 7.4 | .52   |
| Positive blood culture [n/N (%)] | 12/29 (41.4) | 13/28 (46.4) | 30/45 (66.6) | .25   |

SD indicates standard deviation.  
$^*$ Some patients had >1 bone involved.  
$^+$ Irregular (ilium, pubis, ischium) and flat (skull, sternum, scapulae, ribs) bones.
There were 69 male and 33 female patients (male to female ratio: 2.1:1) with no significant gender differences observed among the 3 groups. Eight (28%) of the 29 children with GABHS AHO were white, 16 (55%) were black, 4 (14%) were Hispanic, and 1 (3%) was of other race. The racial/ethnic breakdown of patients with *S. aureus* AHO showed 18 (40%) white, 18 (40%) black, 4 (9%) Hispanic, and 5 (11%) others. Only 2 (7%) of the 28 children with pneumococcal AHO were white, 21 (75%) were black, 4 (14%) were Hispanic, and 1 (4%) was of other racial/ethnic classification. The differences in proportions of white children with AHO among the 3 groups were statistically significant (*P* = .009). On pairwise comparisons, the proportion of white children with AHO caused by GABHS did not differ significantly from that of children with *S. pneumoniae* and *S. aureus* AHO. However, statistically significant differences were observed in relationship to a recent history of varicella. Five (17%) children with GABHS AHO had varicella, whereas none of the patients with *S. pneumoniae* and *S. aureus* AHO had a similar history. The age of the 5 patients with varicella-associated AHO ranged from 11 months to 6 years. There was no correlation of superficial infection of varicella lesions and the location of osteomyelitis, and none of the patients had necrotizing fasciitis.

The most common presenting features of AHO were fever, localized swelling, redness, tenderness with decreased range of motion, limping, and failure to bear weight. Children with GABHS AHO had a mean (± standard deviation) duration of symptoms of 4.8 ± 2.8 days, and 5 (18%) of them received antibiotics for a mean duration of 2.6 ± 1.7 days before admission. These findings were similar to those from patients with *S. pneumoniae* and *S. aureus* AHO. Patients with GABHS AHO had a mean admission temperature of 38.9 ± 1.3°C, higher than that of patients with AHO caused by *S. pneumoniae* (38.2 ± 1.0°C; *P* = .027) and *S. aureus* (38.1 ± 1.1°C; *P* = .016). There was no statistically significant difference in mean admission temperature between patients with *S. pneumoniae* and *S. aureus* AHO (*P* = .69). On admission, the mean (±standard deviation) peripheral WBCs were 17.0 ± 7.8, 16.3 ± 5.5, and 10.6 ± 4.9 × 10^3/mm^3 for patients with GABHS, *S. pneumoniae*, and *S. aureus* AHO, respectively. The difference in admission WBC count was statistically significant between GABHS and *S. aureus* AHO (*P* < .0001) but not between GABHS and *S. pneumoniae* AHO. Using the frequency distribution of pooled data from all children in the study, we determined the 75th percentiles for admission temperature and WBCs. For admission temperature, the 75th percentile was 39.2°C and for admission WBCs was 16 875/mm^3. Forty-eight percent (48%) of children with GABHS AHO had admission temperature >39.2°C compared with 18% of children with *S. aureus* and *S. pneumoniae* AHO. With regard to admission WBCs, 48% of children with GABHS had higher counts. However, only 11% of children with *S. aureus* and 29% with *S. pneumoniae* had admission WBCs >16 875/mm^3.

Blood culture was taken from all patients and proved positive in 54% of the cases. Synovial fluid was obtained from 39 patients and confirmed the cause in 22 patients. In 13 patients, the diagnosis of septic arthritis was supported by the description of the synovial fluid or the synovial fluid WBC count. A bone specimen for culture was obtained by needle aspiration or open bone biopsy in 76% of the children and confirmed the cause in 55% of them.

The most common sites of infection in GABHS AHO were femur (23%), calcaneus (19%), tibia (16%), and humerus (10%). Two children had involvement of >1 bone. The frequency of occurrence of infection of tubular and cuboidal bones was similar among the 3 microorganisms. However, irregular (ilium, pubis, ischium) and flat (eg, skull, sternum) bones were more often infected with *S. aureus* than with GABHS and *S. pneumoniae* (*P* = .026). Concurrent adjoining septic arthritis was present in 22%, 28%, and 61% of children with GABHS, *S. aureus*, and *S. pneumoniae* AHO, respectively. GABHS, like *S. aureus*, was less likely to cause adjoining septic arthritis in children with AHO compared with *S. pneumoniae* (*P* = .01).

### TABLE 2. Treatment and Outcome of Children With AHO Caused by GABHS, *S. pneumoniae*, and *S. aureus*

<table>
<thead>
<tr>
<th>Treatment and Outcome</th>
<th>AHO</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>GABHS (n = 29)</td>
</tr>
<tr>
<td>Surgical procedures*</td>
<td></td>
</tr>
<tr>
<td>Needle aspiration</td>
<td>13</td>
</tr>
<tr>
<td>Incision and drainage</td>
<td>7</td>
</tr>
<tr>
<td>None</td>
<td>8</td>
</tr>
<tr>
<td>Total duration of antibiotic therapy (d, mean ± SD)</td>
<td>50.0 ± 19.7</td>
</tr>
<tr>
<td>Duration of parenteral antibiotics (d, mean ± SD)</td>
<td>20.4 ± 11.7</td>
</tr>
<tr>
<td>Duration of fever (d, mean ± SD)</td>
<td>3.8 ± 4.1</td>
</tr>
<tr>
<td>Hospital length of stay (d, mean ± SD)</td>
<td>14.7 ± 7.2</td>
</tr>
<tr>
<td>Patients with sequelae [n (%)]</td>
<td>2 (6.8)</td>
</tr>
</tbody>
</table>

* In 5 patients, no data on surgical procedures were recorded.
Surgical procedures, antibiotic therapy, and outcome of children with AHO caused by the 3 organisms are summarized in Table 2. Data on bone surgical procedures were recorded for 97 patients: 38 had needle aspiration, 39 had incision and drainage, and 20 had no surgical procedure performed. No differences related to surgical procedures were observed among the 3 groups.

All patients were initially treated with parenteral administration of antibiotics followed by oral therapy. Although there were no differences among the 3 groups in the duration of intravenous antibiotics, the total treatment was shorter for patients with S pneumoniae AHO (42.2 ± 10.5 days) compared with patients with GABHS (50.0 ± 19.7 days) and S aureus (71.0 ± 44.7 days) AHO (P = .002).

In patients with GABHS AHO, the mean duration of fever after admission and the length of hospitalization were 3.8 ± 4.1 and 14.7 ± 7.2 days, respectively. These findings were similar to those from patients with AHO caused by the other 2 pathogens. Among the 3 groups, significant differences were observed in time needed for ESR to return to normal levels (≤20 mm/h; Fig 1). Time to ESR normalization was longer for cases of AHO caused by GABHS compared with that of cases of AHO caused by S pneumoniae, and the difference approached statistical significance (P = .06). Similarly, children with S aureus AHO took a significantly longer time to normalize their ESR compared with those with AHO caused by S pneumoniae (P = .006). However, there was no significant difference in time to normalization of ESR between cases of AHO caused by GABHS and S aureus (P = .26).

All patients were followed in the Infectious Diseases outpatient clinic and, when necessary, by orthopedic surgeons. All cases had a follow-up of at least 2 months. The median duration of follow-up for the 102 patients in the study was 8 months (range: 2–108). Sequelae were documented in 7 patients (GABHS, 2; S pneumoniae, 3; and S aureus, 2). Sequelae included limb length discrepancy and persistent lytic lesion (1), flexion contracture of the elbow (1), hip contracture (3), destructive changes with limited range of motion (1), and avascular necrosis of the femoral head (1). Five of the 7 patients with sequelae had adjacent septic arthritis (hip, 4; elbow, 1). Patients with adjacent septic arthritis were at higher risk of developing sequelae compared with those without arthritis (P = .03).

DISCUSSION

GABHS is the causative pathogen for a small but consistent proportion of childhood AHO.12 Although in a few reported series there was no difference in the proportion of cases caused by GABHS and S pneumoniae, in most of them, GABHS was, after S aureus, the most common pathogen of AHO, causing up to 10% of bacteriologically confirmed cases.12 It is interesting that we also found no difference in the proportion of AHO caused by GABHS and S pneumoniae. However, it should be pointed out that in 6 cases excluded from the study (polymicrobial cause), GABHS was among the identified organisms, but there was no polymicrobial case with S pneumoniae among the causative agents. Although childhood AHO caused by other bacteria (eg, S aureus, S pneumoniae, H influenzae type b) has been well characterized,3,5,9–11 detailed description of childhood AHO caused by GABHS is lacking in the medical literature. This study is the first such characterization of childhood AHO caused by this microorganism.

In our study, the age of children with GABHS AHO was consistent with the peak incidence of GABHS infections in preschool and early school-aged children.13 Similarly, the significantly lower age of children with pneumococcal AHO is representative of the higher incidence of pneumococcal infections in younger children compared with older children and adults.10,11,14 In contrast, S aureus affects a much broader age group and accounts for 80% to 90% of cases of osteomyelitis in children older than 2 years.3,8 Previous studies, with overwhelming cases of S aureus osteomyelitis, found no racial differences.4,8 Similarly, we found that children with GABHS AHO were as likely to be white as nonwhite.

During the last 15 years, numerous reports have documented an increasing frequency of invasive infections caused by GABHS.15 Although the association of invasive GABHS infections and varicella has been well recognized,16,17 only sporadic cases of GABHS osteomyelitis associated with varicella have been reported.18,19 In 1989, Kain et al19 reported 1 case of GABHS AHO associated with varicella infection and also reviewed the literature. They found only 7 cases of AHO associated with a history of varicella, and all of them were caused by GABHS. Of interest was that 17% of our children with GABHS AHO had a recent history of varicella.

Other differences observed among the 3 groups of AHO included mean admission temperature and WBC count, anatomic site of infection, involvement of adjacent joints, and duration of antibiotic therapy. Previous studies investigating different indices of inflammation reported that many patients were afebrile.
brile during admission and that WBC count was a poor indicator of AHO, because only 33% of children had leucocytosis (WBCs >12,000/mm$^3$) at the time of admission. It is worth noting that $S$ aureus was the predominant causative agent in those studies, being responsible for almost 90% of cases. It therefore seems inappropriate to generalize these findings to all cases of AHO, particularly to those caused by other microorganisms.

As evident from our study, GABHS, $S$ pneumoniae, and $S$ aureus affect mainly the tubular bones, and the anatomic site of infection was not predictive of the bacterial agent causing the infection. The only exception was the involvement of irregular (ilium, pubis, and ischium) and flat (skull, sternum, scapulae, and ribs) bones, which were predominantly affected by $S$ aureus.

With regard to the incidence of adjacent septic arthritis, our findings confirmed previous reports indicating the high incidence of concurrent septic arthritis in patients with $S$ pneumoniae AHO. These findings may reflect the younger age of children infected with this pathogen. In infants and toddlers, the bone cortex is relatively thin and the periosteum is loose. In addition, the joint capsule tends to extend distal to the epiphyseal plate, and nutrient metaphyseal vessels extend capillary channels to the epiphysis. These anatomic features favor the spread of bone infection to adjacent joint space.

Although some investigators call for the use of C-reactive protein in patients with AHO, in our institution, ESR continues to be the major laboratory index used to monitor treatment response in patients with osteoarticular infections. Our results revealed that despite insignificant differences in mean admission ESRs, time to normalization of ESR was longer for patients with $S$ aureus and GABHS AHO compared with those with $S$ pneumoniae AHO (Fig 1). These findings mirror the duration of treatment in these groups. With regard to $S$ pneumoniae AHO, these findings were unexpected because 61% of our children with $S$ pneumoniae AHO had adjoining septic arthritis. Previous studies noted that in patients with AHO and adjoining septic arthritis, ESRs remained abnormal for a prolonged period. However, the study population in those earlier reports consisted mainly of patients with $S$ aureus infections. For example, in the study by Unkila-Kallio et al., $S$ aureus was responsible for 41 of their 46 patients. Indeed, these findings, in conjunction with our observations, suggest that the time to ESR normalization may be organism specific. However, it is likely that patients who are infected with the same organism exhibit abnormal ESR levels for a longer period when AHO is complicated by adjoining septic arthritis.

CONCLUSIONS

GABHS is responsible for a relatively small but consistent proportion of cases of AHO in childhood. Although the signs and symptoms seem to be indistinguishable from those caused by other microorganisms, it should be considered in preschool- and early school-aged children who are suspected of having osteomyelitis and whose clinical and laboratory features are characterized by high fever and marked leukocytosis. GABHS should also be highly considered in cases of osteomyelitis associated with varicella infection.

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