Best Evidence Statement (BESt)

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Treatment of Acute Hematogenous Osteomyelitis (AHO)

Clinical Question

P (population/problem)	In otherwise healthy children with acute hematogenous osteomyelitis (AHO)
I (intervention)	does early transition from intravenous (IV) antibiotic therapy to oral therapy
C (comparison)	compared to prolonged intravenous therapy (>7 days)
O (outcome)	achieve equally effective cure rates for osteomyelitis with fewer complication occurrences?

Definitions

Pediatric acute hematogenous osteomyelitis (AHO)	Infection of the bone via the bloodstream in children (ages 0-18)
Early transition	7 days or less of IV therapy
Prolonged IV therapy	Greater than 7 days of IV therapy
Cure of osteomyelitis	Resolution of the infection within 6 months and no development of chronic osteomyelitis
Complication occurrence	Readmission or return to emergency department due to complications of therapy within 6 months
Complications of prolonged IV therapy	Blood stream infection, local skin infections and irritation, and malfunction and dislodgement of long-term IV therapy central venous catheters (CVC), which includes peripherally inserted central catheters (PICC) lines

Target Population

Children 0-18 years of age with acute hematogenous osteomyelitis

Recommendations:

1. It is recommended that transition from IV to oral antibiotic therapy be considered within the first seven days of treatment for hematogenous osteomyelitis to reduce complications of IV therapy *(Le Saux 2002 [1b], Peltola 2010 [2a], Kolyvas 1980 [2b], Peltola 1997 [2b], Ruebner 2006 [4a], Zaoutis 2009 [4a])*.

2. It is recommended that the clinician discuss the risks and benefits of short versus prolonged IV therapy with families *(Le Saux 2002 [1b], Ruebner 2006 [4a], Zaoutis 2009 [4a])*.

Discussion/summary of evidence

Equally Effective Outcomes

Both forms of treatment are equally effective in curing AHO *(Le Saux 2002 [1b], Peltola 2010 [2a], Jaberi 2002 [2a], Kaplan 1982 [2b], Tetzlaff 1978 [3a], Bachur 2007 [4a], Jagodzinski 2009 [3a], Vinod 2002 [4a])*. A systematic review of 11 prospective studies, including both cohort and RCT studies, comparing short courses of IV antibiotic treatment (seven days or less) to long courses of treatment (greater than seven days) reported no significant difference with a 95.2% cure rate for shorter treatments and a 98.8% cure rate for longer treatments at six months *(Le Saux 2002 [1b])*. All studies suitable for inclusion were cohorts, either retrospective or prospective, or RCT studies that clearly addressed the antimicrobial and its route, duration of therapy, and outcome after six months of follow-up *(Le Saux 2002 [1b])*.

A randomized trial by Kaplan et al. *(1982 [2b])* met the inclusion criteria for the above systematic review but was excluded for dissimilar methodology. However, it reports equivalent outcomes of therapy among 13 children who received nafcillin/methicillin IV therapy for a mean of 27 days followed by oral dicloxacillin for a mean of 3.7 weeks and 12 children who received clindamycin IV therapy for a mean of 5.8 days followed by oral clindamycin for a mean of 4.7 weeks. After at least six months of follow up, nine children in the long-term treatment group and 11 children in the short-term treatment group were graded as having an "excellent" outcome, or cure of osteomyelitis *(Kaplan 1982 [2b])*.

A retrospective cohort study with risk adjustment and propensity score modeling of 1969 pediatric patients reported a treatment failure rate of 5% among patients who received prolonged intravenous therapy and 4% among those who received oral therapy. The median time to treatment failure was 16.5 days for the prolonged therapy group and 14.0 days for the oral therapy group. There were no differences between the two groups in terms of disease severity, length of hospital stay, in-hospital therapy, surgical intervention, infecting organism, site of infection, and demographic characteristics *(Zaoutis 2009 [4a])*.

A prospective randomized trial examining the optimal duration of treatment randomly assigned 131 patients to a 20-day treatment or a 30-day treatment with either clindamycin or a first-generation cephalosporin. Antibiotics were initially administered intravenously for a mean 3.7 days for the 20-day treatment and 4.1 days for the 30-day treatment. The remainders of both lengths of treatment were completed with oral antibiotics. 129 out of the 131 children experienced full recovery after 12 months *(Peltola 2010 [2a])*.

Complications associated with long-term intravenous treatment

Patients discharged on intravenous antibiotic therapy are more susceptible to CVC-related infections and have higher rates of readmissions and emergency department visits than patients discharged on oral therapy *(Ceroni 2003 [4a], Le 2010 [4a])*. A retrospective cohort study found that, among 75 patients receiving prolonged intravenous treatment, 41% had a CVC-related complication that resulted in readmission to the hospital or an ED visit. Five patients in the same study were discharged on oral therapy and none of them returned to the hospital *(Ruebner 2006 [4a])*. In the study by Zaoutis et al, there was an increased risk of any rehospitalization within 6 months of diagnosis for children treated with long course intravenous therapy due to catheter-associated complications *(Zaoutis 2009 [4a])*. Children who receive oral therapy will not experience CVC-related complications, which include CVC malfunction or displacement, catheter-associated bloodstream infection, fever with negative blood culture results, and local skin infection, and are relatively common *(Ruebner 2006 [4a])*.

Health Benefits, Side Effects and Risks

Health Benefits

The health benefits in terms of cure rate are equivalent in the published body of evidence. Long-term intravenous therapy may be preferred by families and children who do not take oral medicine well or are concerned about adherence. Potential benefits of oral therapy to children and their families include elimination of the discomfort of the insertion of PICC lines, potential ease of at-home treatment, and lower costs.

Side Effects

Both oral and intravenous therapy can have side effects such as allergic reactions, nausea, suppressed bone marrow production, and rashes.

Risks

Oral therapy could fail, especially if the child is vomiting or does not consistently take the medicine. Failed oral therapy could result in failure to cure and development of chronic osteomyelitis.

References/citations (evidence grade in *[ ]; see Table of Evidence Levels following references*)

Note: When using the electronic version of this document, ☜ indicates a hyperlink to the PubMed abstract.

1. **Le Saux, N.; Howard, A.; Barrowman, N. J.; Gaboury, I.; Sampson, M. and Moher, D.**: Shorter courses of parenteral antibiotic therapy do not appear to influence response rates for children with acute hematogenous osteomyelitis: A systematic review. *BMC Infectious Diseases,* 216, 2002, *[1b]* ☜
2. **Bachur, R. and Pagon, Z.**: Success of short-course parenteral antibiotic therapy for acute osteomyelitis of childhood. *Clinical Pediatrics,* 46(1): 30-35, 2007, *[4a]* ☜
3. **Ceroni, D.; Regusci, M.; Pazos, J. M.; Saunders, C. T. and Kaelin, A.**: Risks and complications of prolonged parenteral antibiotic treatment in children with acute osteoarticular infections. *Acta Orthopaedica Belgica,* 69(5): 400-404, 2003, *[4a]* ☜
4. **Jaberi, F. M.; Shahcheraghi, G. H. and Ahadzadeh, M.**: Short-term intravenous antibiotic treatment of acute hematogenous bone and joint infection in children: A prospective randomized trial. *Journal of Pediatric Orthopedics,* 22(3): 317-320, 2002, *[2a]* ☜
5. **Jagodzinski, N. A.; Kanwar, R.; Graham, K. and Bache, C. E.**: Prospective evaluation of a shortened regimen of treatment for acute osteomyelitis and septic arthritis in children. *Journal of Pediatric Orthopedics,* 29(5): 518-525, 2009, *[3a]* ☜
6. **Kaplan S L, Mason E O, Feigen R D.**: Clindamycin versus nafcillin or methicillin in the treatment of *S. aureus* osteomyelitis in children. *Southern Medical Journal,*75(2): 138–142, 1982, *[2b]*. ☜
7. **Kolyvas, E.; Ahronheim, G.; Marks, M. I.; Gledhill, R.; Owen, H. and Rosenthall, L.**: Oral antibiotic therapy of skeletal infections in children. *Pediatrics,* 65(5): 867-871, 1980, *[2b]* ☜
8. **Le, J.; San Agustin, M.; Hernandez, E. A.; Tran, T. T. and Adler-Shohet, F. C.**: Complications associated with outpatient parenteral antibiotic therapy in children. *Clinical Pediatrics,* 49(11): 1038-1043, 2010, *[4a]* ☜
9. **Peltola, H.; Paakkonen, M.; Kallio, P.; Kallio, M. J. and Osteomyelitis-Septic Arthritis Study Group.**: Short- versus long-term antimicrobial treatment for acute hematogenous osteomyelitis of childhood: Prospective, randomized trial on 131 culture-positive cases. *The Pediatric Infectious Disease Journal,* 29(12): 1123-1128, 2010, *[2a]* ☜
10. **Peltola, H.; Unkila-Kallio, L. and Kallio, M. J.**: Simplified treatment of acute staphylococcal osteomyelitis of childhood. the Finnish study group. *Pediatrics,* 99(6): 846-850, 1997, *[2b]* ☜
11. **Ruebner, R.; Keren, R.; Coffin, S.; Chu, J.; Horn, D. and Zaoutis, T. E.**: Complications of central venous catheters used for the treatment of acute hematogenous osteomyelitis. *Pediatrics,* 117(4): 1210-1215, 2006, *[4a]* ☜
12. **Tetzlaff, T. R.; McCracken, G. H.,Jr and Nelson, J. D.**: Oral antibiotic therapy for skeletal infections of children. II. therapy of osteomyelitis and suppurative arthritis. *The Journal of Pediatrics,* 92(3): 485-490, 1978, *[3a]*
13. **Vinod, M. B.; Matussek, J.; Curtis, N.; Graham, H. K. and Carapetis, J. R.**: Duration of antibiotics in children with osteomyelitis and septic arthritis. *Journal of Paediatrics and Child Health,* 38(4): 363-367, 2002, *[4a]* ☜
14. **Zaoutis, T.; Localio, A. R.; Leckerman, K.; Saddlemire, S.; Bertoch, D. and Keren, R.**: Prolonged intravenous therapy versus early transition to oral antimicrobial therapy for acute osteomyelitis in children. *Pediatrics,* 123(2): 636-642, 2009, *[4a]* ☜

Note: Full tables of evidence grading system available in separate document:

- Table of Evidence Levels of Individual Studies by Domain, Study Design, & Quality (abbreviated table below)
- Grading a Body of Evidence to Answer a Clinical Question
- Judging the Strength of a Recommendation (abbreviated table below)

Table of Evidence Levels (see note above)

Quality level	*Definition*
1a† or 1b†	Systematic review, meta-analysis, or meta-synthesis of multiple studies
2a or 2b	Best study design for domain
3a or 3b	Fair study design for domain
4a or 4b	Weak study design for domain
5	Other: General review, expert opinion, case report, consensus report, or guideline

†a = good quality study; b = lesser quality study

Table of Recommendation Strength (see note above)

Strength	***Definition***
"Strongly recommended"	There is consensus that benefits clearly outweigh risks and burdens (or visa-versa for negative recommendations).
"Recommended"	There is consensus that benefits are closely balanced with risks and burdens.
No recommendation made	There is lack of consensus to direct development of a recommendation.

Dimensions: In determining the strength of a recommendation, the development group makes a considered judgment in a consensus process that incorporates critically appraised evidence, clinical experience, and other dimensions as listed below.

1. Grade of the Body of Evidence (see note above)
2. Safety / Harm
3. Health benefit to patient *(direct benefit)*
4. Burden to patient of adherence to recommendation *(cost, hassle, discomfort, pain, motivation, ability to adhere, time)*
5. Cost-effectiveness to healthcare system *(balance of cost / savings of resources, staff time, and supplies based on published studies or onsite analysis)*
6. Directness *(the extent to which the body of evidence directly answers the clinical question [population/problem, intervention, comparison, outcome])*
7. Impact on morbidity/mortality or quality of life

Supporting information

Introductory/background information

Acute hematogenous osteomyelitis is the most common form of osteomyelitis seen in children that is caused by the localization of bloodborne pyogenic in the metaphysic of bones. The most common pathogen responsible for AHO is *Staphylococcus aureus*, but other organisms identified in patients include *Kingella kingae, Streptococcus pneumoniae,* and *Streptococcus pyogenes*.

Traditionally, the most common approach to treatment for AHO has consisted of intravenous antibiotic therapy in the hospital, followed by 4-6 weeks of IV therapy at home via administration by a central venous catheter. However, more recent studies have shown that home oral antibiotic therapy is equally effective and safe in curing AHO.

Group/team members

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Search Strategy

1) OVID Databases: MEDLINE, Cochrane Database of Systematic Reviews
   Search Terms: osteomyelitis/dt, osteomyelitis/th
   infusions, intravenous/ae
   catheterization, central/ae
   administration, oral
   antibiotics
   ped$, child$
   Filters: Publication date: 1980 to December 28, 2010
   humans
   English language
   "all child (0 to 18 years)"
2) Additional articles identified by clinicians
3) Additional articles identified from reference lists of reviewed articles

Applicability issues

Process measures may include percentage of families engaged in treatment decision-making and percentage who select short course IV therapy followed by oral therapy.
Outcome measures include CVC complications, readmissions, and rate of chronic osteomyelitis (i.e. failure of therapy).
We developed a shared decision-making aid to help the clinicians engage the families in decision-making. We modified this aid based on feedback from clinicians and families.

Note

This Best Evidence Statement addresses only key points of care for the target population; it is not intended to be a comprehensive practice guideline. These recommendations result from review of literature and practices current at the time of their formulation. This Best Evidence Statement does not preclude using care modalities proven efficacious in studies published subsequent to the current revision of this document. This document is not intended to impose standards of care preventing selective variances from the recommendations to meet the specific and unique requirements of individual patients. Adherence to this Statement is voluntary. The clinician in light of the individual circumstances presented by the patient must make the ultimate judgment regarding the priority of any specific procedure.

Reviewed against quality criteria by two independent reviewers.