Acute Bacterial Osteoarticular Infections: Eight-Year Analysis of C-Reactive Protein for Oral Step-Down Therapy

WHAT’S KNOWN ON THIS SUBJECT: Pediatric osteoarticular infections can be treated with successful microbiologic and clinical outcomes with a transition from parenteral to oral therapy. The best way to determine the timing of this transition is neither well studied nor standardized.

WHAT THIS STUDY ADDS: A total of 193 (99.5%) of 194 pediatric patients with acute bacterial osteoarticular infections were successfully transitioned to oral therapy, determined by using a combination of clinical findings and C-reactive protein levels, representing the largest single-center data set analyzed.

abstract

BACKGROUND: One of the most important decisions in the treatment of osteoarticular infections is the time at which parenteral therapy can be changed to oral therapy. C-reactive protein (CRP) is an acute inflammatory indicator with a half-life of 19 hours and thus can be helpful in assessing the adequacy of therapy for bacterial infections. At our institution, a combination of CRP and clinical findings is used to determine the transition to oral therapy.

METHODS: A search of 8 years of electronic records identified children with osteoarticular infections. Only children with culture-positive acute bacterial arthritis (ABA) or acute bacterial osteomyelitis (ABO) were studied further. A primary chart review of demographic and clinical data was conducted, and a secondary chart review of complicated outcomes was performed.

RESULTS: Of 194 total patients, complicated outcomes occurred in 40, of which 35 were prolonged therapy. Only 1 microbiologic failure occurred, presumably due to a retained intra-articular fragment of infected bone. CRP was highest initially among patients with simultaneous ABO + ABA and among those with complicated outcomes, and was lower at the transition to oral therapy in the complicated outcome group (1.5 vs 2.1 mg/dL; P = .012).

CONCLUSIONS: The combination of clinical findings and CRP is a useful tool to transition children with osteoarticular infections to oral therapy. Complicated outcomes were associated with higher early CRP at diagnosis and lower CRP at the end of parenteral therapy, suggesting that clinicians were more conservative with prolonged initial parenteral therapy in this group. Pediatrics 2012;130:e821–e828

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KEY WORDS
acutely bacterial arthritis, acute bacterial osteomyelitis, C-reactive protein, osteomyelitis, septic arthritis

ABBREVIATIONS
ABA — acute bacterial arthritis
ABO — acute bacterial osteomyelitis
CRP — C-reactive protein
ESR — erythrocyte sedimentation rate
IV — intravenous
MRSA — methicillin-resistant Staphylococcus aureus
MSSA — methicillin-susceptible Staphylococcus aureus
RCHSD — Rady Children’s Hospital San Diego

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The treatment of osteoarticular infections has changed dramatically over the past 3 decades. Although extended intravenous (IV) courses of antibiotics were once considered mandatory, it has become clear that for uncomplicated, hematogenous osteomyelitis in children, an initial IV course of antibiotics can be safely followed by oral therapy.\(^1,2\) Despite evidence that shorter parenteral courses are safe and effective, many children still receive prolonged IV therapy for osteoarticular infections, especially those caused by methicillin-resistant \textit{Staphylococcus aureus} (MRSA).\(^3\) The length of IV and oral therapy has not been well established, and it is unlikely that a single treatment pathway can be applied to all children with osteoarticular infections. Once effective antimicrobial therapy and surgery (if needed) have been provided, the expected course is resolution of fever, decrease in pain, return of function, and normalization of laboratory indicators of systemic inflammation (serum \textit{C-reactive protein} [CRP] and erythrocyte sedimentation rate [ESR]), the combination of which could help guide the transition to oral therapy. CRP is an acute-phase reactant that is elevated in rheumatologic, oncologic, and infectious processes.\(^4\) Because of its half-life of 19 hours,\(^5\) CRP can be used as an objective measure of treatment over the first days of therapy and has been studied by Scandinavian investigators.\(^6-8\) CRP has been used at our institution as the key laboratory factor in support of clinical and microbiologic recovery, helping determine the timing of the switch to oral therapy in osteoarticular infections. The use of CRP to guide the transition to oral therapy is not universally used in the United States and is the object of this retrospective analysis. We describe the outcomes and limitations of this approach in children with culture-positive osteoarticular infections over a recent 8-year period.

**METHODS**

**Clinical Background**

The approach to managing osteoarticular infections by the infectious diseases and orthopedic surgery divisions at Rady Children’s Hospital San Diego (RCHSD) during the past 2 decades is to continue IV therapy until an appropriate clinical response occurs, supported by a CRP level \(<2\) to \(3\) mg/dL (normal: \(<0.9\) mg/dL), at which time oral step-down therapy is initiated. After the transition to oral therapy, children are routinely evaluated as outpatients and typically complete 3 to 4 weeks of total (IV + oral) therapy for acute bacterial arthritis (ABA) and 6 weeks of total therapy for acute bacterial osteomyelitis (ABO).\(^9\) Dosages of oral therapy used are those recommended by Nelson et al.\(^9,10\) Discontinuation of oral antibiotics is based on clinical recovery and normal ESR (typically \(<10\) mm/hour) at the end of therapy, with a plain radiograph of the involved bone or joint documenting lack of sequestrum and evidence of bone healing. Long-term evaluation at 1 year after hospitalization occurs in the orthopedics clinic.

**Chart Review**

Protocol for this study was reviewed and approved by the institutional review boards of the University of California San Diego and RCHSD. Children aged \(\geq 1\) month to \(<18\) years admitted to RCHSD with a diagnosis of osteomyelitis and/or septic or pyogenic arthritis between January 1, 2000, and November 30, 2007, were identified by using the \textit{International Classification of Diseases, Ninth Revision, Clinical Modification} diagnosis code for osteomyelitis (730.01–730.39) or septic arthritis (711.01–711.99). Charts were then reviewed by authors (B.W., M.K.R., and C.R.C.) to determine eligibility for inclusion. Inclusion and exclusion criteria (Table 1) were developed to limit the chart review to acute, culture-positive bacterial infections. Culture-positive ABO was defined as evidence of bone infection on the basis of the following: (1) clinical suspicion according to patient history and physical examination; (2) abnormal bone imaging or histologic examination of surgically obtained bone specimens consistent with ABO; and (3) culture from blood, bone, and/or joint fluid positive for a bacterial pathogen known to cause ABO. Culture-positive ABA was defined as evidence of a joint infection by: (1) clinical suspicion according to patient history and physical examination; (2) arthrocentesis fluid with \(>50,000\) white blood cells/mL; and (3) arthrocentesis fluid or blood culture positive for a pathogen known to cause ABA.

Demographic data, clinical details, radiologic reports, and laboratory test results (including bacterial culture results, arthrocentesis fluid cellular analyses, and pathologist reports on submitted surgical tissue samples) were recorded. Data related to the hospitalization and medical treatment from progress notes, including response to therapy, length of stay, inpatient antimicrobial therapy (agents, route, and dosage) were noted. Data were collected on outpatient management, including the type and dosage of outpatient parenteral and oral antimicrobial therapy prescribed, the duration of therapy, the duration of follow-up, and osteoarticular complications or other long-term sequelae. Ten percent of charts were reviewed by 2 investigators to confirm consistency of data abstraction.

“Uncomplicated outcome” was defined as receiving a standard course of therapy, with a good clinical response, appropriate transition to oral therapy, appropriate duration of therapy, and lack of any osteoarticular sequelae on long-term evaluation. Follow-up was deemed adequate to exclude complication if: (1) the child attended orthopedic
TABLE 1 Inclusion and Exclusion Criteria

<table>
<thead>
<tr>
<th>Inclusion Criteria</th>
<th>Exclusion Criteria</th>
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<tbody>
<tr>
<td>Inpatient admission to RCHSD before January 1, 2000, and November 30, 2007</td>
<td>No clinical diagnosis of ABO or ABA at discharge (incorrectly coded)</td>
</tr>
<tr>
<td>Age ≥ 1 mo and &lt;18 y at admission</td>
<td>Chronic ABO or ABA (≥14 d of symptoms at presentation)</td>
</tr>
<tr>
<td>ICD-9-CM at any time during hospitalization</td>
<td>No positive result on bacterial culture from blood, bone, or joint fluid</td>
</tr>
<tr>
<td>730.01—730.39 (osteomyelitis)</td>
<td>Nonhematogenous route</td>
</tr>
<tr>
<td>711.01—711.99 (pyogenic arthritis)</td>
<td>Soft tissue trauma</td>
</tr>
<tr>
<td>003.24 (Salmonella osteomyelitis)</td>
<td>Chronic wounds</td>
</tr>
<tr>
<td>003.25 (Salmonella arthritis)</td>
<td>Implanted hardware</td>
</tr>
<tr>
<td>088.50 (Gonococcal arthritis)</td>
<td>Surgical site infection</td>
</tr>
<tr>
<td>036.82 (meningococcal arthritis)</td>
<td>Osteomyelitis of the orbits, sinuses, or mastoids</td>
</tr>
<tr>
<td>Chart review confirmation of ABO and/or ABA</td>
<td>Tuberculosis osteoarticular infections</td>
</tr>
<tr>
<td>Clinical description consistent with ABO and/or ABA</td>
<td>Fungal osteoarticular infections</td>
</tr>
<tr>
<td>Radiologic or histologic evidence of ABO and/or ABA</td>
<td>Comorbid conditions</td>
</tr>
<tr>
<td>Positive culture from blood, bone, or synovial fluid</td>
<td>Immunodeficiency</td>
</tr>
</tbody>
</table>


clinic visits at least through completion of the active antibiotic treatment with a specific physical assessment for complications of the infection at each visit, with the last routine assessment scheduled for 1 year after the infection for children with no sequelae; or (2) the child was seen at our institution for another reason after the recommended orthopedics follow-up, and the child had no sequelae from the osteoarticular infection.

“Complicated outcome” was defined as follows: the need for prolonged antibiotic treatment without other complication (>4 weeks for ABA and >6 weeks for ABO), the development of late cartilaginous degeneration of the joint requiring additional therapy (physical therapy or surgery), chronic osteomyelitis, recurrent osteomyelitis, avascular necrosis of bone adjacent to the site of osteomyelitis, contracture, malunion, limb—length discrepancy, relapse/recurrence of the infection, or readmission to the hospital due to orthopedic complications or complications of therapy. For those children defined as having complicated outcomes, a secondary individual chart review was completed by a pediatric infectious diseases physician (J.B.) to determine the reason for prolonged therapy and assess for complications of the infection. Reasons for prolonged therapy were characterized as: (1) severe disease with persisting clinical findings or laboratory evidence of inflammation as assessed by elevation of ESR at 4 to 6 weeks; (2) no clinical or laboratory requirement for prolonged therapy but additional concerns expressed by the parents or physician with a decision to prolong treatment; or (3) miscommunication between treating physicians or physicians and parents, or other social or logistical reasons that led to prolonged therapy.

Statistical Analysis

Fisher’s exact test was used to compare rates of occurrence in categorical data. Due to asymmetry, 2 groups having continuous data were compared by using the rank sum test and 3 groups by using the Kruskal-Wallis test. When the latter was significant, 2 groups within the 3 were compared by using the rank sum test with a Bonferroni correction on the significance level. Statistical significance was taken as ≤ .05, except as ≤ .017 for the Bonferroni corrections.

RESULTS

Demographic Characteristics

A total of 1012 possible subjects were identified by using International Classification of Diseases, Ninth Revision, Clinical Modification codes; 323 were ultimately determined to have a documented or presumed diagnosis other than ABO or ABA. Of the 689 who had a confirmed diagnosis of documented or presumed osteoarticular infection, only 208 met initial criteria (Table 1) for the final analysis. The exclusions were primarily for children who had negative results on culture (n = 245). Fourteen (7%) of the 208 patients did not have adequate documented follow-up. The remaining 194 patients were included in the final analysis.

Microbiology and Antimicrobial Therapy

The most common organisms identified were methicillin-susceptible Staphylococcus aureus (MSSA) (61%), Streptococcus pyogenes (13%), MRSA (7.2%), and Kingella kingae (6.2%) (Table 2). MRSA was responsible for 9% of all ABO cases but did not cause any cases of isolated ABA. In contrast, K. kingae was responsible for 19% of all ABA cases but only 3% of all ABO cases. Multiple surgeries were performed significantly more frequently in MRSA infections compared with MSSA infections (8 of 14 [57%] vs 25 of 119 [21%]; P = .028). Complicated outcomes and sequelae tended to be more frequent in those infected with MRSA (5 of 14 [36%]) than those infected with MSSA (26 of 119 [22%]) (P = .328).

Nine children with MRSA infections received empirical therapy with vancomycin, and 7 were transitioned to clindamycin within 8 days. The 2 remaining children...
Thirty-five children received prolonged therapy. Twelve (34%) children had an ESR that did not normalize during the standard treatment course, with the child receiving appropriately prolonged therapy until the ESR was normal. Nine of these children had severe and/or multifocal infections, often requiring multiple surgeries. Two children had elevated inflammatory markers from causes unrelated to the osteoarticular infection, but treatment was continued until the inflammatory markers returned to normal.

An additional 12 children were identified as having inappropriately prolonged treatment courses, including 5 cases in which the treating physician wished to treat longer than the standard treatment course despite normalization of laboratory values and 3 children in whom miscommunication between orthopedics and infectious diseases physicians resulted in prolonged therapy. A comparison of osteomyelitis caused by MSSA and MRSA revealed that patients with MRSA infections were receiving therapy for ≥7 weeks (8 of 14 [57%]) more frequently than those with MSSA infections (33 of 119 [28%]) (P = .033). In addition, IV therapy of ≥3 weeks tended to be more common for MRSA (4 of 14 [29%]) than MSSA (13 of 119 [11%]) (P = .082).

### Long-Term (Anatomic) Complications and Clinical/Microbiologic Relapse

Nine children had long-term complications of infection (Table 3). Only 2 children were evaluated for suspected microbiologic failure. One child had microbiologic failure after completion of IV therapy and receipt of oral step-down therapy; a 17-year-old male with MSSA hip joint/acetabular osteoarthritis (ESR 8 mm/hour at completion of oral therapy) presented with pain 2 weeks after completion of a total of 6 weeks of therapy and had a recurrent, culture-positive MSSA hip joint infection.
infection. An MRI performed during the initial hospitalization, and reviewed at rehospitalization, suggested the presence of devitalized, infected bone fragments within the joint. This finding represented the single microbiologic failure in 194 children (99.5% success rate) treated with a full course of appropriate antibiotics at therapeutic dosages and with normal inflammatory markers at the end of IV (CRP) and oral (ESR) therapy. A second child with clinical failure was in fact a documented microbiologic cure: a 4.5-year-old male with MSSA tibia osteomyelitis had increasing pain 10 days after transition to oral therapy. MRI was used to document a subperiosteal abscess that was surgically drained and found to be sterile. No child developed chronic osteomyelitis.

**Laboratory Findings**

Analysis of CRP levels, absolute neutrophil count, white blood cell count, and ESR revealed higher levels of inflammation in the complicated group during the acute illness (Table 4). The most significant difference in maximum CRP was noted in children with concurrent ABO + ABA, compared with those having either ABO or ABA alone (Table 2) (P < .001). However, the CRP level at the transition to oral antibiotics was lower in the complicated group (1.5 ± 1.4 mg/dL) than in the uncomplicated group (2.1 ± 1.9 mg/dL) (P = .012), whereas the end-of-therapy ESR was slightly higher in the complicated group (13.8 ± 7.7 mm/hour) compared with the uncomplicated group (10.2 ± 5.9 mm/hour) (P = .008). Platelet counts were reviewed for children with complicated courses to assess any discrepancy between CRP and platelet count at the time of oral step-down therapy. No child with a complicated course was found to have a persistent elevation of platelets at the time of transition to oral step-down therapy.

**Reinstitution of IV Antibiotic Therapy and Other Complications**

Three children required reinstitution of IV therapy after switching to oral therapy: 1 family could not afford to purchase oral therapy after discharge; a second child had a sterile subperiosteal abscess (described earlier); and a third had a relapse of an MSSA hip infection (described earlier). Other complications occurred in 2 children: a peroneal nerve injury and a readmission for inpatient management of postoperative hip pain in which no infectious complications were identified.

**DISCUSSION**

The treatment of pediatric ABO before 1980 consisted of a prolonged IV antimicrobial treatment course. Clinical experience and case series documented success with IV + oral treatment courses of 4 to 6 weeks.1,2,9–17 Recently, Peltola et al18 provided a retrospective analysis of 131 children with ABO receiving treatment courses as short as 20 days.

**TABLE 4** Laboratory Indices Comparing the 154 Cases of Uncomplicated Cures With the 40 Cases of Complicated Outcomes

<table>
<thead>
<tr>
<th>Index</th>
<th>Uncomplicated Cure</th>
<th>Complicated Outcome</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRP mg/dL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Admission</td>
<td>8.7 ± 7.4</td>
<td>10.5 ± 7.2</td>
<td>.474</td>
</tr>
<tr>
<td>Maximum</td>
<td>11.7 ± 8.8</td>
<td>15.7 ± 8.1</td>
<td>.002</td>
</tr>
<tr>
<td>Oral</td>
<td>2.1 ± 1.9</td>
<td>1.5 ± 1.4</td>
<td>.012</td>
</tr>
<tr>
<td>ANC (cells/µL)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Admission</td>
<td>8821 ± 4872</td>
<td>12 272 ± 4753</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Maximum</td>
<td>9007 ± 5182</td>
<td>13 787 ± 5208</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Oral</td>
<td>4269 ± 2401</td>
<td>4132 ± 1751</td>
<td>.760</td>
</tr>
<tr>
<td>WBC (cells/µL)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Admission</td>
<td>11.8 ± 5.2</td>
<td>14.6 ± 5.2</td>
<td>.001</td>
</tr>
<tr>
<td>Maximum</td>
<td>12.4 ± 5.0</td>
<td>16.5 ± 5.6</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Oral</td>
<td>8.3 ± 3.6</td>
<td>8.8 ± 3.1</td>
<td>.279</td>
</tr>
<tr>
<td>ESR, mm/h</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Admission</td>
<td>53.8 ± 27.0</td>
<td>65.8 ± 34.4</td>
<td>.031</td>
</tr>
<tr>
<td>Maximum</td>
<td>68.1 ± 32.0</td>
<td>94.8 ± 35.4</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Discharge from hospital</td>
<td>56.9 ± 27.5</td>
<td>71.6 ± 32.9</td>
<td>.212</td>
</tr>
<tr>
<td>End of therapy</td>
<td>10.2 ± 5.9</td>
<td>13.8 ± 17.7</td>
<td>.008</td>
</tr>
</tbody>
</table>

Time points measured included at admission; the maximum value (any time point), the transition to oral antibiotics, hospital discharge, and end of therapy. Data are presented as mean ± SD. ANC, absolute neutrophil count; WBC, white blood cell count.
(89% caused by MSSA, but no children with MRSA) prospectively followed up in Finland. Globally, pediatric osteoarticular infections represent a heterogeneous group of pathogens and a heterogeneous group of poorly defined disease severity. A short treatment regimen universally applied to all children may not be appropriate for all cases and all pathogens but may be considered in the child with a susceptible pathogen, mild or moderate disease severity, a brisk response to appropriate antimicrobial and surgical therapy, and in a compliant family with ready access to medical care.

Community-acquired MRSA infection is associated with greater morbidities than MSSA infection, including venous thrombosis in lower-extremity osteomyelitis, prolonged hospitalization, prolonged fever, and the need for multiple surgeries. In addition, the non-β-lactam antimicrobial agents used to treat MRSA may not be as effective as the β-lactam antimicrobial agents that have been the mainstay of treatment of MSSA ABO. In fact, not only have slower responses to vancomycin been documented, but in a group of adults treated with IV therapy with mainly contiguous (trauma related) osteomyelitis, recurrence was more likely in patients who received vancomycin than in those who received penicillinase-stable penicillins for MSSA. In the community-acquired MRSA era, a reliable strategy for identifying patients likely to respond to shorter IV treatment courses with outcomes equivalent to long-course IV therapy is needed.

We present here a series of patients from a single institution over 8 years, in which the combination of both clinical (resolution of fever, decrease in pain, and improvement in function) and laboratory parameters (near-normal CRP) were used to determine the timing of the transition to oral antibiotics. We provide an analysis of 194 culture-proven acute osteoarticular infections. Although the majority of patients had ABO alone, 16% (32 of 194) were diagnosed with isolated ABA and 25% (49 of 194) had both ABA and ABO. Patients in the ABO + ABA group had higher CRP early in the illness and longer IV courses (Table 2), presumably as a consequence of initial osteomyelitis that was more severe or that was not recognized early in the disease course that may have eroded into the joint.

The distribution of pathogens in our series was typical of pediatric hematogenous acute osteoarticular infections for the period studied: 61% of cases caused by MSSA and only 7.2% caused by MRSA. The global increase in the prevalence of community-acquired MRSA has been well documented, especially in the 8-year span of our study. Although we had relatively few MRSA cases, higher ESR and CRP levels were noted in patients with MRSA than with MSSA at presentation, an association previously reported. Children infected with MRSA had longer IV courses before transition to oral therapy based on CRP criteria, suggesting increased virulence and inflammation of MRSA or less efficacious therapy of MRSA with non-β-lactam antimicrobial agents compared with β-lactam antimicrobial agents for MSSA.

Thirty-five of the 40 children with complicated outcomes were classified as such due to prolonged therapy. For those patients with justified prolonged therapy, the most common reasons were persistent inflammation (as measured by using ESR) and multilocular or severe disease, which alone seemed to justify a more conservative treatment course. Whether longer treatment was actually required for these children is not addressed in our study. Twelve cases of prolonged therapy, representing 6% of the 194 patients, were felt to be inappropriate and included reasons such as continuation of antibiotic therapy despite consultative advice to discontinue, social and logistical reasons, and miscommunication between the medical and surgical teams. This analysis reveals areas of potential improvement in the multidisciplinary approach to patients with osteoarticular infections.

Nine patients were found to have clinical complications related to the infection. Most complications were identified during the initial hospitalization as being severe cases or having associated comorbid conditions. All of the patients with complications such as avascular necrosis of the femoral head or growth plate damage responded well to initial therapy, with no indication of microbiologic failure. In fact, of the 194 patients, only 1 was identified with a microbiologic failure after the step-down oral therapy protocol. In retrospect, this child was thought to have had a fragment of infected bone in the joint space, not removed at the time of initial surgical debridement.

Keeping in mind the many reasons for complicated outcomes, it is interesting to note that although the maximum CRP levels, absolute neutrophil count, and white blood cell count were significantly higher at admission among those with complications (Table 4), the CRP level at the time of transition to oral therapy was lower. This trend suggests that clinicians might have anticipated or noted a complication due to more severe disease during the acute illness, so a longer, more conservative course was undertaken. Therefore, it seems that children with more extensive injury to the bone and/or more aggressive pathogens received more aggressive, prolonged IV therapy before taking any additional risks of oral therapy, such as nonadherence or inadequate antibiotic exposure in infected tissues.

Our review has flaws inherent in any retrospective analysis. Patients who did not respond to therapy or developed long-term sequelae may not have returned to our institution for follow-up, although we believe that this would be unlikely given that RCHSD is the only
major pediatric center in our region that includes a large pediatric orthopedics program. Children who had negative results on bacterial culture at the time of hospitalization were not included in the analysis but may have had bacterial infections with a poor outcome. Finally, compliance with oral therapy was not documented.

CONCLUSIONS

We describe the outcomes of 194 children with acute bacterial osteoarticular infections treated at a single institution over an 8-year period, with transition to oral step-down therapy when fever and pain were resolving, function was returning, and a serum CRP level was <3 mg/dL. Using this strategy, all but 1 child was cured, yielding a microbiologic success rate of 99.5%. Long-term outcomes were similar to those expected with the more traditional extended IV antibiotic courses. More prolonged parenteral treatment courses may be required for those infected with MRSA and for those with more severe infection. This approach to antimicrobial management should be tested in a prospective, randomized comparative fashion. The additional hypothesis that shorter total courses of therapy than those used in our review, possibly using the CRP rather than the ESR to assess the end of antimicrobial therapy, may be adequate in certain low-risk children but also requires prospective, controlled investigation.

REFERENCES


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