International Journal of
Science Inventions Today
www.ijsit.com
ISSN 2319-5436
Review Article

ANTIBIOTICS USE IN OSTEOMYELITIS IN CHILDREN: REVIEW ARTICLE

Rajiv Jaiswal[1] and She Yuan Jun[2]

Department of Orthopedic Surgery, Clinical Medical college of Yangtze University, Jingzhou Central Hospital Jingzhou, Hubei Province PR China

ABSTRACT

Osteomyelitis is an infection of bone sustained most commonly by bacteria, although fungal etiology is rarely described, particularly in immune-compromised children .When adult are affected is usually because their resistance is lowered .The causal organism in both adult and children usually Staphylococcus .Anti-staphylococcal penicillin such as oxacillinor flucoxacillin and/or a cephalosporin are recommended as first line treatment.

INTRODUCTION

Osteomyelitis is an infection of bone sustained most commonly by bacteria, although fungal etiology is rarely described, particularly in immune-compromised children [1]. According to the time period between diagnosis and symptom onset, osteomyelitis is classified as acute (<2 weeks), sub-acute (2 weeks–3 months), or chronic (>3 months). Bacteria may reach bone marrow through the bloodstream, or spreading from nearby tissue. Infection can also be subsequent to an injury that exposes bone to a contaminated environment [1]. The estimated incidence of acute osteomyelitis is about 8 cases per 100,000 children/year [2,3] Children under 5 years of age are affected in about 50% of the cases, with a M:F ratio of 2:1. Acute osteomyelitis is approximately two times more frequent than septic arthritis, and its incidence is steadily increasing. Gafur et al. [4] observed that the incidence of acute osteomyelitis has tripled over the last 20 years while the incidence of septic arthritis remained constant. Early detection is crucial given that a delay in the diagnosis of only 4 days is a risk factor for long-term sequelae .

Possible complications include septic arthritis, subperiosteal abscess, pyomyositis, deep vein thrombosis, sepsis, and multiorgan failure. Even if the mortality is less than 1%, permanent disabilities can occur, such as growth arrest with limb length discrepancy. Moreover, acute osteomyelitis can evolve to the chronic form. Most of pediatric osteomyelitis originates as a bloodstream infection. The route of entry may be the respiratory tract, particularly for K. kingae, S. pyogenes and S. pneumoniae, while the skin may be a common port of entry for S. aureus [3]. Less frequently, acute osteomyelitis spreads from contiguous tissues or from direct inoculation following trauma or surgery.

Its clinical presentation and imaging can be highly variable, and culture can be negative in 34 to 60% of histologically proven osteomyelitis cases.[11] Delayed treatment can result in overwhelming sepsis, chronic infection, bony deformity, and/or growth retardation.[5,7,10–13] Complications generally arise within one year of discharge and the rate ranges from 10 to 25%; risk factors for complications include infection with Staphylococcus aureus, disease in infancy, and a 4-to- 5-day delay from symptom onset to treatment.[8,11,14] Optimal treatment for pediatric osteomyelitis remains controversial.[5–9,15–17] Surgical treatment to reduce the bacterial load is increasingly popular owing to the rising incidence of methicillin-resistant S. aureus.[6,18] Drainage enables collection of a larger sample for culture to guide antibiotic therapy.[11] Traditionally, surgery is indicated when there is concurrent septic arthritis, failure of clinical improvement after 48 to 72 hours of antibiotic treatment, and/or radiological evidence of a pelvic abscess >2 cm.[5,6,9,19] Although many children recover quickly with medical treatment alone,[5,16] surgery is still performed in up to 50% of patients.[6,9,12]

Key Words: Role of antibiotic in osteomyelitis

Antibiotic treatment:

Caring for children with acute haematogenous osteomyelitis is a multidisciplinary challenge and requires collaboration between pediatricians, infectious diseases specialists, orthopedic surgeons, microbiologists and radiologists. Copley et al. [25] confirmed the effectiveness of a multidisciplinary approach in terms of efficiency of clinical investigations, rates of identifications of causative pathogens and length of hospital stays. The main goal of this common effort is to establish an early and effective antibiotic therapy.

The choice of a specific antibiotic is based on the identification of the causative infectious organism and on local epidemiological data on resistance. Anti-staphylococcal penicillin such as oxacillin or flucoxacillin and/or a cephalosporin are recommended as first line treatment. Some authors [1] have suggested to use antibiotics affective against MRSA while awaiting for culture results, especially in settings with more than 10% of S. aureus isolates are MRSA or if risk factors are present. This approach is, however, not generally accepted since it is thought that this may contribute to the spread of antibiotic resistant strains. In a recent review [24] different regimens depending on MRSA local prevalence where proposed. The duration and routes of administration of antibiotics is currently under debate [30]. Historically, osteomyelitis was treated with intravenous antibiotics for 4–6 weeks. In the only randomized trial [31] that has addressed the issue of the duration of therapy, patients who showed a good clinical response after 2–4 days of intravenous treatment and where shifted to oral treatment for further 20 days, had the same outcome of children treated with continued IV therapy for 30 days. This approach has been adopted in many centers, although it is usually patient tailored, depending on the organism being treated, local bacterial sensitivity epidemiological data, availability of oral equivalent antibiotic, and severity of the osteomyelitis [32]. However, the generalization of the results of the only available trial [31] study is debatable. It has been highlighted that the study population is unique and, indeed, that MSSA had been isolated in almost 90% of cases, showing a peculiar epidemiology.

More recently, Keren et al. [32] retrospectively evaluated data from 2060 children with osteomyelitis: 1005 received a brief IV antibiotic treatment (7 days), followed by oral therapy and 1055 received IV therapy for 4–6 weeks. Similar treatment failure rates were observed (approximately 5%), while almost 15% of children receiving prolonged IV therapy developed deep vein thrombosis. These results support the trend to rapidly shift from IV to oral therapy, at least in children that show a good clinical response in terms of resolution of fever, pain and restoration of function, combined with progressive normalization of inflammatory markers. On the other hand, it has to be acknowledged that, given the retrospective observational nature of the study, criticism to this approach exists. Faust et al. [33] noted that the two treatment groups in the study by Keren [32] were not perfectly homogeneous: the children treated with oral antibiotics were more frequently younger than one year of age and in worse socio-economic conditions. Others [34] pointed out that many data regarding the severity of the disease (i.e., duration of

symptoms before admission, duration of fever, trend of inflammatory markers) were lacking.

Tamma et al. [35] speculated that children on prolonged IV therapy had more severe disease and emphasized the lack of information about the discrepancies between antibiotic used and susceptibility of the isolated pathogen. Pending the results of other clinical studies, a reasonable approach could be to perform a short (5–7 days) IV therapy with a subsequent shift to oral administration in uncomplicated cases, in children over 3 months of age. Prolonged treatment (at least 14–21 days, to be decided case by case) could be reserved to children under 3 months of age, to complicated cases (such as multifocal osteomyelitis), to immune-compromised patients, and to patients at high risk of complications (i.e., sickle cell anemia, sepsis, extensive destruction of bone, isolation or high suspicion of antibiotic resistant microorganism).

In some cases, transition to oral therapy can be difficult in the clinical setting, since the limited availability of oral antibiotics. The dosage of oral antibiotic therapy is under debate as well. In a recent review published by Peltola et al. [24], same doses as per parenteral route are recommended for oral treatment. Faust et al. [33], on the other hand, recommend much lower oral doses. Moreover, the successful use of trimethoprim/sulfamethoxazole (TMP/SMX) for oral treatment of MRSA acute osteomyelitis has been reported from the U.S. [36]. In proven or suspected infections by MRSA, we consider different therapeutic options for the switch to oral treatment, including also a combination therapy with TMP/SMX plus rifampicin.

The most common causative infectious organisms are Staphylococcus aureus (70%–90% of positive cultures) followed by Streptococcus pyogenes, Streptococcus pneumoniae and Gram negative bacilli. Streptococci and Gram negative bacilli cause up to 60% of infections in children under the age of 4 [20]. For this reason, a combined antibiotic therapy, covering Gram positive and Gram negative strains, (ceftazidime plus oxacillin) should be chosen. However it should be underlined that the increased prevalence of Gram negative organisms is also due to K. kingae infection, and the incidence is increasing predominantly due to improved detection methods, including polymerase chain reaction. Over the last 10 years, the pattern of pathogens involved has changed . On one hand, causative pathogens such as Haemophilus influenzae type B, once the most common Gram negative organism involved in paediatric osteomyelitis, have become rare as a consequence of the vaccination campaigns. On the other hand, cases associated with Kingella kingae infection are rising as are methicillin-resistant S. aureus (MRSA) cases, albeit with wide geographical variations. In fact, MRSA is responsible for up to 9%–30% of osteomyelitis in children [24–26].

Osteomyelitis due to MRSA is usually more aggressive, with higher inflammation markers, prolonged hospital stays and increased possibility to undergo surgical treatment. Therefore, these forms are associated with a higher likelihood of developing complications such as deep vein thrombosis, pulmonary embolism, multifocal infections, subperiosteal abscesses formation, multiorgan failure and progression to chronic osteomyelitis. The association with these complications is more frequent in the event of Panton-Valentine Leukocidin (PVL)-producing isolates. Geographical differences have been reported. In the U.S. the

predominant PVL-producing S. aureus strains are MRSA [27].

On the other hand, in Europe, PVL-producing S. aureus strains are more commonly MSSA which have been associated with severe osteoarticular infections in children [28,29]. Several studies have demonstrated PVL production is stimulated by subinhibitory concentrations of betalactams [29], which is the case in abscesses, therefore clindamycin or other antibiotic drugs inhibiting protein synthesis are recommended especially in the presence of pulmonary infections by these strains.

CONCLUSIONS

Acute osteomyelitis in children is a serious disease that, when detected and treated early, can heal without severe sequelae [37]. It is of primary importance to recognize the signs and symptoms at the onset of the disease and to properly use the available diagnostic tools [38,39]. Recommendations for the duration of intravenous antimicrobial therapy have not been stated. Moreover, local different prevalence of antibiotic resistant strains may justify different therapeutic approaches. Of note, the widely adopted short course antibiotic therapy has not been investigated in poor resource countries, where the timing of diagnosis is delayed and other comorbidities such as anemia, malnutrition and HIV infection may influence the outcomes. According to Elena et al [40], at the moment, every child with acute osteomyelitis should receive a "tailored therapy", based on epidemiological resistance data, age, initial response to first intravenous antibiotic regimen, availability of oral drugs for the suspected causative infectious agent, potential compliance of the family to oral therapy after discharge, risk of adverse events and costs.

REFERENCES

1. Howard-Jones, A.R.; Isaacs, D. Systematic review of duration and choice of systemic antibiotics therapy for acute haematogenous bacterial osteomyelitis in children. J. Paediatr. Child Health **2013**, 49, 760–768.
2. The Pediatric Orthopedic Society of North America (POSNA). Acute Osteomyelitis. 2013. Available online: www.posna.org/education/StudyGuide/acuteOsteomyelitis.asp (accessed on 25 May 2016).
3. Yeo, A.; Ramachandran, M. Acute haematogenous osteomyelitis in children. BMJ **2014**, 348, 66
4. Gafur, O.A.; Copley, L.A.B.; Hollmig, S.T.; Browne, R.H.; Thornton, L.A.; Crawford, S.E. The impact of the current epidemiology of pediatric musculoskeletal infection on evaluation and treatment guidelines. J. Pediatr. Orthop. **2008**, 28, 777–785.
5. Dartnell J, Ramachandran M, Katchburian M. Haematogenous acute and subacute paediatric osteomyelitis: a systematic review of the literature. J Bone Joint Surg Br 2012;94:584–95.
6. Dodwell ER. Osteomyelitis and septic arthritis in children: current concepts. Curr Opin Pediatr 2013;25:58–63.
7. Peltola H, Unkila-Kallio L, Kallio MJ. Simplified treatment of acute staphylococcal osteomyelitis of

childhood. The Finnish Study Group. Pediatrics 1997;99:846–50.

8. Gutierrez K. Bone and joint infections in children. Pediatr Clin North Am 2005;52:779–94.

9. Howard-Jones AR, Isaacs D. Systematic review of duration and choice of systemic antibiotic therapy for acute haematogenous bacterial osteomyelitis in children. J Paediatr Child Health 2013;49:760–8.

10. Bonhoeffer J, Haeberle B, Schaad UB, Heininger U. Diagnosis of acute haematogenous osteomyelitis and septic arthritis: 20 years experience at the University Children's Hospital Basel. Swiss Med Wkly 2001;131:575–81.

11. Wu JS, Gorbachova T, Morrison WB, Haims AH. Imaging-guided bone biopsy for osteomyelitis: are there factors associated with positive or negative cultures? AJR Am J Roentgenol 2007;188:1529–34.

12. Frank G, Mahoney HM, Eppes SC. Musculoskeletal infections in children. Pediatr Clin North Am 2005;52:1083–106.

13. Steer AC, Carapetis JR. Acute hematogenous osteomyelitis in children: recognition and management. Paediatr Drugs 2004;6:333–46.

14. Roine I, Arguedas A, Faingezicht I, Rodriguez F. Early detection of sequela-prone osteomyelitis in children with use of simple clinical and laboratory criteria. Clin Infect Dis 1997;24:849–53.

15. Wheeler AM, Heizer HR, Todd JK. Influence of culture results on management and outcome of pediatric osteomyelitis and/ or septic arthritis. J Pediatric Infect Dis Soc 2012;1:152–6.

16. Le Saux N, Howard A, Barrowman NJ, Gaboury I, Sampson M, 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 Infect Dis 2002;2:16.

17. Weichert S, Sharland M, Clarke NM, Faust SN. Acute haematogenous osteomyelitis in children: is there any evidence for how long we should treat? Curr Opin Infect Dis 2008;21:258–62.

18. Tuason DA, Gheen T, Sun D, Huang R, Copley L. Clinical and laboratory parameters associated with multiple surgeries in children with acute hematogenous osteomyelitis. J Pediatr Orthop 2014;34:565–70.

19. Connolly SA, Connolly LP, Drubach LA, Zurakowski D, Jaramillo D. MRI for detection of abscess in acute osteomyelitis of the pelvis in children. AJR Am J Roentgenol 2007;189:867–72.

20. Russell, C.D.; Ramaesh, R.; Kalima, P.; Murray, A.; Gaston, M.S. Microbiological characteristics of acute osteoarticular infections in children. J. Med. Microbiol. **2015**, 64, 446–453.

21. Peltola, H.; Pääkkönen, M. Acute osteomyelitis in children. New Engl. J. Med. **2014**, 370, 352–360

22. Copley, L.A.; Kinsler, A.; Gheen, T.; Shar, A.; Sun, D.; Browne, R. The impact of evidence-based clinical practice guidelines applied by a multidisciplinary team for the care of children with osteomyelitis. J. Bone Joint Surg. Am. **2013**, 95, 686–693
23. Hawkshead, J.J.; Patel, N.B.; Steele, R.W.; Heinrich, S.D. Comparative severity of pediatric osteomyelitis attributable to methicillin-resistant versus methicillin-sensitive Staphylococcus aureus. J. Pediatr. Orthop. **2009**, 29, 85–90.
24. Boyle-Vavra, S.; Daum, R.S. Community-acquired methicillin-resistant Staphylococcus aureus: The role of Panton-Valentine leukocidin. Lab. Investig. **2007**, 87, 3–9
25. Tong, S.Y.; Davis, J.S.; Eichenberger, E.; Holland, T.L.; Fowler, V.G., Jr. Staphylococcus aureus Infections: Epidemiology, pathophysiology, clinical manifestations, and management. Clin. Microbiol. Rev. **2015**, 28, 603–661.
26. Dohin, B.; Gillet, Y.; Kohler, R.; Lina, G.; Vandenesch, F.; Vanhems, P.; Floret, D.; Etienne, J. Pediatric one and joint infections caused by Panton-Valentine leukocidin-positive Staphylococcus aureus. Pediatr. Infect. Dis. J. **2007**, 26, 1042–1048. [CrossRef] [PubMed]
27. Dumitrescu, O.; Boisset, S.; Badiou, C.; Bes, M.; Benito, Y.; Reverdy, M.E.; Vandenesch, F.; Etienne, J.; Lina, G. Effect of antibiotics on Staphylococcus aureus producing Panton-Valentine leukocidin. Antimicrob. Agents Chemother. **2007**, 51, 1515–1519. [CrossRef] [PubMed]
28. Zaoutis, T.; Localio, A.R.; Leckerman, K.; Saddlemire, S.; Bertoch, D.; Keren, R. Prolonged intravenous therapy versus early transition to oral antimicrobial therapy for acute osteomyelitis in children. Pediatrics **2009**, 123, 636–642. [CrossRef] [PubMed]
29. Peltola, H.; Pääkkönen, M.; Kallio, P.; Kallio, M.J. 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. Pediatr. Infect. Dis. J. **2010**, 29, 1123–1128. [CrossRef] [PubMed]
30. Keren, R.; Shah, S.S.; Srivastava, R.; Rangel, S.; Bendel-Stenzel, M.; Harik, N.; Hartley, J.; Lopez, M.; Seguias, L.; Tieder, J.; et al. Pediatric research in inpatient settings network comparative effectiveness of intravenous vs. oral antibiotics for postdischarge treatment of acute osteomyelitis in children. JAMA Pediatr. **2015**, 169, 120–128. [CrossRef] [PubMed]
31. Faust, S.N.; Clark, J.; Pallett, A.; Clarke, N.M. Managing bone and joint infection in children. Arch. Dis. Child. **2012**, 97, 545–553. [CrossRef] [PubMed]
32. Michelow, I.C.; Mandell, J.G. Sequential intravenous oral antibiotic therapy for osteomyelitis: How short is long enough? JAMA Pediatr. **2015**, 169, 698–699. [CrossRef] [PubMed]
33. Tamma, P.D.; Milstone, A.M. Outpatient antibiotic therapy for acute osteomyelitis in children: Balancing safety and efficacy. JAMA Pediatr. **2015**, 169, 108–109. [CrossRef] [PubMed]
34. Messina, A.F.; Namtu, K.; Guild, M.; Dumois, J.A.; Berman, D.M. Trimethoprim-sulfamethoxazole therapy for children with acute osteomyelitis. Pediatr. Infect. Dis. J. **2011**, 30, 1019–1021. [CrossRef] [PubMed]

35. Tafin-Kampé, K.; Kamsu-Foguem, B. Acute osteomyelitis due to Staphylococcus aureus in children: What is the status of treatment today? Pediatr. Infect. Dis. **2013**, 5, 122–126. [CrossRef]
36. Martin, A.C.; Anderson, D.; Lucey, J.; Guttinger, R.; Jacoby, P.A.; Mok, T.J.; Whitmore, T.J.; Whitewood, C.N.; Burgner, D.P.; Blyth, C.C. Predictors of outcome in pediatric osteomyelitis: Five year experience in a single tertiary center. Pediatr. Infect. Dis. J. **2016**, 35, 387–391. [CrossRef] [PubMed]
37. Int. J. Environ. Res. Public Health **2016**, 13, 539 , Review - A Case of Acute Osteomyelitis: An Update on Diagnosis and Treatment , Elena Chiappini , Greta Mastrangelo and Simone Lazzeri