

Oral Versus Parenteral Antibiotics for Osteoarticular Infections: You PICC

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A previously healthy 8-year-old girl presented to the emergency department with right hip pain and inability to bear weight on the right lower extremity. She had been afebrile at home, although was receiving ibuprofen for pain. Inflammatory markers were elevated, including a C-reactive protein (CRP) of 76.4 mg/L and an erythrocyte sedimentation rate of 40 mm per hour. A radiograph of the pelvis did not show any obvious joint effusion. Given the concern for septic hip, orthopedics was consulted and she was taken to the operating room for aspiration of her right hip joint. Aspiration showed cloudy yellow fluid with a white blood cell count >85 000. Orthopedics proceeded with incision and drainage and she was admitted for parenteral antibiotics. She was empirically started on cefazolin. The broth from her hip culture grew coagulase-negative *Staphylococcus* species, but the fluid culture was negative, and this was presumed to be a contaminant. The orthopedic and infectious disease teams made a joint decision to treat empirically with cefazolin for a total of 4 weeks for presumed septic hip. A peripherally inserted central catheter (PICC) was placed on hospital day 3 and she was discharged on hospital day 4. At the time of discharge, the patient had no hip pain, was afebrile, able to bear weight, and had a CRP of 8.8 mg/L.

Four days after discharge, the patient presented to the emergency department with pain, erythema, and swelling above the site of her PICC line. A duplex ultrasound of the arm showed a deep vein thrombus. Her PICC line was removed and she was started on enoxaparin for 3 months. She was discharged on oral high-dose cephalexin. Total duration of treatment was 16 days; antibiotics were then discontinued based on a normal clinical examination and inflammatory markers.

This case illustrates the harm that can occur from the decision to proceed with long-term parenteral therapy for osteoarticular infections, a historical practice that has come into question over the past several decades. Recent evidence suggests that shorter, enteral courses of antibiotics may be sufficient therapy for both osteomyelitis and septic arthritis.¹⁻⁵ Potential complications of treatment failure in osteoarticular infections are severe, including avascular necrosis, growth plate damage, or degeneration of the joint.⁶ Fear of these outcomes likely plays a role in the decision to proceed with aggressive therapy. However, a number of studies have found no significant difference in the rates of treatment failure among patients who received an early transition to oral antibiotics.¹⁻⁴

Appropriate timing of transition to oral therapy remains somewhat controversial based on available literature. Arnold et al⁶ used a combination of clinical improvement and a CRP <3.0 mg/dL as a guide to transition to oral antibiotics, with only 2.5% of patients experiencing a complication, such as avascular necrosis, physis injury with growth arrest, degenerative arthritis, or microbiologic relapse. Other studies also used clinical improvement, but accepted a normalizing CRP as a criterion for transition to oral antibiotics with good long-term outcomes.^{1,7} As interest in this topic has grown, larger retrospective reviews have emerged that further support an early

www.hospitalpediatrics.org

DOI:10.1542/hpeds.2015-0245

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HOSPITAL PEDIATRICS (ISSN Numbers: Print, 2154-1663; Online, 2154-1671).

FINANCIAL DISCLOSURE: The authors have indicated they have no financial relationships relevant to this article to disclose.

FUNDING: No external funding.

POTENTIAL CONFLICT OF INTEREST: The authors have indicated they have no potential conflicts of interest to disclose.

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transition to oral antibiotics. In 2009, Zaoutis et al⁸ looked at 1969 patients with osteomyelitis, 948 of whom received oral antibiotics at discharge. The treatment failure rate, as defined by rehospitalization with osteomyelitis, a complication of osteomyelitis, or a surgical procedure related to the musculoskeletal system, was 4%, which was not significantly different from those who received prolonged parenteral therapy. Similarly, Keren et al⁹ looked at 2060 patients with osteomyelitis and again found no difference in the rate of treatment failure between those who received oral antibiotics at discharge and those who received prolonged intravenous therapy. In this study, treatment failure was defined as a change in antibiotic, prolongation of antibiotic therapy, conversion from oral to intravenous antibiotics, abscess, pathologic fracture, or a procedure related to the musculoskeletal system.⁹ Both authors used propensity scoring to adjust for patient-level confounders that may have contributed to selection of treatment strategy.^{8,9} Although these 2 reviews focus on patients with osteomyelitis, their results align with smaller, earlier studies of patients with septic arthritis.¹⁻⁴ This body of literature supports the early transition to oral antibiotics in patients whose pain and fever are resolving, when function of the extremity is returning, and the CRP is normalizing.

Critics of oral antibiotic treatment argue that there have been no randomized controlled trials assessing efficacy between oral and intravenous antibiotics. However, there are also no randomized controlled trials to support prolonged intravenous therapy.¹ In patients with osteoarticular infections, it would be difficult to achieve the necessary power in a randomized controlled trial to show a clinical significance.¹ Even without a randomized controlled trial, we cannot ignore the numerous studies that have supported the effectiveness of an early transition to oral antibiotics.

One must also consider the harms associated with each treatment modality. The main difference between oral and

prolonged intravenous therapy is that intravenous medication must be given via a catheter, often a PICC line. PICC lines are associated with many complications, including line infections requiring further courses of antibiotics, mechanical complications that can cause pain and vascular damage, or thrombotic complications requiring several months of anticoagulation. In a recent retrospective analysis of children with PICC lines placed for prolonged intravenous antibiotic therapy for treatment of osteomyelitis, 15% had complications requiring a visit to the emergency department or rehospitalization.⁹ A cohort study looking at complications of PICC lines placed for any indication found that 20.8% had complications requiring PICC removal.¹⁰ Another study looking specifically at non-critically ill pediatric patients found thrombotic complications in 3.2%.¹¹ In fact, catheter placement is the greatest risk factor for thrombus formation in children.¹¹ Having a PICC line also has a significant impact on a child's quality of life. Depending on the frequency of dosing, they may be connected to an intravenous pump for several hours per day. This can sometimes affect school or sleeping schedules, and can be difficult on parents as well. The child is also limited as to participation in certain activities while the PICC line is in place. It is clear that a PICC line poses an often unnecessary risk to the patient as well as negatively affects the child's quality of life. These harms could be avoided with early transition to oral therapy.

In this case, our patient had to endure the negative consequences and associated risks of enoxaparin as well. The duration of enoxaparin therapy for a deep vein thrombosis is twice daily subcutaneous injections for 3 months (although it should be noted that optimal duration of therapy is unclear; evidence for duration is Grade 2C).¹² For children, these injections can often be painful and difficult to administer. In addition, routine monitoring of anti-Xa levels is recommended in children.¹² Our patient was required to have blood draws every other week, requiring frequent trips to a laboratory. There are also potential serious side effects of enoxaparin, including

significant bleeding, heparin-induced thrombocytopenia, and osteoporosis.¹² Although the latter 2 are not directly addressed in the literature, bleeding was found in 25% of patients in 1 review, with 2.9% having major bleeding.¹³ This risk of bleeding translates to limited activity during treatment. This can further impact a child's quality of life.

When considering both the risks and benefits of different treatment modalities in osteoarticular infections, current evidence suggests that patients treated more aggressively suffer untoward effects without evidence of improved outcomes. As physicians, we sometimes err on the side of more aggressive treatment without fully considering the adverse effects of that decision. When a family hears that their child's infection may lead to joint destruction without adequate therapy, they often feel that taking the most aggressive approach is warranted. They may consent to long-term parenteral therapy without fully understanding the associated risks, and without the knowledge that current literature suggests that oral therapy is a rational approach to osteoarticular infections. Implementation of a shared decision-making tool that provides evidence-based information to families and assists providers in their discussion of risks and benefits with parents has proven to increase the number of patients discharged from the hospital on oral antibiotics.¹⁴

The decision to transition to oral antibiotics is not always black and white; individual circumstances must be closely evaluated by care providers when making recommendations to a family. However, for many patients, early transition to oral antibiotics is the right decision, and may reduce harm and cost, and improve quality of life. Pediatric hospitalists, infectious disease specialists, and orthopedic surgeons are often part of the team taking care of these patients, and should work together to provide the best evidence-based care for each individual. In patients such as the one presented here, who are otherwise healthy and are improving clinically with reduction in inflammatory markers, a transition to oral

antibiotics is often the most appropriate course of action. This case serves as a valuable reminder of the therapeutic complexity of our work, and challenges us to provide a level of shared decision-making with families that includes potential harms associated with aggressive treatment approaches.

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Hospital Pediatrics 2016;6;434

DOI: 10.1542/hpeds.2015-0245 originally published online June 23, 2016;

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Hospital Pediatrics 2016;6:434

DOI: 10.1542/hpeds.2015-0245 originally published online June 23, 2016;

The online version of this article, along with updated information and services, is located on the World Wide Web at:

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