Impact of Antibiotic Pretreatment on Bone Biopsy Yield for Children With Acute Hematogenous Osteomyelitis

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abstract

OBJECTIVE: Pediatric acute hematogenous osteomyelitis (AHO) is a relatively common reason for hospitalization, but many variables require additional study, including the impact of antibiotic treatment on bone biopsy culture yield.

METHODS: This was a retrospective study of children 60 days to 18 years old with AHO seen from 2011 to 2012 in whom bone biopsy cultures were obtained.

RESULTS: A total of 67 children had biopsies; median age was 7 years; 40 were pretreated with antibiotics. Microbiologic confirmation was obtained for 72%: in 34%, both blood and bone cultures were positive; in 33%, bone cultures alone were positive; and 4% had only positive blood cultures. There was no difference in bone biopsy cultures for children who did and did not receive antibiotics before biopsy (28/40 [70%] vs 17/27 [63%], odds ratio 1.37, 95% confidence interval 0.49–3.86). For pretreated patients, the mean duration of therapy was longer in children with negative cultures (79 vs 40 hours, $P = .04$). Bacteremia was seen in 26 (39%), and was more common in antibiotic-pretreated children (55% vs 15%, odds ratio 7, 95% confidence interval 2.1–24.1). Among the 41 nonbacteremic children, bone cultures provided the only microbiologic diagnosis for 22 (54%): 20 *Staphylococcus aureus,* 2 *Streptococcus pyogenes.*

CONCLUSIONS: In conclusion, although bone biopsy results were not affected by previous antibiotic administration, a longer duration of antibiotic therapy before bone biopsy was associated with lower culture yield. In one-third of children, only the bone biopsy resulted in an organism being isolated. As it may take longer to sterilize bone than blood, a bone biopsy/culture should be considered a crucial part of the AHO evaluation to increase diagnostic yield.

Acute hematogenous osteomyelitis (AHO) is the most common form of pediatric osteomyelitis. Pathogen-directed therapy is preferable to empirical treatment and appropriate therapy depends on identification of a causative organism; however, blood culture results are positive in only 23% to 60% of cases.[1–6] The addition of a bone biopsy culture or other tissue culture has been shown to increase the organism detection rate to 45% to 80%.[1,4–8]

There are limited data on the yield of bone biopsies and the effect of prebiopsy antibiotics on pathogen recovery in osteomyelitis. Several small retrospective studies in adults suggest that there is between a 16% to 56% lower rate of pathogen recovery in fine-needle aspirates obtained after the initiation of antibiotics[9–11]; however, a larger retrospective review that included both percutaneous and open bone biopsies did not show a difference in culture yield (percentage of all specimens yielding a positive culture).[12] The effect of pre–bone biopsy antibiotic exposure

on pathogen recovery in children with AHO is unknown. Some practitioners may withhold antibiotic therapy until after a bone biopsy is obtained because of concerns that antibiotics will reduce the likelihood of a positive culture result, whereas others may be uncomfortable withholding antibiotics. Understanding the impact of pre–bone biopsy antibiotic exposure on pathogen recovery could assist practitioners in making decisions about when to initiate antibiotic therapy in patients with known or suspected AHO. We sought to analyze the association between initiation of antibiotics before bone biopsy and subsequent culture yield.

METHODS

This was a retrospective cohort study of children aged 60 days to 18 years hospitalized at a large children's hospital from 2011 to 2012 with a diagnosis of AHO (versus contiguous osteomyelitis) who underwent a bone biopsy. Patients were identified from 3 sources: hospital discharge diagnoses (International Classification of Diseases, Ninth Revision codes 730, 730.2, 730.3, 730.8, and 730.9), records of the infectious disease service, and microbiology laboratory. A diagnosis of AHO was established based on compatible signs and symptoms of disease confirmed by MRI changes consistent with osteomyelitis (defined as bone marrow signal intensity alterations consistent with inflammation with or without associated marrow necrosis, suppuration, periosteal reaction, or cortical bone destruction),[13] and histopathologic specimens consistent with osteomyelitis (defined as positive blood or bone culture or histologic changes on bone biopsy consistent with osteomyelitis). Patients were excluded if they were immunocompromised (asplenia,

HIV, malignancy, primary immune disorders, chronic immunosuppressive therapy, or sickle cell disease), had received antibiotic therapy for >1 week's duration at the time of presentation, had chronic osteomyelitis (defined as symptoms compatible with osteomyelitis present for >2 weeks and radiographic evidence of devitalized bone or pathology consistent with chronic osteomyelitis), had penetrating trauma or postoperative infections, had cultures obtained only from subperiosteal fluid collections or abscesses, or were transferred from a referring hospital with incomplete documentation of antibiotic or laboratory data. Records were reviewed to identify patient demographics, clinical symptoms, physical examination, and laboratory, microbiologic, pathology, and radiographic findings. Records also were abstracted for the timing and selection of antibiotics. The study was approved by the local institutional review board. Frequencies were calculated for descriptive variables. Continuous variables were analyzed with t tests or Wilcoxon rank sum.

Dichotomous variables were analyzed with χ^2 or Fisher's exact test. Stata 11 (Stata, Inc., College Station, TX) was used for analyses.

RESULTS

A total of 181 patients were diagnosed with AHO (Figure) and 112 met inclusion criteria, of whom 67 (60%) received bone biopsy. Thirty-seven biopsies (55%) were operative and 30 (45%) were performed by interventional radiology; the culture yields were 86% and 43%, respectively (odds ratio [OR] 8.4, 95% confidence interval [CI] 2.6–27.4). The demographics of the study population are described in Table 1 and compared with children not receiving bone biopsy. The clinical and laboratory findings are described in Table 2. Of the children receiving bone biopsies, only 2 (3%) were described as toxic-appearing.

Twenty-six children (39%) were bacteremic with 23 (88%) of 26 having *Staphylococcus aureus* (12 methicillin-susceptible *S aureus* [MSSA], 11
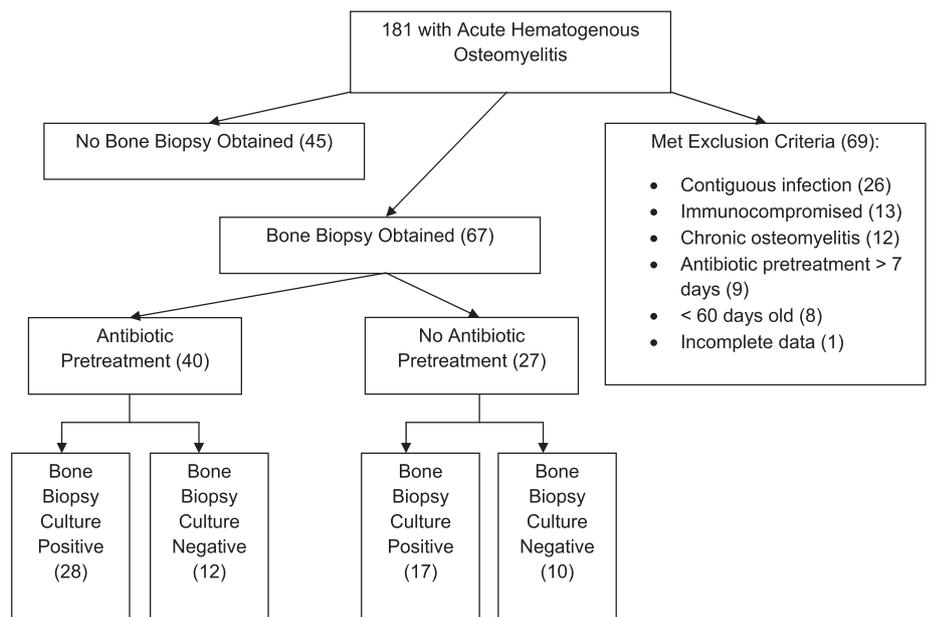

FIGURE Children diagnosed with AHO, 2011–2012.

TABLE 1 Comparison of the Demographics of the Study Population With Children Not Receiving Bone Biopsy

Variable	Complete Study Population, n = 112	Population Without Biopsy, n = 45	Population With Biopsy, n = 67	P
Boys	71 (63)	31 (69)	40 (60)	.43
Age				
Median, y	7	7 (16)	7 (10)	.55
2–12 mo	5 (4)	1 (2)	4 (6)	.40
1–4 y	31 (28)	15 (33)	16 (24)	
5–12 y	64 (57)	21 (47)	43 (64)	
13–18 y	12 (11)	8 (18)	4 (6)	
Medical comorbidity				
None	107 (96)	45 (100)	62 (93)	.79
Other[a]	5 (4)	0	5 (7)	
Blood culture				
Positive	40 (36)	14 (31)	26 (39)	.43
Negative	72 (64)	31 (69)	41 (61)	
Site				
Tibia/fibula	31 (28)	4 (9)	27 (40)	.44
Femur	19 (17)	7 (16)	12 (18)	
Foot	17 (15)	6 (13)	11 (16)	
Pelvis	15 (13)	12 (27)	3 (4)	
Humerus	9 (8)	6 (13)	3 (4)	
Spine	8 (7)	3 (7)	5 (7)	
Forearm	4 (4)	1 (2)	3 (4)	
Patella	4 (4)	3 (7)	1 (1)	
Hand	2 (2)	2 (4)	0	
Other[b]	3 (3)	1 (2)	2 (3)	

Numbers may not sum to 100% due to rounding. Values are n (%) unless otherwise indicated.
[a] One child each had intestinal atresia, Menke disease, solitary kidney, spina bifida, and 1 new-diagnosis chronic granulomatous disease.
[b] One child who did not receive a biopsy had scapular AHO; 2 children with clavicular and rib osteomyelitis received biopsies.

methicillin-resistant *S aureus* [MRSA]), 2 (8%) *Streptococcus pyogenes*, and 1 (4%) group B *Streptococcus*. All children who had both positive blood and bone biopsy cultures grew the same organism in both. Sixty percent (40/67) of children who underwent bone biopsy received antibiotics before the biopsy. Children who received antibiotics did not differ in physical examination findings, but were more likely to have a higher peripheral white blood cell count and C-reactive protein, as well as being more likely to have a joint effusion visualized on MRI (Table 2). The most common antibiotics used before biopsy were vancomycin (19/40, 48%) and clindamycin (17/40, 43%). This reflected local antibiotic resistance patterns. The local rates of MRSA were high (>60%) among all skin/

soft tissue infections, and rates of clindamycin resistance increased to 20% during the study period.

There was no difference in bone biopsy culture results for those children who did and did not receive antibiotics before biopsy (28/40 [70%] vs 17/27 [63%], OR 1.37, 95% CI 0.49–3.86). For patients who received an antibiotic before biopsy, the mean duration of therapy was 79 vs 40 hours in children with negative and positive cultures, respectively (P = .039). Among the 41 children who were not bacteremic, bone cultures provided the only microbiologic diagnosis for 22 (54%): 16 MSSA, 4 MRSA, 2 *S pyogenes*. Overall, microbiologic confirmation was obtained in 48/67 (72%) children: 23/67 (34%) both blood and

bone cultures, 22 (33%) bone cultures alone, and 3 (4%) blood cultures alone. There was a trend toward children with MSSA being more likely to have a positive bone culture than blood culture when compared with MRSA (for MSSA, of 27 children with a positive bone culture, 11 were bacteremic [41%] vs 73% with MRSA; OR 4, 95% CI 1.0–15.9).

Fourteen children (21%) had complications, with the most common being a need for repeat operative intervention (6), new abscess formation (3), multifocal osteomyelitis (2), and pathologic fracture (2). Twelve had received antibiotics before biopsy.

DISCUSSION

This study demonstrated several interesting associations. First, antibiotic pretreatment was not associated with a decrease in bone biopsy culture yield when antibiotic use was treated as a dichotomous outcome. However, longer antibiotic durations before biopsy were associated with reduced culture yield. Importantly, for many children in our study, the only microbiologic diagnosis was derived from a bone biopsy.

Bone biopsy yield did not appear to be associated with antibiotic pretreatment in this pediatric cohort. This may be because of differences in illness severity. Children who were pretreated with antibiotics were more likely to be bacteremic, and had higher white blood cell counts and inflammatory markers than children who were not pretreated. As this was a retrospective cohort study, children were not randomized to a given intervention. A higher proportion of bacteremic children receiving antibiotics likely reflects clinical recognition of increased disease severity. Despite pretreatment, these children

TABLE 2 Clinical and Radiographic Laboratory Findings in Children Undergoing Bone Biopsy

Finding	Antibiotic Pretreatment Group, n = 40[a]	No Antibiotic Pretreatment Group, n = 27	Statistical Variable, P or OR (95% CI)
Symptoms[b]			
Pain	37/40 (93%)	20/27 (74%)	P = .08
Fever	38/40 (95%)	27/27 (100%)	P = .51
Swelling	20/22 (91%)	9/13 (69%)	P = .17
Signs[b]			
Tenderness	33/37 (89%)	22/24 (92%)	P = .99
Decreased range of motion	25/27 (93%)	15/19 (79%)	P = .21
Erythema	18/29 (62%)	5/14 (36%)	P = .19
Warmth	19/23 (83%)	9/12 (75%)	P = .67
Swelling	30/34 (88%)	13/18 (72%)	P = .25
Laboratory findings, means			
WBC, cells/mm³	12 300	9600	P = .02
Hemoglobin, g/dL	11.8	11.4	P = .14
Platelets, cells/μL	256 000	352 000	P < .001
ESR, mm/h	53	52	P = .84
CRP, mg/L	18	8	P = .01
MRI findings,[c] n (%)			
Marrow edema	23 (58)	17 (63)	0.8 (0.29–2.17)
Myositis	22 (55)	12 (44)	1.53 (0.57–4.08)
Joint effusion	24 (60)	8 (30)	3.56 (1.26–10.08)
Periosteal reaction	9 (23)	4 (15)	3.62 (0.72–18.34)
Histopathology			
Nonviable bone	26/29 (90%)	13/19 (68%)	4 (0.86–18.6)
Acute inflammation	21/26 (81%)	8/15 (53%)	3.68 (0.90–15.01)
Gram stain positive	2/40 (5%)	1 (4%)	1.37 (0.12–15.89)
Blood culture, n (%)			
Positive	22 (55)	4 (15)	7.03 (2.05–24.07)
Negative	18 (45)	23 (85)	
Bone biopsy Gram stain, n (%)			
Positive	18 (45)	7 (26)	2.33 (0.81–6.76)
Negative	22 (55)	20 (74)	
Bone biopsy culture, n (%)			
Positive	28 (70)	17 (63)	1.37 (0.49–3.86)
Negative	12 (30)	10 (37)	

Numbers may not sum to 100% due to rounding. CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; WBC, white blood cell count.

[a] Antibiotic pretreatment (number with positive cultures/number receiving antibiotic before bone biopsy): vancomycin 15/19 (79%), clindamycin 6/13 (46%), ceftriaxone 4/4 (100%), oral β-lactam 2/3 (67%), and nafcillin 1/1.

[b] Number with documented positive findings/number with finding documented.

[c] Many patients had >1 MRI finding.

may have had positive bone biopsy cultures because of their bacterial load. In many instances, a bacteremic child underwent an intervention by surgery or interventional radiology not because a bone biopsy was pursued for a microbiologic diagnosis, but rather because the child had a purulent fluid collection that needed to be drained. In other instances, the antibiotics received (eg, ceftriaxone or amoxicillin/clavulanate) in the outpatient setting would not have provided coverage for the most common organisms causing AHO.

Although antibiotic receipt before biopsy was not associated with culture results when considered as a dichotomous variable, the duration of antibiotic use before biopsy was associated with culture yield. This is an important consideration when clinicians are faced with the dilemma of withholding antibiotics pending a biopsy. A child admitted over a weekend may not receive a biopsy until the next weekday when procedural sedation may be more feasible. Although clinicians may feel comfortable withholding antibiotics for a short period pending biopsy, others may question the justification behind hospitalizing a child with a suspected bone infection for observation off of antibiotics.

For one-third of the patients, the etiology of AHO was determined only via bone biopsy. This is concordant with previously published literature.[1–8] This may be because it takes longer to sterilize bone than blood. In an era of increasing antibiotic resistance, isolation of a pathogen becomes critical to targeting not only initial parenteral antibiotics, but also assisting with the decision to transition from intravenous to oral therapy. Some infectious disease clinicians may feel more comfortable transitioning a child to oral therapy if an etiology and antibiotic susceptibilities are available.

There were limitations to this study. Given the retrospective nature, not all variables were documented for all patients and this was particularly true for elements of the history and physical examination. We excluded children who had received antibiotics for more than 1 week to exclude children who received antibiotics for other presumed etiologies (eg, acute otitis media) before recognition of the full spectrum of AHO. There was a selection bias in which children received antibiotics before biopsy, which antibiotics were administered, and likely illness severity; all of these are possible factors that could have accounted for the results. Indications for bone biopsy were not always evident from the medical record. The hospital implemented

a new clinical pathway for AHO in 2011 that strongly recommended bone biopsy and led to increased cases during the last year of the study period. The sample size was relatively small, and a multicenter study would add substantially to the existing data.

In conclusion, although bone biopsy results were not affected by antibiotic receipt, a longer duration of antibiotic therapy before bone biopsy was associated with lower culture yield. In one-third of children, only the bone biopsy culture produced a microbiological diagnosis. Clinicians should coordinate with subspecialists to obtain early bone biopsy in children with suspected osteomyelitis.

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