CQR is a recurring section in Hospital Pediatrics where authors start with a relevant clinical question, find and synthesize the recent literature and provide their best answer to the question in conclusion.

Route and Length of Therapy of Acute Uncomplicated Hematogenous Osteomyelitis: Do We Have the Answers Yet?

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KEY WORDS
osteomyelitis, therapeutics, child

ABBREVIATIONS
AHOM: acute hematogenous osteomyelitis
CRP: C-reactive protein
ESR: erythrocyte sedimentation rate
IV: intravenous
MSSA: methicillin-sensitive *Staphylococcus aureus*

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Acute hematogenous osteomyelitis (AHOM) is not uncommonly encountered in hospitalized pediatric patients, occurring in 1 in 5000 children per year or 1% of pediatric hospitalizations.[1] There are published data regarding the length of antibiotic therapy, with many studies supporting an initial short intravenous (IV) course of therapy followed by an oral course of several weeks. Le Saux[2] performed a systematic review that supported short-course IV therapy for AHOM. Peltola[3] published the largest prospective study to date addressing treatment of AHOM, which supported short-course IV therapy followed by oral therapy for a total of 20 days. However, in practice, it is not so straightforward. It is not unusual for practitioners to recommend a long IV course of therapy, even in the face of an uncomplicated case of AHOM. Uncomplicated AHOM has been variably defined, but in general it would refer to osteomyelitis in a patient with <14 days of symptoms, no underlying medical conditions, and infection not associated with trauma and not requiring extensive surgical intervention[3–6]. This review synthesizes the available literature and addresses 2 clinical questions: (1) Is it reasonable to use short-course IV therapy in uncomplicated AHOM in pediatric patients? and (2) What is the appropriate total duration of therapy for uncomplicated AHOM in pediatric patients?

METHODS

AHOM is defined as <2 weeks of clinical symptoms with associated laboratory and imaging findings characteristic of AHOM and without any source for exogenous spread to the bone, such as may occur with penetrating trauma.

The Pub Med and Google Scholar databases were used to conduct searches. Google Scholar was used to aid in finding open-access articles that might not be listed in PubMed. The search followed Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[7] Google scholar search terms included "osteomyelitis in infants and children," "antibiotics," and "duration," with no filters. Three PubMed searches included the terms "intravenous therapy," "oral antibiotics," and "acute osteomyelitis in children" with the filter "humans"; "antibiotic therapy," "children," "acute osteomyelitis," and "bone infection," with the filter "humans"; and "short," "therapy," "acute" and "osteomyelitis" with the filters "humans," "Child: birth–18 years," "Adolescent: 13–18 years," "Infant: 1–23 months," "Preschool child: 2–5 years," and "Child: 6–12 years."

Additionally, our literature review targeted articles published after the systematic review written by Le Saux in 2002.[2]

RESULTS

Six studies were ultimately used for the present review.[1,3–6,8] A detailed description of the search is shown in Fig 1. The studies included in this review are listed in Table 1 and the details of the treatment, bacteriology, antibiotics used, and outcomes are shown in Table 2.

As can be seen from Table 1, the studies are variable as to their type. Three were prospective,[3,5,8] 2 were retrospective chart reviews,[4,6] and 1 was a retrospective database study.[1] The studies also varied greatly in regard to sample size. The largest study was conducted by Zaoutis et al with data collection for 1969 subjects,[1] whereas Jaberi et al's study had the smallest cohort of only 12 patients.[8] Additionally the location and actual year(s) of data of collection are varied. The largest prospective study, by Peltola et al,[3] collected patients over 22 years (Table 1).

Length of IV Therapy

The length of IV therapy with ranges for each study is shown in Table 2. Two of the studies compared short and long courses.[1,8] In a retrospective database study, Zaoutis et al defined a short-course parenteral therapy as ≤10 days.[1] Jaberi et al defined 10 days and 21 days for short- and long-course parenteral therapy, respectively.[8] The remaining 4 studies reported an average length of IV therapy of <7 days.[3–6] Peltola et al and Jagodzinski et al used a priori criteria to guide transition time from IV to oral therapy.[3,5] Jaberi et al used a priori criteria either to stop therapy at the short-course time period or convert to long-course IV therapy[8] (Table 2).

Long-term complications were rare, occurring in only 2 studies,[1,3] and in none of the studies did complication rates differ by duration of IV therapy. Defining complications as readmissions to the hospital within 6 months of initial admission for a related illness, Zaoutis et al reported complication rates of 4.7% and 5% for patients receiving the short and long courses of IV therapy, respectively[1] (Table 2). Peltola et al reported 2 complications: 1 patient received IV therapy for 3 days and the other for 13 days.[3]

Total Duration of Therapy

Five of the studies addressed total duration of therapy[3–6,8] (Table 2). The average total duration of therapy for the studies ranged from 20 to 38 days (Table 2). None of the studies reviewed had comparison groups that received combined therapy longer than 30 days. Two of the prospective studies used criteria to guide total length of therapy. Peltola et al used the following criteria: C-reactive protein (CRP) <20 mg/L and resolution of most clinical signs and symptoms of AHOM.[3] Jagodzinski et al used the following criteria: a combination of clinical signs and symptoms and continued therapy until the erythrocyte sedimentation rate normalized.[5] They reported 2 patients who had therapy extended because of the presence of lytic lesions on plain radiographs, although this finding was not consistently used as a reason to extend therapy.[5]

Peltola reported the only complications in the studies addressing total duration of therapy. One patient had an asymptomatic 8-degree varus

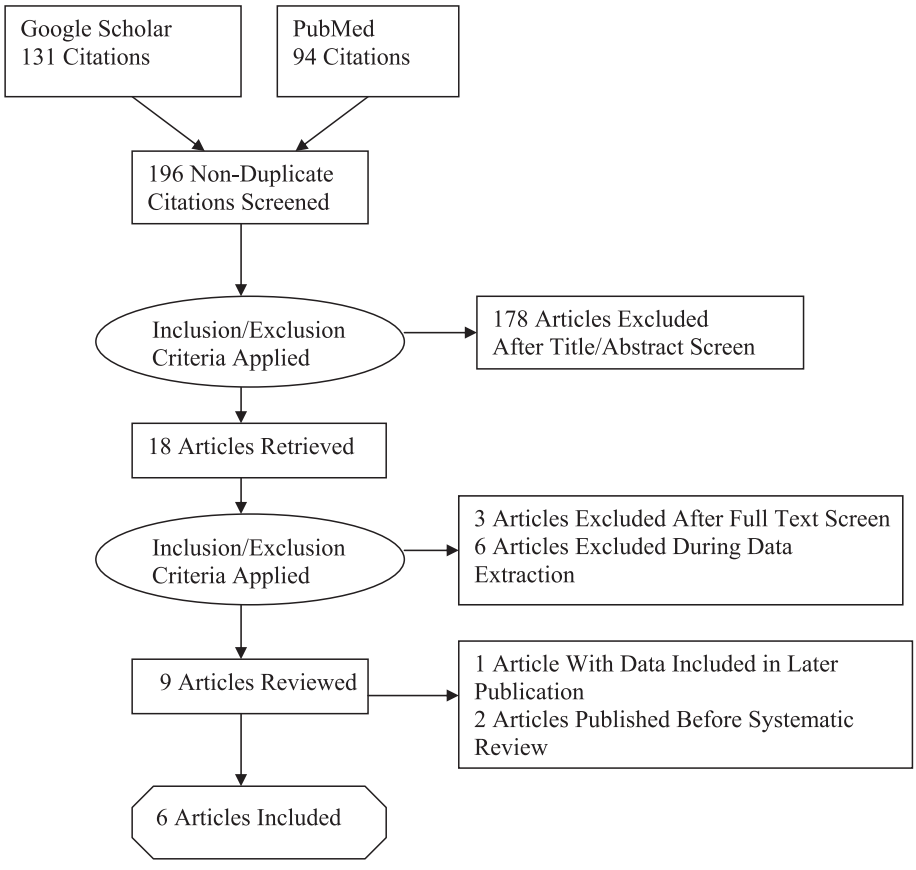

FIGURE 1 Flow diagram of search results.

TABLE 1 Studies Included in Review

Study First Author	Year Published (Time Period of Study)	Study Type	Sample Size	Country
Peltola	2010 (1983–2005)	Prospective	131	Finland
Jagodzinksi	2009 (2001–2007)	Prospective	37	England and Australia
Zaoutis	2009 (2000–2005)	Retrospective (database search)	1969	US (29 hospitals)
Bachur	2007 (1995–2000)	Retrospective (chart review)	29	US (Boston)
Jaberri	2002 (1996–1998)	Prospective	12	Iran
Vinod	2002 (1997)	Retrospective (chart review)	32	Australia

deformity and the other had ankle pain with exercise. The first patient received antibiotics for 118 days and the second for 80 days[3] (Table 2).

DISCUSSION

Although there is a significant amount of published data regarding treatment of AHOM, in practice there remains significant variability in treatment.[1] Given the rarity of long-term complications in uncomplicated AHOM in children, it is no surprise that it is so difficult to determine with certainty how best to treat these patients. Jagodzinski et al noted that it was not feasible to conduct a randomized clinical trial due to "power analysis and cost."[5] At present, Pediatric Research in Inpatient Settings is beginning a multicenter study addressing the treatment of osteomyelitis and other infections, and recommendations from the Pediatric Infectious Diseases Society/Infectious Diseases Society of America Committee for the Diagnosis and Management of Bone and Joint Infections are forthcoming.

The data presented in this review provide a basis to answer 2 questions about the management of uncomplicated AHOM. Is it reasonable to use short-course IV therapy in uncomplicated AHOM in pediatric patients? The exact length of IV therapy is unclear; however, a curtailed course of IV therapy, then switching to oral therapy, is indicated. The majority of the studies suggest that 7 days is sufficient for the vast majority of patients with uncomplicated AHOM. Improving clinical signs and symptoms coupled with falling serum CRP concentrations provide a basis for safely transitioning to oral therapy. What is the appropriate total duration of therapy for uncomplicated AHOM? The ranges from the studies reviewed are broad, but in general it appears that 21 to 28 days of therapy is adequate for the majority of cases of uncomplicated AHOM, particularly in the face of a resolved clinical picture accompanied by normalization of

TABLE 2 Study Details

Study	Duration IV in Days (Range)	Total Duration of Therapy in Days (Range)	Antibiotics Used	*S aureus*–Positive Culture: % of All Isolates (Reported MSSA vs MRSA)	Percent With Complication
Peltola	3.9[a] (0–14)	20: 67 patients; 30: 64 patients (10–43)	Clindamycin, first-generation cephalosporin	89 (all MSSA)	1.5 (2 patients)
Jagodzinki	3.75[b] (2–15)	21 d after IV (28 patients); extended (9 patients)[c]	Penicillinase-resistant penicillin	100[d]	0
Zaoutis	<10 vs >10	NA	First-generation cephalosporin, penicillinase-resistant penicillin clindamycin	MSSA average 32.5; MRSA average 7.5[e]	4.7 vs 5[f]
Bachur	4[b] (0–7)	32 (20-49)	First-generation cephalosporin	85 (all MSSA)	0
Jaberi	10 or 21	28 d after IV	Cephalosporin with aminoglycoside	100[d]	0
Vinod	3[b]	38[g] (20–46)	First-generation cephalosporin, penicillinase-resistant penicillin	65[d]	0

d, days; MRSA, methicillin-resistant *S aureus*.
[a] Average of 2 study groups.
[b] Median.
[c] Specifics not reported.
[d] Authors did not report MSSA versus MRSA.
[e] Average of short and long IV groups combined.
[f] Short- versus long-course IV.
[g] Converted from weeks.

serum CRP and erythrocyte sedimentation rate.

Given that most of the patients included in this review were infected with methicillin-sensitive *Staphylococcus aureus* (MSSA), the application of these recommendations to children infected with community-acquired methicillin-resistant *S aureus* must be made with care.[9] Martinez-Aguilar compared the natural history of skeletal infections in children with both MSSA and MRSA[10]; the total duration of therapy was comparable for both groups and was affected mostly by complicating factors such as deep vein thrombosis or accompanying pyomyositis. Compared with children with MSSA infections, those with infected with MRSA remained febrile longer and had longer hospitalizations; however, there was no difference in long-term outcomes between the 2 groups.[10] Additionally, as noted by Lazarevic, molecular determinants of *S aureus* isolates have not correlated with clinical outcome.[11]

CONCLUSIONS

Although the data are challenging to synthesize, it is reasonable to make an evidence-based decision regarding the duration of IV therapy and the total duration of antibiotics for patients with uncomplicated osteomyelitis. For children with uncomplicated AHOM, transition to oral antibiotics should occur when the child is clinically improved and the CRP has normalized, which will typically take between 3 and 7 days for children infected with MSSA. Total direction of therapy should range from 21 to 28 days.

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